The Chemistry of Dienes and Polyenes. Volume 2
Edited by Zvi Rappoport

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The chemistry of
dienes and polyenes

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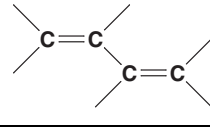

The chemistry of **dienes and polyenes**

Volume 2

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ZVI RAPPOPORT

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To

Ron Johnson

and

the late
Nir Poraz

To give and not to take

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Foreword

The first volume on *The Chemistry of Dienes and Polyenes* in the series 'The Chemistry of Functional Groups' (edited by Z. Rappoport) was published in 1997 and included 21 chapters — its table of contents appears at the end of this volume following the indexes. It was recognized then that several topics were not covered and a promise was made that a second volume covering these topics would be published in a few years.

The present volume contains 13 chapters written by experts from 11 countries, and treats topics that were not covered, or that are complementary to topics covered in Volume 1. They include chapters on mass spectra and NMR, two chapters on photochemistry complementing an earlier chapter on synthetic application of the photochemistry of dienes and polyenes. Two chapters deal with intermolecular cyclization and with cycloadditions, and complement a chapter in Volume 1 on intramolecular cyclization, while the chapter on reactions of dienes in water and hydrogen-bonding environments deals partially with cycloaddition in unusual media and complements the earlier chapter on reactions under pressure. The chapters on nucleophiliic and electrophilic additions complements the earlier chapter on radical addition. The chapter on reduction complements the earlier ones on oxidation. Chapters on organometallic complexes, synthetic applications and rearrangement of dienes and polyenes are additional topics discussed.

The literature coverage is up to the end of 1998 or early 1999.

I would be grateful to readers who call my attention to any mistakes in the present volume.

Jerusalem
January 2000

ZVI RAPPOPORT

The Chemistry of Functional Groups Preface to the series

The series 'The Chemistry of Functional Groups' was originally planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the preparation, properties and reactions of the functional group treated and on the effects which it exerts both in the immediate vicinity of the group in question and in the whole molecule.

A voluntary restriction on the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series and in textbooks (i.e. in books which are usually found in the chemical libraries of most universities and research institutes), should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the topic. Therefore each of the authors is asked not to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level.

It is realized that no plan can be devised for a volume that would give a complete coverage of the field with no overlap between chapters, while at the same time preserving the readability of the text. The Editors set themselves the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters. In this manner, sufficient freedom is given to the authors to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter deals with the general and theoretical aspects of the group.

(b) Chapters discuss the characterization and characteristics of the functional groups, i.e. qualitative and quantitative methods of determination including chemical and physical methods, MS, UV, IR, NMR, ESR and PES — as well as activating and directive effects exerted by the group, and its basicity, acidity and complex-forming ability.

(c) One or more chapters deal with the formation of the functional group in question, either from other groups already present in the molecule or by introducing the new group directly or indirectly. This is usually followed by a description of the synthetic uses of the group, including its reactions, transformations and rearrangements.

(d) Additional chapters deal with special topics such as electrochemistry, photochemistry, radiation chemistry, thermochemistry, syntheses and uses of isotopically labelled compounds, as well as with biochemistry, pharmacology and toxicology. Whenever applicable, unique chapters relevant only to single functional groups are also included (e.g. 'Polyethers', 'Tetraaminoethylenes' or 'Siloxanes').

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the authors and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, some volumes may be published without giving consideration to the originally planned logical order of the chapters.

Since the beginning of the Series in 1964, two main developments have occurred. The first of these is the publication of supplementary volumes which contain material relating to several kindred functional groups (Supplements A, B, C, D, E, F and S). The second ramification is the publication of a series of 'Updates', which contain in each volume selected and related chapters, reprinted in the original form in which they were published, together with an extensive updating of the subjects, if possible, by the authors of the original chapters. A complete list of all above mentioned volumes published to date will be found on the page opposite the inner title page of this book. Unfortunately, the publication of the 'Updates' has been discontinued for economic reasons.

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editors.

The publication of this series would never have been started, let alone continued, without the support of many persons in Israel and overseas, including colleagues, friends and family. The efficient and patient co-operation of staff-members of the publisher also rendered us invaluable aid. Our sincere thanks are due to all of them.

The Hebrew University
Jerusalem, Israel

SAUL PATAI
ZVI RAPPOPORT

Sadly, Saul Patai who founded 'The Chemistry of Functional Groups' series died in 1998, just after we started to work on the 100th volume of the series. As a long-term collaborator and co-editor of many volumes of the series, I undertook the editorship and this is the second volume to be edited since Saul Patai passed away. I plan to continue editing the series along the same lines that served for the first hundred volumes and I hope that the continuing series will be a living memorial to its founder.

The Hebrew University
Jerusalem, Israel
May 2000

ZVI RAPPOPORT

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
AIBN	azoisobutyronitrile
Alk	alkyl
All	allyl
An	anisyl
Ar	aryl
Bn	benzyl
Bz	benzoyl (C_6H_5CO)
Bu	butyl (also *t*-Bu or Bu^t)
CD	circular dichroism
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAH	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
EI	electron impact
ESCA	electron spectroscopy for chemical analysis
ESR	electron spin resonance
Et	ethyl
eV	electron volt
Fc	ferrocenyl

FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_3)
GLC	gas liquid chromatography
Hex	hexyl(C_6H_{13})
c-Hex	cyclohexyl(C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
i-	iso
Ip	ionization potential
IR	infrared
ICR	ion cyclotron resonance
LAH	lithium aluminium hydride
LCAO	linear combination of atomic orbitals
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	metal
M	parent molecule
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MS	mass spectrum
n	normal
Naph	naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Pc	phthalocyanine
Pen	pentyl(C_5H_{11})
Pip	piperidyl($C_5H_{10}N$)
Ph	phenyl
ppm	parts per million
Pr	propyl (also *i*-Pr or Pr^i)
PTC	phase transfer catalysis
Pyr	pyridyl (C_5H_4N)
R	any radical
RT	room temperature

s-	secondary
SET	single electron transfer
SOMO	singly occupied molecular orbital
t-	tertiary
TCNE	tetracyanoethylene
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TLC	thin layer chromatography
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl or tetramethylsilane
Tol	tolyl(MeC_6H_4)
Tos or Ts	tosyl(*p*-toluenesulphonyl)
Trityl	triphenylmethyl(Ph_3C)
Xyl	xylyl($Me_2C_6H_3$)

In addition, entries in the 'List of Radical Names' in *IUPAC Nomenclature of Organic Chemistry*, 1979 Edition, Pergamon Press, Oxford, 1979, p. 305–322, will also be used in their unabbreviated forms, both in the text and in formulae instead of explicitly drawn structures.

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CHAPTER **1**

Mass spectrometry and gas-phase ion chemistry of dienes and polyenes

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I. INTRODUCTION

As compared to other functional groups, mass spectrometry of olefins is special, and this holds for dienes and polyenes as well. The reason for this lies in the gas-phase ion chemistry of C−C double bonds. Unsaturated C−C bonds have medium ionization energies and are readily attacked by protons and other electrophiles and, in this sense, react similarly to other unsaturated functional groups. However, they are 'symmetrical' in that they connect, by definition, identical atoms, viz. carbons. Moreover, they are constituents of the carbon skeleton of organic molecules, not pending groups which are prone to be lost from the molecular framework by fragmentation. For these reasons, molecular ions, or ions in general, that contain C−C double (and triple) bonds easily undergo isomerization. Thus, removal of an electron from the π electron system of the >C=C< unit or addition of an electrophile to it may cause much more perturbation to the gaseous ion than, for example, ionization or protonation of a carbonyl group. The well-known loss of stereospecificity of *cis*- or *trans*-configurated double bonds under most mass spectrometric ionization conditions presents another problem in gaseous ions derived from dienes and polyenes.

On the other hand, unimolecular reactions of a molecular ion triggered by $>C^{+\bullet}-C<$ or $>C^{+}-CH<$ units are comparable to those triggered by other electron-deficient centres. For instance, formal abstraction of a hydrogen atom or a hydride, respectively, by these cationic groups and proton transfer from the allylic α-C−H bonds to other parts of the molecular ions can be understood similarly well as the corresponding reactions of related heteroatomic unsaturated groups. A lucid example is the McLafferty reaction, which occurs in the radical cations of olefins as it does in the radical cations of carbonyl groups. Also, allylic cleavage may be considered a well-behaved fragmentation reaction for olefins.

Yet, there is another complication with double (and triple) bonds. Things get more complicated because of the sp^2 (and sp) hybridization of the carbon atoms involved. Fragmentation of a bond attached directly to the unsaturated C−C unit (i.e. α-C−X) generates an sp^2- (or even sp-) hybridized carbenium ion, the formation of which requires much more energy than, e.g., allylic cleavage. Therefore, highly unsaturated carbon frameworks of dienes and polyenes in which the double bonds are either cumulated, conjugated or homoconjugated require relatively high internal excitation to undergo skeletal fragmentation. For the same reason, in turn, mass spectrometry of aromatic ions is relatively straightforward.

All these features have rendered mass spectrometry of dienes and polyenes somewhat diverse. In view of analytical applicability of mass spectrometry for distinguishing between isomeric olefins, there has been pertinent interest in the interplay of fundamental and applied aspects of mass spectrometry. Thus, besides the traditional investigation of the unimolecular chemistry of gaseous ions generated from these compounds, there has been a considerable body of research on the bimolecular gas-phase ion chemistry of alkenes and their higher unsaturated analogues, aiming mostly at the localization of the double bond(s) within the compound under investigation. Much effort has been made to perform 'gas-phase derivatization' of olefins, that is, to generate ionic derivatives which undergo more structure-specific fragmentation than the original substrates do. As the liquid-phase variant, derivatization of the neutral olefins followed by mass spectrometric analysis has also been studied in greater detail.

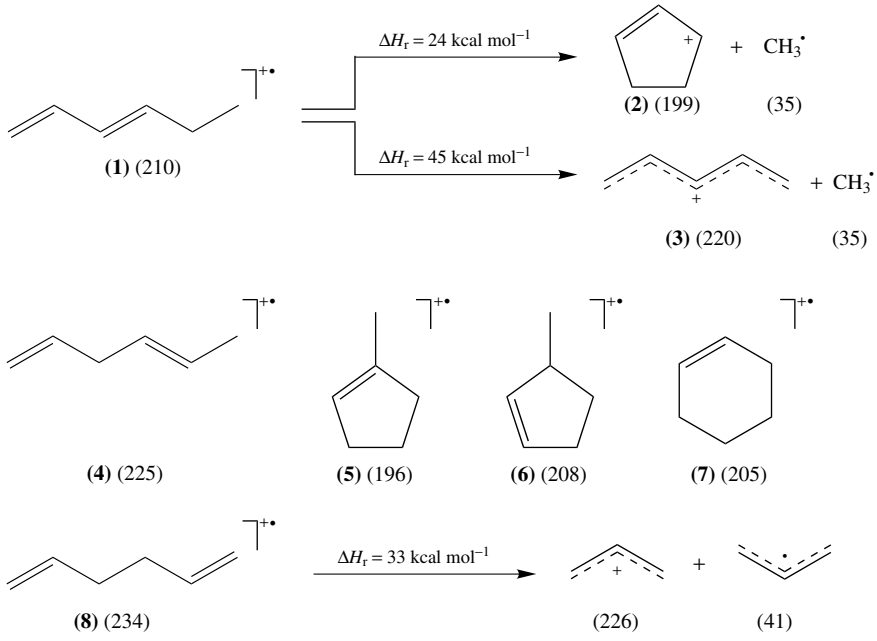
This review will first concentrate on the unimolecular gas-phase chemistry of diene and polyene ions, mainly cationic but also anionic species, including some of their alicyclic and triply unsaturated isomers, where appropriate. Well-established methodology, such as electron ionization (EI) and chemical ionization (CI), combined with MS/MS techniques in particular cases will be discussed, but also some special techniques which offer further potential to distinguish isomers will be mentioned. On this basis, selected examples on the bimolecular gas-phase ion chemistry of dienes and polyenes will be presented in order to illustrate the great potential of this field for further fundamental and applied research. A special section of this chapter will be devoted to shed some light on the present knowledge concerning the gas-phase derivatization of dienes and polyenes. A further section compiles some selected aspects of mass spectrometry of terpenoids and carotenoids.

Only a few reviews on mass spectrometry of monoolefins and cyclic isomers have appeared during the last two decades. Within this series, ionized alkenes and cyclopropanes have been discussed[1–3]. With regard to dienes and polyenes, reviews by Dass[4] on (formally) pericyclic reactions and by Tureček and Hanuš[5] and by Mandelbaum[6] on retro-Diels–Alder reactions in gaseous radical cations have to be noted. The gas-phase ion chemistry of ionized alkylbenzenes, a classical field of organic mass spectrometry ever since, was also reviewed in 1990 and overlaps in part with that of ionized cycloolefins such as cycloheptatriene, norbornadiene and cyclopentadiene[7]. Gaseous protonated alkylbenzenes, which can be considered positively charged olefinic species rather than aromatic ones, have been of particular interest and reviewed several times during the last decade[8–10]. It is noted here for curiosity that the EI mass spectra of terpenes and other highly unsaturated olefins show many prominent peaks that indicate the formation of both $[M - H]^+$ and $[M + H]^+$ ions of alkylbenzenes (cf Section VII)[11,12].

II. GASEOUS RADICAL CATIONS OF SOME DIENES AND POLYENES: THERMOCHEMISTRY OF SOME TYPICAL REACTIONS

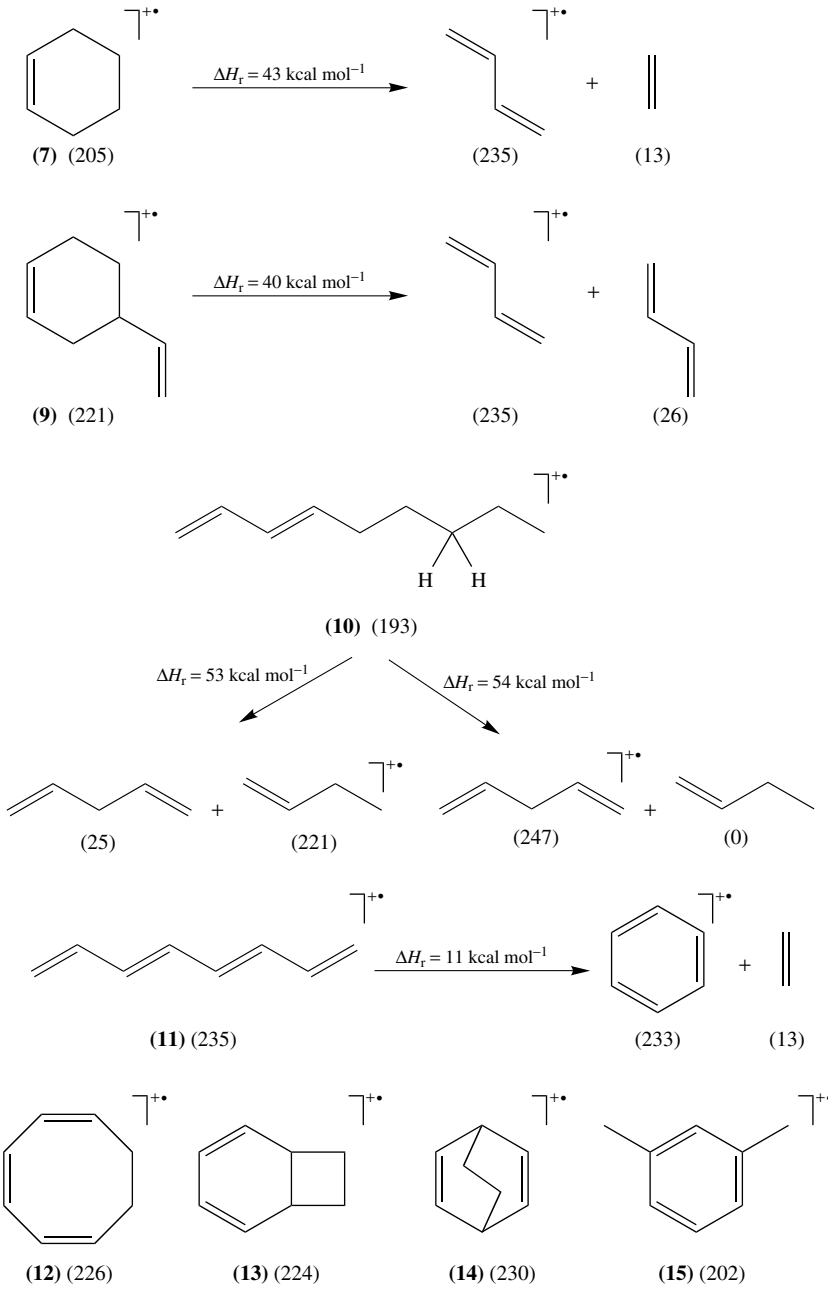
As mentioned in the Introduction, diene and polyene ions cannot undergo facile fragmentation reactions unless suitable saturated carbon centres are present at which C–C (or C–X) bond cleavage can occur to generate stable fragments. On the other hand, the availability of one or more unsaturated C–C bonds in the vicinity of a formally charged centre can easily give rise to bonding interaction, i.e. cyclization reactions. Moreover, 1,2-H shifts may lead to reorientation of the individual double bonds and open additional paths for C–C bonding between parts of the same or formally isolated π-electron systems. As a consequence, isomerization by cyclization is prevalent in the odd- and even-electron ions of dienes and polyenes, and negatively charged ions of these compounds also tend to undergo cyclization quite easily.

This section is mainly intended to demonstrate, by using some selected examples, the relative ease of cyclization reactions of organic cations containing two or several C−C double bonds. In fact, a multitude of such ring-forming isomerization processes take place prior to fragmentation but most of them remain obscured due to the reversibility of these processes. Only a few of them lead directly to energetically favourable exit channels, i.e. to specific fragmentation of the reactive intermediates. From the examples collected in Schemes 1 and 2, the reader may recognize some general trends on the energy requirements of the cyclization processes preceding the actual fragmentation reaction of ionized dienes and polyenes. The heats of formation of the reactant ions and their fragments are given in kcal mol^{-1} below the structural formulae. The collection is restricted to the radical cations since the thermochemical data on these are better known than on the even-electron cations. It may be noted, however, that the wealth of thermochemical data on organic cations and anions is steadily growing[13] and the reader is referred to recent compilations which are readily accessible nowadays[14].



SCHEME 1

In Scheme 1, the radical cations of the linear hexadienes and some cyclic isomers are contrasted. The heats of formation, ΔH_r, as determined from the heats of formation of the species involved, as well as the heats of formation of the isomeric radical cations themselves clearly reveal the favourable stability of the cyclic isomers and/or fragment ions. Thus, instead of the linear pentadienyl cation **(3)**, the cyclopenten-3-yl cation **(2)** is eventually formed during the loss of a methyl radical from ionized 1,3-hexadiene **(1)**. Since 1,2-H$^+$ shifts usually have low energy requirements (5–12 kcal mol^{-1}), interconversion of the linear isomers, e.g., **4**, and subsequent formation of the cyclic isomers, in particular of the ionized methylcyclopentenes **5** and **6**, can take place easily on the level of the



(7) (205) (235) (13)

(9) (221) (235) (26)

(10) (193)

(25) (221) (247) (0)

(11) (235) (233) (13)

(12) (226) **(13)** (224) **(14)** (230) **(15)** (202)

SCHEME 2

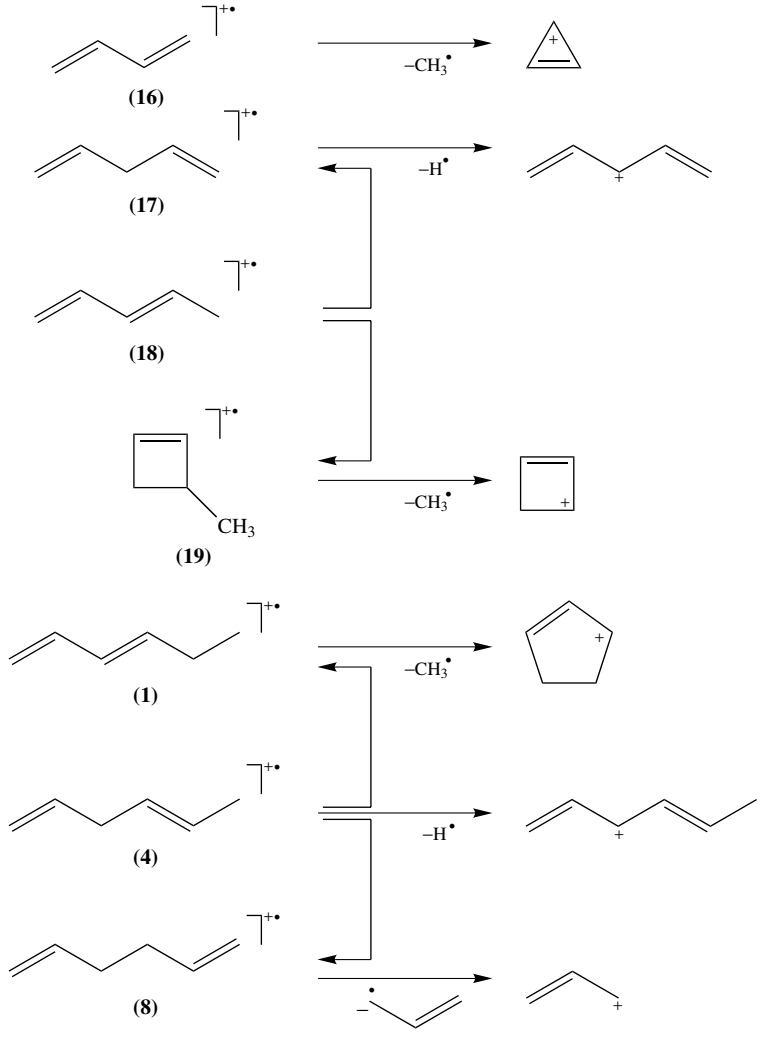
radical cations. It is also obvious that the direct bis-allylic C−C bond cleavage of ionized 1,5-hexadiene **(8)** is a kinetically fast process, but thermochemically it is still rather unfavourable as compared to isomerization to the methylcyclopentene radical cations followed by $CH_3^{\bullet}$ loss. Details of the gas-phase chemistry of $C_6H_{10}^{+\bullet}$ ions are discussed in Section III.

In Scheme 2, three types of elimination reactions from ionized dienes and polyenes are contrasted, again merely as examples for more complex reactant systems. The retro-Diels–Alder (RDA) reaction of ionized cyclohexenes (cf **7**) often occurs also in suitable diene and polyene analogues, e.g. in vinylcyclohexene radical cations (cf **9**). As can be seen from Scheme 2, the thermochemical energy requirements of the RDA reaction are relatively high, and again higher than those for $CH_3^{\bullet}$ loss. The McLafferty reaction of ionized 1,3-alkadienes, involving the rearrangement of a γ-$H^{\bullet}$ atom to the ionized double bond with subsequent cleavage of the allylic C−C bond, requires even more energy than the fragmentation processes discussed above, as shown for the case of 1,3-nonadiene **(10)**. Part of the endothermicity originates from the deconjugation of the 1,3-diene system and, in fact, McLafferty reactions are relatively rare with ionized dienes and polyenes. Finally, the expulsion of an arene from the radical cations of conjugated polyenes represents a lucid example for the intermediacy of cyclized isomers during the fragmentation of polyene ions such as **11**. Scheme 2 also shows that cyclic $C_8H_{10}^{+\bullet}$ ions, in particular ionized 1,3,5,7-cyclooctatriene **(12)** but also the bicyclic isomers **13** and **14**, are again more stable than acyclic ones, and all of them are much less stable than the *o*-xylene radical cations such as **15**. However, an intramolecular metathetic reaction between two remote C−C double bonds, viz. $\Delta(1)$ and $\Delta(7)$ in the case of 1,3,5,7-octatetraene **(11)**, leads to C(2)−C(7) and C(1)−C(8) bond formation. Thus, a stable arene unit is released, either as the ionic or the neutral fragment, leaving a neutral or ionized olefin, respectively. The reaction is believed to involve ionized bicyclo[4.2.0]octa-2,4-dienes (cf **13**) as intermediates, and charged fragments $[M - \text{arene}]^{+\bullet}$ (not shown in Scheme 2) prevail when the C−C double bond in the olefinic fragment is part of a larger conjugated π-electron system, as is the case in carotenoids (cf Section VII). The energy requirements of the arene elimination are intriguingly low for the parent case, but also for the higher analogues where a neutral arene is eliminated.

III. UNIMOLECULAR ISOMERIZATION AND FRAGMENTATION

A. Selected Linear Dienes: Allylic Cleavage and Isomer Distinction

As mentioned in the Introduction, isomerization is a common feature of the radical cations of dienes and polyenes. This holds unless allylic cleavage of one or two C−C bonds offers a both energetically and entropically favourable exit channel and the reacting ions are relatively highly excited. Thus, for 1,3-butadiene radical cations **(16)** a minimum of 57 kcal mol^{-1} is required to expel a $CH_3^{\bullet}$ radical and form the cyclopropenyl cation, *c*-$C_3H_3^{+}$ (Scheme 3). Aromaticity of the latter ion helps to let the reaction run but propargyl ions, $HC{\equiv}C{-}CH_2^{+}$, may also be formed. The high barrier towards fragmentation enables profound rearrangement of these relatively small ions. In the case of the pentadiene ions **17** and **18**, the least energy-demanding direct cleavage would be the loss of an $H^{\bullet}$ atom, but preceding cyclization to **19** offers a means to expel a $CH_3^{\bullet}$ radical as well. This is one of the simplest examples in which for highly unsaturated ions the number of sp^3-hybridized atomic centres is increased, thus opening the way for an energetically relatively favourable (allylic) cleavage (Scheme 3). Similar mechanisms apply for most of the next higher homologues, but here 1,2-H shifts — well known to occur in neutral olefins and allyl radicals — give rise to formation of the 1,5-hexadiene radical cation, which undergoes the least energetically expensive double allylic C−C bond cleavage (cf



SCHEME 3

Section II). Thus, the $C_3H_5^+$ (m/z 41) fragment ion generates an intensive peak in all of the standard (70 eV) EI mass spectra of the isomeric hexadienes. However, the molecular ion peak ($C_6H_{10}^{+\bullet}$, m/z 82) also gives relatively strong signals for all isomers, except for 1,5-hexadiene **(8)**, where it is completely absent[15]. Similar specificity has been observed for isomeric terpenes such as allo-ocimene, a triene containing a 1,4-diene substructure, and myrcene, bearing a 1,5-diene unit. In contrast, homosqualene presents an example of a 1,5-diene which undergoes both specific double allylic cleavage and single allylic cleavage after attaining conjugation by repeated H shift[16]. In general, allylic cleavage is a relatively specific process for higher branched alkenes and for alkadienes and -polyenes containing highly substituted double bonds and/or extended conjugated double bonds[17,18]. Special

methods such as field ionization (FI) mass spectrometry helps to make highly structure-specific allylic C–C bond cleavage become dominant[19,20]. EI-induced allylic cleavage has also been studied for a number of 1,2-alkadienes[21].

A number of papers discuss the behaviour of small diene ions in terms of gas-phase ion chemistry. Holmes[22] investigated the mass spectra of isomeric C_5H_8 hydrocarbons by deuterium labelling and found that the hydrogen atoms lose their identity prior to fragmentation. The standard EI spectra (obtained at 70 eV electron energy) of 1,3-pentadiene, isoprene and cyclopentene exhibit only minor differences. $H^{\bullet}$ atom loss from the molecular ion ($M^{+\bullet}$) produces the most abundant fragment ions, $C_5H_7^+$, and it may be argued that the highest $[(M - H)^+]/[M^{+\bullet}]$ ratio, found for cyclopentene, is due to the both energetically and entropically favourable formation of the allylic *c*-$C_5H_7^+$ cation. Clearly, the $C_5H_8^{+\bullet}$ molecular ions attain a common structure or mixture of isomeric structures prior to fragmentation. The almost identical mass spectra of piperylene and isoprene suggest that, in fact, not only hydrogen but also carbon scrambling occurs in these ions. Interestingly, the mass spectrum of spiropentane is most structure-specific in that the $C_4H_4^{+\bullet}$ ion (m/z 40) is particularly abundant, reflecting the preformation of the strained C_2H_4 units eliminated as ethene. Nevertheless, complete scrambling occurs in the spirocyclic isomer as well, in particular in the long-lived, metastable ions.

Metastable ions are those which survive the acceleration region of a sector-field mass spectrometer but fragment somewhere during the flight. If mass selection has been effected before fragmentation, the mass-analysed ion kinetic energy (MIKE) spectrum of the particular ions, or mixtures of ions, of the selected m/z ratio are obtained, reflecting the isomerization of these relatively weakly excited ions. When stable ions (i.e. those which would not undergo spontaneous fragmentation) are excited during their flight, e.g. by collision or by laser irradiation, the mass-selected, originally non-excited and thus non-interconverting ions can be sampled through their more or less structure-specific, collision-induced dissociation (CID)[23]. Much work has been devoted to the structure elucidation of organic ions, in particular to the classical problem of isomeric $C_7H_8^{+\bullet}$ and $C_7H_7^+$ ions[7,24]. Besides simply exciting the ions, they can be oxidized by stripping off another electron from a cation ('charge stripping', CS, or 'collisional ionization') or two electrons from an anion ('charge reversal', CR), or reduced by single electron transfer (in neutralization/reionization mass spectrometry, NRMS). Subsequent fragmentation, e.g. of the dications formed in the CS process, results in structure-specific mass spectra of doubly charged fragment ions. Maquestiau and coworkers[25] and Holmes and coworkers[26] have demonstrated this method to be useful for the identification of unsaturated radical cations including various $C_5H_8^{+\bullet}$ isomers.

Gross and coworkers[27] have generated the radical cations of fourteen acyclic and cyclic C_5H_8 isomers by using a soft ionization method, viz. 'charge exchange' (CE) with ionized carbon disulphide. This limits the excitation energy of the molecular ions, in this case $C_5H_8^{+\bullet}$, to a well-defined amount and thus the extent of isomerization is low. By using the combination of charge exchange and charge stripping (CE/CS) mass spectrometry, piperylene, cyclopentene and isoprene were found to undergo individual, i.e. structure-specific fragmentation. In these cases, substantial energy barriers exist, preventing the ions from interconversion at low internal energies. In all other cases, barriers towards isomerization are much lower. Thus, the remaining linear radical cations, i.e. ionized 1,2-, 1,4- and 2,3-pentadienes and the linear ionized pentynes, as well as vinylcyclopropane and 3-methylcyclobutene, readily adopt the 1,3-pentadiene structure prior to charge stripping, whereas the branched acyclic radical ions and ionized 1-methylcyclobutene are converted to ionized isoprene. As a consequence of the differently high isomerization barriers, adjustment of the pressure of the CS_2 charge exchange gas in the CI source may be used to

affect the internal energy of the $C_5H_8^{+\bullet}$ ion population which, in turn, is reflected by characteristic changes of the CS spectra.

Detailed measurements have been performed on the formation and fragmentation of radical cations of C_5H_8 hydrocarbons including the heats of formation of the $C_5H_7^+$ ions[22,28]. The proton affinities (PA) of cyclopentadiene (as well as of its heteroaromatic derivatives) have been determined by Houriet and his associates[29] using ion cyclotron resonance (ICR) mass spectrometry. Similar to pyrrole, furan and thiophene, protonation at the terminal positions of the diene system ('C_α') of cyclopentadiene is thermodynamically more favourable than at the C_β positions, with cyclopentadiene exhibiting the largest PA difference (*ca* 8 kcal mol^{-1}). Semi-empirical calculations suggested a non-classical, pyramidal structure for the product of C_β protonation. More recent computational work adds detailed information on the thermochemical stabilities of the individual $C_5H_7^+$ ions[30]. In fact, the allylic *c*-$C_5H_7^+$ ion was both measured[29] and calculated[30] to be *ca* 21 kcal mol^{-1} more stable than the open-chain pentadienyl cation and *ca* 19 kcal mol^{-1} more stable than the homoallylic, non-classical cyclopenten-4-yl cation. Since the experimental work discussed above provides only semi-quantitative, if any, information on low-lying isomerization barriers, computational approaches to the energy hypersurface of gaseous ions have gained much importance.

The $C_5H_8^{+\bullet}$ ion manifold has been used also by other groups as a test case to explore the possibilities of using special mass spectrometric techniques to distinguish the ionic isomers and, thereby, their neutral precursors. An interesting additional degree of freedom available in CID and CS measurements is to vary the collision energy and the number of collisions. Thus, energy-resolved mass spectrometry (ERMS) was studied with $C_5H_8^{+\bullet}$ ions by Jennings, Cooks and coworkers[31] and revealed the potential to identify isomers, viz. ionized 1,3- and 1,4-pentadiene, which were found to be indistinguishable otherwise. Beynon and coworkers[32] compared energy-dependent collision-induced dissociation, high-energy CID and a refined charge stripping technique comprising electron capture of the doubly charged ions (CS/EC). Although this work reflects the sensitivity of structure elucidation of highly unsaturated radical cations, it confirms that distinction is possible, in particular with CS techniques, between the branched acyclic (isoprene-type) and cyclic (cyclopentene) isomers. Besides CS and CS/EC mass spectrometry of mass-selected stable singly charged ions, doubly charged ions already generated in the EI ion source can be mass-selected after acceleration and subsequently subjected to electron capture. Such doubly-charged-ion ('2*E*') mass spectra have been examined by Moran and coworkers[33] for a large set of alkenes including acyclic and cyclic alkadienes. Double ionization energies of a particular C_5H_8 isomer, 1,1-dimethylallene, concerning the triplet state of $C_5H_8^{2+}$ were determined by Harris and coworkers[34].

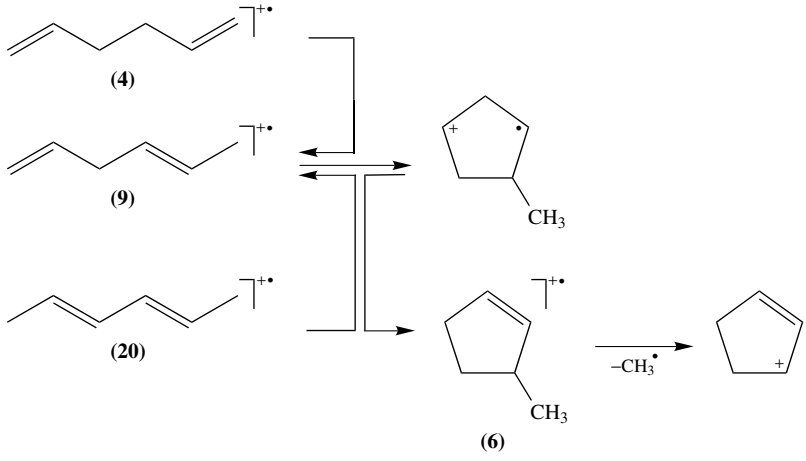
An alternative mass spectrometric technique to distinguish alkenes and more highly unsaturated radical cations is photodissociation mass spectrometry. In this method, laser light of variable wavelength is focused onto the beam of mass-selected ions and rapid, structure-specific dissociation may be achieved. By using this technique, $C_5H_8^{+\bullet}$ ions were probed by Wagner-Redeker and Levsen[35] and found to exhibit clearly distinct wavelength-dependent dissociation. For example, ionized 1,2- and 1,3-pentadiene not only exhibit extremely different cross sections in the wavelength range of $450 \leqslant \lambda \leqslant 535$ nm, but also clearly distinct mass spectra. Many related studies using light-induced excitation of gaseous olefinic ions have been reported. Dunbar and coworkers[36] investigated the photodissociation of six hexadiene radical cations. The spectra of the 1,3- and the 2,4-hexadienes were distinguishable and, by using laser light in the visible region ($478 \leqslant \lambda \leqslant 510$ nm), even all of the three stereoisomeric 2,4-hexadiene ions gave distinct spectra. Less long-lived stereoisomeric 2,4-hexadiene (and 1,3-pentadiene) radical cations studied by

Krailler and Russell[37] were found to give indistinguishable photodissociation mass spectra but different wavelength-dependence of the kinetic energy released upon fragmentation. Dunbar and coworkers[36] also showed that ionized 1,4-hexadiene is readily converted to the 2,4-isomer(s) whereas ionized 1,5-hexadiene is not. Thus, the radical cations of the conjugated dienes do not suffer H shift or rotation about the ionized double bonds under these conditions; likewise, H shifts do not take place in the isomer containing 'fully isolated' double bonds, but they do occur in the isomer containing the 1,4-diene unit. In the latter case, activation by two adjacent vinylic groups certainly drives the formal 1,3-H shift, whereas single allylic activation is not sufficient. Note that in the case of the ionized 1,5-isomer, competition due to the particularly favourable cleavage of the central C−C bond cannot occur (see below).

Photodissociation-photoionization mass spectrometry (PDPIMS) represents another technique involving photolysis of gaseous ions. In this approach, the neutral precursors are first photodissociated with ultraviolet laser light and the neutral fragments produced then softly ionized by coherent vacuum UV irradiation. A special feature of the method is that isomerization of the neutral precursor can be detected. Among the cases reported for dienes, Van Bramer and Johnston[38] recently described the identification of various alkene isomers by PDPIMS, including various C_6H_{10} isomers. By using 9.68 and 10.49 eV photons for ionization of the neutral fragments, the four conjugated hexadienes were found to exhibit highly individual PDPI mass spectra. Distinct from the other three isomers, 1,5-hexadiene gave intense allyl fragments, in line with the facile cleavage of the central, two-fold allylic C−C bond, followed by ionization to $C_3H_5^+$ ions. This method is certainly interesting for direct analytical application.

In more early but very extensive and impressive work on $C_6H_{10}^{+\bullet}$ ions, eight of the ten possible linear hexadienes and related unsaturated isomers have been investigated by Wolkoff, Holmes and Lossing[39]. A total of thirty $C_6H_{10}^{+\bullet}$ ions were studied. By again combining several experimental methods such as deuterium labelling, ionization and appearance energy measurements and metastable peak shape analysis, the authors conclude that the allylic *c*-$C_5H_7^+$ ion is the only structure of the $[M - CH_3]^+$ ions formed from all these precursors. Successive 1,2-H and 1,3-H shifts were postulated to interconvert alkyne, allene and diene isomers, with preferential intermediacy of the conjugated diene radical cations such as **20** and ionized 3-methylcyclopentene **(6)** as the key isomer undergoing the final $CH_3^\bullet$ loss (Scheme 4). These results suggest that the $C_5H_7^+$ ion with the cyclopenten-3-yl structure is the origin of the ubiquitous m/z 67 signal giving the base or second most prominent peak in the EI mass spectra of heptadienes, octadienes and some higher homologues. A related study was focused on the $CH_3^\bullet$ loss from 1,5-hexadiene radical cations **8** generated both by field ionization (FI) and by EI and confirmed the isomerization of $C_6H_{10}^{+\bullet}$ ions by formation of a five-membered rather than a six-membered ring[40].

Recently, another useful method for the distinction of easily isomerizing olefinic radical cations has been developed by Tureček and Gu[41]. The whole set of positive ions generated in the EI source from isomeric hexadienes and 3-methyl-1,3-pentadiene were accelerated and then neutralized by passing through a zone filled with Xe or NO gas. The fast neutrals are then reionized by collisions with O_2 in a cell floated at high negative electric potential to exclude all of the fragment ions which were generated during the neutralization and reionization processes from transmission. The cationic products that had survived the whole flight path were then mass analyzed. In the case of the $C_6H_{10}^{+\bullet}$ ions, the 'survivor-ion' mass spectra yield better isomer differentiation than standard EI mass spectra, and the origin of this effect has been ascribed, inter alia[42], to the enhanced survival chance of most highly unsaturated ions as compared to those containing saturated



SCHEME 4

carbon centres and thus being able to fragment relatively easily, e.g. by allylic cleavage (cf Section I).

B. Linear Dienes that Cannot Undergo Allylic Cleavage: Allene and Butadienes

A number of studies using the same or closely related methodology deal with lower homologues of the pentadienes and hexadienes. They will only be mentioned here briefly. For isomerization of ionized butadienes by electrocyclic reactions, see Section III.D.

Allene and the butadiene radical cations have been studied extensively with respect to isomerization and fragmentation. Very recently, Hayakawa and coworkers[43] published their investigation on the dissociation of electronically excited C_3H_4 isomers generated during charge reversal (CR, also called 'charge inversion') with metal vapours in the mass spectrometer. In previous work[44], these authors reported that unequivocal discrimination is possible between ionized allene and ionized propyne using this technique. This is in line with early experimental work by Stockbauer and Rosenstock[45], Levsen and coworkers[46] and also with *ab initio* calculations by Frenking and Schwarz[47]. However, ionized propyne tends to isomerize to allene radical cation prior to fragmentation, as found by photoionization and photodissociation measurements by Parr and coworkers[48] and by van Velzen and van der Hart[49]. The latter authors suggest that the energy barrier for interconversion of these $C_3H_4^{+\bullet}$ isomers by consecutive 1,2-H shifts is similarly high, as is that for the loss of $H^\bullet$ yielding *c*-$C_3H_3^+$. A more recent work by van der Hart[50] offers a detailed computational analysis of the allyl radical and allyl cationic intermediates formed by the first 1,2-H shift. The CID and CS spectra of ionized cyclopropene have been compared with those of ionized allene and propyne[51]. A completely different approach by Cornaggia[52] may be mentioned; he used Coulomb explosion mass spectrometry to determine the geometry of the carbon skeleton of $C_3H_4^{+\bullet}$ ions. Also, photoionization and photodissociation of allene clusters (dimers and trimers) has been studied[53] (cf Section V.A).

Early EI studies by King[54] suggested that 1,3-butadiene radical cations suffer isomerization and complete hydrogen scrambling prior to loss of $H^\bullet$ and C_2H_2. Later, Gross, Nibbering and coworkers[55] showed by field ionization kinetic (FIK) measurements that

hydrogen scrambling prior to loss of $CH_3^{\bullet}$, giving *c*-$C_3H_3^+$, is complete within *ca* 10^{-11} s while carbon scrambling is relatively slow. It is only with metastable ions of lifetimes of $10^{-5}-10^{-4}$ s that the carbon atoms lose their identity, too. Besides their unimolecular reactivity[56], in particular in pericyclic reactions (see Section III.D), gaseous $C_4H_6^{+\bullet}$ ions have also been investigated in detail by photodissociation techniques. Bunn and Baer[57] studied the isomerization of ionized 1,3-butadiene and 1- and 2-butyne by coincidence methods. Laser light (e.g. at $\lambda = 510$ nm) which photodissociates the butadiene radical ions does not affect the butyne ions. However, when the internal energy of the butyne ions was increased in a controlled manner, photodissociation set in at 10.6 eV, i.e. at some 1.8 eV (42 kcal mol^{-1}) above the ground state of the 1,3-butadiene ions. This value was interpreted to reflect the activation barrier towards hydrogen shift to form both of the isomeric butyne radical cations. In a more recent study, Baer and coworkers[58] investigated the details of the energetics and dynamics of the unimolecular isomerization of 1,3-butadiene radical cations, including the intermediacy of ionized 3-methylcyclopropene, prior to $CH_3^{\bullet}$ loss. The isomerization barrier towards the skeletal rearrangement was determined to be *ca* 46 kcal mol^{-1} and only 8 kcal mol^{-1} below the threshold of dissociation giving pure *c*-$C_3H_3^+$ ions[59]. Two-colour laser multiphoton ionization (MPI) and dissociation of 1,3-butadiene was measured by Chupka and coworkers[60]. The geometry of ionized 1,3-butadiene as determined by matrix infrared and resonance Raman spectroscopy by Bally and coworkers[61,62] may be mentioned here.

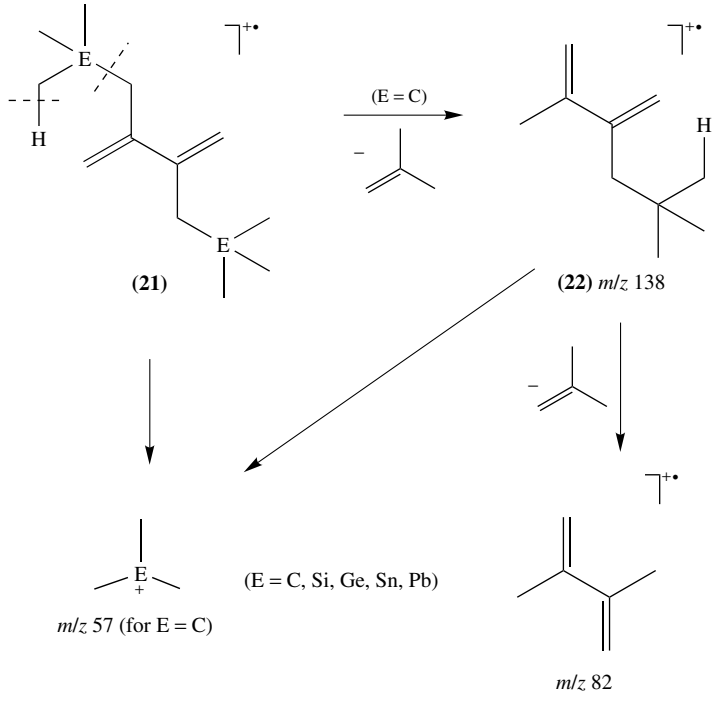
Not surprisingly, the presence of a hydroxy group in ionized 1,3-butadiene strongly affects the overall mechanism of the $CH_3^{\bullet}$ loss. Tureček, Gäumann and coworkers[63] generated the highly stable dienol ion radical cation of 2-hydroxybutadiene radical cations by a retro-Diels–Alder reaction (see Section III.E) and showed, by extensive deuterium and ^{13}C labelling, that the highly stable acryloyl cations, $H_2C{=}CH{-}CO^+$, are formed, rather than hydroxycyclopropenylium ions. The EI mass spectra of several fluoro- and fluorochloro-substituted 1,3-butadienes have also been reported[64].

C. Linear Dienes and Polyenes: McLafferty Reactions

As mentioned in the Introduction, the ionized C–C double bond can trigger a characteristic hydrogen rearrangement reaction which, in turn, leads to allylic cleavage of the intermediate. Whereas the McLafferty reaction of ionized heteroatomic double bonds and aromatic nuclei is highly characteristic for the structure of the precursor molecule, the analytical value for this process with olefins decisively depends on the site stability of the unsaturation. Therefore, alkene ions which tend to undergo facile hydrogen shifts or even scrambling may give McLafferty rearrangement reactions which do not reflect the original structure. Of course, the presence of suitable saturated carbon centres is necessary to allow the γ-hydrogen migration to occur at all. In suitable cases, the relatively low energy requirements for the McLafferty reaction may help to compete with isomerization by H shifts. In the case of monoolefins, the McLafferty reaction was found to be rather unspecific for 1,2-alkyl-substituted dienes but quite specific for 1,1-dialkyl- and all more highly alkyl-substituted congeners[65]. For dienes and polyenes, however, fragmentation by McLafferty reactions is extremely rare, much in contrast to the fragmentation behaviour of alkylbenzene radical cations[7]. It is quite obvious that isomerization by C–C bond formation between the unsaturated sites predominates in ionized alkadienes and alkapolyenes, provided such cyclization reactions are sterically possible. Interestingly, in their comprehensive review published in 1974 on the McLafferty reaction, Bursey and coworkers[66] have commented on the suppression of the γ-H rearrangement to C–C double bonds when arene or/and carbonyl functions are also available in the radical cation[67]. Thus, in

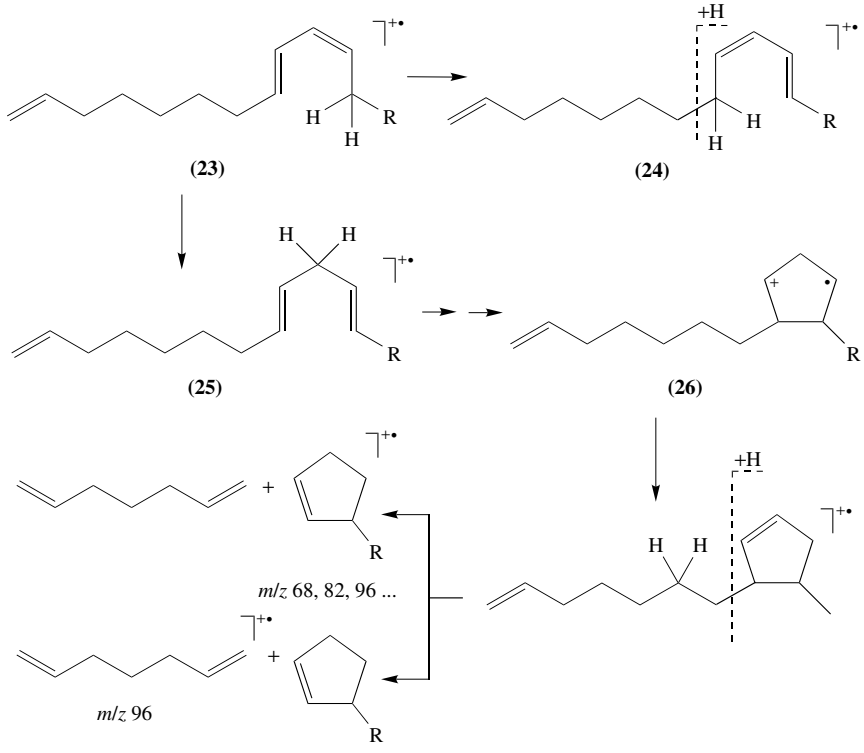
a case where the γ-H rearrangement to a C−C double bond was found to compete with that to a C−O double bond, the former is shifted to an internal position of the aliphatic chain prior to the actual McLafferty process[68].

Since C−C double bond shifts are even more frequent in ionized dienes and polyenes, clear-cut McLafferty reactions are extremely rare for these compounds. 2,3-Alkyl-substituted 1,3-butadienes may present an exception if 1,2-H shifts are also suppressed. An interesting example was reported by Bates and coworkers[69] for 2,3-neopentyl-1,3-butadiene (**21**, E = C) (Scheme 5). Despite the high tendency to undergo allylic cleavage yielding $C_4H_9^+$ ions (m/z 57), a peak of considerable relative intensity was observed at m/z 138 for the loss of C_4H_8 (isobutene). The $[M - C_4H_8]^{+\bullet}$ ions **(22)**, in which an ionized 1,3-diene unit has been preserved, suffers another McLafferty reaction to give $[M - 2\ C_4H_8]^{+\bullet}$ ions with m/z 82, of likewise moderate intensity. Without any doubt, ionized 2,3-dimethyl-1,3-butadiene is formed in this sequence of elimination reactions. The analogues containing Si, Ge, Sn and Pb, instead of carbon, at the neopentane centres did not give the corresponding element-organic alkadiene ions owing to the more facile allylic cleavage and the low stability of the corresponding element-organic isobutenes.



SCHEME 5

Another, and quite telling, example concerns the structure-specific elimination of olefins from acyclic trienes (Scheme 6). Bestmann and coworkers[70] found that the EI spectra of (8*E*,10*Z*)-1,8,10-dodecatriene (**23**, R = H), (11*E*,13*Z*)-1,11,13-pentadecatriene and some of their homologues display characteristic peaks at m/z 68, 82, 96 etc., corresponding to the formation of ionized alkadienes $C_{5+n}H_{8+2n}{}^{+\bullet}$, along with a neutral diene. The peaks



SCHEME 6

corresponding to the complementary charge distribution were also observed. Measurements at low ionization energy clearly favoured these rearrangement reactions, a typical behaviour for slow reorganization processes requiring only low activation energies but long ion lifetimes. Although no clear-cut mechanism has been forwarded, it is obvious that the (ionized) 1,3-butadiene unit triggers hydrogen rearrangements such as specific ones, e.g. 1,5-H shifts leading to **24** and subsequent allylic C−C bond cleavage, but also unspecific ones, i.e. by repeated 1,2-H shifts. In the present case, the latter process would convert the 1,3-diene **(23)**, to the 1,4-diene **(25)** which is prone to cyclization. The alkylalkenyl-substituted cyclopentene **(26)** thus formed can undergo a 1,2-H shift followed by the McLafferty reaction to yield even-mass fragments which are characteristic for the initial 1,3-butadiene unit.

However, things may become even more difficult. In a recent communication, Miyashi and coworkers[71] discussed the possibility of the Cope rearrangement in the radical cations of five dimethyldiphenyl-substituted 1,5-hexadienes and three isomeric dimethyldiphenyl-substituted bicyclo[2.2.0]hexanes. The 70 eV EI spectra of these compounds exhibit slight differences and the cleavage of the bis-allylic C−C bond is a minor fragmentation channel only. Unexpectedly, the base peak (m/z 158) corresponds to the elimination of 104 mass units. The authors attribute this to a McLafferty reaction as major exit from the putative equilibrium of the isomers produced by the Cope rearrangement. However, in view of the general tendency of highly unsaturated alkylbenzene radical cations to undergo cyclization[7], various other isomerization paths seem likely to intervene.

In concluding this section, the EI mass spectra of some 'true' polyolefins may be discussed. Remarkably, the normal 1, 5, 9, ... sequence of double bonds in oligoterpenes does not permit elimination processes such as the McLafferty reaction. Several double bond shifts would enable this type of reaction to occur. Although structure-specific allylic or bis-allylic cleavage occurs in large isoprenoids, random H migrations may compete and suppress structure-specific analytical information. Bhalerao and Rapoport[72] performed a systematic study of several isoprenyl ketones bearing three to five isoprene units, one of which is saturated, as model cases for higher isoprenoids. Extensive hydrogen migration was observed, and the major primary fragmentations were found to be alkyl loss ($C_nH_{2n+1}^+$, $1 \leqslant n \leqslant 6$). Only in one case do the spectra contain an abundant even-mass fragment ion (m/z 136) corresponding to the mass of a monoterpene unit, $C_{10}H_{16}$. However, formation of this radical cation requires double 1,2-H shift along the chain and is thus non-diagnostic for analytical purposes. As the authors stated, this shows the 'limitations of [conventional EI] mass spectrometry for detection of the position of a saturated isoprene unit in polyisoprenoids'. Likewise, some olefin eliminations have been reported[73] for the EI spectra of carotenoids, but the details of the mechanism appear doubtful in view of nowadays general insights into the complexity of ionic rearrangements.

D. Butadiene and Cyclobutene

The interconversion of butadiene radical cations and ionized cyclobutene represents a model case for a formal pericyclic process. Much work has been invested to study not only the distinguishability of these isomers and their derivatives by mass spectrometry, but also to check the role of orbital symmetry in the ionic species. Dass[4] has addressed the latter problem in depth in a review on pericyclic reactions in radical cations in both the gas and condensed phases and no further survey on the papers mentioned there will be given here. The topic pertains also to the ring-opening of ionized benzocyclobutene to ionized *ortho*-quinodimethane (cf Section V) and various other phenyl-, methyl- and carboxy-substituted derivatives. In this context, we restrict ourselves here mentioning that an upper limit of 7 kcal mol^{-1} only has been determined by CE mass spectrometry for the activation barrier of the cycloreversion of the parent cyclobutene radical cations[74]. The energy requirement for the cycloreversion of ionized 1- and 3-substituted cyclobutenes were found, by experiment, to be markedly different. Obviously, dissociation of the (in a sense bis-allylic) strained C−C bond is much more facile when the substituent is at C-3, i.e. at the α position to the bond to be cleaved[75]. Also, it may be pointed out that the agglomeration of several double bonds in olefins containing aromatic nuclei gives rise to various cyclization paths. For example, 1-phenylcyclobutene and 2-phenyl-1,3-butadiene radical cations were shown to isomerize to ionized 1-methylindene[76]. This behaviour holds also for other alkylbenzenes containing unsaturated bonds in the side chain[7].

Mandelbaum and coworkers[77] reported on the partial retention of the stereochemical identity of the 1,3-butadiene skeleton prior to fragmentation in the EI mass spectra of the isomeric dimethyl 3,4-diethylmuconates. Whereas the radical cations of the *trans*,*trans*-isomer exhibits loss of methanol, those of the *cis*,*cis*- and the *cis*,*trans*-isomers both expel a methoxy radical during cyclization to the respective pyrylium cations. In a subsequent work[78], the EI mass spectra of the dimethyl esters of the stereoisomeric dimethyl muconates and some 3,4-disubstituted derivatives have also been studied with respect to electrocyclic ring closure to the corresponding dimethyl cyclobut-3-ene-1,2-dicarboxylates. To a great extent, both the stereoisomers and constitutional isomers were found to behave in a distinct way and it was concluded that electrocyclization is largely suppressed by specific neighbouring group interactions involving the carboxylate and the 3,4-alkyl groups.

The proton affinities of 1,2- and 1,3-butadiene and of 2-butyne have been determined by Lias and Ausloos[79] using equilibrium measurements in an Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer. Surprisingly, they were found to be almost identical. The bimolecular reactivity of the $C_4H_7^+$ cations formed from the three isomers was also reported.

E. Cyclic Dienes and Polyenes: Retro-Diels–Alder and (Apparent) Diels–Alder Reactions

One of the most characteristic fragmentation reactions of ionized cycloalkenes is the expulsion of a C_2 unit from the ring as an olefin. In the simplest case, cyclohexene radical cations undergo dissociation of the allylic C−C bonds to produce neutral ethene and ionized 1,3-butadiene. Substituents on the cyclohexene ring may favour the allylic cleavage but also invert the distribution of the positive charge, to generate ionized ethene and neutral butadiene pair of fragments. Further, H shifts may precede fission of the C−C bond(s) and lead to RDA products of non-specific masses. Fortunately, the highly excited molecular ions produced in the standard 70 eV EI mass spectra are sufficiently short-lived to favour the allylic cleavage reactions over competing rearrangement processes. In contrast, long-lived cyclohexene radical cations, i.e. metastable ions, are known to undergo extensive H shifts[80,81].

Mass spectrometric retro-Diels–Alder reactions are particularly interesting for the characterization of complex alicyclic molecular frameworks. Just as Diels–Alder reactions in synthetic organic chemistry allow one to construct complex structures by a single preparative step, the retro-Diels–Alder reaction yields literally 'clear-cut' analytical information although more than one bond has to be broken. Moreover, the formal analogy between the retro-Diels–Alder reaction of neutral reactants and the cycloreversion of radical cations in the mass spectrometer offers the potential to use this fragmentation as a probe for the stereochemistry of the cyclic or polycyclic compounds under investigation. An important question directly associated with this problem refers to the concertedness or non-concertedness of pericyclic reactions in (open-shell) radical cations. Therefore, extensive work has been done on the applicability of the RDA-type fragmentation in mass spectrometry. Since a number of comprehensive reviews have appeared during the past decades, the following discussion will be restricted to a few selected examples on dienes and polyenes and in particular to more recent work on this class of alkenes.

An interesting prototype case which has been under intense study concerns the RDA reaction of the radical cations of 4-vinylcyclohexene. By using appropriate deuterium labelling, Smith and Thornton[82] studied the distribution of the positive charge between the two formally identical 1,3-butadiene fragments, one involving an original intra-ring C_4 subunit and the other a C_4 subunit including the original vinyl group. A considerable preference for charge retention in the latter fragment was observed. Since this is at odds with the Stevenson–Audier rule[83], which would predict strictly equal probability for ionization of the two butadiene fragments, the degree of concertedness of the C−C bond cleavage and the conservation of orbital symmetry was invoked to explain the experimental results[84,85]. Tureček and Hanuš[86] investigated the parent 4-vinylcyclohexene and four higher congeners generating two identical diene fragments. For 4-vinylcyclohexene and the 1,4-dimethyl derivative, these authors found only a slight preference for the charged butadiene and isoprene fragments, respectively, whereas the 1,Δ^1-dimethyl isomer (limonene), dicyclopentadiene and dicyclohexadiene all exhibited symmetrical charge distribution. As a tentative rationalization, unsymmetrical retention of charge in the fragments was attributed to unsymmetrical charge distribution in the molecular ions.

Notably, the labelling studies with the ionized vinylcyclohexenes enabled the distinction of the two moieties in the molecular ions that eventually yield the diene fragments. In fact, H atom shifts were found to be relatively slow in the ions undergoing the RDA processes, in contrast to ionized cyclohexene which is known to suffer fast and extensive hydrogen scrambling after field ionization (FI) even at very short ion lifetimes[80]. Obviously, once again, dissociation of the particularly weak bis-allylic C−C bond present in the 4-vinylcyclohexene-type radical cations is sufficiently fast to largely suppress isomerization by 1,2- or 1,3-H shifts.

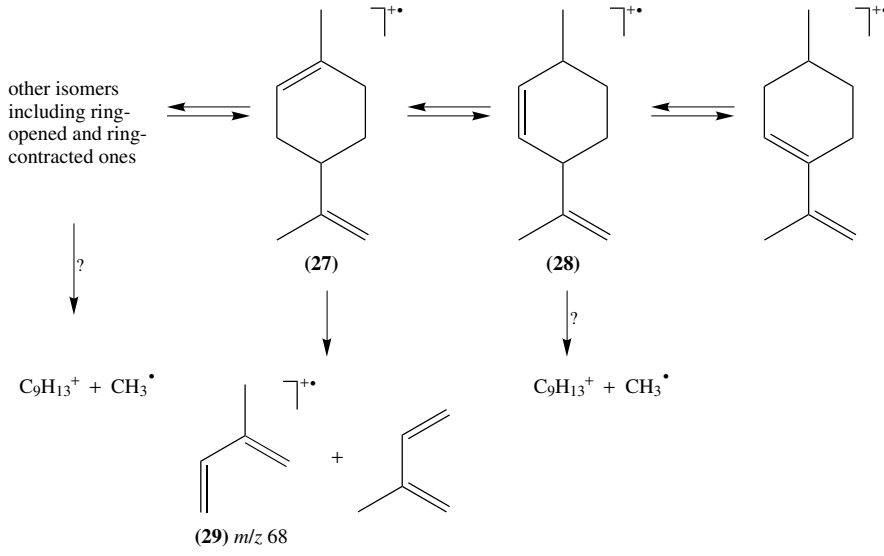
In this context, the striking difference of the standard 70 eV EI mass spectra of the isomeric cyclooctadienes may be mentioned here (see below)[87]. Whereas the radical cations of the stereoisomeric 1,5-cyclooctadienes, containing two bis-allylic C−C bonds, give the products of the two-fold allyl cleavage as the base peak ($[C_4H_6]^{+\bullet}/[M]^{+\bullet} \approx 10 : 1$), the *cis*,*cis*-1,4- and *cis*,*cis*-1,3-cyclooctadiene ions are reluctant to do so ($[C_4H_6]^{+\bullet}/[M]^{+\bullet} \approx 1 : 3$). Clearly again, 1,2- and 1,3-H shifts cannot efficiently compete with dissociation of the bis-allylic C−C bond.

The EI-induced fragmentation of gaseous [4 + 2]- and [2 + 2]dicyclopentadiene radical cations has been studied by Roth and coworkers[88] using Fourier transform ion cyclotron resonance mass spectrometry, and compared to the cleavage of these ions in solution using chemically induced dynamic nuclear polarization (CIDNP). Both in the gas and in the liquid phase, the isomers of the molecular ions formed by single C−C bond cleavage were observed. It is noteworthy that these distonic ions were termed 'non-vertical radical' cations.

In the case of the parent $C_8H_{12}{}^{+\bullet}$ system, the reverse process of the RDA reaction, i.e. the formal Diels–Alder addition of a 1,3-butadiene radical cation to neutral 1,3-butadiene, has been studied in great detail. Groenewold and Gross generated the adduct ions in a usual CI source of a sector-field mass spectrometer. Characterization of the adduct ions by CID revealed the presence of a mixture of isomers, the composition of which strongly depends on the internal energy imposed on the adducts. 4-Vinylcyclohexene ions and an acyclic $C_8H_{12}{}^{+\bullet}$ isomer, probably with distonic structure, were identified as the major components and a stepwise mechanism, rather than a concerted one, was invoked[89]. In contrast, Bauld and coworkers[90] had suggested a concerted, albeit non-synchronous path for the formal 'cation-radical Diels–Alder' reaction on the basis of semiempirical and *ab initio* molecular orbital (MO) calculations. Later, the complexity of the $C_8H_{12}{}^{+\bullet}$ ion hypersurface was clearly demonstrated by Chen and Williams[91] using electron-spin resonance (ESR) spectroscopy of the bicyclo[3.2.1]oct-2-ene radical cations generated by skeletal rearrangement of 4-vinylcyclohexene upon radiolytic oxidation in freon matrix at 77 K.

Gross and coworkers[92] demonstrated that both $C_8H_{12}{}^{+\bullet}$ isomers reside in distinct potential wells and can be characterized by CID in both sector-field and FT-ICR mass spectrometers. The mass spectrometric experiments were in line with calculation in that the ionized bicyclic isomer appears to be more stable than 4-vinylcyclohexene ions, and with the radiolytic results in that a closely related bicyclic isomer, viz. ionized bicyclo[2.2.2]octene, is not easily formed upon ionization of the other C_8H_{12} hydrocarbons. The retro-Diels–Alder reaction of ionized bicyclo[2.2.2]octa-2,5-dienes leading to expulsion of the initially saturated bridge as an alkene gives rise to the base peak in the EI spectra[93].

Limonene, one of the most prominent natural monoterpenes (cf Section VII), represents a particular derivative of 4-vinylcyclohexene since it has been studied with respect to the pronounced energy dependence of its fragmentation behaviour (Scheme 7). Counterintuitively, and in contrast to 4-vinylcyclohexene, the radical cations of limonene **(27)** do not undergo the retro-Diels–Alder reaction if the internal energy of the ions is low. As



SCHEME 7

pointed out by Boyd and coworkers[94], ionization at 70 and even at 20 eV leads to abundant ionized and neutral isoprene expected for the RDA process, the $C_5H_8^{+\bullet}$ ions (m/z 68) giving rise to the base peak in the spectra, but neither the metastable ion (B/E linked scan) spectra nor CID spectra of stable ions exhibit a peak at m/z 68. Rather, loss of $CH_3^{\bullet}$ prevails as the primary fragmentation process. The origin of the m/z 68 peak from the singly charged molecular ion of limonene, $C_{10}H_{16}^{+\bullet}$ (m/z 136), is beyond any doubt since occurrence of a thermal RDA reaction or doubly charged $C_{10}H_{16}^{2+}$ ions were excluded. Moreover, the structure of the $C_5H_8^{+\bullet}$ ions formed from the high-energy molecular ions was confirmed to resemble that of ionized isoprene **(29)**. Deuterium labelling revealed extensive hydrogen scrambling prior to fragmentation, including the splitting into the moieties formed by the RDA path. As a consequence, low-energy molecular ions, e.g., **27**, obviously undergo even more extensive isomerization generating isomers such as **28** from which less energetically demanding C−C bond cleavages can occur, in particular loss of $CH_3^{\bullet}$. Later, the pronounced energy dependence of the fragmentation of ionized limonene was used by Cooks and coworkers as a probe to study the effects of energy deposition by surface-induced dissociation (SID) and energy- and angle-resolved mass spectrometry[95] and also under various conditions of tandem mass spectrometry present in triple quadrupole and FT-ICR instruments[96]. More recent work addressed the same problem using electron-induced dissociation (EID), by which electrons are collided with the ions of interest[97].

Many other ion−molecule reactions involving highly unsaturated hydrocarbon ions and neutral olefins or the equivalent strained cycloalkanes have been studied by mass spectrometry[98]. For example, we may mention here the addition of ionized cyclopropane and cyclobutane to benzene radical cations giving the respective *n*-alkylbenzene ions but also isomeric cyclodiene ions such as ionized 8,9-dihydroindane and 9,10-dihydrotetralin, respectively. Extensive studies have been performed on the 'dimerization' product of charged and neutral styrene[4].

In their recent landmark femtosecond-resolved mass spectrometry studies, Zewail and coworkers[99] have used mass spectrometry for monitoring the time-resolved unimolecular fragmentation of neutral norbornene and norbornadiene. In both cases, the RDA reactions occurred, but only in the norbornadiene case was the well-known $H^{\bullet}$ loss giving rise to $C_7H_7^+$ ions found to compete. Still, non-concertedness and biradicaloid character of the intermediates is being addressed by femtosecond dynamic studies. In this context, Kompa and coworkers[100] have compared the expulsion of H^+ from femtosecond-laser-irradiated 1,3-cyclohexadiene and 1,3,5-hexatriene. The closed-shell cation analogy of the RDA reaction of norbornene is the cycloreversion of bicyclo[3.2.1]oct-6-en-3-yl cations, which have been studied very recently by the present authors[101] in the context of the isomerization of protonated cycloheptatrienes[11]. The reverse reaction type, viz. cycloaddition of the allyl cation to 1,3-butadiene, has been recently studied by Pascual-Teresa and Houk[102] using *ab initio* calculations. In all cases mentioned, the results point to stepwise paths of cycloreversion or cycloaddition, respectively.

F. Selected Cycloalkadienes and Cycloalkapolyenes

Mass spectrometry of certain cyclic dienes and polyenes deserves special discussion owing to their prototypical isomerization and fragmentation behaviour. Among them, $C_5H_6^{+\bullet}$ ions from 1,3-cyclopentadiene, $C_6H_8^{+\bullet}$ ions from the cyclohexadienes, $C_7H_8^{+\bullet}$ and $C_7H_9^+$ ions from 1,3,5-cycloheptatriene and its isomers, as well as ions derived from 1,3,5,7-cyclooctatriene and its less unsaturated analogues will be treated here briefly.

Methylenecyclopropene and Cyclobutadiene. The radical cations of these smallest cycloalkadienes have been of high interest owing to their fundamental importance in physical organic chemistry[103]. Lifshitz and coworkers[104] were the first to find indications for the formation of isomeric $C_4H_4^{+\bullet}$ ions upon EI of benzene[105]. Using their distinct bimolecular reactivity in an ICR mass spectrometer, Ausloos[106] detected the presence of both a linear and a second, non-linear $C_4H_4^{+\bullet}$ isomer in the $[M - C_2H_2]^{+\bullet}$ ions generated by EI of benzene and suggested them to be ionized methylenecyclopropene. Bowers and coworkers[107] confirmed these results by CID spectrometry and elucidated the quantitative composition of the $C_4H_4^{+\bullet}$ ion mixture. Further experimental data on the $C_4H_4^{+\bullet}$ manifold were contributed by McLafferty and coworkers[108,109] by using CID mass spectrometry and neutralization–reionization mass spectrometry of the $C_4H_4^{+\bullet}$ ions generated, e.g. from Nenitzescu's hydrocarbon, tricyclo[4.2.2.$0^{2,5}$]deca-3,7,9-triene, as well as CID spectrometry of the $C_4H_7N^{+\bullet}$ adducts formed from $C_4H_4^{+\bullet}$ with ammonia[110]. Besides these $C_4H_4^{+\bullet}$ isomers, ionized vinylacetylene and butatriene were also distinguished by this method. Quantitation of the four isomers in mixtures of $C_4H_4^{+\bullet}$ ions generated from a large variety of neutral precursors was also performed[111]. For example, benzene radical cations were found to give 70% of ionized methylenecyclopropene and 30% of vinylacetylene, whereas ionized cyclobutadiene is the main product generated from CO loss of the radical cations of the benzoquinones, besides other suitable sources. The presence of minor amounts of butatriene radical cations (10%), besides a major fraction of ionized vinylacetylene (60%) and cyclic isomer(s) (30%, probably ionized methylenecyclopropene) was also determined by van der Hart[112] using photodissociation of benzene and 1,5-hexadiyne as precursors. Later, Cooks and coworkers[113] generated these $C_4H_4^{+\bullet}$ isomers in a directed way. Pure *c*-$C_4H_4^{+\bullet}$ ions were also generated by Jacobsen and coworkers[114] starting from *cis*-3,4-dichlorobutene and performing a well controlled ion/molecule reaction with bare Fe^+ ions in the cell of an FT-ICR mass spectrometer. The identity of these ions was probed by characteristic ion/molecule reactions (see Section V).

Schwarz and coworkers[115] used 1,2,3-butatriene, along with 1,3-butadiyne, as a precursor for the generation of neutral 1,2,3-butatrienylidene in a neutralization/reionization mass spectrometric sequence ($C_4H_4 \rightarrow C_4H_2^{-\bullet} \rightarrow C_4H_2 \rightarrow C_4H_2^{+\bullet}$).

Cyclopentadienes. Maquestiau, Beynon and coworkers[116] have studied the charge-stripping and collision-induced dissociation spectra of ionized cyclopentadiene and of the $C_5H_6^{+\bullet}$ ions generated from various precursors including dicyclopentadiene. Evidence for the presence of both cyclic and acyclic isomers was obtained. Cooks and coworkers[117] confirmed these results by applying surface-induced dissociation spectrometry, an alternative method using the excitation of mass-selected ions by bombarding them onto a surface and measuring the ionic fragments being 'reflected', to a similar set of $C_5H_6^{+\bullet}$ ions generated, *inter alia*, from norbornadiene, dicyclopentadiene and 2-methylenenorbornane.

The EI mass spectra of methyl-substituted cyclopentadienes were studied by Harrison and coworkers[118] and their fragmentation behaviour was found to be very similar to that of the isomeric cyclohexadienes. Major fragmentation paths were suggested to lead to protonated alkylbenzenes such as benzenium ($C_6H_7^+$) and toluenium ($C_7H_9^+$) ions. Obviously, formation of antiaromatic cyclopentadienyl cations is circumvented; however, other isomers may also be formed along with the (most stable) arenium-type fragment ions (see below). Open-chain 1,3,5-hexatriene isomers were also found to give similar EI mass spectra.

Cyclohexadienes and 1,3,5-Hexatrienes. Not only the standard EI mass spectra but also the CID spectra of the isomeric cyclohexadienes are indistiguishable, as shown by McLafferty and coworkers[119]. Owing to the conjugated π electron system, the 1,3-isomer has a significantly lower ionization energy than the 1,4-isomer ($\Delta IE = 13$ kcal mol^{-1})[14] but fragmentation to, e.g., $C_6H_7^+$ ions, whose structure has been a matter of debate in several aspects (see below)[120–122], is preceded by fast hydrogen scrambling. Among other sources, fragmentation of ionized 4-vinylcyclohexene and 1,5-cyclooctadiene generates cyclohexadiene radical cations as the major product[85,119]. Among other isomers, 1,3,5-hexatriene radical cations do not convert completely to the cyclohexadiene ions, as also shown by CID spectrometry[119]. Photodissociation of stereoisomeric 1,3,5-hexatrienes was stated to be identical[123]. The interconversion of 1,3-cyclohexadiene and its open-chain isomer has been reviewed together with related formally electrocyclic reactions in lower and higher analogues[4]. Schweikert and coworkers[124] recently demonstrated that plasma desorption (PD) mass spectra of the two isomeric cyclohexadienes are distinct, in contrast to their EI and CID spectra. It has to be noted that PD spectrometry not only yields the radical cations $M^{+\bullet}$ but also the protonated molecules $[M + H]^+$, along with their fragments, and the abundance ratio of these ions was found to be quite distinct. A comparative resonant two-photon ionization (R2PI) time-of-flight (TOF) mass spectrometry study on jet-cooled 1,3-cyclohexadiene and 1,3,5-hexatriene was performed by Share and Kompa[125]. The photodissociation study of Baumgärtel and coworkers[53] on allene clusters, which essentially produce ionized dimers and trimers, $(C_3H_4)_2^{+\bullet}$ and $(C_3H_4)_3^{+\bullet}$, reveal that the latter aggregates behave very similarly to those of the covalently bound radical cations. For example, the ionized allene dimer reacts similarly to the cyclohexadiene radical cations forming abundant $C_6H_7^+$ ions by loss of $H^\bullet$.

Various substituted 1,3-cyclohexadienes and their open-chain isomers, the respective 1,3,5-hexatrienes, have been studied by EI mass spectrometry with special regard to the stereospecificity of the mutual pericyclic interconversion. A brief discussion including the parent systems, ionized 1,3-cyclohexadiene and 1,3,5-hexatriene has been provided by Dass in his review on pericyclic reactions of radical cations[4]. McLafferty and coworkers[119] have shown that the two parent isomers are (almost) indistinguishable

by CID spectrometry. Thus, the barrier towards interconversion is very low as compared to those of fragmentation and the occurrence of the pericyclic process, in analogy to the neutral counterparts, appears to be rapid. Interestingly, *cis*- and *trans*-5,6-dimethyl-1,3-cyclohexadiene and the three corresponding acyclic $C_8H_{12}^{+\bullet}$ isomers, viz. *cis*,*cis*,*cis*-, *cis*,*cis*,*trans*- and *trans*,*cis*,*trans*-2,4,6-octatriene, also exhibit very similar EI mass spectra, as demonstrated by Rennekamp and Hoffman[126]. Loss of $CH_3^{\bullet}$ is the most prominent fragmentation in all cases, with a slight preference for the cyclic isomers, in which a direct exit path exists by dissociation of the allylic C−C bonds. Furthermore, $CH_3^{\bullet}$ loss and the other fragmentation channels (expulsion of $H^{\bullet}$, H_2 and the ensemble of both) were found to be associated with identical kinetic energy release (T_{kin}) values. No clear evidence for the role of orbital-symmetry control is deduceable from these studies. From a general view, it appears rather likely that other isomerization paths such as five-membered ring formation and extensive hydrogen shifts make up a highly complex hypersurface in these highly unsaturated radical cations.

Fulvene Radical Cations, Protonated Fulvene, and Isomeric $C_6H_6^{+\bullet}$ and $C_6H_7^{+}$ Ions. The radical cations of fulvene are isomeric to those of benzene and the open-chain $C_6H_6^{+\bullet}$ ions which have been studied in great detail with regard to the skeletal rearrangement of the prototype aromatic species prior to fragmentation. This topic has been reviewed earlier[7]. The chemistry of ionized fulvene and its derivatives has also been studied in various ways but is less understood than that of the linear $C_6H_6^{+\bullet}$ ions. An early work of Hanus and Dolejšek[127] showed that the EI-induced unimolecular fragmentation of 6-methylfulvene is very similar to that of toluene, 1,3,5-cycloheptatriene and some other C_7H_8 isomers. Rosenstock and coworkers[128] early indicated that the fulvene radical cation is the next stable $C_6H_6^{+\bullet}$ isomer beyond the benzene ion, which is only some 10 kcal mol^{-1} more stable[129]. Photoelectron spectroscopy had suggested an even smaller energy difference[130]. In recent years, more quantitative data have become available by combining techniques such as ion/molecule reactions, photodissociation mass spectrometry and computational approaches. Owing to distinct ion/molecule reactivity as compared to ionized benzene, fulvene ions reside in a relatively deep energy well[131]. The critical energy for $C_6H_6^{+\bullet}$ ion interconversion still lies some 58 kcal mol^{-1} above the heat of formation of the fulvene ion, as determined in computational work by van der Hart[132]. Yet, isomerization is possible since fragmentation is even more energy demanding.

Protonated fulvene (fulvenium) ions have been studied to a much lesser extent, although they represent isomers of benzenium ions, the prototype species for the major intermediates formed during electrophilic aromatic substitution. Based on ICR mass spectrometry, Lias and Ausloos[133] pointed out that loss of $H^{\bullet}$ from the ionized cyclohexadienes, *trans*-1,3,5-hexatriene and the methylcyclopentenes leads to a mixtures of two isomeric $C_6H_7^{+}$ ions, one being the benzenium ion and the other a less acidic species. Similar mixtures were obtained by ion/molecule reactions of ionized and neutral allene and propyne. The 'non-benzenium' ion was assigned the structure of protonated fulvene, and the C(1)-protonated form was suggested to be the most stable $C_6H_7^{+}$ isomer next to protonated benzene. Zhu and Gäumann[134] drew similar conclusions from infrared multiphoton dissociation of 1,4-cyclohexadiene radical cations formed under ICR conditions. Fulvenium ions were also identified as the product of ion/molecule reactions involving allyl bromide[135], vinyl chloride[136] and 1,3-butadiene[137]. In analogy to the isomeric $C_6H_6^{+\bullet}$ ions derived from fulvene and benzene, the difference in stability was found to be rather small, and a recent theoretical study by Bouchoux and coworkers[138] suggested C(1)-protonated fulvene to be by only 10 kcal mol^{-1} less stable than the benzenium ion. The details of the hypersurface were also calculated and, in further analogy

to the case of the radical cations, substantial energy barriers towards the skeletal rearrangement were calculated for the $C_6H_7^+$ ions. In the context of the ring contraction of protonated 1,3,5-cycloheptatriene and its 7-methyl derivative, $C_7H_9^+$ and $C_8H_{11}^+$, we have recently determined the thermochemical properties of protonated 6-methyl- and 6,6-dimethylfulvene[139].

For mass spectrometry and gas-phase chemistry of negative ions derived from fulvene, see Section IV.A.

Cycloheptatriene, Norbornadiene, Methylenecyclohexadienes (Isotoluenes) and Bicyclo[3.2.0]heptadienes. The gas-phase ion chemistry of ionized 1,3,5-cycloheptatriene is closely related to that of ionized toluene, in particular, and to that of norbornadiene and other 'non-aromatic' $C_7H_8^{+\bullet}$ isomers. This extensive body of work will not be discussed here since a detailed review on this topic has been published by one of these authors in the context of the gas-phase chemistry of the alkylbenzene radical cations[7,140]. This chemistry pertains also to the well-known isomerization of the even-electron $C_7H_7^+$ ions and to their formation from the respective parents, e.g. $C_7H_8^{+\bullet}$. A related, albeit chemically different field concerns protonated cycloheptatriene, i.e. the even-electron $C_7H_9^+$ ions[141], and alkylcycloheptatrienes, which are closely related to protonated toluene and higher alkylbenzenium ions. A parallel review by one of these authors[8] on protonated alkylbenzenes has been published, and recent investigations on protonated alkylcycloheptatrienes have highlightened the complexity of this gas-phase ion chemistry[11,142]. To a minor extent, ionized[135] and protonated[138] fulvenes have also been investigated with respect to their interconversion to their (mainly arene-derived) isomers.

More recent work on the chemistry of gaseous 1,3,5-cycloheptatriene radical cations concerns the energetics and dynamics of the interconversion with ionized toluene and the competing losses of $H^\bullet$ from both isomers. Lifshitz and coworkers[22,143] have reported on the details of the energy surface of the $C_7H_8^{+\bullet}$ ions. Most importantly, the critical energies for interconversion was determined to be only *ca* 4 and 5 kcal mol^{-1} below that of $H^\bullet$ loss from *c*-$C_7H_8^{+\bullet}$ and *c*-$C_6H_5CH_3^{+\bullet}$, respectively, and the potential wells for both isomers are very deep (28 and 45 kcal mol^{-1} below the isomerization barrier). This is in line with the previous findings that the radical cations of cycloheptatriene and toluene exhibit distinct CID spectra and time-resolved photodissociation[7]. As a consequence, energy-dependent interconversion of isomeric ions can occur to a significant extent in mass spectrometers in which the ions survive several collisions. This problem was recently addressed by Yost and coworkers[144], who reported on the marked dependence of the ion breakdown behaviour of toluene and cycloheptatriene radical cations on the resonant excitation time in a quadrupole ion-trap mass spectrometer. The doubly charged ion (2*E*) mass spectra of cycloheptatriene and toluene were reported by Moran and coworkers[145] to be remarkably different. Distinct from the spectrum of toluene, $[M - 6\ H]^+$ ions, generated from the corresponding doubly charged cations of cycloheptatriene, give rise to the predominant peak in the spectrum.

Gross and coworkers[146] recently published the CID spectra of ionized 7-methyl-1,3,5-cycloheptatriene generated by charge exchange with carbon disulphide [CE(CS_2)]. The spectra were found to be similar but not identical to those of ionized ethylbenzene and showed only minor dependence on the CE gas pressure (i.e. on the ions internal energy). Thus, partial interconversion was invoked. This result is in line with the previous finding by Grotemeyer and Grützmacher[147] that metastable 7-methylcycloheptatriene radical cations are kinetically trapped as stable ethylbenzene or xylene ions. Furthermore, the results are reminiscent of even earlier work by Kuck and Grützmacher[148] who found that metastable 7-(β-phenylethyl)-1,3,5-cycloheptatriene radical cations partially retain their

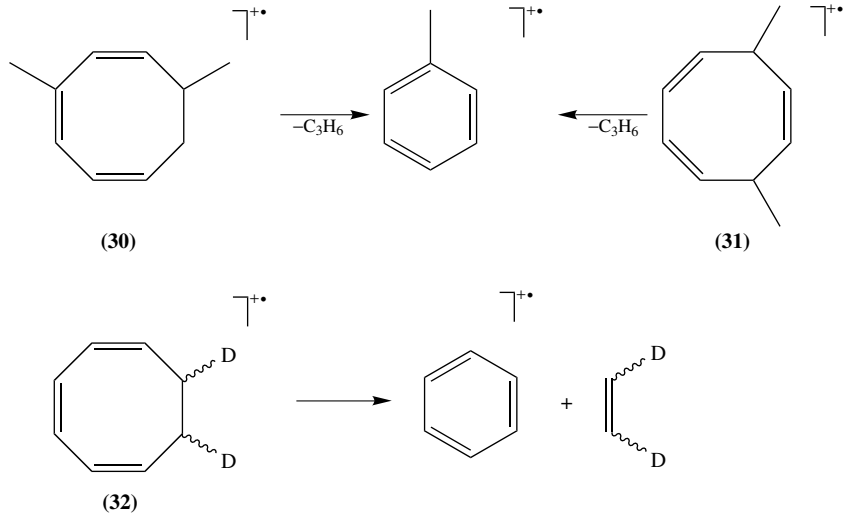
structure and partially rearrange into ionized 1,3-diphenylpropane and the isomeric 1-phenyl-2-tolylethane radical cations. The EI and FI mass spectra of cycloheptatriene and of 7,7'-ditropyl have been reported, and only the latter were found to exhibit a molecular ion peak[149].

The intermediacy of the radical cations of isotoluenes (methylenecyclohexadienes) and their derivatives is a common feature in organic mass spectrometry; however, it is widely ignored because of the rather difficult experimental access to neutral isotoluenes. Again, the reader is referred to the discussion on methylenecyclohexadienes in the 1990 review on ionized alkylbenzenes[7]. An early paper by Lifshitz and Bauer[150] on mass spectrometry of bicyclo[3.2.0]hepta-2,6-diene, another C_7H_8 isomer, as well as of bicyclo[3.2.0]hept-6-ene and one of its isomers, cyclohepta-1,3-diene, may also be mentioned in this context.

Cyclooctadienes, Cyclooctatrienes and Cyclooctatetraene. As mentioned in Section III.E, the 70 eV EI mass spectra of the isomeric cyclooctadienes are strikingly different[87]. Not surprisingly, the three possible stereoisomeric 1,5-cyclooctadienes give similar spectra, the product ions $C_4H_6^{+\bullet}$ of the apparent [4 + 4] cycloreversion, i.e. loss of 1,3-butadiene, generating the base peak at m/z 54. A significant difference is recognized for the most highly strained *trans*,*trans*-isomer whose spectrum lacks the otherwise abundant $C_3H_5^+$ ions (m/z 41). Contrary to the 1,5-isomers, the EI mass spectra of 1,3- and 1,4-cyclooctadiene both exhibit significantly more abundant molecular ions ($C_8H_{12}^{+\bullet}$), reflecting the higher stability or, respectively, more facile accessibility of the conjugated π electron system. Also, loss of $C_2H_5^\bullet$ gives rise to the base peak at m/z 79 with these isomers. This process and the analogous loss of $CH_3^\bullet$ certainly generate protonated benzene ($C_6H_7^+$) and toluene ($C_7H_9^+$, m/z 93), again reflecting the interaction of the unsaturated C−C bonds in these $C_8H_{12}^{+\bullet}$ isomers prior to fragmentation. In contrast to the PDMS spectra of the cyclohexadienes (see above), the PD mass spectra of 1,3- and 1,5-cyclooctadienes were found to be different and showed the same trend as the EI spectra. $C_5H_7^+$ and $C_6H_7^+$ ions represent the major fragment ions under PD conditions[124]. The latter ions were again interpreted as benzenium ions, whose formation is particularly efficient for the conjugated diene in competition with allylic C−C bond cleavage.

The EI-induced fragmentation of various cyclooctadienes and cyclooctatrienes and of the respective bicyclo[3.3.0]octene and octadiene isomers was investigated by Pentz in a thesis of 1975[151]. The high-energy (70 eV) EI spectra of 3,8-dimethylcycloocta-1,3,5-triene **(30)** and of 5,8-dimethylcycloocta-1,3,6-triene **(31)** were found to be quite distinct and the low-energy (12 eV) spectra exhibit the elimination of propene as the exclusive fragmentation path. Interestingly, the ionized [7,8-D_2]-labelled isotopomer **32** of the parent 1,3,5-cyclooctatriene **12** (Scheme 2) was found to expel $C_2H_2D_2$ with relatively low selectivity (*ca* 60%) at 70 eV electron energy but with higher selectivity (*ca* 90%) at low internal energies (Scheme 8). This indicates that hydrogen scrambling is largely suppressed in the molecular ions from which the ionized arene is expelled and that this reaction is energetically highly favourable (cf Scheme 2). In contrast, loss of $CH_3^\bullet$ is preceded by much more extensive hydrogen scrambling.

Later, gaseous 1,3,5-cyclooctatriene radical cations **12** were also studied by CID mass spectrometry, together with the ions generated from the acyclic isomer, 1,3,5,7-octatetraene **(11)**, and some bicyclic isomers, viz. bicyclo[2.2.2]octa-2,5-diene (dihydrobarrelene) **(14)** and bicyclo[4.2.0]octa-2,4-diene **(13)** (Scheme 2)[148]. The ions were formed by CE with $CS_2^{+\bullet}$ and strong dependence of the spectra on the CE gas pressure, i.e. on the internal energy contents, was observed, indicating facile interconversion of the isomers. It is noteworthy that elimination of ethene from these $C_8H_{10}^{+\bullet}$ ions is less pronounced for dihydrobarrelene ions[89], from which this path would formally correspond to a retro-Diels–Alder process, than for 1,3,5-cyclooctatriene ions. Interestingly, the spectra were



(30) (31) (32)

SCHEME 8

clearly distinct from those of ionized 7-methyl-1,3,5-cycloheptatriene and ionized styrene. Calculations suggested ionized cyclooctatriene to be the most stable isomer, in contrast to experimental data.

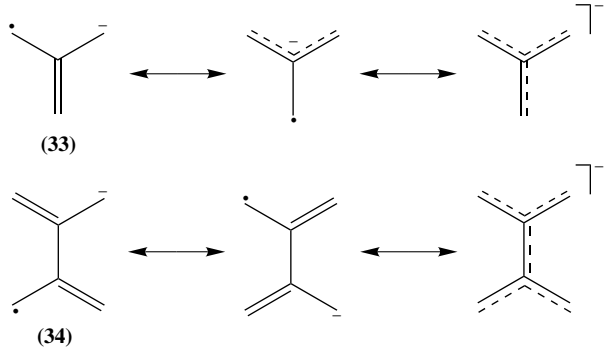
There appears to be not much knowledge available on the fragmentation of gaseous cations formed from 1,3,5,7-cyclooctatetraene besides the standard EI mass spectra. These are known to be quite similar to those of styrene[14c]. In an attempt to elucidate the potential of combining field ionization and collision-induced dissociation (FI/CID) to differentiate isomeric cations, Levsen and Beckey[152] compared the fragmentation of $C_8H_8^{+\bullet}$ radical cations generated from cyclooctatetraene and styrene. Again, the spectra were found to be rather similar, with the exception of the $[M - C_2H_3]^+$ ions (m/z 77), which were significantly more abundant in the CID spectrum of styrene, suggesting partial retention of structural specificity in these isomers. In contrast to the gas phase, the structural reorganization of $C_8H_{10}^{+\bullet}$ ions has been investigated in condensed media in much detail[153].

IV. GASEOUS ANIONS GENERATED FROM DIENES AND POLYENES

Knowledge about mass spectrometry and gas-phase chemistry of carbanions of dienes and polyenes is increasing although it still falls short of that on the respective carbocations. The relatively facile access to allyl anions from alkenes in the plasma of a negative chemical ionization (NCI) source and of flowing afterglow tubes has enabled investigations on unusual highly unsaturated, even- and odd-electron anions of fundamental interest. A lucid example is the recent comprehensive investigation of the thermochemistry of allene, methylacetylene, the propargyl radical and of related carbanions by DePuy and his associates[154], who have extensively used the flowing afterglow (FA) methology, and in particular the selected ion flow tube (SIFT) technique. Also, negative ion mass spectrometry of dienes and polyenes has brought about relevant analytical applications. A brief overview will be given in the following paragraphs.

A. Trimethylenemethane and Related Radical Anions

Among the 'small' ions, the trimethylenemethane radical anion, $(CH_2)_3C^{-\bullet}$ **(33)**[155], and the tetramethyleneethane radical anion, $(CH_2)_2C{=}C(CH_2)_2^{-\bullet}$ **(34)**[156] (Scheme 9), have been of particular interest and several of their derivatives have been prepared in the gas phase. Recent work has been reviewed by Lee and Grabowski[157]. These species and carbanions in general can be generated either by the reaction of either $O^{-\bullet}$ ions in the NCI source or in the flowing afterglow flow tube using N_2O/CH_4 mixtures, or by the sequential reaction of F^- ions, generated from NF_3 and neutral F_2.

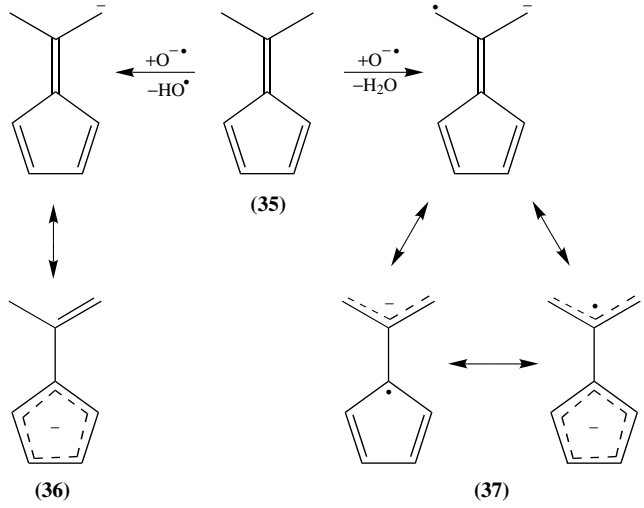


SCHEME 9

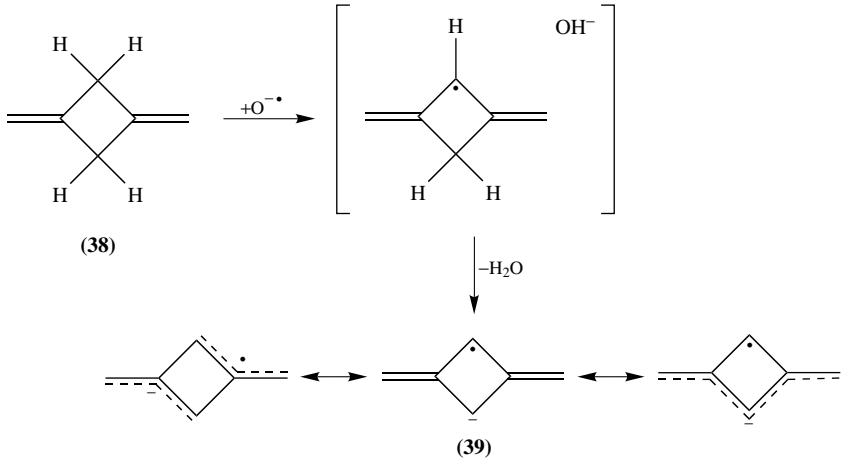
An impressive demonstration for the potential to generate 'larger' trimethylenemethane-type radical anions has been given in a more recent work using 6,6-dimethylfulvene **(35)** as the neutral precursor[158]. As shown in Scheme 10, reaction of $O^{-\bullet}$ ions with this cross-conjugated polyene in a flowing afterglow apparatus generates the radical anion of (cyclopentadienylidene)di(methylene)methane **(37)** by subsequent highly regioselective proton and hydrogen atom abstraction. Deuterium labelling of the methyl groups revealed that a fraction of at least 94% of H^+ and $H^\bullet$ transferred originate from the methyl groups. The distonic radical carbanion was demonstrated to be a better nucleophile than the related even-electron carbanion of 6,6-dimethylfulvene **(36)**, studied earlier[159], and to display both radical and carbanionic reactivity towards various partners. Higher analogues of 6,6-dimethylfulvene were also studied. Negative-ion mass spectra of several 6,6-di-substituted fulvenes were reported by Tolstikov and coworkers[160].

The sequential removal of $H^\bullet$ and H^+ from isobutene-type structural units (so-called '$H_2{}^{+\bullet}$ abstraction') was also used to generate the radical anion of 'non-Kékulé benzene', i.e. 1,3-dimethylenecyclobutane-1,3-diyl **(39)** (Scheme 11). As shown by Hill and Squires[161], this highly unusual, distonic $C_6H_6{}^{-\bullet}$ isomer can be produced in pure form by reaction of $O^{-\bullet}$ with 1,3-dimethylenecyclobutane **(38)**. Working in a flowing afterglow mass spectrometer, subsequent reactions were again used to characterize this radical anion and differentiate it from other $C_6H_6{}^{-\bullet}$ isomers.

The radical anion of the parent trimethylenemethane **(33)** has been generated and characterized by photoelectron spectroscopy by Squires, Lineberger and coworkers[162], making use of the high affinity of fluoride ions towards the trimethylsilyl (TMS) group[163]. Starting from the α-bis(trimethylsilyl)isobutene **(40)**, sequential TMS^+ abstraction by F^- and dissociative electron transfer to an F_2 molecule generates an $F^\bullet$ atom and an ion/neutral complex consisting of an F^- ion and the 2-(TMS-methyl)allyl radical (Scheme 12).



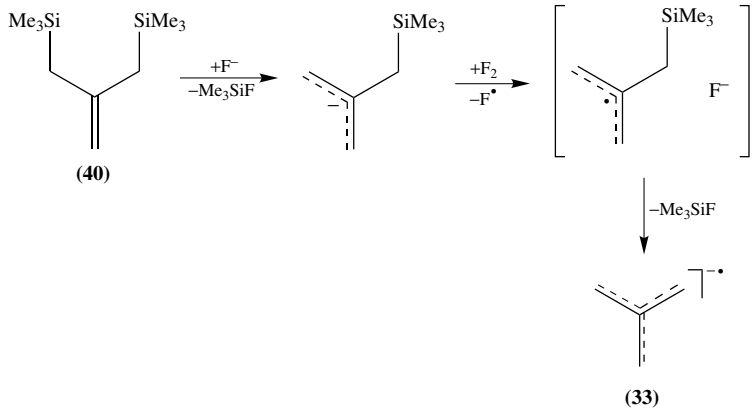
SCHEME 10



SCHEME 11

Intra-complex TMS^+ abstraction by F^- yields the trimethylenemethane radical anion **33**. Similarly, a number of other (mostly aromatic) distonic radical anions have been generated. Using the same approach, several other highly unsaturated distonic negative ions, such as the benzyne radical anions, were also studied[164].

It is obvious that the isobutene unit provides a good starting point for the generation of trimethylenemethane radical anions. However, even isobutane units can be used to produce these more highly unsaturated species. In a preliminary work aimed at two- and three-fold deprotonation processes in solution, Kuck, de Meijere and coworkers[165] have subjected triquinacene **(41)** and the tribenzotriquinacenes **44** to NCI conditions with



SCHEME 12

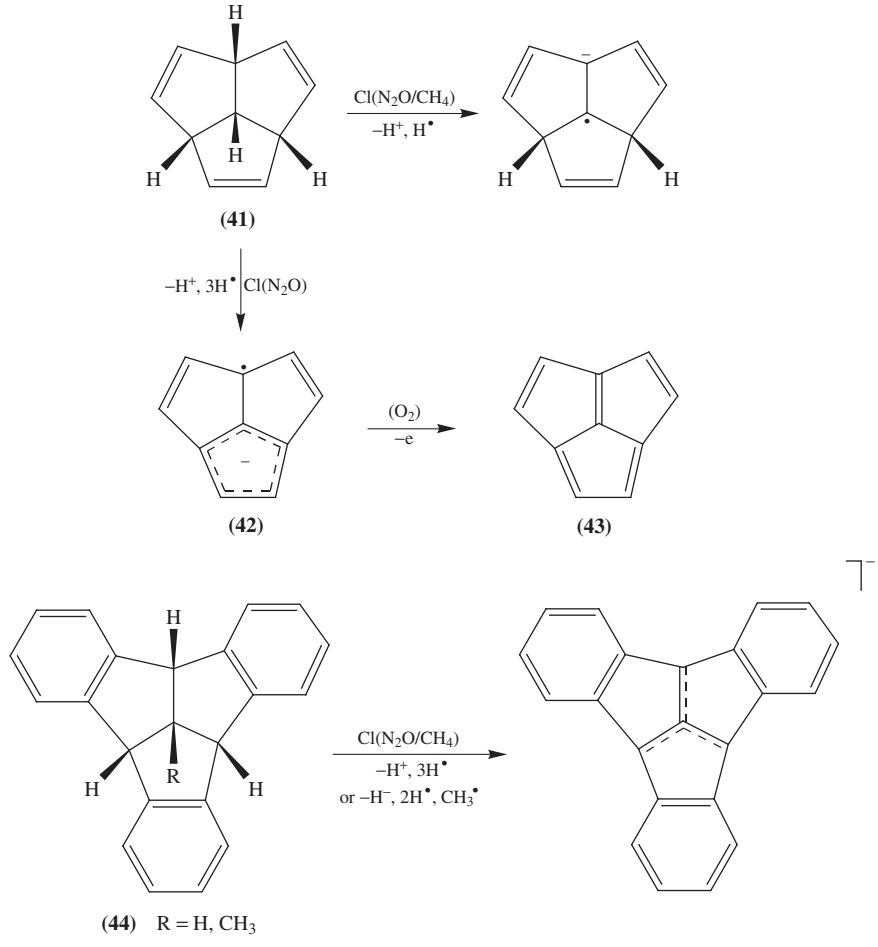
CH_4/O_2 and CF_4 as the reactant gases and observed the formation of $[M - 4\ H]^{-\bullet}$ ions in the CI plasma (Scheme 13)[166]. Thus, repeated deprotonation and electron transfer processes appear to offer an efficient access to more highly unsaturated and/or ring condensed trimethylenemethane radical anions. The $[M - 4\ H]^{-\bullet}$ ion is considered identical to the molecular radical anion **(42)** of acepentalene **(43)**, which was generated as a short-lived species from the former by neutralization–reionization mass spectrometry[167]. Efforts to apply Squires' methodology to triquinacene **41** and the tribenzotriquinacenes **44** have been made[168].

B. Deprotonation of 1,3,5-Cycloheptatriene: *cyclo*-$C_7H_7^-$ and the Benzyl Anion

In contrast to the tropylium cation, the cycloheptatrienyl anion should be antiaromatic in the planar geometry. Although the *c*-$C_7H_7^-$ anion is considerably less stable (*ca* 27 kcal mol^{-1})[169] than the benzyl anion, it appears to be kinetically stabilized by a substantial energy barrier, and evidence for its existence in the gas phase has been reported[170,171]. Wilkins, Staley and coworkers[172] demonstrated by FT-ICR spectrometry that gas-phase deprotonation of cycloheptatriene **(45)** with OD^- and ND_2^- gives rise to isomerization to the benzyl anion because H/D exchange with D_2O and ND_3, respectively, leads exclusively to the D_1- and D_2-isotopomers involving neutral toluene **46**, (Scheme 14). In contrast, ring contraction of cycloheptatriene does not occur with the less basic anion CD_3O^- although slow but progressive H/D exchange is observed with CD_3OD[154]. Formation of an ion molecule complex [*c*-$C_7H_7^- \cdot H_2O$] has been invoked to explain the relatively fast rearrangement of cycloheptatriene in the presence of OD^-/D_2O. The anion CID spectrum of deprotonated 7-methyl-1,3,5-cycloheptatriene has been reported by Nibbering and coworkers[173] and compared to those of the $C_8H_9^-$ anions generated from other olefinic isomers such as 1,3,5-cyclooctatriene and spiro[2.5]octa-4,6-diene as well as from ethylbenzene.

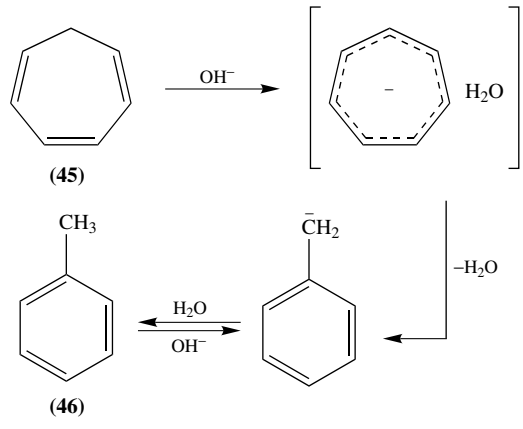
C. Deprotonation of Bicyclo[3.2.1]alkadiene, Some Other Cycloalkadienes and Cyclooctatetraene: Bishomoaromaticity and Transannular Cyclization

Another interesting bicyclic $C_8H_9^-$ anion has been investigated by Lee and Squires[174], again by using the flowing afterglow methodology (Scheme 15). Gas-phase deprotonation

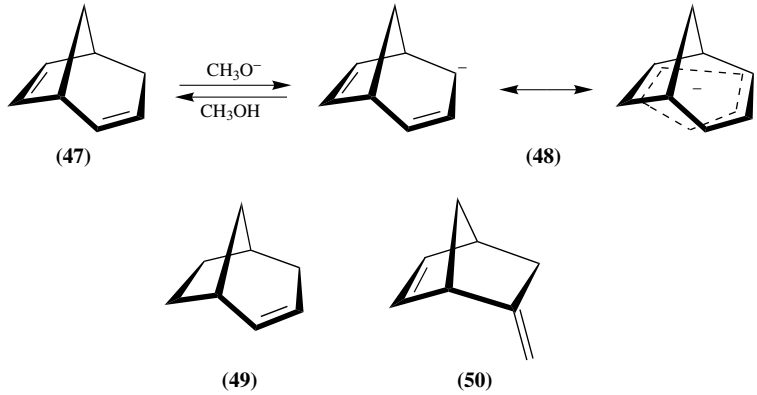


SCHEME 13

of bicyclo[3.2.1]octa-2,6-diene **(47)** by OH^- and OMe^- yields the bicyclo[3.2.1]octa-2,6-dien-3-yl anion **(48)** which, as a characteristic feature for its structural identity, incorporates two deuterium atoms in the respective reaction with D_2O. Most strikingly, the gas-phase acidity of the diene was found to be much higher (ΔK_a *ca* -10 kcal mol^{-1}) than that of an isomer, 5-methylene-2-norbornene **(50)**, and the less unsaturated bicyclo[3.2.1]oct-2-ene (**49**). The major part of the increase in acidity (ΔK_a *ca* -6.4 kcal mol^{-1}) has been attributed to strong bis-homoconjugative stabilization of the bicyclo[3.2.1]octa-2,6-dien-3-yl anion. Slightly increased gas-phase acidities have been measured for 1,3-cyclohexadiene, 1,3-cyclooctadiene and 1,5-cyclooctadiene and the role of homoaromaticity in the conjugate anions considered there as well. In contrast to the above-mentioned dienes, 2,5-norbornadiene, known to be a relatively weak C−H acid[171], turned out to undergo gas-phase deprotonation and slow H/D exchange exclusively at the olefinic C−H bonds. It is also noteworthy that the acidifying effect of homoaromaticity falls by far short of 'regular'



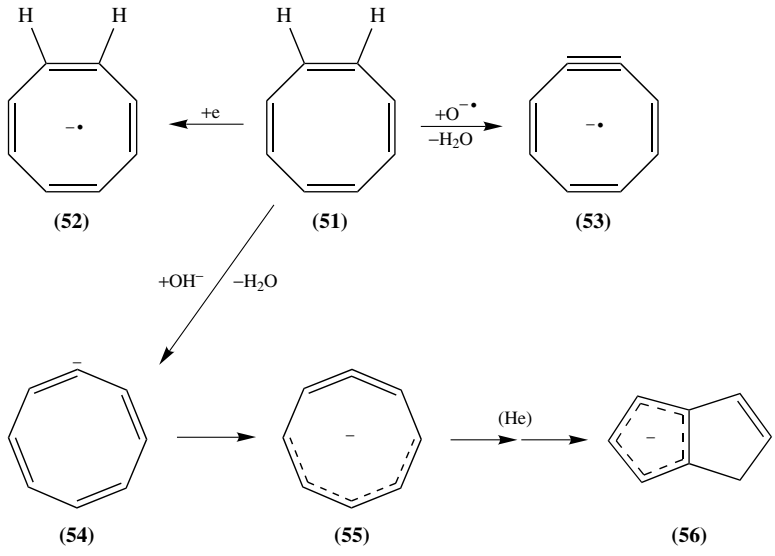
SCHEME 14



SCHEME 15

aromaticity: The gas-phase acidity of cyclopentadiene is by *ca* 24 kcal mol^{-1} higher than that of bicyclo[3.2.1]octa-2,6-diene **(47)** and by 16 kcal mol^{-1} higher than that of 1,3-cyclohexadiene.

The particular acidity of cyclopentadienes has become evident in a recent extended work by Bierbaum and coworkers[175] on the gas-phase properties of various anions derived from cyclooctatetraene **(51)**. The molecular radical anion $C_8H_8^{-\bullet}$ **(52)** as well as the $[M - H]^-$ and $[M - 2\ H]^{-\bullet}$ ions, i.e. $C_8H_7^-$ **(54)** and $C_8H_6^{-\bullet}$ **(53)**, respectively, were generated in a flowing afterglow mass spectrometer and the gas-phase basicities, H/D exchange and other bimolecular reactions of these species were determined. The initial structure of the $C_8H_7^-$ ions was characterized as a monocyclic species bearing both an allene and a pentadienyl anion unit. i.e. **55** rather than **54**. Upon collision with the helium atoms downstream the reaction tube, isomerization to a less-strained diquinane anion, the bicyclo[3.3.0]octa-1,3,6-trien-5-yl anion **(56)**, takes place (Scheme 16). The relatively high stability of this $C_8H_7^-$ isomer became evident from its generally low reactivity. Moreover, the proton affinity of the bicyclic $C_8H_7^-$ ion **56** was determined to be very



SCHEME 16

close to that of the cyclopentadienide anion, about 24 kcal mol^{-1} higher than that of the initial monocyclic isomer. Thus, the conjugated hydrocarbon, bicyclo[3.3.0]octa-1,3,6-triene is by 24 kcal mol^{-1} less acidic than cyclooctatetraene. Note that the bicyclic anion can be regarded as the addition product of hydride ion to pentalene.

Recently, Cooks and coworkers[176] determined the electron affinity (EA) of 1,3,5,7-cyclooctatetraene by using the kinetic method, that is, by performing CID of the cluster anions of the cycloolefin with a number of reference molecules of known EA. The value obtained (EA $= 0.58 \pm 0.10$ eV) was found to be in excellent accordance with that reported previously by Wentworth and Ristau[177].

V. BIMOLECULAR REACTIONS OF DIENES AND POLYENES

Bimolecular ion/molecule reactions of dienes and polyenes have been extensively studied for several reasons. Some of them have been mentioned implicitly in the previous sections, that is, in order to structurally characterize the gaseous cations derived from these compounds. In this section, bimolecular reactivity of cationic dienes, in particular, with various neutral partners will be discussed, and some anion/molecule reactions will be mentioned also (cf Section IV). In addition, the reactions of neutral dienes with several ionic partners will also be discussed. Of this latter category, however, the vast chemistry of reactions of neutral dienes with metal cations and metal-centred cations will not be treated here. Several reviews on this topic have been published in the last decade[178].

A. Ionized Dienes and Neutral Molecules

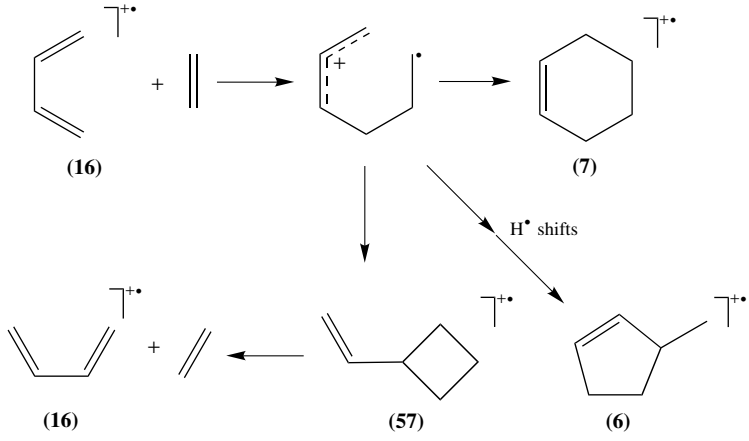
Allene Radical Cations. The bimolecular reactivity of the radical reactions of allene and propyne has been a longstanding matter of interest. Myher and Harrison[179] studied the ion/molecule reactions of ionized C_3H_4 with the respective neutral precursor in a medium-pressure chemical ionization source. $C_6H_7^+$ ions were found to be amongst

the most prominent charged adducts. Subsequently, Bowers, Jennings and coworkers[180] investigated this system by ICR mass spectrometry and found that the $C_6H_7^+$ ions result from a direct condensation reaction between $C_3H_5^+$ and C_3H_4. Later, a photoionization mass spectrometric study by Tanaka and coworkers[181] revealed that the yield of the $C_6H_7^+$ ions is much larger with allene and propyne as compared to cyclopropene, another isomer. Obviously, the reactivity of the ion/molecule complexes formed in the course of the exothermic reaction depends strongly on the internal energy contents. Lifshitz and coworkers[182,183] studied the energy-dependent photoionization of allene in detail and considered the allene dimer to be formed by covalent coupling of the central carbon atoms, thus leading to the non-Kékulé structure of tetramethyleneethane, $^{\bullet}(CH_2)_2C{-}C(CH_2)_2^+$ (cf Scheme 9 for the radical anion). The different energy dependences of allene and propyne were explained by RRKM model calculations[184]. Photoelectron-secondary ion coincidence mass spectrometry was applied by Niehaus and coworkers[185] to tackle the energy dependence problem. ICR studies by Anicich and coworkers[186] on allene, vinylacetylene and diacetylene, amongst other olefins, revealed that by far the largest fraction of ion/molecule reactions (>90%) leads to condensation reactions, i.e. to hydrocarbon ions larger than those of the starting system. Several groups assumed that the $C_6H_7^+$ product ions have the structure of protonated benzene (benzenium ions)[187]. Subsequently, Lias and Ausloos[133] devoted a detailed ICR investigation to this structural problem and concluded that the $C_6H_7^+$ ions formed from the ion/molecule reactions of allene and propyne, as well as by unimolecular fragmentation of various cyclic and acyclic olefins (cf Section III), consist of at least two isomers, viz. the benzenium ion and, most probably, protonated fulvene (fulvenium ions).

Cyclobutadiene Radical Cations. Ionized cyclobutadiene represents a stable species in the gas phase. This prototype species has been studied, amongst other $C_4H_4^{+\bullet}$ isomers, by its ion/molecule reactions under various conditions. Collision-induced dissociation (CID) of the adducts of *c*-$C_4H_4^{+\bullet}$ with ammonia was found to be distinctive from those of the $C_4H_7N^{+\bullet}$ adduct ions obtained with ionized methylenecyclopropene and vinylacetylene[110]. The CID behaviour as well as the association reactions of *c*-$C_4H_4^{+\bullet}$ ions with e.g. 1,3-butadiene, furan and thiophene were studied by Cooks and coworkers[113] in a pentaquadrupole mass spectrometer and revealed dramatic differences from the corresponding reactions of ionized methylenecyclopropene and the acyclic $C_4H_4^{+\bullet}$ ions. The gas-phase reaction between *c*-$C_4H_4^{+\bullet}$ ions and acetylene has also been measured[188].

Butadiene Radical Cations. Cycloaddition reactions between the radical cations of 1,3-butadiene and its derivatives with various neutral olefins have been a subject of intense research over the past decades because of the fundamental importance of this type of pericyclic reactions in organic chemistry. Reviews concerning Diels–Alder reactions involving radical cationic species in the gas phase and in general organic chemistry are mentioned here[4,90c,189]. Cycloaddition reactions of ionized 1,3-butadiene **(16)** with ethene and of ionized furan with neutral 1,3-butadiene were discussed by Gross and coworkers[190]. Very recently, Bouchoux and Salpin[137] presented convincing FT-ICR evidence on the prototypical addition of ionized **16** to ethene (Scheme 17). The reaction was shown to occur via an intermediate acyclic distonic ion which subsequently cyclizes to ionized vinylcyclobutane **(57)** which then undergoes [2 + 2] cycloreversion to generate the starting components with mutually interchanged methylene groups. In competition, cyclization also gives ionized cyclohexene **(7)**, whereas various H shifts lead to acyclic diene and methylcyclopentene radical cations **(6)**.

In an early ICR study, Gross and coworkers[191] reacted ionized 1,3-butadiene **(16)** with several C_5 alkenes and found characteristically different fragmentation of the ionic



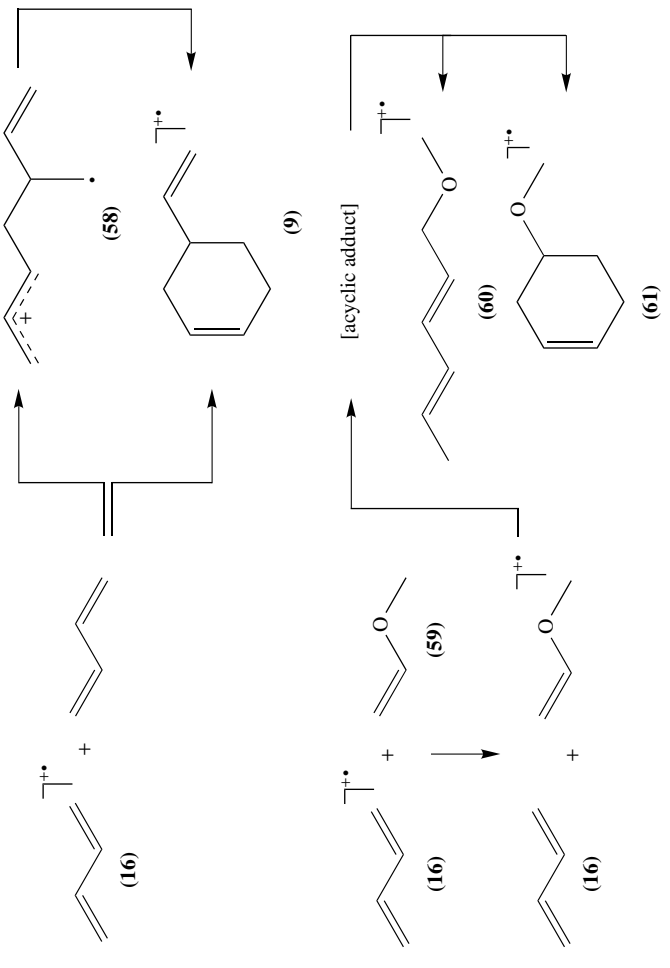
SCHEME 17

adducts, which themselves were not detectable due to the lack of collisional cooling at the time of the experiment. The distinct reactivities of the six C_5H_{10} isomers pointed to a potential means to identify these neutral isomers by ICR mass spectrometry. Interestingly, the highest substituted alkene, i.e. 2-methylbut-2-ene, reacted by charge exchange only. In a later work, the ionic adduct was stabilized by collisions with neutral gas in the ICR cell prior to collision-induced decomposition. Energy-dependent formation of two dimeric adducts was identified, one being the [2 + 4] cycloadduct **9** and the other a branched, acyclic isomer, to which the structure of a distonic ion **(58)** was assigned (Scheme 18)[89].

Nibbering, Jennings and coworkers[192] reported on the [2 + 4] cycloaddition of ionized 1,3-butadiene **16** with methyl and ethyl vinyl ether **(59)** and identified the (again short-lived) adduct to be the 4-methoxycyclohexene radical cation **61**, from which methanol or ethanol, respectively, are eliminated regioselectively. Later, FT-ICR mass spectrometry work by Groenewold and Gross[193], using collisional cooling as well as CID spectrometric studies in a sector-field instrument, revealed that the cycloaddition process occurs stepwise and that both the acyclic adduct **(60)** and the [4 + 2] cycloadduct **(61)** can be identified (Scheme 18). The reaction starting with ionized 1,3-butadiene involves charge exchange prior to the formation of the covalent adduct. In contrast to the aforementioned cases, ionized 1,3-butadiene reacts with acrolein and methyl vinyl ketone as the ene component, and α,β-unsaturated ketones react as dienes to yield 2-vinyl-2,3-dihydropyrans[194].

The gas-phase reactions of the fulvene radical cation with neutral 1,3-butadiene, alkenes and 2-propyl iodide have been investigated by Russell and Gross[131a] using ICR mass spectrometry. Unlike ionized benzene, ionized fulvene undergoes no C−C coupling with 2-propyl iodide. On the basis of deuterium and ^{13}C labelling, the reaction of ionized fulvene with 1,3-butadiene was suggested to occur by [6 + 4] cycloaddition to yield tetrahydroazulene radical cations. Cycloadditions of neutral fulvene were also studied in this work.

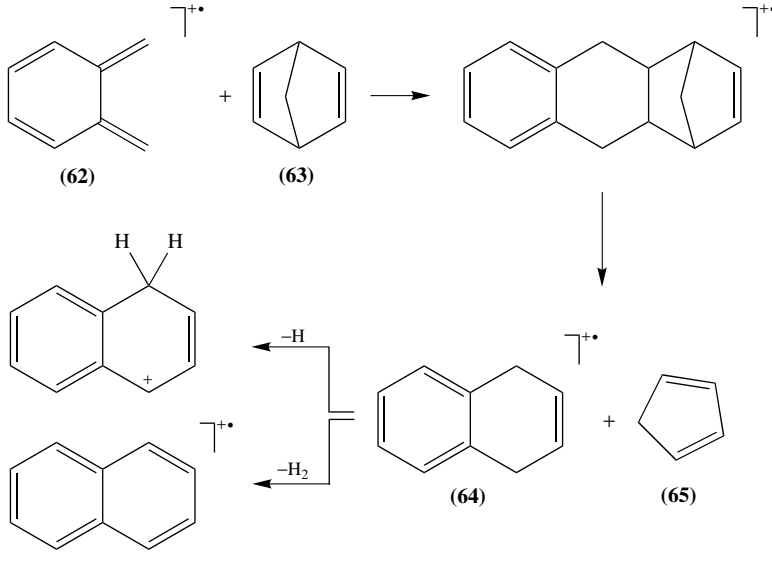
The radical cations of the quinodimethanes (xylylenes) represent particularly interesting members of the family of $C_8H_8^{+\bullet}$ isomers. Ionized *ortho*-quinodimethane is formed from a variety of neutral precursors such as benzocyclobutene (by ring opening), *ortho*-methylbenzyl alcohol and its esters and ethers (by 1,4-elimination) and from 1,4-dihydrobenzo[*c*]thiophene *S*,*S*-dioxide (by 1,1-elimination of SO_2). Gross and coworkers[195] generated the $C_8H_8^{+\bullet}$ species in a high-pressure ion source and characterized them by



SCHEME 18

the reaction with neutral styrene. The *ortho*-quinodimethane structure was deduced from labelling evidence and 2-phenyltetralin was suggested to be the product of a [4 + 2] cycloaddition. CID spectrometry of the cycloaddition product formed from ionized benzocyclobutene and from [β,β-D_2]-styrene and [3,3-D_2]-2-phenyltetralin confirmed the identity of these ions and thus the intermediacy of the *ortho*-quinodimethane radical cations[196].

In a very recent FT-ICR study employing an external ion source, Grützmacher and Barkow[197] compared the bimolecular reactivity of ionized *ortho*-quinodimethane **(62)** formed by water loss from 2-methylbenzyl alcohol under EI conditions with the benzocyclobutene radical cations formed from the neutral hydrocarbon by charge exchange and styrene radical cations formed by EI. Ionized benzocyclobutene was found to be distinguishable from the *ortho*-quinodimethane ions by its inertness towards neutral alkenes. A highly diagnostic probe reaction for ionized *ortho*-quinodimethane **62** has also been found in this work (Scheme 19): These ions undergo a [4 + 2] cycloaddition with neutral norbornadiene **(63)** followed by [4 + 2] cycloreversion of the Diels–Alder adduct to give ionized 1,4-dialin (1,4-dihydronaphthalene, **64**) and neutral cyclopentadiene **(65)**, as well as the products of subsequent $H^{\bullet}$ and H_2 loss. The possible formation of ionized quinodimethanes during the loss of benzene from long-lived radical cations of 1,2-diphenylethane, and of SO_2 and benzene from ionized dibenzyl sulphone, was also discussed recently[198]. However, the probe reaction with norbornadiene turned out to be negative[199].



SCHEME 19

B. Neutral Dienes and Odd-electron Reagent Ions

Neutral dienes have been reacted with a large variety of ions in the gas phase. Besides the cases concerning the same reactants discussed above but with reversed charge distribution, e.g. those of neutral 1,3-butadiene with ionized alkenes, there are interesting studies of reactions of 1,3-dienes with even-electron cations and studies on ion/molecule

reactions of anions derived from dienes. Again, the reader is also referred to Section III describing the unimolecular gas-phase ion chemistry of dienes.

The reactions of neutral allene and other unsaturated hydrocarbons with carbon ions ($C^{+\bullet}$) have been studied by Bohme and coworkers[200] using the flowing afterglow (selected ion flow tube, SIFT) technique, in order to gain insight into the fundamentals of the build-up mechanisms of carbon skeletons. Parent[201] reacted $C^{+\bullet}$, $Si^{+\bullet}$ and $Si_2C_2^{+\bullet}$ with allene and propyne in an FT-ICR mass spectrometer and found distinct reactivity towards insertion into single bonds. Isoprene has been amongst the various olefins which Španěl and Smith[202] recently subjected to reactions with $H_3O^{+\bullet}$, NO^+ and $O_2^{+\bullet}$. The ion/molecule reactions occurring between 3-methylbuta-1,2-diene and *ortho*-hydroxythiophenol under CI conditions were reported by Traldi and coworkers[203].

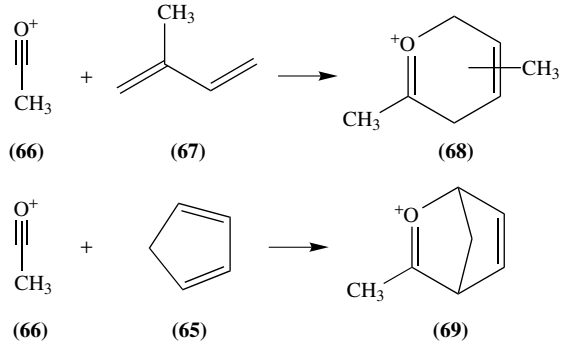
Various organic radical cations have been reacted with neutral dienes. The investigations by Groenewold and Gross[193] mentioned above also included the reactions of neutral 1,3-butadiene and ionized methyl vinyl ether (cf Scheme 18). Two distinct addition products were identified when benzene radical cations were reacted with neutral 1,3-butadiene, viz. ionized 2-phenylbut-2-ene and ionized 1-methylindane, depending on the internal energy of reactants[204]. Cooks and coworkers[205] studied the reactions of ionized pyrene and the corresponding $[M - H]^+$ and $[M - H_2]^{+\bullet}$ ions with neutral isoprene using a quadrupole ion-trap mass spectrometer. Dass[206] observed significantly different CID behaviour of the adduct ions formed from neutral 1,3- and 1,4-pentadienes with ionized ketene. Similarly, Bouchoux and Penaud-Berruyer[207] found that ion/molecule reactions between ionized vinylamine and twelve neutral C_4, C_5 and C_6 dienes lead to characteristically different products depending on whether the diene is conjugated or non-conjugated. Again, stepwise $[4 + 2]$ cycloaddition was inferred to occur in the case of the 1,3-dienes whereas metathetic $[2 + 2]$ cycloaddition appeared to be the key step with 1,4- and 1,5-dienes. The latter behaviour strictly parallels the regiospecific reactivity of ionized vinylamine with simple alkenes[208] and leads to one of the useful methods for double bond localization in unsaturated hydrocarbon chains (cf Section VI).

Some special cases for reactions of radical cations with neutral dienes deserve mention here as well. Nibbering and coworkers[209] demonstrated that the distonic dimethylmethylenesulphonium ion, $(CH_3)_2S^+CH_2^\bullet$, reacts with 1,4-cyclohexadiene predominantly by $H^\bullet$ abstraction and competing radical addition to one of the double bonds. The adduct undergoes several structure-specific fragmentation reactions, such as $CH_3^\bullet$ loss and elimination of $(CH_3)_2S$. Another special case is the investigation of the reactivity of fullerene $C_{60}^{+\bullet}$ ions with several neutral acyclic and cyclic dienes in the SIFT mass spectrometer[210]. In contrast to the acyclic 1,3-dienes, 1,3-cyclopentadiene and 1,3-cyclohexadiene formed $C_{65}H_6^{+\bullet}$ and $C_{66}H_8^{+\bullet}$ adducts in which the diene unit is assumed to be added across a [6.6] bond of the fullerene skeleton. The same authors also reacted neutral 1,3-butadiene with C_{60}^{2+} and C_{70}^{2+} dications and observed the doubly charged adduct ions along with the products of charge exchange[211,212]. A study on the adducts of $C_5H_5^+$ ions and C_{60} is also mentioned[213].

C. Neutral Dienes and Even-electron Reagent Ions

Unsaturated even-electron cations have been used in the gas phase to react with olefins, including dienes, in a way that characterizes their structure. In most cases, these ion/molecule reactions take place by $[4 + 2]$ cycloadditions followed by specific elimination of even-electron neutrals. A most suitable instrumental setup for these studies are triple-quadrupole and pentaquadrupole mass spectrometers in which the ion/molecule addition reactions take place subsequent to the selection of the reagent ion. In most

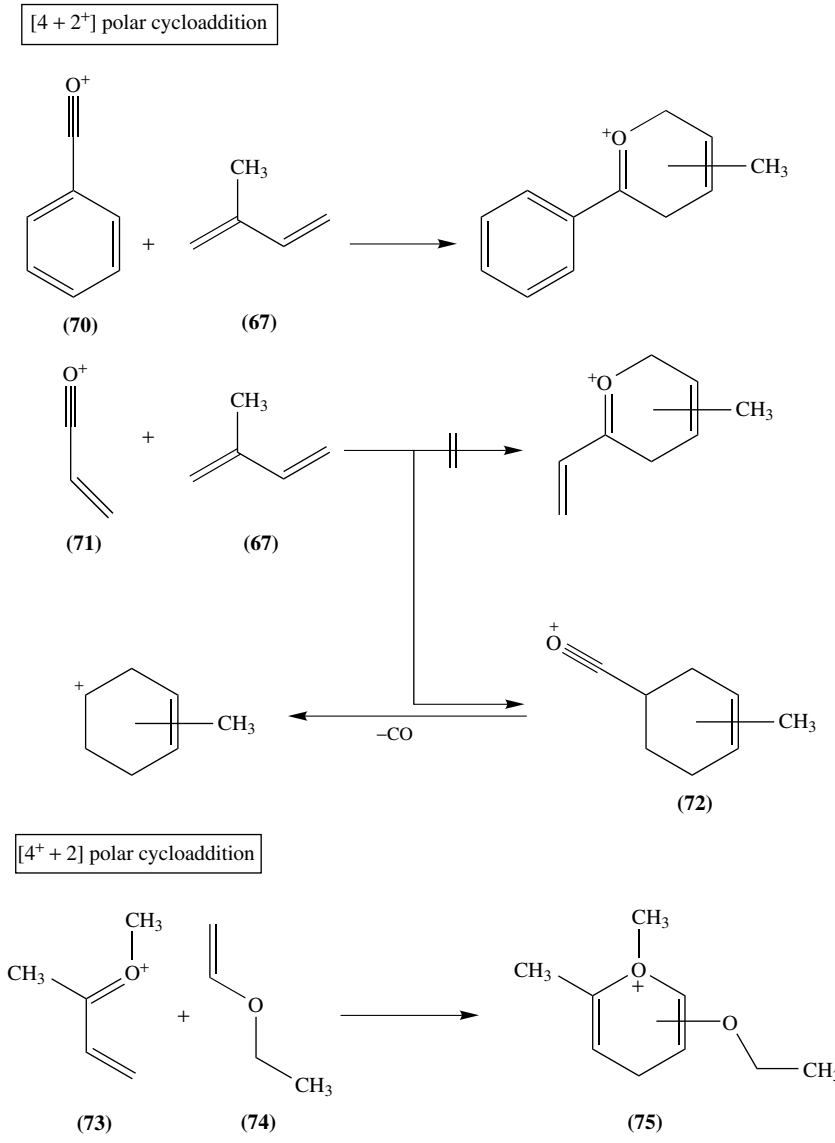
cases, the adduct is stabilized by collision cooling and can be re-excited by collision in the next quadrupole. Triple-stage pentaquadrupole (so-called 'QqQqQ') mass spectrometers even allow one to identify the ionic adduct by performing structure-specific CID. Eberlin[214] has recently reviewed this method and its applications. A prototype $[4 + 2^+]$ cycloaddition concerning dienes is the reaction of acetyl cations **66** with isoprene **67** and cyclopentadiene **65** to give the corresponding oxonium ions **68** and **69** as shown by Cooks and coworkers[215] (Scheme 20). Note that the charged 'ene' is the 2^+ component in these 'polar' cycloaddition reactions. Collision-induced dissociation reverts this addition generating the initial reactants. Several analogous reactions have been studied, such as the cycloaddition of thioacetyl cations with isoprene. Unlike the product formed with acetyl cations, this cycloadduct was found to expel C_2H_4 and H_2S. A large variety of other acyl cations has been reacted in the same way with 1,3-butadiene, isoprene and 1,3-cyclopentadiene (Scheme 20)[216].



SCHEME 20

Many variants of the $[4 + 2^+]$ polar cycloaddition are possible including the reactions of unsaturated acyl cations. Cooks, Eberlin and coworkers also investigated the reactions of various nitrilium and immonium cations with isoprene. Again, cycloaddition is a common reaction path; however, protonated nitriles tend to undergo proton transfer to the relatively highly basic neutral diene[217]. Protonated quinones and the *O*-Me^+ adducts of quinones, α,β-unsaturated aldehydes and ketones and also protonated saturated ketones have been cycloadded to 1,3-butadiene. Peculiar combinations of reactants are possible, e.g. the reaction of the *O*-Me^+ adduct of cyclohexen-3-one with 2,3-dimethoxybutadiene, the cycloadduct of which was found to undergo mainly the retro-Diels–Alder process upon CID. In the same work, Cooks and coworkers[218] also demonstrated a cycloaddition occurring with inverse electron demand (Scheme 21): The *O*-Me^+ adduct of 2-butenone **73** adds to ethyl vinyl ether **74** by $[4^+ + 2]$ ion/molecule reaction since the cycloadduct **75** fragments differently as compared to the putative $[4 + 2^+]$ isomer. Whereas benzoyl cations **70** react with isoprene **67** in the expected $[4 + 2^+]$ orientation, cycloaddition of acryloyl cations **(71)** was suggested to take place at the α,β-unsaturated double bond, thus generating isocyclic $[4 + 2^+]$ cycloadducts **72** instead of a heterocyclic (dihydropyrylium-type) ion[219].

The reaction of thioacetyl cations with 2,5-dimethyl-1,5-hexadiene under low-pressure conditions in an FT-ICR mass spectrometer leads to elimination of propene. At variance from the $[4 + 2^+]$ polar cycloadditions observed under high-pressure conditions in the QqQqQ instrument, Caserio and coworkers[220] invoked electrophilic attack of the CH_3CS^+



SCHEME 21

cation at an inner position of the diene unit leading to a five-membered cycloadduct, from which a thiophenium cation is formed upon C_3H_6 elimination. It appears possible that the corresponding $[4 + 2^+]$ cycloadduct is formed initially and that ring contraction is a subsequent isomerization step, which becomes evident only in cases where a stable olefin can be expelled. Another interesting case was reported by Morizur and coworkers[221] who reacted the dimethoxyphosphenium ion, $(CH_3O)_2P^+$, with 2,3-dimethylbutadiene in

a quadrupole ion trap mass spectrometer. A cheletropic $[4 + 2^+]$ cycloaddition generates a 1,1-dimethoxyphosphoniocyclopent-3-ene ion which, under CID conditions, undergoes the retro-cheletropic reaction and competitive loss of methanol, to yield a phosphacyclopentenyl cation. Finally, a classical ICR paper by Ausloos and coworkers[222] may be mentioned which describes the reaction of benzyl cations with 1,3-butadiene, besides various monoalkenes. The primary $C_{11}H_{13}^+$ adduct, presumably the linear 5-phenylpent-1-en-3-yl cation rather than a formal $[4 + 2^+]$ cycloadduct bearing a seven-membered ring, expels ethene as the predominant reaction, suggesting the formation of the 1-indanyl cation as the final product.

D. Reactions of Diene-derived Anions

Some ion/molecule reactions of several even- and odd-electron carbanions derived from dienes and polyenes have already been mentioned (Section IV) in the context of their unimolecular gas-phase chemistry. Some additional aspects will be presented here concerning their bimolecular reactions. Using the flowing afterglow technique, the number of acidic C−H bonds and hidden isomerization reactions can be determined in the carbanions by H^+/D^+ exchange with D_2O. This was shown by Shapiro, DePuy and coworkers[223] for a large set of $[M - H]^-$ ions including those of the butadienes and butynes. Only two hydrogens are exchanged in the anions generated from 1,2-butadiene, 1-butyne and 2-butyne whereas the 1,3-butadiene carbanion undergoes mainly D^+ abstraction from D_2O. Thus, 1,3-butadiene is deprotonated at one of the inner C−H bonds. When Lewis acids are allowed to react with carbanions, the formation of diagnostic addition products may be observed. In line with this, the same authors demonstrated[224] that the $[M - H]^-$ ion of 1,3-butadiene reacts with N_2O by attack of one of the inner carbons at the terminal nitrogen atom of the neutral reagent since the adduct expels CH_2O. Information on the site of deprotonation of allene was gained by reacting its carbanion with CS_2, as shown in a very recent work by DePuy and coworkers[225]. A complex isomerization was discovered in the primary adduct, $CH_2CCHCS_2^-$, by which the C(1) and C(3) atoms of the allenyl anion and the CS_2 carbon atom become equivalent. The reaction with COS and CO_2 were also studied.

DePuy and coworkers[226] also reported on the rate constants of H^+/D^+ exchange of OH^- with several weakly acidic olefins, including 1,3-butadiene and norbornadiene, under flowing afterglow conditions. Another interesting FA investigation[227] dealt with the proton transfer processes that occur in long-lived ion/molecule complexes formed from D_2O and allylic carbanions, including the carbanion of isoprene. In all cases, the H^+/D^+ exchange does not reach the statistical limit within the lifetime of the complexes.

A series of papers have appeared describing the bimolecular chemistry of gaseous anions derived from 1,3-cyclopentadiene. McDonald and coworkers[228] reacted the *c*-$C_5H_5^-$ anion with several alcohols in a flowing afterglow apparatus and observed, surprisingly, that ion/molecule adducts such as [*c*-$C_5H_5^-$ CF_3CH_2OH] react with further alcohol molecules by anion switching, leaving neutral cyclopentadiene and the corresponding alcohol dimer anion, as well as higher clusters anions. The cyclopentadienyl anion and the cyclopentadienylidene radical anion, *c*-$C_5H_4^{-\bullet}$, were found to undergo nucleophilic 1,4-addition with α,β-unsaturated compounds, viz. acrylonitrile and methyl acrylate[229,230]. A detailed study[231] was focused on the gas-phase chemistry of the *c*-$C_5H_4^{-\bullet}$ radical anion, generated from diazocyclopentadiene by electron attachment, followed by N_2 loss, or by sequential $H^+/H^\bullet$ abstraction (cf Section IV). This unusual species also reacts by Michael addition with acrylonitrile, methyl acrylate and vinyl chloride, but also with a variety of other electrophiles.

VI. LOCALIZATION OF THE C−C BOND UNSATURATION

The determination of the sites of the C−C double bonds in unsaturated fatty acid derivatives and other lipids plays an outstanding role in the analytical application of mass spectrometry. Much work has been published on the localization of double bonds in monoolefins, and a number of extensive reviews has appeared on the topic[232−235]. Two major methodologies have been employed. In the first one, unsaturated C−C bonds are converted to appropriate derivatives by synthesis in the liquid phase, which are then subjected to mass spectrometric analysis mostly by using standard EI techniques. These methods will be mentioned only briefly in the next section, including some recent work which has not yet been mentioned in the reviews. The second methodology takes advantage of the bimolecular reactivity of *neutral* olefins with ionic reagents in the gas phase, i.e. in the chemical ionization source of a mass spectrometer, or in the cell of an ion trap or ICR mass spectrometer. A diversity of reagent ions has been investigated during the past decades, and much of this chemistry has also been treated in the reviews.

Double bond localization in dienes and polyenes has also attracted much attention but the examples are less widespread than with simple olefins. However, the specific reactivity of 1,3-dienes deserves special notice and recent work will be presented in detail to some extent in the following sections.

A. Liquid-phase Derivatization Followed by Mass Spectrometry

Classical methods of derivatization of double bonds in dienes and polyenes comprise the oxidation of the olefin with osmium tetroxide or with permanganate, followed by methylation of the 1,2-diols[236,237]. Alternatively, bromination of the double bonds in the presence of methanol gives the corresponding multiple α-bromo-β-methoxy adducts[238]. Also, the oligohydroxy derivative obtained from the diene or polyene can be converted to the multiple bis-trimethylsilyl derivatives[239,240]. In all cases, structure-specific cleavage of the C−C single bond generated by derivatization occurs readily, owing to activation by the electron-rich groups added to the original double bond. Cleavage of the multiple α,β-bis(trimethylsilyloxy)ethylene units proved to be particularly prominent.

Still another related method consists in reacting dienes with dimethyl disulphide in the presence of iodine, to produce the corresponding bis(α,β-dimethylmercapto) derivative[241−243]. Again, characteristic fragmentation is obtained in the standard EI spectra. However, this method involves complications if the double bonds are separated by less than four methylene groups due to the formation of cyclic thioethers.

A special method developed by Vouros and coworkers[244] for 1,3-dienes makes use of the facile Diels–Alder reaction with 4-phenyl-1,2,4-triazolin-3,5-dione. Cycloaddition converts the original 1,3-butadiene unit of the olefin into a 1,2,3,6-tetrahydropyridazine unit, from which the pending alkyl groups are lost by diagnostic C−C bond cleavage. Hogge and coworkers[245] performed combined epoxidation/hydrogenation for double-bond localization of polyunsaturated compounds. Vetter and coworkers[246] recently reported on further methods for the double-bond localization in polyunsaturated fatty acids making use of charge-remote fragmentation[247].

B. Gas-phase Derivatization by Chemical Ionization

When a neutral olefin forms covalent adducts with ionic reactants at one of its C−C double bonds, a new single C−C bond is formed which, owing to the influence of the substituents added during the ion/molecule reaction, may undergo facile dissociation. The

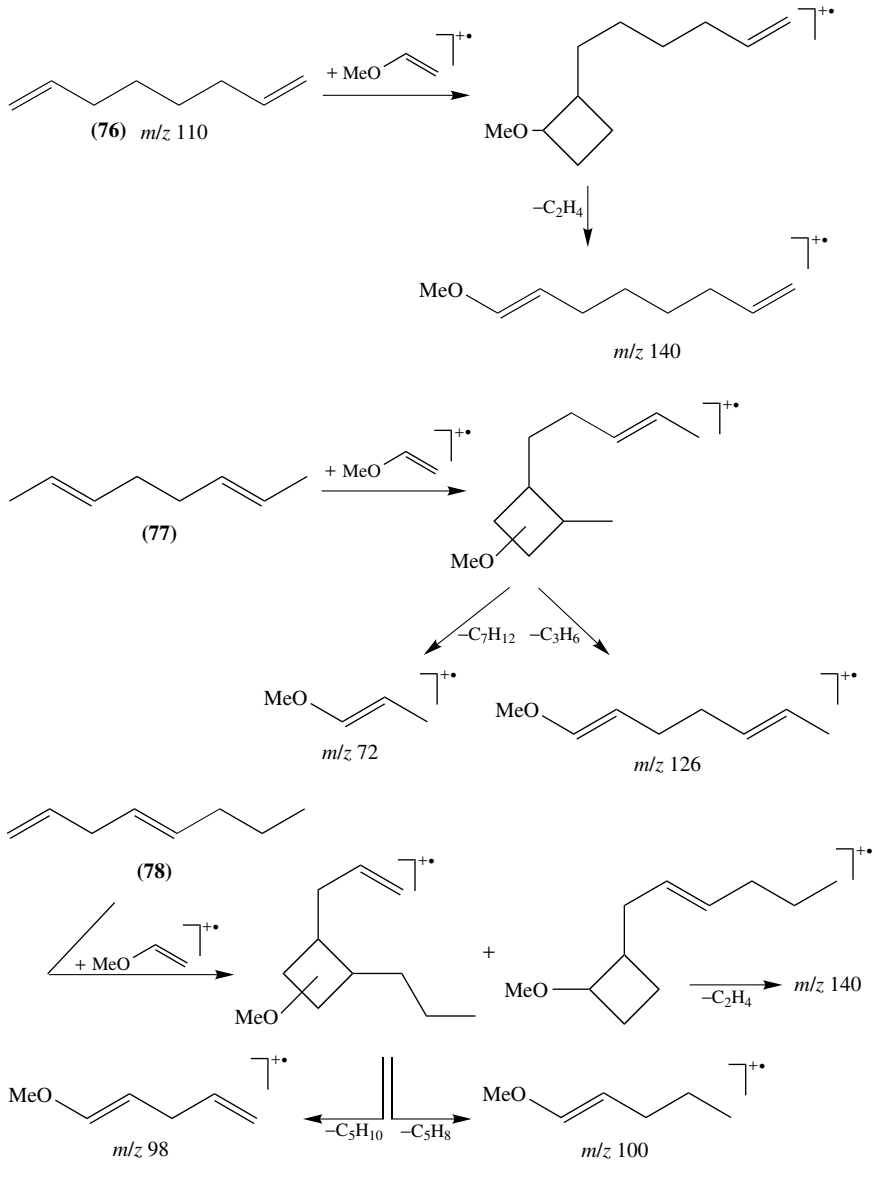
fragment ions formed are then characteristic indicators for the position of the unsaturation in the olefin under investigation. Due to the fact that double bonds are easily shifted in cationic (and even sometimes anionic) olefins, ion/molecule reactions between ionic olefins and neutral reagents are much less specific than are those involving neutral olefins and ionic reagents. During the last three decades, much work has been invested to develop methods for the localization of double and triple bonds in olefins, in particular in long-chain unsaturated aliphatic chains such as in fatty acids, by performing ion/molecule reactions in the dilute gas phase of a mass spectrometer. To this end, gas-phase derivatization of the olefin within the CI ion source is a most suitable approach. However, double-bond localization can also be carried out by selecting suitable ions within ion traps, FT-ICR cells and quadrupole mass spectrometers and allowing them to react subsequently with the olefin under investigation. Of course, this approach is more limited than the first one since the sample olefin has to be sufficiently volatile.

Jennings and coworkers[248] were the first to report on a mass spectrometric method of locating double bonds by use of gas-phase ion/molecule reactions. Ionized alkyl vinyl ethers proved to be highly suitable reagent ions, and the principle of this gas-phase method for double-bond localization is illustrated for prototype dienes **76–78** in Scheme 22. At the same time, Hunt and coworkers[249,250] introduced nitric oxide (NO) as a reagent gas in CI mass spectrometry and studied the reactions of the NO^+ and $[NONO]^{+\bullet}$ ions with alkenes and also with several acyclic dienes and 1,3,5-cycloheptatriene. Thereafter, several groups have contributed to the development and only some classical work concerning simple alkenes may be mentioned here.

Extended reviews on double bond localization have been published by Budzikiewicz[251] and Harrison[252]. Besides the [2 + 2] cycloaddition, addition of gaseous alkyl cations, metal cations, ionized amines and of NO^+ offers a wide variety of reagents to locate double bonds. In an overview that appeared in 1990, Vairamani and coworkers[253,254] have collected various, in part rather special, reagent gases used for this purpose in chemical ionization mass spectrometry. Some of these reactions occurring with 1,3-dienes under CI conditions have employed dimethyl ether as the reactant gas. Double-bond localization has been performed not only in conventional sector-field instruments but also in ion traps, in which ionized alkenes such as cyclooctene radical cations may be used as reagent ions[255], and in FT-ICR mass spectrometers using Fe^+ as the reagent ion[256].

In the remainder of this section, some cases concerning dienes and polyenes will be treated, and we restrict ourselves mainly to the more recent literature. Using standard chemical ionization techniques with isobutane as the reactant gas, Doolittle and coworkers[257] demonstrated that conjugated dienes which may contain terminal functionalities such as aldehyde, alcohol and formate groups react with the major reagent ion, $t\text{-}C_4H_9^+$, to give structure-specific fragmentation. Limitations were encountered with dienes bearing the functional group proximal to the unsaturation and identification of stereoisomeric dienes proved also to be difficult. In closely related work and at the same time, Einhorn and coworkers[258,259] used isomeric butyl chlorides, instead of isobutane, as the reactant gases and found that the reactions of conjugated dienes, $R^1(CH{=}CH)_2R^2$, with $t\text{-}C_4H_9^+$ cations yield highly diagnostic fragment ions of the composition $C_4H_8(R^1)^+$ and $C_4H_8(R^2)^+$.

As mentioned above, gas-phase coordination of unsaturated C−C bonds to metal cations constitutes another means for double-bond localization. Peake and Gross[260] determined the fragmentation of Fe^+/olefin complexes by CID spectrometry and reported highly characteristic differences for several constitutional octadiene isomers. High-resolution mass spectrometry proved to be necessary in certain cases due to the isobaric masses of Fe and even two units of C_2H_4 and/or CO[261]. Although not based on gas-phase ion/molecule

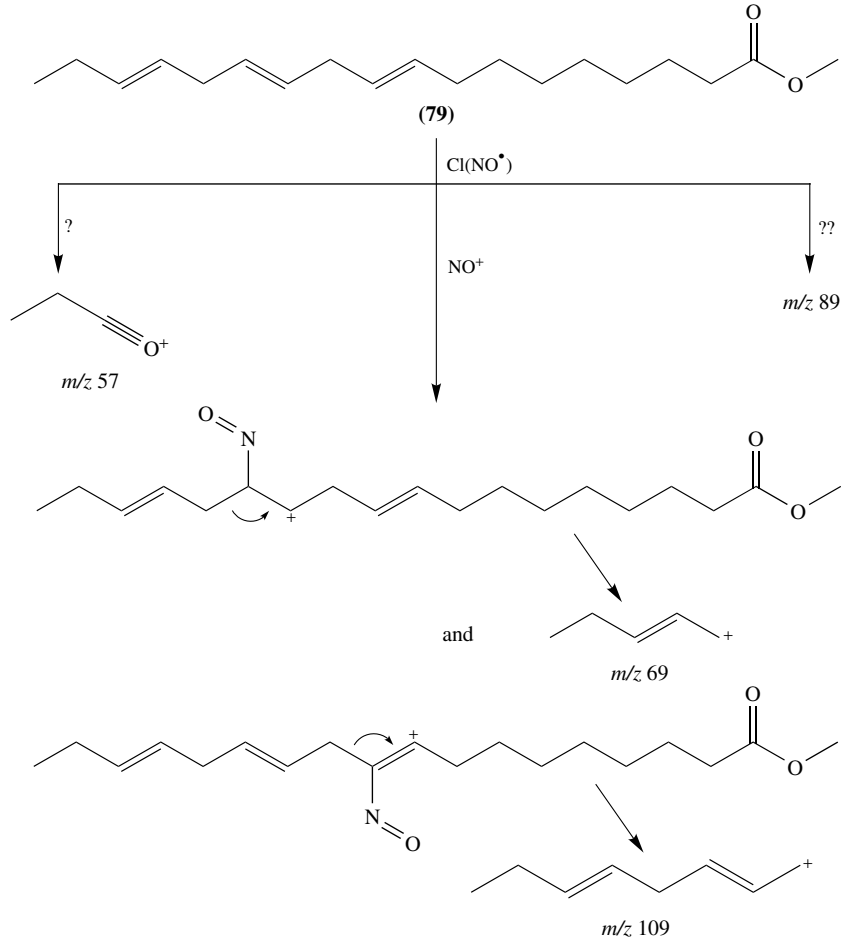


SCHEME 22

reactions, a study by Canty and Colton reporting electrospray ionization (ESI) mass spectrometry of several cyclic dienes and polyenes may be mentioned here[262].

Concerning special reactant gases used in CI mass spectrometry of dienes and polyenes, some more recent results are also of interest. It is noted that the distinction of isomers bearing C−C double bonds using CI mass spectrometry relies, in appropriate cases, on

the $[4 + 2^+]$ cycloaddition processes discussed in the previous section, as suggested by Keough[263]. Along the same line, Lange[264] reported the use of oxirane as the reactant gas for CI mass spectrometry. Several olefins including 1,3-alkadienes and doubly and triply unsaturated fatty acids were examined and the $[M + 43]^+$ ion was found to be characteristic for 1,3-dienes. It appears reasonable that $C_2H_3O^+$ ions, formed in the CI(oxirane) plasma, presumably as acetyl cations, are able to undergo cycloaddition with 1,3-dienes. Distinction of stereoisomeric dienes was also reported. Furthermore, acetone has been tested as a reactant gas for CI mass spectrometry of olefins. The spectra of a few alkadienes have been reported in this context[265].



SCHEME 23

Finally, a recent study on the localization of the double bonds in dienes will be examplified. As an extension of the data presented in his reviews[251], Budzikiewicz and

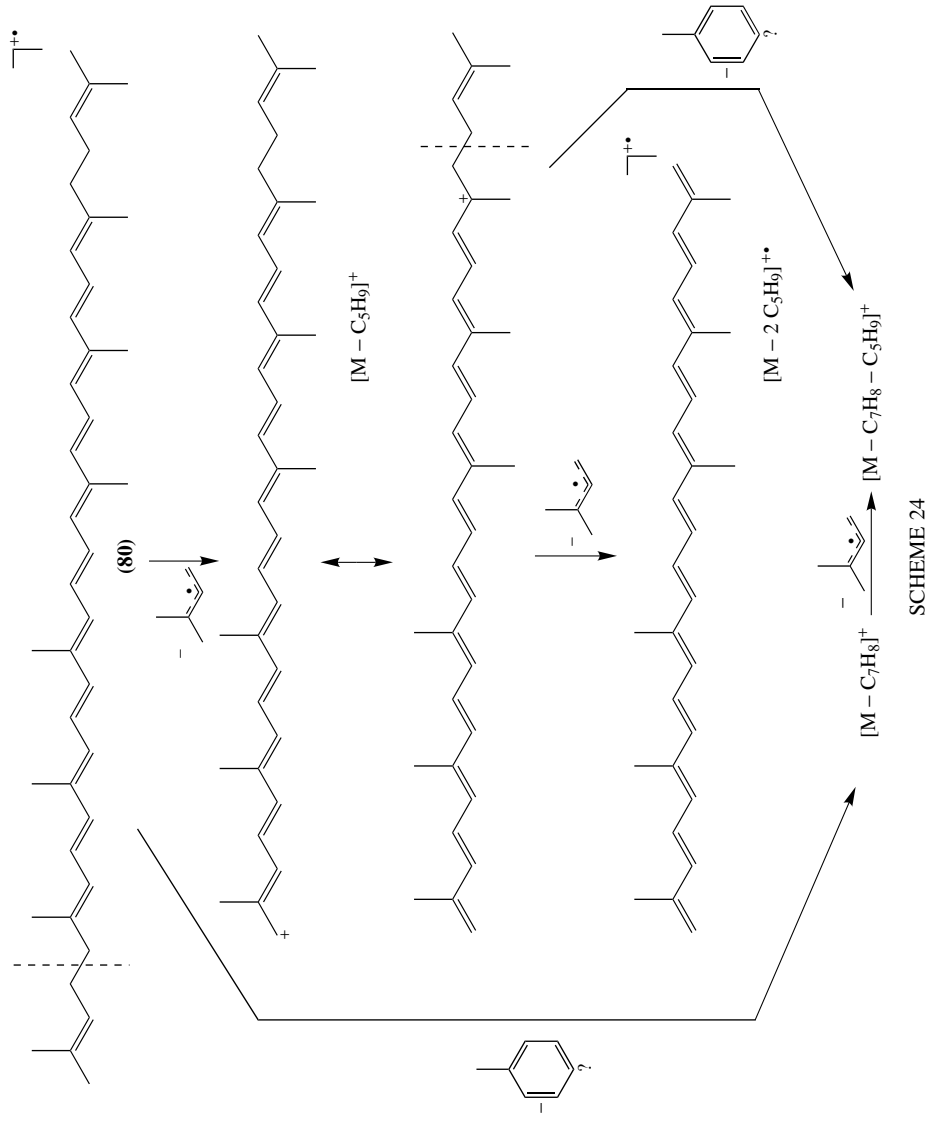
coworkers[266] have reported on the fragmentation of several non-conjugated alkadiene hydrocarbons and of methyl linolenate, a two-fold homoconjugated alkatriene carboxylic ester, using nitric oxide, which is one of the most widely studied reagent gases used for this purpose. Complex rearrangement processes have been identified. However, as stated by the authors, the details of the parameters that influence the CI(NO) mass spectra have remained unclear, in spite of the tremendous work invested in this topic. Most importantly, the temperature of the ion source and possibly other parameters of the experimental setup strongly affect the diagnostically valuable analytical information, as demonstrated for the linolenate. Under suitable conditions, however, structure-specific acyl cations can be recognized in all cases, originating from (possibly surface-catalysed) oxidative cleavage of the C−C double bonds. Also, diagnostic allylic cations are formed, probably resulting from the direct gas-phase electrophilic attack of NO^+ on the double bonds of unsaturated fatty acids such as **79** (Scheme 23). Both of these types of fragment ions, amongst others, help to determine the position of the double bond close to the end of the hydrocarbon chain, whereas localization of double bonds close to the functionalized terminus of **79** was found to be difficult. Still, it is noteworthy that the recurring formation of quite abundant fragment ions (m/z 89) of obvious specificity, being formed from dienes bearing a terminal 1-buten-1-yl group, is not yet understood. There is no doubt that 'unexpected' peaks will keep mass spectrometry a field of both mystery and fascination[267].

VII. MASS SPECTROMETRY OF MONO- AND OLIGOTERPENES, TERPENOIDS AND CAROTENOIDS

Owing to the vast occurrence of oligoterpenes in biological systems, instrumental analytical methods concerning these compounds have gained enormous interest during the past decades. Mass spectrometry of terpenoids and isoprenoids has become particularly important because of the extremely low detection limit as compared to other spectrometric techniques. From the mechanistically rather complicated isomerization reaction taking place in highly unsaturated radical cations, in particular, a detailed understanding of the gas-phase ion chemistry, as the origin of fragmentation behaviour, is difficult for terpenoid and carotenoid ions, too. Nevertheless, major fragmentation paths of these species have been found to correspond to the principles discussed in the previous sections for smaller diene and polyene ions. Thus, allylic and bis-allylic C−C bond cleavage, retro-Diels–Alder reactions and, most importantly, cyclization processes by C−C bond formation between the double bonds give rise to the most characteristic peaks in the positive-ion mass spectra of terpenoid and isoprenoid compounds.

Before returning to the deluge of literature that has built up on mass spectrometry of natural polyenes, the most impressive and highly diagnostic fragmentation reactions of carotenoid radical cations will be presented since this reflects the 'well-behaved', i.e. rational, gas-phase ion chemistry of these compounds. The major routes are collected in Scheme 24 for the case of lycopene (**80**)[268]. Bis-allylic cleavage leads to the $[M - C_5H_9]^+$ ions which lose another prenyl radical, as a notable exception of the even-electron rule. The other fragmentation path which is highly characteristic for carotenoids and other polyconjugated polyenes is the expulsion of neutral arenes, such as toluene and *meta*-xylene, from inner-chain units. Combinations of both fragmentation reactions provide also useful analytical information, although the sequence of the consecutive fragmentation is not unequivocal.

The expulsion of arenes from the inner sections of the polyene chain is very important for the determination of the positions of the side groups. Depending on the mutual distance of the methyl groups, either neutral toluene (92 u) and/or xylene (106 u) [u corresponds to Da = atomic mass unit, a symbol recommended by IUPAC] are eliminated from the



SCHEME 24

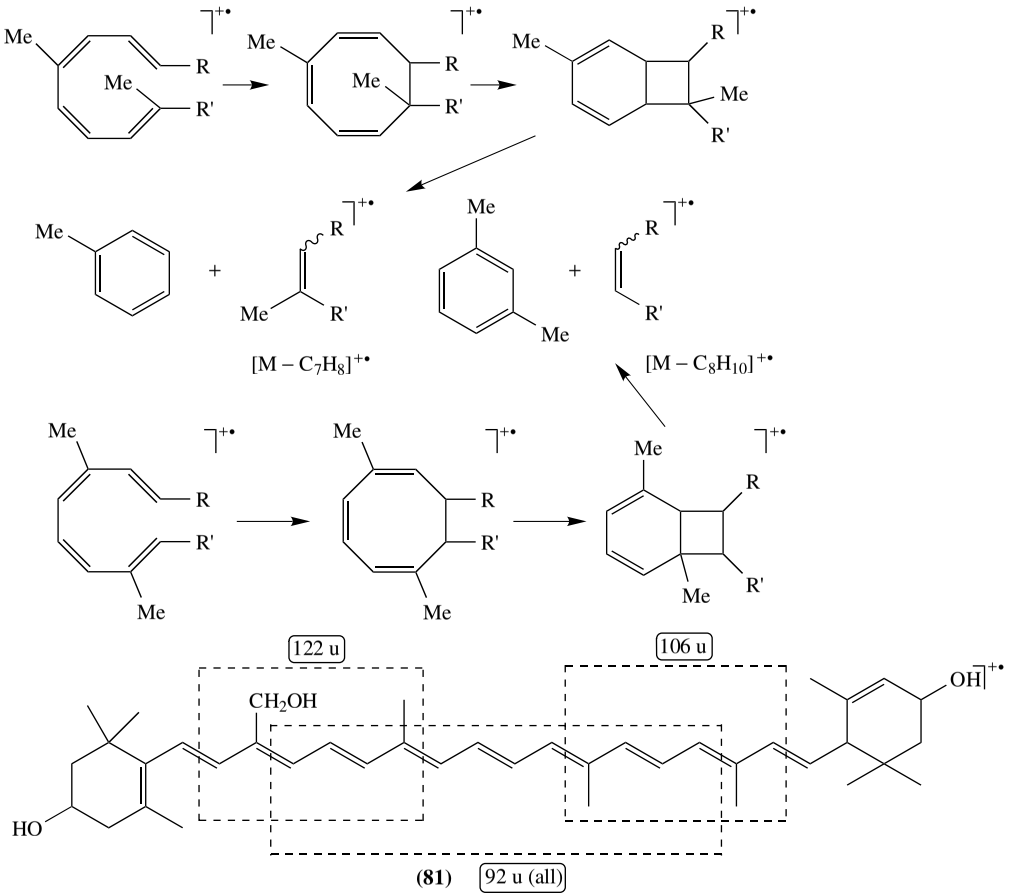
radical cations. In contrast to simple 1,3,5,7-octatetraene radical cations such as **(11)** (Scheme 2), the positive charge remains on the non-aromatic polyene fragment formed, owing to the lower ionization energy of the latter as compared with the arene. In the specific example of loroxanthin **(81)** shown in Scheme 25, the loss of 122 u indicates the presence of a hydroxymethyl group[269].

The elimination of arenes is not limited to the radical cations of the carotenoids. Just as the neutral compounds themselves also tend to undergo (thermal) cyclization followed by arene loss, the protonated analogues, e.g. ion **82** generated by CI or fast atom bombardment (FAB) mass spectrometry are prone to eliminate one or even two arene molecules as well (Scheme 26)[270].

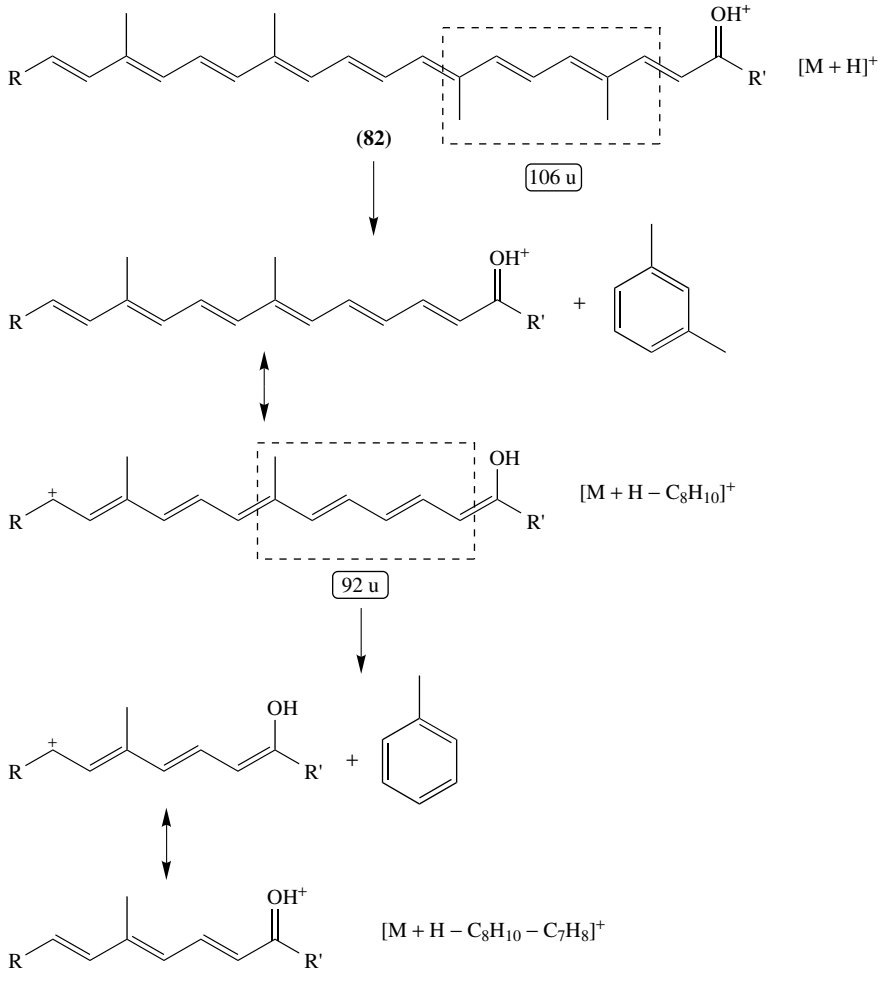
Mass spectrometry and gas-phase ion chemistry of monoterpenes have been reviewed several times during the last four decades[12]. In recent years, more attention has been drawn to the gas-phase ion chemistry taking place upon ionization of terpenes. Fernandez and coworkers[271] determined the gas-phase basicity and proton affinity of limonene by proton transfer equilibrium measurements in an FT-ICR mass spectrometer. Theoretical calculations suggest that protonation at the external C−C double bond occurs with concomitant 1,2-H shift of the proton at C(1) to C(7), yielding a tertiary, endocyclic carbocation instead of a secondary, exocyclic one. Basic and Harrison[272] have compared the standard 70 eV EI mass spectra of ten monoterpenes as well as the MIKE and CID spectra of the molecular radical cations. The isomers were found to be distinguishable, although long-lived (metastable) ions apparently undergo enhanced interconversion. Thus, double-bond migration appears to be limited in these cases but pairs of isomers give very similar MIKE spectra. The fragmentation of the ubiquitous $[M - CH_3]^+$ ions (m/z 121), $[M - C_2H_5]^+$ ions (m/z 107) and $[M - C_3H_7]^+$ ions ($C_7H_9^+$, m/z 93) was also studied by MIKE spectrometry. The MIKE spectra exhibit very similar fragmentation, and two paths for the formation of the $C_7H_9^+$ ions from the molecular ions were elucidated. Most intriguingly, comparison of charge stripping (CS) spectra of the $C_7H_9^+$ ions with those of protonated toluene and 1,3,5-cycloheptatriene led to the conclusion that the $C_7H_9^+$ ions from the monoterpenes have the dihydrotropylium rather than the toluenium structure. The structural specificity of the EI mass spectra can be enhanced by working at low electron energies, as shown by Brophy and Maccoll[273] in their study comprising nineteen monoterpenes. In almost all cases, the [m/z 93] / [m/z 121] intensity ratio provides a characteristic feature of the isomers. Previous investigations by Schwarz and coworkers[274] had also shown that the molecular ions of the monoterpenes are rather reluctant to isomerization whereas the $C_7H_9^+$ ions undergo extensive interconversion to a common structure or mixture of structures. Interestingly, the structural ambiguity of $C_7H_9^+$ ions has been known as long as the much better recognized problem of the six- and seven-ring isomers of the $C_7H_7^+$ ions (i.e. benzyl vs tropylium) and $C_7H_8^{+\bullet}$ ions (i.e. ionized toluene vs ionized cycloheptatriene). With regard to the monoterpenes, Friedman and Wolf[275] had already suggested in 1957 a monocyclic structure for the ion at m/z 93 in the EI spectrum of camphene.

Formation of dihydrotropylium ions is a key feature of the $C_7H_9^+$ hypersurface. Currently, efforts in our laboratory[276] have concentrated on the presence of different $C_7H_9^+$ isomers by probing their bimolecular reactivity. Thus, gas-phase titration in the FT-ICR mass spectrometer has revealed that mixtures of $C_7H_9^+$ ions are formed by protonation of 1,3,5-cycloheptatriene, 6-methylfulvene and norbornadiene as the neutral precursors but that, in contrast to the results obtained by CS mass spectrometry, fragmentation of the radical cations of limonene yields almost exclusively toluenium ions[275].

An impressive number of comprehensive reviews have appeared since the first overview on the structure elucidation of carotenoids by spectroscopic methods by Weedon appeared



SCHEME 25



SCHEME 26

in 1969[277]. This early review already collected the major fragmentation routes reflected by the EI spectra of the terpenoids containing 1,5-hexadiene units, viz. bis-allylic C−C bond cleavage, and the carotenes, viz. cyclization of the unsaturated chain leading to the elimination of toluene and xylene from inner positions of the chain (see above). The mechanisms of these and other important fragmentation reactions have been discussed in the 1971 review on carotenoids by Vetter and coworkers[278]. Only one year later, two further review articles appeared, one by Enzell and coworkers[279] concerning mass spectrometry of terpenes and terpenoids, and another by Elliott and Waller[280] on mass spectrometry of vitamins and cofactors. In the former article, the standard EI mass spectra of monoterpenes, sesquiterpenes and many higher terpenoids, including the carotenes, are presented and discussed with many mechanistic suggestions for the major fragmentation paths. The latter review is focused on the EI mass spectra of vitamins A and D and their

derivatives. Subsequently, Budzikiewicz[281] gave an exemplatory view on the potential of EI mass spectrometry, concentrating in detail on the expulsion of arene molecules from the inner-chain positions of the radical cations of several carotenoids. In 1980, a supplemental volume of the series on biochemical applications of mass spectrometry appeared to which Enzell and Wahlberg contributed extensive overviews on the mass spectrometric fragmentation of terpenoids[282] and carotenoids[283]. Degraded isoprenoids, as present in substantial amounts in tobacco, contribute to the diversity of these polyene compounds, and another extensive review dealing with the mass spectra of tobacco isoprenoids appeared in 1984[284]. Stereochemical aspects reflected in the mass spectra of terpenes and terpenoids have been discussed in a separate survey[285]. A collection of spectral data of more than 300 sesquiterpene hydrocarbons, including the EI mass spectra, has appeared recently[286]. In their latest overview on mass spectrometry of carotenoids, Enzell and Back[287] gave an exhaustive presentation and discussion on the topic, including various ionization techniques such as EI, FAB and CI, and examples on the application of tandem mass spectrometry such as MIKE spectrometry and the B/E linked scan techniques. Moreover, state-of-the-art combination of chromatographic techniques with mass spectrometry was discussed for carotenoids. While the major part of the discussion is again devoted to the mechanism of the elimination of in-chain units from the polyene skeleton in the radical cations formed upon EI (see above), even the mass spectra of carotenoid conjugates such as fatty and retinoic acid esters, sulphates and glycosides are included.

Several original papers must be mentioned that deal with mass spectrometric techniques which the numerous reviews do not comprise. Kaufmann and coworkers[268,288] studied the mass spectrometric analysis of carotenoids and some of their fatty acid esters using matrix-assisted laser desorption/ionization (MALDI) mass spectrometry and its post-source-decay (PSD) variant. Some advantages concerning the thermal instability and limited solubility were discussed, but the fragmentation paths of the carotenoid cations were found to be essentially the same as those observed with conventional techniques.

Different from many other classes of organic compounds, the carotenoids have relatively high electron affinities. Capture of thermal electrons in the NCI plasma by a low-lying π^* orbital of the extended system of conjugated double bonds is facile and therefore electron capture negative chemical ionization (ECNCI) mass spectrometry is particular useful with carotenes and carotenoids. McClure and Liebler[289] have recently demonstrated the characterization of β-carotene and three of its oxidation products by ECNCI tandem mass spectrometry, i.e. by performing collision-induced dissociation (CID) of the molecular radical anions and recording the fragment anions by B/E linked scanning. It is noteworthy that, in contrast to the positively charged molecular ions formed under EI, CI, FAB and MALDI conditions, the negative charge molecular ions do not undergo expulsion of arenes from the inner segments of the polyene chain. Instead of those rearrangement processes, the fragment anions formed originate from (apparently) simple cleavages of both single and double C−C bonds in a highly characteristic manner. Mechanistic explanations have not yet been provided. It may be suspected, however, that cyclization by C−C bond formation between unsaturated centers intervenes also in the radical anions as well. Also, owing to the particularly high electron affinity, the detection limits in carotenoid analysis by ECNCI mass spectrometry are considerably lower than under positive-ion conditions. The conversion of β-carotene to retinol under in-vivo conditions has been studied recently by ECNCI and atmospheric pressure chemical ionization (APCI) mass spectrometry[290]. Very recent work utilizing coupling of the ECNCI techniques with gas chromatography[291] and liquid chromatography[292] for monitoring of retinol and carotenoids, respectively, is also mentioned here. Analytical studies on carotenoids using other ionization techniques

such as fast-atom bombardment (FAB)[293], electrospray ionization (ESI)[294] and atmospheric pressure chemical ionization[295], field desorption (FD)[296] and plasma desorption mass spectrometry have been published[297].

Selva and coworkers[298–302] reported on their experiences to apply various mass spectrometric techniques to the analysis of β-carotene and carotenoids and their adducts formed in aqueous solution. EI mass spectrometry and field desorption (FD) mass spectrometry were applied to aqueous mixtures of β-carotene and β-cyclodextrin, and the polyene was found to be detectable[298]. Tandem mass spectrometry can be applied to identify β-carotenone as a minor component in complex carotenoid mixtures. EI/MIKE spectrometry of the molecular ion (m/z 600) was used in this case[299]. A previous study was focused on the characterization of *seco*-carotenoids using EI/MIKE and CID spectrometry[300]. The more recent ionization methods, viz. MALDI and its variant working without a matrix, laser desorption/ionization (LDI), as well as electrospray ionization (ESI) mass spectrometry, have also been applied to this topic. MALDI and LDI mass spectrometry were used to analyse mixtures of β-carotene and γ-cyclodextrin in aqueous solution. Adduct ions were not observed using these methods[301].

Also, a brief note has appeared concerning electrospray ionization mass spectrometry of mixtures of β-carotene with β- and with γ-cyclodextrin in aqueous methanol solutions. Whereas negative ion ESI produced 1:1 adduct ions of β-carotene with both of the cyclodextrin isomers, positive ESI gave these adducts only in the case of β-cyclodextrin[302].

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IX. REFERENCES

1. A. G. Loudon and A. Maccoll, in *The Chemistry of Alkenes*, Vol. 2 (Ed. J. Zabicky), Chap. 7, Wiley-Interscience, London, 1970, pp. 327–358.
2. M. N. Mruzek, in *The Chemistry of Double-bonded Functional Groups*, Vol. 2, Part 2 (Ed. S. Patai), Chap. 2, Wiley, Chichester, 1989, pp. 53–79.
3. H. Schwarz, in *The Chemistry of the Cyclopropyl Group*, Part 1 (Ed. Z. Rappoport), Chap. 4, Wiley, Chichester, 1987, pp. 173–211.
4. C. Dass, *Mass Spectrom. Rev.*, **9**, 1 (1990).
5. F. Tureček and V. Hanuš, *Mass Spectrom. Rev.*, **3**, 85 (1984).
6. A. Mandelbaum, in *Applications of Mass Spectrometry to Organic Stereochemistry* (Ed. J. S. Splitter), VCH, New York, 1994, pp. 299–324.
7. D. Kuck, *Mass Spectrom. Rev.*, **9**, 181 (1990).
8. D. Kuck, *Mass Spectrom. Rev.*, **9**, 583 (1990).
9. S. Fornarini, *Mass Spectrom. Rev.*, **15**, 365 (1996).
10. S. Fornarini and M. E. Crestoni, *Acc. Chem. Res.*, **31**, 827 (1998).
11. M. Mormann and D. Kuck, *J. Mass Spectrom.*, **34**, 384 (1999).
12. For early reviews, see:
    (a) H. Budzikiewicz, C. Djerassi and D. H. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry*, Vol II: Steroids, Terpenoids, Sugars and Miscellaneous Classes, Chap. 24, Holden-Day, San Francisco, 1964, pp. 141–164.
    (b) J. H. Beynon, R. A. Saunders and A. E. Williams, *The Mass Spectra of Organic Molecules*, Chap. 3.2, Elsevier, Amsterdam, 1968, pp. 112–122.

13. See, for example: D. Kuck, *Angew. Chem.*, **112**, 129 (2000); *Angew. Chem., Int. Ed. Engl.*, **39**, 125 (2000).
14. (a) S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin and W. G. Mallard, *J. Phys. Chem. Ref. Data*, **17**, Suppl. 1 (1988).
(b) E. P. L. Hunter and S. G. Lias, *J. Phys. Chem. Ref. Data*, **27**, 413 (1998).
(c) W. G. Mallard and P. J. Linstrom (Eds.), *NIST Chemistry Webbook*, NIST Standard Reference Database No. 69; March 1998; National Institute of Standards and Technology: Gaithersburg, MD 20899 (http://webbook.nist.gov).
15. F. W. McLafferty and D. B. Stauffer, *The Wiley/NBS Registry of Mass Spectral Data*, Vol. 1, Wiley, New York, 1989, p. 16.
16. F. W. McLafferty and F. Tureček, *Interpretation of Mass Spectra*, 4th edn., University Science Books, Mill Valley, 1993, p. 230–231.
17. K. Levsen and E. Hilt, *Justus Liebigs Ann. Chem.*, 257 (1976).
18. J. C. A. Marques, A. Falick, A. Heusler, D. Stahl, P. Tecon and T. Gäumann, *Helv. Chim. Acta*, **67**, 425 (1984).
19. (a) K. Levsen, R. Weber, F. Borchers, H. Heimbach and H. D. Beckey, *Anal. Chem.*, **50**, 1655 (1978).
(b) K. Levsen, *Fundamental Aspects of Organic Mass Spectrometry*, Verlag Chemie, Weinheim, 1978, pp. 186–196 and 273–279.
20. S. A. Rang, A.-M. A. Müürisepp, M. M. Liitma and O. G. Eisen, *Org. Mass Spectrom.*, **13**, 181 (1978).
21. A. A. Polyakova, K. I. Zimina, A. A. Petrov and R. A. Kheml'nitskii, *J. Gen. Chem. USSR (Engl. Transl.)*, **30**, 2949 (1960).
22. J. L. Holmes, *Org. Mass Spectrom.*, **8**, 247 (1974).
23. Synonymous terms used: *C*ollisional *a*ctivation (CA) and *c*ollision-*a*ctivated *d*issociation (CAD).
24. C. Lifshitz, *Acc. Chem. Res.*, **27**, 138 (1994).
25. A. Maquestiau, Y. Van Haverbeke, R. Flammang, C. de Meyer and A. Menu, *Org. Mass Spectrom.*, **12**, 706 (1977).
26. J. L. Holmes, J. K. Terlouw, P. C. Burgers and R. T. B. Rye, *Org. Mass Spectrom.*, **15**, 149 (1980).
27. C. Dass, D. A. Peake and M. L. Gross, *Org. Mass Spectrom.*, **21**, 741 (1986).
28. F. P. Lossing and J. C. Traeger, *Int. J. Mass Spectrom. Ion Phys.*, **19**, 9 (1976).
29. R. Houriet, H. Schwarz, W. Zummack, J. G. Andrade and P. v. R. Schleyer, *Nouv. J. Chim.*, **5**, 505 (1981).
30. P. v. R. Schleyer, T. W. Bentley, W. Koch, A. J. Kos and H. Schwarz, *J. Am. Chem. Soc.*, **109**, 6953 (1987).
31. R. S. Mason, K. R. Jennings, S. Verma and R. G. Cooks, *Org. Mass Spectrom.*, **20**, 727 (1985).
32. J. M. Curtis, A. G. Brenton, J. H. Beynon and R. K. Boyd, *Org. Mass Spectrom.*, **22**, 779 (1987).
33. J. R. Appling, K. M. Musier and T. F. Moran, *Org. Mass Spectrom.*, **19**, 412 (1984).
34. S. R. Andrews, D. E. Parry and F. M. Harris, *Rapid Commun. Mass Spectrom.*, **8**, 913 (1994).
35. W. Wagner-Redeker and K. Levsen, *Org. Mass Spectrom.*, **16**, 538 (1981).
36. R. C. Benz, R. C. Dunbar and P. C. Claspy, *J. Am. Chem. Soc.*, **103**, 1799 (1981).
37. R. E. Krailler and D. H. Russell, *Anal. Chem.*, **57**, 1211 (1985).
38. S. E. Van Bramer and M. V. Johnston, *Org. Mass Spectrom.*, **27**, 949 (1992).
39. P. Wolkoff, J. L. Holmes and F. P. Lossing, *Can. J. Chem.*, **58**, 251 (1980).
40. P. Wolkoff and J. L. Holmes, *J. Org. Chem.*, **47**, 3342 (1982).
41. (a) F. Tureček and M. Gu, *Org. Mass Spectrom.*, **27**, 1335 (1992).
(b) F. Tureček and M. Gu, *J. Mass Spectrom.*, **30**, 144 (1995).
42. M. Gu and F. Tureček, *Org. Mass Spectrom.*, **29**, 85 (1994).
43. S. Hayakawa, H. Endoh, K. Arakawa and N. Morishita, *Int. J. Mass Spectrom. Ion Processes*, **171**, 209 (1997).
44. S. Hayakawa, H. Endoh, K. Arakawa, N. Morishita and T. Sugiura, *Int. J. Mass Spectrom. Ion Processes*, **151**, 89 (1995).
45. R. Stockbauer and H. Rosenstock, *Int. J. Mass Spectrom. Ion Phys.*, **27**, 185 (1978).
46. W. Wagner, K. Levsen and C. Lifshitz, *Org. Mass Spectrom.*, **15**, 271 (1980).

47. G. Frenking and H. Schwarz, *Int. J. Mass Spectrom. Ion Phys.*, **52**, 131 (1983).
48. A. C. Parr, A. J. Jason, R. Stockbauer and K. E. McCulloh, *Int. J. Mass Spectrom. Ion Phys.*, **30**, 319 (1979).
49. P. N. T. van Velzen and W. J. van der Hart, *Org. Mass Spectrom.*, **16**, 237 (1981).
50. W. J. van der Hart, *Int. J. Mass Spectrom. Ion Processes*, **151**, 27 (1995).
51. A. A. Mommers, P. C. Burgers, J. L. Holmes and J. K. Terlouw, *Org. Mass Spectrom.*, **19**, 7 (1984).
52. C. Cornaggia, *Phys. Rev. A*, **52**, R4328 (1995).
53. E. Rühl, B. Brutschy, P. Bisling and H. Baumgärtel, *Ber. Bunsenges. Phys. Chem.*, **92**, 194 (1988).
54. A. B. King, *J. Phys. Chem.*, **68**, 1409 (1964).
55. D. H. Russell, M. L. Gross, J. van der Greef and N. M. M. Nibbering, *J. Am. Chem. Soc.*, **101**, 2086 (1979).
56. J. L. Franklin and A. Mogenis, *J. Phys. Chem.*, **71**, 2820 (1967).
57. T. L. Bunn and T. Baer, *J. Chem. Phys.*, **85**, 6361 (1986).
58. J. W. Keister, T. Baer, M. Evans, C. Y. Ng and C.-W. Hsu, *J. Phys. Chem. A*, **101**, 1866 (1997).
59. P. C. Burgers, J. L. Holmes, A. A. Mommers and J. E. Szulejko, *J. Am. Chem. Soc.*, **106**, 521 (1984).
60. A. M. Woodward, W. A. Chupka and S. D. Colson, *J. Phys. Chem.*, **88**, 4567 (1984).
61. W. Tang, X.-L. Zhang and T. Bally, *J. Phys. Chem.*, **97**, 4373 (1993).
62. T. Keszthelyi, R. Wilbrandt and T. Bally, *J. Mol. Struct.*, **410–411**, 339 (1997).
63. F. Tureček, F. Maquin, N. Hill, D. Stahl and T. Gäumann, *Org. Mass Spectrom.*, **23**, 91 (1988).
64. B. G. Syrvatka, M. M. Gil'burd and A. L. Bel'ferman, *J. Org. Chem. USSR (Engl. Transl.)*, **9**, 1144 (1973).
65. M. Kraft and G. Spiteller, *Org. Mass Spectrom.*, **2**, 865 (1969).
66. D. G. I. Kingston, J. T. Bursey and M. M. Bursey, *Chem. Rev.*, **74**, 215 (1974).
67. H. Budzikiewicz, C. Fenseleau and C. Djerassi, *Tetrahedron*, **22**, 1391 (1966).
68. J. R. Dias, Y. M. Sheikh and C. Djerassi, *J. Am. Chem. Soc.*, **94**, 473 (1972).
69. R. B. Bates, J. J. White and K. H. Schramm, *Org. Mass Spectrom.*, **22**, 295 (1987).
70. O. Vostrowsky, K. Michaelis and H. J. Bestmann, *Justus Liebigs Ann. Chem.*, 1001 (1982).
71. H. Ikeda, T. Takasaki, Y. Takahashi and T. Miyashi, *J. Chem. Soc., Chem. Commun.*, 367 (1993).
72. U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 105 (1971).
73. K. Schmidt, G. W. Francis and S. Liaaen-Jensen, *Acta Chem. Scand.*, **25**, 2476 (1971).
74. M. L. Gross and D. H. Russell, *J. Am. Chem. Soc.*, **101**, 2082 (1979).
75. C. Dass, T. M. Sack and M. L. Gross, *J. Am. Chem. Soc.*, **106**, 5780 (1984).
76. C. Dass and M. L. Gross, *J. Am. Chem. Soc.*, **105**, 5724 (1983).
77. E. Gil-Av, J. H. Leftin, A. Mandelbaum and S. Weinstein, *Org. Mass Spectrom.*, **4**, 475 (1970).
78. A. Mandelbaum, S. Weinstein, E. Gil-Av and J. H. Leftin, *Org. Mass Spectrom.*, **10**, 842 (1975).
79. S. G. Lias and P. Ausloos, *Int. J. Mass Spectrom. Ion Processes*, **81**, 165 (1987).
80. (a) P. J. Derrick, A. M. Falick and A. L. Burlingame, *J. Am. Chem. Soc.*, **94**, 6794 (1972).
    (b) P. J. Derrick, A. M. Falick and A. L. Burlingame, *J. Am. Chem. Soc.*, **96**, 615 (1974).
81. P. Wolkoff and J. L. Holmes, *Can. J. Chem.*, **57**, 348 (1979).
82. E. P. Smith and E. R. Thornton, *J. Am. Chem. Soc.*, **89**, 5079 (1967).
83. (a) D. P. Stevenson, *Disc. Faraday Soc.*, **10**, 35 (1951).
    (b) H. E. Audier, *Org. Mass Spectrom.*, **2**, 283 (1969).
84. R. C. Dougherty, *J. Am. Chem. Soc.*, **90**, 5788 (1968).
85. E. F. Brittain, C. H. J. Wells and H. M. Paisley, *J. Chem. Soc. B*, 503 (1969).
86. F. Tureček and V. Hanuš, *Org. Mass Spectrom.*, **15**, 4 (1980).
87. (a) G. M. Whitesides, G. L. Goe and A. C. Cope, *J. Am. Chem. Soc.*, **89**, 7136 (1967).
    (b) G. M. Whitesides, G. L. Goe and A. C. Cope, *J. Am. Chem. Soc.*, **91**, 2608 (1969).
88. W. D. Reets, Jr, H. D. Roth, M. L. Schilling and C. J. Abelt, *Int. J. Mass Spectrom. Ion Processes*, **72**, 155 (1986).
89. G. S. Groenewold and M. L. Gross, *J. Am. Chem. Soc.*, **106**, 6569 (1984).

90. (a) N. L. Bauld, D. J. Bellville, R. Pabon, R. Chelsky and G. Green, *J. Am. Chem. Soc.*, **105**, 2378 (1983).
(b) D. J. Bellville and N. L. Bauld, *Tetrahedron*, **42**, 6167 (1986).
(c) N. L. Bauld, *Tetrahedron*, **45**, 5307 (1989).
91. G.-F. Chen and F. Williams, *J. Am. Chem. Soc.*, **113**, 7792 (1991).
92. D. Vollmer, D. L. Rempel and M. L. Gross, *J. Am. Chem. Soc.*, **117**, 1669 (1995).
93. D. A. Lightner, J. K. Gawroński and T. D. Bouman, *J. Am. Chem. Soc.*, **102**, 5749 (1980).
94. D. Harris, S. McKinnon and R. K. Boyd, *Org. Mass Spectrom.*, **14**, 265 (1979).
95. M. Vincenti, S. R. Horning and R. G. Cooks, *Org. Mass Spectrom.*, **23**, 585 (1988).
96. S. R. Horning, J. M. Wood, R. R. Gord, B. S. Freiser and R. G. Cooks, *Int. J. Mass Spectrom. Ion Processes*, **101**, 219 (1990).
97. J. R. Gord, S. R. Horning, J. M. Wood, R. G. Cooks and B. S. Freiser, *J. Am. Soc. Mass Spectrom.*, **4**, 145 (1993).
98. R. W. Holman, C. D. Warner, R. N. Hayes and M. L. Gross, *J. Am. Chem. Soc.*, **112**, 3362 (1990).
99. B. A. Horn, J. L. Herek and A. H. Zewail, *J. Am. Chem. Soc.*, **118**, 8755 (1996).
100. S. A. Trushin, W. Fuss, T. Schikarski, W. E. Schmid and K. L. Kompa, *J. Phys. Chem.*, **106**, 9386 (1997).
101. M. Mormann and D. Kuck, unpublished results.
102. B. de Pascual-Teresa and K. N. Houk, *Tetrahedron Lett.*, **37**, 1759 (1996).
103. See, for example:
(a) W. T. Borden, E. R. Davidson and D. Feller, *J. Am. Chem. Soc.*, **103**, 5725 (1981).
(b) D. W. Kohn and P. Chen, *J. Am. Chem. Soc.*, **115**, 2844 (1993).
104. (a) C. Lifshitz and M. Weiss, *Int. J. Mass Spectrom. Ion Phys.*, **34**, 311 (1980).
(b) C. Lifshitz, D. Gibson, K. Levsen and I. Dotan, *Int. J. Mass Spectrom. Ion Phys.*, **40**, 157 (1981).
105. T. Baer, G. D. Willett, D. Smith and J. S. Phillips, *J. Chem. Phys.*, **70**, 4076 (1979).
106. P. Ausloos, *J. Am. Chem. Soc.*, **103**, 3931 (1981).
107. W. Wagner-Redeker, A. J. Illies, P. R. Kemper and M. T. Bowers, *J. Am. Chem. Soc.*, **105**, 5719 (1983).
108. J. C. Ray, Jr., P. O. Danis, F. W. McLafferty and B. K. Carpenter, *J. Am. Chem. Soc.*, **109**, 4408 (1987).
109. M.-Y. Zhang, C. Wesdemiotis, M. Marchetti, P. O. Danis, J. C. Ray, Jr., B. K. Carpenter and F. W. McLafferty, *J. Am. Chem. Soc.*, **111**, 8341 (1989).
110. C. Wesdemiotis, M.-Y. Zhang and F. W. McLafferty, *Org. Mass Spectrom.*, **26**, 671 (1991).
111. M.-Y. Zhang, B. K. Carpenter and F. W. McLafferty, *J. Am. Chem. Soc.*, **113**, 9499 (1991).
112. W. J. van der Hart, *Org. Mass Spectrom.*, **23**, 187 (1988).
113. B. J. Shay, M. N. Eberlin, R. G. Cooks and C. Wesdemiotis, *J. Am. Soc. Mass Spectrom.,* **3**, 518 (1992).
114. R. Bakhtiar, J. J. Drader and D. B. Jacobsen, *Org. Mass Spectrom.*, **28**, 797 (1993).
115. N. Goldberg, D. Sülzle and H. Schwarz, *Chem. Phys. Lett.*, **213**, 593 (1993).
116. (a) R. Flammang, P. Meyrant, A. Maquestiau, E. E. Kingston and J. H. Beynon, *Org. Mass Spectrom.*, **20**, 253 (1985).
(b) E. E. Kingston, J. H. Beynon, T. Ast, R. Flammang and A. Maquestiau, *Org. Mass Spectrom.*, **20**, 546 (1985).
117. M. A. Mabud, T. Ast and R. G. Cooks, *Org. Mass Spectrom.*, **22**, 418 (1987).
118. A. G. Harrison, P. Haynes, S. McLean and F. Meyer, *J. Am. Chem. Soc.*, **87**, 5099 (1965).
119. T. E. Smith, S. R. Smith and F. W. McLafferty, *Org. Mass Spectrom.*, **13**, 254 (1978).
120. J. L. Franklin and S. R. Carroll, *J. Am. Chem. Soc.*, **91**, 6564 (1969).
121. (a) M. I. Gorfinkel, T. P. Sosedkina and V. A. Koptyug, *J. Gen. Chem. USSR (Engl. Transl.)*, **37**, 1373 (1967).
(b) M. I. Gorfinkel, I. S. Isaev, I. A. Shleider and V. A. Koptyug, *J. Gen. Chem. USSR (Engl. Transl.)*, **39**, 1333 (1969).
122. M. N. Glukhovtsev, A. Pross, A. Nicolaides and L. Radom, *J. Chem. Soc., Chem. Commun.*, 2347 (1995).
123. R. C. Dunbar and H. H. I. Teng, *J. Am. Chem. Soc.*, **100**, 2279 (1978).
124. R. L. Betts, M. A. Park and E. A. Schweikert, *J. Mass Spectrom.*, **30**, 305 (1995).
125. P. E. Share and K. L. Kompa, *Chem. Phys.*, **134**, 429 (1989).

126. M. E. Rennekamp and M. K. Hoffman, *Org. Mass Spectrom.*, **10**, 1075 (1975).
127. V. Hanuš and Z. Dolejšek, *Collect Czech. Chem. Commun.*, **28**, 6562 (1963).
128. H. M. Rosenstock, K. E. McCulloh and F. P. Lossing, *Int. J. Mass Spectrom. Ion Phys.*, **25**, 327 (1977).
129. See also: W. Roth, cited as personal communication in Reference 14a.
130. E. Heilbronner, R. Gleiter, H. Hopf, V. Hornung and A. de Meijere, *Helv. Chim. Acta*, **54**, 783 (1971).
131. (a) D. H. Russell and M. L. Gross, *J. Am. Chem. Soc.*, **102**, 6279 (1980).
(b) W. J. van der Hart, L. J. de Koning, N. M. M. Nibbering and M. L. Gross, *Int. J. Mass Spectrom. Ion Processes.*, **72**, 99 (1986).
132. (a) W. J. van der Hart, *Int. J. Mass Spectrom. Ion Processes*, **130**, 173 (1994).
(b) W. J. van der Hart, *J. Am. Soc. Mass Spectrom.*, **6**, 513 (1995).
133. S. G. Lias and P. Ausloos, *J. Chem. Phys.*, **82**, 3613 (1985).
134. Z. Zhu and T. Gäumann, *Org. Mass Spectrom.*, **28**, 1111 (1993).
135. T. Gäumann, G. Zhao and Z. Zhu, *Rapid Commun. Mass Spectrom.*, **8**, 1 (1994).
136. J. A. Herman, K. Herman and T. B. McMahon, *Can. J. Chem.*, **69**, 2038 (1991).
137. (a) G. Bouchoux and J.-Y. Salpin, *Rapid Commun. Mass Spectrom.*, **8**, 325 (1994).
(b) G. Bouchoux, J.-Y. Salpin and M. T. Nguyen, to be published.
138. G. Bouchoux, M. Yáñez and O. Mó, *Int. J. Mass Spectrom.*, **185/186/187**, 241 (1999).
139. M. Mormann, J.-Y. Salpin and D. Kuck, *Eur. Mass Spectrom.*, in press.
140. For an early review, see: M. K. Hoffman, *Z. Naturforsch.*, **29a**, 1077 (1974).
141. (a) D. H. Williams and G. Hvistendahl, *J. Am. Chem. Soc.*, **96**, 6755 (1974).
(b) G. Hvistendahl and D. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 881 (1975).
142. J.-Y. Salpin, M. Mormann, M. T. Nguyen and D. Kuck, to be published.
143. C. Lifshitz, Y. Gotkis, A. Ioffe, J. Laskin and S. Shaik, *Int. J. Mass Spectrom. Ion Processes*, **125**, R7 (1993).
144. C. Basic, J. E. Eyler and R. A. Yost, *Org. Mass Spectrom.*, **29**, 329 (1994).
145. B. P. Mathur, E. M. Burgess, D. E. Bostwick and T. F. Moran, *Org. Mass Spectrom.*, **16**, 92 (1981).
146. K. N. Wiegel, R. W. Holman and M. L. Gross, *Int. J. Mass Spectrom. Ion Processes*, **146/147**, 239 (1995).
147. (a) J. Grotemeyer and H.-F. Grützmacher, *Org. Mass Spectrom.*, **17**, 353 (1982).
(b) J. Grotemeyer and H.-F. Grützmacher, in *Current Topics in Mass Spectrometry and Chemical Kinetics* (Eds. J. H. Beynon and M. L. McGlashan), Heyden, London, 1982, pp. 29–59.
148. D. Kuck and H.-F. Grützmacher, *Org. Mass Spectrom.*, **14**, 86 (1979).
149. J. Møller, C. Th. Pedersen, E. Egsgaard and E. Larsen, *Org. Mass Spectrom.*, **15**, 456 (1980).
150. C. Lifshitz and S. H. Bauer, *J. Phys. Chem.*, **67**, 1629 (1963).
151. (a) R. Pentz, *Massenspektrometrische Untersuchungen von C_8-Cycloalkenen: Zerfallsmechanismen von Cyclooctadi- und -trienen und von [3.3.0]-Bicyclooctenen und octadienen*, Doctoral Thesis. Universität Hamburg, Germany, 1975.
(b) R. Pentz and H.-F. Grützmacher, unpublished results.
152. K. Levsen and H. D. Beckey, *Org. Mass Spectrom.*, **9**, 570 (1974).
153. See, for example: T. Bally, L. Truttmann and F. Williams, *J. Mol. Struct. (Theochem.)*, **398–399**, 255 (1997).
154. M. S. Robinson, M. L. Polak, V. M. Bierbaum, C. H. DePuy and W. C. Lineberger, *J. Am. Chem. Soc.*, **117**, 6766 (1995).
155. P. G. Wenthold, J. Hu and R. R. Squires, *J. Am. Chem. Soc.*, **116**, 6961 (1994).
156. J. Lee, P. K. Chou, P. Dowd and J. J. Grabowski, *J. Am. Chem. Soc.*, **115**, 7902 (1993).
157. J. Lee and J. J. Grabowski, *Chem. Rev.*, **92**, 1611 (1992).
158. J. Zhao, P. Dowd and J. J. Grabowski, *J. Am. Chem. Soc.*, **118**, 8871 (1996).
159. M. D. Brickhouse and R. R. Squires, *J. Am. Chem. Soc.*, **110**, 2706 (1988).
160. I. I. Furlei, E. A. Burmistrov, F. Z. Galin, V. N. Iskandarova, V. K. Mavrodiev and G. A. Tolstikov, *J. Acad. Sci. USSR, Ser. Chem. (Engl. Transl.)*, **8**, 1618 (1986).
161. B. T. Hill and R. R. Squires, *J. Chem. Soc., Perkin Trans. 2*, 1027 (1998).
162. P. G. Wenthold, J. Hu, R. R. Squires and W. C. Lineberger, *J. Am. Chem. Soc.*, **118**, 475 (1996).
163. P. G. Wenthold, J. Hu, B. T. Hill and R. R. Squires, *Int. J. Mass Spectrom.*, **179/180**, 173 (1998).

164. P. G. Wenthold, J. Hu and R. R. Squires, *J. Am. Chem. Soc.*, **118**, 11865 (1996).
165. D. Kuck, A. Schuster, B. Ohlhorst, V. Sinnwell and A. de Meijere, *Angew. Chem.*, **101**, 626 (1989); *Angew. Chem., Int. Ed. Engl.*, **28**, 595 (1989).
166. For a review, see: D. Kuck, *Top. Curr. Chem.*, **196**, 167 (1998).
167. R. Haag, D. Schröder, T. Zywietz, H. Jiao, H. Schwarz, P. v. R. Schleyer and A. de Meijere, *Angew. Chem.*, **108**, 1413 (1996); *Angew. Chem., Int. Ed. Engl.*, **35**, 1317 (1996).
168. D. Kuck, A. de Meijere and R. R. Squires, unpublished results. See also Reference 13.
169. J. E. Bartmess and R. T. Mclver, Jr., in *Gas Phase Ion Chemistry*, Vol. 2 (Ed. M. T. Bowers), Chap. 11, Academic Press, New York, 1979, pp. 87–121.
170. C. H. DePuy and V. M. Bierbaum, *Acc. Chem. Res.*, **14**, 146 (1981).
171. C. A. Wight and J. L. Beauchamp, *J. Am. Chem. Soc.*, **103**, 6499 (1981).
172. R. L. White, C. L. Wilkins, J. H. Heitkamp and S. W. Staley, *J. Am. Chem. Soc.*, **105**, 4868 (1983).
173. W. P. M. Maas, P. A. van Veelen and N. M. M. Nibbering, *Org. Mass Spectrom.*, **24**, 546 (1989).
174. R. E. Lee and R. R. Squires, *J. Am. Chem. Soc.*, **108**, 5078 (1986).
175. S. Kato, R. Gareyev, C. H. DePuy and V. M. Bierbaum, *J. Am. Chem. Soc.*, **120**, 5033 (1998).
176. J. W. Denault, G. Chen and R. G. Cooks, *J. Am. Soc. Mass Spectrom.*, **9**, 1141 (1998).
177. W. E. Wentworth and W. J. Ristau, *J. Phys. Chem.*, **73**, 2126 (1969).
178. (a) B. S. Freiser (Ed.), *Organometallic Chemistry*, Klewer Academic Publ., Dordrecht, 1996.
(b) A. Fontijn (Ed.), *Gas Phase Metal Reactions*, North-Holland, Amsterdam, 1992.
(c) K. Eller and H. Schwarz, *Chem. Rev.*, **91**, 1121 (1991).
(d) D. H. Russell (Ed.), *Gas Phase Inorganic Chemistry*, Plenum, New York, 1989.
(e) S. W. Buckner and B. S. Freiser, *Polyhedron*, **7**, 1583 (1988).
(f) J. Allison, *Prog. Inorg. Chem.*, **34**, 627 (1986).
179. J. J. Myher and A. G. Harrison, *J. Phys. Chem.*, **72**, 1905 (1968).
180. M. T. Bowers, D. D. Elleman, R. M. O'Malley and K. J. Jennings, *J. Chem. Phys.*, **74**, 2583 (1970).
181. A. Nato, M. Niwa, K. Honma, I. Tanaka and I. Koyano, *Int. J. Mass Spectrom. Ion Phys.*, **34**, 287 (1980).
182. C. Lifshitz, Y. Gleitman, S. Gefen, U. Shainok and I. Dotan, *Int. J. Mass Spectrom. Ion Phys.*, **40**, 1 (1981).
183. C. Lifshitz and Y. Gleitman, *Int. J. Mass Spectrom. Ion Phys.*, **40**, 17 (1981).
184. C. Lifshitz and Y. Gleitman, *J. Chem. Phys.*, **77**, 2383 (1982).
185. D. van Pijkeren, J. van Eck and A. Niehaus, *Chem. Phys.*, **103**, 383 (1986).
186. V. G. Anicich, G. A. Blake, J. K. Kim, M. J. McEwan and W. T. Huntress, Jr., *J. Phys. Chem.*, **88**, 4608 (1984).
187. R. Wolfschütz, H. Schwarz and K. Levsen, unpublished work quoted in References 183 and 184.
188. M. F. Jarrold, W. Wagner-Redeker, A. J. Illies, N. J. Kichner and M. T. Bowers, *Int. J. Mass Spectrom. Ion Processes*, **58**, 63 (1984).
189. J. Mattay, *Nachr. Chem. Tech. Lab.*, **36**, 376 (1988).
190. M. L. Gross, D. H. Russell, R. Phongbetchara and P.-H. Lin, *Adv. Mass Spectrom.*, **7A**, 129 (1978).
191. M. L. Gross, P.-H. Lin and S. J. Franklin, *Anal. Chem.*, **44**, 974 (1972).
192. R. van Doorn, N. M. M. Nibbering, A. J. V. Ferrer-Correia and K. R. Jennings, *Org. Mass Spectrom.*, **13**, 729 (1978).
193. G. S. Groenewold and M. L. Gross, *J. Am. Chem. Soc.*, **106**, 6575 (1984).
194. L. W. Castle and M. L. Gross, *Org. Mass Spectrom.*, **24**, 637 (1989).
195. E. K. Chess, P.-H. Lin and M. L. Gross, *J. Org. Chem.*, **48**, 1522 (1983).
196. G. S. Groenewold, E. K. Chess and M. L. Gross, *Org. Mass Spectrom.*, **19**, 519 (1984).
197. H.-F. Grützmacher and A. Barkow, *Acta Chem. Scand.*, **51**, 619 (1997).
198. D. Kuck, A. Bruder, D. V. Ramana, *Int. J. Mass Spectrom. Ion Processes*, **167/168**, 55 (1997).
199. A. Barkow, Doctoral Thesis, Bielefeld, 1997.
200. D. K. Bohme, A. B. Rakshit and H. I. Schiff, *Chem. Phys. Lett.*, **93**, 592 (1982).
201. D. C. Parent, *Int. J. Mass Spectrom. Ion Processes*, **138**, 307 (1994).
202. P. Španěl and D. Smith, *Int. J. Mass Spectrom.*, **181**, 1 (1998).
203. G. Podda, A. Sturaro and P. Traldi, *Org. Mass Spectrom.*, **21**, 723 (1986).

204. R. W. Holman, M. D. Rozeboom, M. L. Gross and C. D. Warner, *Tetrahedron*, **42**, 6235 (1986).
205. B. D. Nourse, K. A. Cox and R. G. Cooks, *Org. Mass Spectrom.*, **27**, 453 (1992).
206. C. Dass, *Org. Mass Spectrom.*, **28**, 940 (1993).
207. G. Bouchoux and F. Penaud-Berruyer, *Org. Mass Spectrom.*, **29**, 366 (1994).
208. G. Bouchoux and J.-Y. Salpin, *Rapid Commun. Mass Spectrom.*, **11**, 1001 (1997).
209. M. W. van Amsterdam, P. O. Staneke, S. Ingemann and N. M. M. Nibbering, *Org. Mass Spectrom.*, **28**, 919 (1993).
210. H. Becker, G. Javahery, S. Petrie and D. K. Bohme, *J. Phys. Chem.*, **98**, 5591 (1994).
211. S. Petrie, G. Javahery, J. Wang and D. K. Bohme, *J. Am. Chem. Soc.*, **114**, 9177 (1992).
212. S. Petrie, G. Javahery, J. Wang and D. K. Bohme, *J. Phys. Chem.*, **96**, 6121 (1992).
213. X. Guo, Z. Liu and S. Liu, *J. Mol. Struct. (Theochem)*, **340**, 169 (1995).
214. M. N. Eberlin, *Mass Spectrom. Rev.*, **16**, 113 (1997).
215. M. N. Eberlin, T. K. Majumdar and R. G. Cooks, *J. Am. Chem. Soc.*, **114**, 2884 (1992).
216. M. N. Eberlin and R. G. Cooks, *J. Am. Chem. Soc.*, **115**, 9226 (1993).
217. M. N. Eberlin, N. H. Morgan, S. S. Yang, B. J. Shay and R. G. Cooks, *J. Am. Soc. Mass Spectrom.*, **6**, 1 (1995).
218. L. Lu, S. S. Yang, Z. Wang, R. G. Cooks and M. N. Eberlin, *J. Mass Spectrom.*, **30**, 581 (1995).
219. M. Soni, J. Amy, V. Frankevich, R. G. Cooks, D. Taylor, A. Mckewan and J. C. Schwartz, *Rapid Commun. Mass Spectrom.*, **9**, 911 (1995).
220. C. Paradisi, H. Kenttämaa, Q. T. Le and M. C. Caserio, *Org. Mass Spectrom.*, **23**, 521 (1988).
221. S. Gevrey, M.-H. Taghanel and J.-P. Morizur, *J. Mass Spectrom.*, **33**, 399 (1998).
222. P. Ausloos, J.-A. J. Jackson and S. G. Lias, *Int. J. Mass Spectrom. Ion Phys.*, **33**, 269 (1980).
223. J. H. Stewart, R. H. Shapiro, C. H. DePuy and V. M. Bierbaum, *J. Am. Chem. Soc.*, **99**, 7650 (1977).
224. V. M. Bierbaum, C. H. DePuy and R. H. Shapiro, *J. Am. Chem. Soc.*, **99**, 5800 (1977).
225. C. H. DePuy, V. M. Bierbaum, M. S. Robinson, G. E. Davico and R. Gareyev, *Tetrahedron*, **53**, 9847 (1997).
226. J. J. Grabowski, C. H. DePuy and V. M. Bierbaum, *J. Am. Chem. Soc.*, **105**, 2565 (1983).
227. R. R. Squires, V. M. Bierbaum, J. J. Grabowski and C. H. DePuy , *J. Am. Chem. Soc.*, **105**, 5185 (1983).
228. R. N. McDonald, A. K. Chowdbury and D. W. Setser, *J. Am. Chem. Soc.*, **102**, 4836 (1980).
229. R. N. McDonald and A. K. Chowdbury, *J. Am. Chem. Soc.*, **102**, 6146 (1980).
230. R. N. McDonald, A. K. Chowdbury and D. W. Setser, *J. Am. Chem. Soc.*, **103**, 7586 (1981).
231. R. N. McDonald, A. K. Chowdbury and D. W. Setser, *J. Am. Chem. Soc.*, **102**, 6491 (1980).
232. P. Vouros, in *Mass Spectrometry*, Part B (Eds. C. Merritt, Jr. and C. N. McEwen), Chap. 2, Marcel Dekker, New York, 1980, pp. 129–251.
233. B. Schmitz and R. A. Klein, *Chem. Phys. Lipids*, **39**, 285 (1986).
234. N. J. Jensen and M. L. Gross, *Mass Spectrom. Rev.*, **6**, 497 (1987).
235. R. J. Anderegg, *Mass Spectrom. Rev.*, **7**, 395 (1988).
236. W. G. Niehaus and R. Ryhage, *Anal. Chem.*, **40**, 1840 (1968).
237. For further examples, see:
    (a) J. H. Tumlinson, R. R. Heath and R. E. Doolittle, *Anal. Chem.*, **46**, 1309 (1974).
    (b) N. J. Jensen and M. L. Gross, *Mass Spectrom. Rev.*, **6**, 497 (1987).
238. N. C. Shantha and T. N. B. Kaimal, *Lipids*, **19**, 871 (1984).
239. G. Janssen and G. Parmentier, *Biomed. Mass Spectrom.*, **5**, 439 (1978).
240. B. Schmitz and H. Egge, *Chem. Phys. Lipids*, **25**, 287 (1979).
241. M. Vincenti, G. Guglielmetti, G. Cassani and C. Tonini, *Anal. Chem.*, **59**, 694 (1987).
242. D. A. Carlson, C.-S. Roan, R. A. Yost and J. Hector, *Anal. Chem.*, **61**, 1564 (1989).
243. (a) C. Pepe, P. Dizabo, J. Dagaut, N. Balcar and M. F. Lautier, *Eur. Mass Spectrom.*, **1**, 209 (1995).
    (b) C. Pepe, H. Sayer, J. Dagaut and R. Couffignal, *Rapid Commun. Mass Spectrom.*, **11**, 919 (1997).
    (c) C. Pepe, H. Sayer and J. Dagaut, *Rapid Commun. Mass Spectrom.*, **12**, 565 (1998).
244. D. C. Young, P. Vouros, B. Decosta and M. F. Holick, *Anal. Chem.*, **59**, 1954 (1987).
245. L. R. Hogge, E. W. Underhill and J. W. Wong, *J. Chromatogr. Sci.*, **23**, 171 (1985).
246. W. Vetter, W. Meister and G. Oesterhelt, *J. Mass Spectrom.*, **33**, 461 (1998).

247. J. Adams, *Mass Spectrom. Rev.*, **9**, 141 (1990).
248. (a) A. J. V. Ferrer-Correia, K. R. Jennings and D. K. Sen Sharma, *J. Chem. Soc., Chem. Commun.*, 973 (1975).
(b) A. J. V. Ferrer-Correia, K. R. Jennings and D. K. Sen Sharma, *Org. Mass Spectrom.*, **11**, 867 (1976).
(c) A. J. V. Ferrer-Correia, K. R. Jennings and D. K. Sen Sharma, *Adv. Mass Spectrom.*, **7A**, 287 (1977).
249. F. Hunt and T. M. Harvey, *Anal. Chem.*, **47**, 2136 (1975).
250. D. F. Hunt, C. N. McEwen and T. M. Harvey, *Anal. Chem.*, **47**, 1730 (1975).
251. (a) H. Budzikiewicz, *Fresenius Z. Anal. Chem.*, **321**, 150 (1985).
(b) H. Budzikiewicz, in *Analytiker-Taschenbuch* (Eds. W. Fresenius, H. Günzler, W. Huber, I. Lüderwald, G. Tölg and H. Wisser) Vol. 5, Springer, Berlin, 1985, pp. 135ff.
(c) H. Budzikiewicz, *Spectrosc. Int.*, **5**, 183 (1987).
(d) H. Budzikiewicz, in *Studies in Natural Products Chemistry*, Vol. 2 (Ed. Atta-ur-Rahman), Elsevier, Amsterdam, 1988, pp. 3–18.
252. A. G. Harrison, *Chemical Ionization Mass Spectrometry, 2nd edn.*, Chap. 5, CRC Press, Boca Raton, FL, 1992, pp. 113–120.
253. M. Vairamani, U. A. Mirza and R. Srinivas, *Mass Spectrom. Rev.*, **9**, 235 (1990).
254. M. Vairamani, *Org. Mass Spectrom.*, **25**, 271 (1990).
255. J. Einhorn, H. I. Kenttämaa and R. G. Cooks, *J. Am. Soc. Mass Spectrom.*, **2**, 305 (1991).
256. (a) D. A. Peake, S.-K. Huang and M. L. Gross, *Anal. Chem.*, **59**, 1557 (1987).
(b) M. L. Gross, *Adv. Mass Spectrom.*, **11A**, 792 (1989).
257. R. E. Doolittle, J. H. Tumlinson and A. Proveaux, *Anal. Chem.*, **57**, 1625 (1985).
258. J. Einhorn, H. Virelizier, A. L. Gemal and J.-C. Tabet, *Tetrahedron Lett.*, **26**, 1445 (1985).
259. J. Einhorn, H. Virelizier, A. Guarrero and J.-C. Tabet, *Biomed. Mass Spectrom.*, **12**, 200 (1985).
260. D. A. Peake, S.-K. Hunang and M. L. Gross, *Anal. Chem.*, **57**, 115 (1985).
261. D. A. Peake, S.-K. Hunang and M. L. Gross, *Anal. Chem.*, **59**, 1557 (1987).
262. A. J. Canty and R. Colton, *Inorg. Chim. Acta*, **220**, 99 (1994).
263. T. Keough, *Anal. Chem.*, **54**, 2540 (1982).
264. (a) C. Lange, *Org. Mass Spectrom.*, **28**, 1285 (1993).
(b) C. Lange, *Org. Mass Spectrom.*, **22**, 55 (1987).
265. M. Vairamani, K. V. Siva Kumar and G. K. Viswanadha Roa, *Org. Mass Spectrom.*, **25**, 363 (1990).
266. H. Budzikiewicz, S. Blech and B. Schneider, *Org. Mass Spectrom.*, **26**, 1057 (1991).
267. D. Kuck, in *Proceedings of the 8th ISMAS Symposium on Mass Spectrometry*, Vol. I (Ed. S. K. Aggarwal) *Indian Society for Mass Spectrometry* (ISMS), Mumbai, 1999, pp. 245–260.
268. R. Kaufmann, T. Wingerath, D. Kirsch, W. Stahl and H. Sies, *Anal. Biochem.*, **238**, 117 (1996).
269. K. Aitzetmüller, H. H. Strain, W. A. Svec, M. Gandolfi and J. J. Katz, *Phytochemistry*, **8**, 1761 (1969).
270. J. Carnevale, E. R. Cole, D. Nelson and J. S. Shannon, *Biomed. Mass Spectrom.*, **5**, 641 (1978).
271. M. T. Fernandez, C. Williams, R. S. Mason and B. J. C. Cabral, *J. Chem. Soc., Faraday Trans.*, **94**, 1427 (1998).
272. C. Basic and A. G. Harrison, *Can. J. Chem.*, **36**, 33 (1991).
273. J. J. Brophy and A. Maccoll, *Org. Mass Spectrom.*, **27**, 1042 (1992).
274. H. Schwarz, F. Borchers and K. Levsen, *Z. Naturforsch. B*, **31**, 935 (1976).
275. L. Friedman and A. P. Wolf, *J. Am. Chem. Soc.*, **80**, 2424 (1958).
276. M. Mormann and D. Kuck, to be published.
277. B. C. L. Weedon, *Fortschr. Chem. Org. Naturst.*, **27**, 81 (1969).
278. W. Vetter, G. Englert, N. Rigassi and U. Schwieter, in *Carotenoids* (Eds. O. Isler, H. Gutmann and U. Solms), Chap. 4, Birkhäuser Verlag, Stuttgart, 1971, pp. 189–266.
279. C. R. Enzell, R. A. Appleton and I. Wahlberg, in *Biochemical Applications of Mass Spectrometry* (Ed. G. R. Waller), Chap. 13, Wiley-Interscience, New York, 1972, pp. 315–385.
280. W. H. Elliott and G. R. Waller, in *Biochemical Applications of Mass Spectrometry* (Ed. G. R. Waller), Chap. 18, Wiley-Interscience, New York, 1972, pp. 499–536.
281. H. Budzikiewicz, *Adv. Mass Spectrom.*, **6**, 163 (1974).

282. C. R. Enzell and I. Wahlberg, in *Biochemical Applications of Mass Spectrometry*, 1st Suppl. Vol. (Eds. G. R. Waller and O. C. Dermer), Chap. 13A, Wiley, New York, 1980, pp. 311–405.
283. C. R. Enzell and I. Wahlberg, in *Biochemical Applications of Mass Spectrometry*, 1st Suppl. Vol. (Eds. G. R. Waller and O. C. Dermer), Chap. 13B, Wiley, New York, 1980, pp. 407–438.
284. C. R. Enzell, I. Wahlberg and R. Ryhage, *Mass Spectrom. Rev.*, **3**, 395 (1984).
285. C. R. Enzell, O. Dahlman and J. Bielawski, in *Applications of Mass Spectrometry to Organic Stereochemistry* (Ed. J. S. Splitter), Chap. 18, VCH, New York, 1994, pp. 509–542.
286. D. Joulain and W. A. König, *The Atlas of Spectral Data of Sesquiterpene Hydrocarbons*, E. B. Verlag, Hamburg, 1998.
287. C. R. Enzell and S. Back, in *Carotenoids*, Vol. 1B: Spectroscopy (Eds. G. Britton, S. Liaanen-Jensen and H. Pfander), Chap. 7, Birkhäuser Verlag, Basel, 1995, pp. 261–320.
288. T. Wingerath, D. Kirsch, R. Kaufmann, W. Stahl and H. Sies, *Meth. Enzymol.*, **299**, 390 (1999).
289. T. D. McClure and D. C. Liebler, *J. Mass Spectrom.*, **30**, 1480 (1995).
290. G. Tang, B. A. Andrien, G. D. Dolnikowski and R. M. Russell, *Meth. Enzymol.*, **282**, 140 (1997).
291. G. Tang, J. Qin and G. G. Dolnikowski, *J. Nutr. Biochem.*, **9**, 408 (1998).
292. M. Careri, P. Lombardi, C. Mucchino and E. Cantoni, *Rapid Commun. Mass Spectrom.*, **13**, 118 (1999).
293. (a) H. H. Schmitz, R. B. van Breemen and S. J. Schwartz, *Meth. Enzymol.*, **213**, 322 (1992).
(b) R. B. Van Breemen, H. H. Schmitz and S. J. Schwartz, *Anal. Chem.*, **65**, 695 (1993).
294. G. J. Van Berkel, K. G. Asano and S. A. McLuckey, *J. Am. Soc. Mass Spectrom.*, **5**, 689 (1994).
295. (a) R. B. van Breemen, D. Nikolic, X. Xu, J. Xiong, M. van Lieshout, C. E. West and A. B. Schilling, *J. Chromatogr. A*, **794**, 245 (1998).
(b) T. Hagiwara, T. Yasumo, K. Funayama and S. Suzuki, *J. Chromatogr. B*, **708**, 67 (1998).
296. (a) C. D. Watts, J. R. Maxwell, D. E. Games and M. Rossiter, *Org. Mass Spectrom.*, **10**, 1102 (1975).
(b) S. Takaichi, *Org. Mass Spectrom.*, **28**, 785 (1993).
297. E. R. Hilf, W. Tuszynski, B. Curdes, J. Curdes, M. Wagner and K. Wien, *Int. J. Mass Spectrom. Ion Processes*, **126**, 101 (1993).
298. A. Mele and A. Selva, *Eur. Mass Spectrom.*, **3**, 161 (1997).
299. A. Selva, F. Cardini and M. Chelli, *Org. Mass Spectrom.*, **29**, 695 (1994).
300. A. Selva and F. Cardini, *Org. Mass Spectrom.*, **28**, 570 (1993).
301. A. Mele, W. Panzeri, A. Selva and E. Canu, *Eur. Mass Spectrom.*, **5**, 7 (1999).
302. A. Selva, A. Mele and G. Vago, *Eur. Mass Spectrom.*, **1**, 215 (1995).

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CHAPTER **2**

NMR spectroscopy of dienes and polyenes

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I. INTRODUCTION

A. Scope and Limitation

From the advent of organic chemistry, dienes (and polyenes) have played a very important role in both the theoretical and synthetic aspects. For example, 1,4-addition of bromine to 1,3-butadiene to form 1,4-dibromo-2-butene rather than 3,4-dibromo-1-butene as the major product was a challenging problem for theoretical chemists, who interpreted the phenomenon in terms of resonance or delocalization of π-electrons[1].

Later, the structural chemists determined the structure of 1,3-butadiene (the bond lengths C1−C2 and C2−C3 are 1.467 and 1.349 Å, respectively, which can be compared with the corresponding values of *trans*-2-butene (1.508 and 1.347 Å), respectively). Another significant aspect of dienes is the Diels–Alder reaction, the reaction between a diene and an olefin with electron-withdrawing substituents to give a six-membered ring[2]. The reaction is designated as $4 + 2$ cycloaddition since the diene has four carbon atoms while the olefin, a dienophile, may represent a two-carbon unit. The mechanism of this useful reaction was not clear until 1964, when Woodward and Hoffmann proposed the so-called Woodward–Hoffmann rule[3]. This proposal has opened a wide world of electrocyclic reactions in which the symmetry of orbitals plays an important role.

NMR spectroscopy has been extensively used in diene chemistry not only for conventional structural analysis but also in dealing with theoretical problems. Among a variety of examples in which NMR spectroscopy played an important role in the latter application, is the unusually large high- and low-field shifts observed for inner protons of cyclic conjugated polyenes (annulenes). Thus, the high-field shifts for $[4n + 2]$annulenes and corresponding low-field shifts for $[4n]$annulenes were interpreted as the indication of aromaticity and antiaromaticity, respectively, of these compounds[4].

Previously, the NMR spectroscopic data for dienes and polyenes were treated as a part of a chapter on alkenes[5], and have not been treated as an independent topic. In view of the important role which dienes and polyenes have generally played in chemistry, the authors believe that the topic can, and should, be treated in an independent chapter.

In this review, chemical shifts and coupling constants of simple dienes will first be summarized, and the theory of chemical shift for dienes and polyenes will then be reviewed. Finally, the recent applications of NMR spectroscopy to a variety of polyenes and dienes and specific systems (allenes, solitons and fullerenes) will be reviewed.

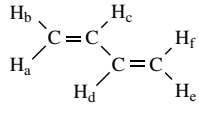
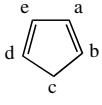
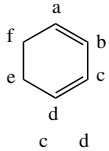
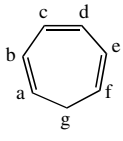
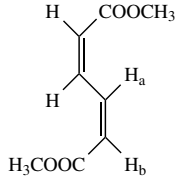
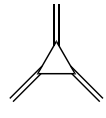
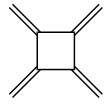
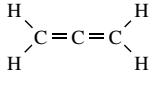
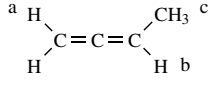
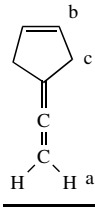
Although we have tried to cover the literature on standard data as much as possible, our emphasis have been focused on new developments of application of NMR spectroscopy to dienes and polyenes. Readers who seek more basic data rather than recent advances are advised to consult books and journal articles dealing with this topic.

B. Chemical Shifts and Coupling Constants

It would be convenient for the readers if a limited amount of selected data are summarized at the beginning of this chapter so that they can have some general idea on the chemical shifts and coupling constants observed for dienes and polyenes.

i. Protons bonded to conjugated carbon atoms. Collections of data on chemical shifts in linear dienes, cyclic dienes and exocyclic multi-methylene systems are given in Table 1 together with references to selected compounds. The characteristic values of the geminal and allylic coupling constants and chemical shifts assembled in Table 1 make these signals very informative. The chemical shifts of some allenic protons are also included in Table 1[6].

TABLE 1. ^{1}H chemical shifts and coupling constants of linear and cyclic dines, exocyclic methylenes and allenes

Compound	^{1}H chemical shift (ppm)	Coupling constant (Hz)	Reference
	(a,f) 5.16 (b,e) 5.06 (c,d) 6.27	$J_{ab} = 1.8, J_{bc} = 10.2, J_{ac} = 17.1,$ $J_{ad} = -0.8, J_{be} = 1.3, J_{ae} = 0.6,$ $J_{af} = 0.7, J_{bd} = -0.9, J_{ed} = 10.4$	6a
	(a,e) 6.5 (b,d) 6.4 (c) 2.90	$J_{ab} = 5.1, J_{bc} = 1.2, J_{ac} = -1.3,$ $J_{ad} = 1.1, J_{ae} = 1.9, J_{bd} = 1.9$	6a
	(a,d) 5.8 (b,c) 5.9 (e,f) 2.15	$J_{ab} = 9.4, J_{bc} = 5.1, J_{ac} = 1.1,$ $J_{ad} = 0.9$	6a
	(a,f) 5.26 (b,e) 6.09 (c,d) 6.50 (g) 2.22	$J_{ab} = 8.9, J_{bc} = 5.5, J_{bd} = 0.8,$ $J_{be} = -0.6, J_{ae} = 0.6, J_{af} = 0, J_{ed} = 11.2,$ $J_{gg} = -13.0, J_{ag} = 6.7, J_{ac} + J_{ad} = 1.5$	6a
	(a) 7.87 (b) 5.94		6b
	5.02		6b
	5.19		6b
	4.67		6b
	(a) 4.50 (b) 4.94 (c) 1.59		6b
	(a) 4.60 (b) 5.52 (c) 3.13		6b

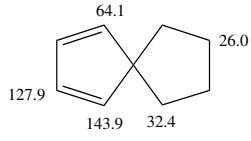
The chemical shifts of exocyclic methylene protons are very close to the calculated value of 4.65 ppm for four-, five- and six-membered rings; not surprisingly the three-membered ring proves to be exceptional. There are also some differences in the effect exerted by carbonyl substitution in rings of different size and in the chemical shifts of radialenes.

In the case of 1,3-butadiene, the chemical shifts of inner (H2, H3) protons and outer (H1, H4) is large, while in the case of cycloalkadienes (e.g. 1,3-cyclopentadiene and 1,3-cyclohexadiene), the difference is very small. It is interesting to note that in 1,3,5-cycloheptatriene, the chemical shifts of three kinds of olefinic protons are very diverse. The effect of the ring size and in the chemical shifts of radialenes was also included.

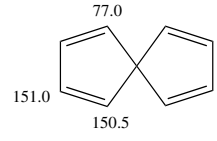
ii. Carbon atoms of linear and branched conjugated dienes. The ^{13}C chemical shifts of simple linear and branched dienes are collected in Table 2[7]. The ^{13}C chemical shifts of conjugated dienes such as 1,3-butadiene or 1,3,5-hexatriene are not significantly different from those in the monoenes.

iii. Unsubstituted cyclopolyenes. The chemical shifts of simple unsubstituted cyclopolyenes are listed in Table 3[7].

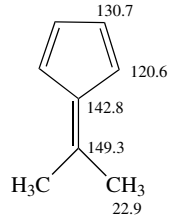
In the spirodiene **3** and tetraene **4** the spiroconjugated carbon nuclei are shifted downfield on going from **3** to **4**, an effect which is due to the interaction between the two π-systems.



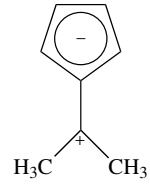
(3)



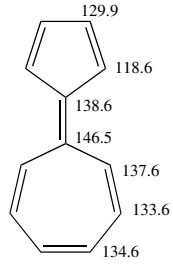
(4)



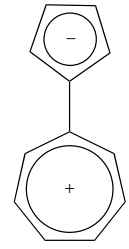
(5)



(5a)



(6)



(6a)

TABLE 2. ^{13}C chemical shifts for linear and branched dienes[7]

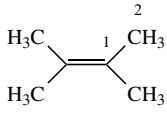
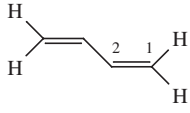
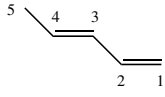
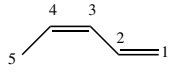
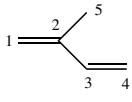
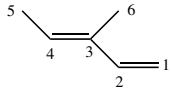
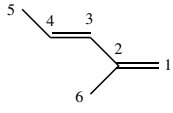
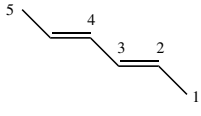
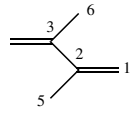
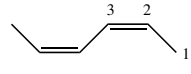
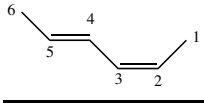
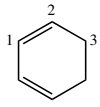
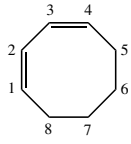
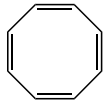
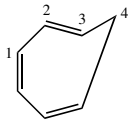
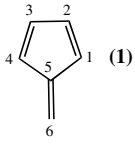
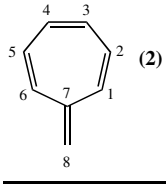
Compound	δ_c (ppm)					
	C1	C2	C3	C4	C5	C6
	123.5	20.4				
	116.6	137.2				
	114.4	137.8	129.5	133.2	17.2	
	116.5	132.5	130.9	126.4	12.8	
	113.0	142.9	140.3	116.4	17.6	
	110.3	142.1	135.5	127.1	11.1	13.6
	114.5	142.2	135.5	125.1	18.8	18.3
	17.5	126.2	132.5			
	113.0	143.8			20.3	
	12.9	124.9	125.3			
	13.0	123.1	127.4	130.2	128.3	18.0

TABLE 3. ^{13}C chemical shifts for unsubstituted cyclopolyenes

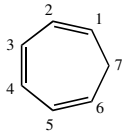
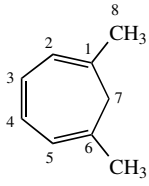
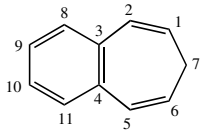
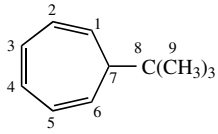
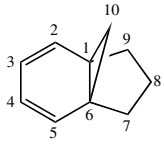
Compound	C1	C2	C3	C4	C5	C6	C7	C8
	132.2	132.8	41.6					
	126.1	124.6	22.3					
	126.5	132.1			23.4	28.5		
	131.5							
	131.0	126.8	120.4	28.1				
 **(1)**	124.9	134.3			152.6	123.4		
 **(2)**	138.3	126.8[a]	130.8[a]				146.6	111.9

[a] Assignment uncertain.

The ^{13}C NMR data for pentafulvene **(1)** and heptafulvene **(2)** (Table 3) and for 6,6-dimethylpentafulvene **(5)** and sesquifulvalene **(6)**, afford evidence of the extent to which polar structures of the types **5a** and **6a** contribute to the ground state. If the chemical shifts are analyzed on the basis of electron density, these hydrocarbons are to be considered as olefinic systems with only a small contribution (10% at most) from the polar structures **5a** and **6a**.

iv. Cyclic conjugated polyenes. Table 4[8] gives the ^{13}C chemical shifts for cycloheptatriene and related compounds. The internal olefinic carbons C3 and C4 of the triene

TABLE 4. ^{13}C chemical shifts of cycloheptatriene and norcaradiene compounds

	C1	C2	C3	C7	C8	C9	C10
	120.4	126.8	131.0	28.1			
	130.6	122.2	128.8	40.1	24.6		
	125.9	127.7	137.2	26.6	130.3	130.8	
	123.0	124.6	130.8	49.4	31.1	27.3	
	37.7	129.0	119.2	32.3	15.7		19.7

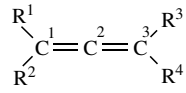
system are the most deshielded in cycloheptatriene. Methyl substitution at C1 deshields C1 and C7 and shields C2 and C3.

v. Allenes. Allenes form a unique class of compounds because of the extremely low field shift of the central allenic carbon C2 (200 to 220 ppm). Table 5[8] presents representative data for a number of substituted allenes. For a given alkyl substituent, there is a linear relationship between the number of substituents and the chemical shift of the central carbon. The shielding is regarded as an additive property, a methyl group shields that carbon by 3.3 ppm, an ethyl group by 4.8 ppm and a *sec*-alkyl group by 7 ppm. Carbons C1 and C3 are shielded by some 30 ppm relative to corresponding ethylene carbons but otherwise display similar substituent effects. Strain in cyclic allenes appears to have little effect.

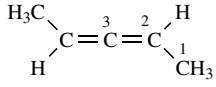
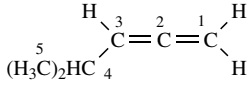
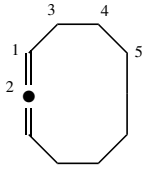
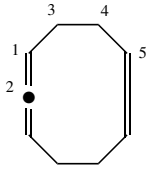
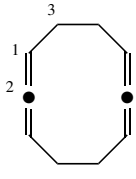
II. THEORY OF NMR CHEMICAL SHIFTS OF POLYENES

Recently, *ab initio* shielding calculations based on well-established theories, IGLO (individual gauge for localized orbitals)[9], GIAO (gauge including atomic orbital)[10] and LORG

TABLE 5. ^{13}C chemical shift of allenes



R^1	R^2	R^3	R^4	C1	C2	C3
H[a]	H[a]	H[a]	H[a]	74.8	213.5	74.8
Me	H	H	H	84.4	210.4	74.1
Me	Me	H	H	93.4	207.3	72.1
Me	H	Me	H	85.4	207.1	85.4
Me	Me	Me	Me	92.6	200.2	92.6
Me	SMe	H	H	99.9	203.6	80.1
Ph	Ph	Ph	Ph	113.6	209.5	113.6
OMe	H	H	H	123.1	202.0	90.3
Br	H	H	H	72.7	207.6	83.8
CN	H	H	H	80.5	218.7	67.2

Compound	C1	C2	C3	C4	C5
	14.6	84.5	206.5		
	76.2	207.8	97.8	27.9	22.9
	92.7	206.5	27.9	25.8[b]	27.2[b]
	90.4	206.7	27.4[b]	29.2[b]	130.4
	90.2	208.3	26.8		

[a] $^{13}C-^{1}H$ coupling (in hertz) in allene: $^{1}J(C-H)$ [167.8], $^{2}J(C-H)$ [3.9], $^{3}J(C-H)$ [7.7].
[b] Assignments uncertain.

(localized orbital/local origin) methods[11] have been widely used not only to assist signal assignments but also to elucidate the electronic structure and conformation of molecules. The use of high-quality basis sets in these types of shielding calculations leads to reasonable results which are within the experimental accuracy.

Inoue and coworkers[12] reported an *ab initio* calculation of the ^{13}C shieldings for some polyenals and their Schiff bases using the LORG method. They reported the results for some polyenes with basis sets of various quality. It was shown that the introduction of polarization functions substantially improves agreement between experiment and theory. They used the program RPAC9.0, which was developed by Bouman and Hansen[13] for *ab initio* shielding calculations, interfacing to the Gaussian-90 program[14]. The geometrical parameters of all the molecules studied were optimized by using 6-31G basis sets and planar frameworks were then assumed for the backbone. The basis sets they used for shielding calculations were the Pople type 6-31G, 6-31+G, 6-31++G, 6-31G*, 6-31G**, 6-311G* and 6-311G**[15].

In the LORG theory, occupied orbitals are localized according to the Foster–Boys criterion[16]. In the calculations described above they chose the LORG centroid assignment[11a].

Table 6 gives the calculated and experimental ^{13}C shieldings for acrolein, crotonaldehyde and hexa-2,4-dienal. The numbering of the carbon atoms is given in Figure 1. The calculated and experimental ^{13}C chemical shift data were converted to the methane reference using the data in Table 7 and in the standard reference[17], respectively.

The author examined the correlation between the calculated and experimental isotropic shieldings. The 6-31G shielding data are in qualitative agreement with the experimental data and completely reproduce the relative order of all the carbon shieldings studied. The 6-31G shieldings for the carbonyl carbons shift are about 20 ppm downfield of the experimental values. If the experimental data are converted to the methane reference using the data reported by Jameson and Jameson[18], this discrepancy still remains large (about 16 ppm).

The RMS error for the 6-31G data is relatively large (9.8 ppm). The origin of this error has been considered to be attributable to electron correlation effects, which were not included in the calculations. The results for the carbonyl shieldings could be improved by using *d*-type polarization functions on carbon and oxygen atoms. The results using 6-31G* and 6-31G** basis sets exhibited a good reproducibility for all the carbons including the carbonyl carbons. The RMS errors for the 6-31G* and 6-31G** results are 3.7 and 3.8 ppm, respectively.

As shown in Table 6, the addition of *p*-type polarization functions to hydrogen atoms in the 6-31G** basis has little effect on the calculated data.

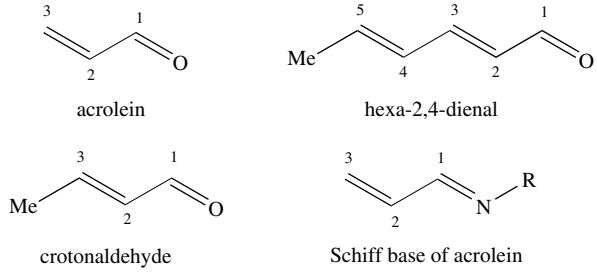


FIGURE 1. Numbering system of carbon atoms for the compounds in Table 6

TABLE 6. Comparison of calculated and experimental ^{13}C chemical shifts for acrolein, crotonaldehyde and hexa-2,4-dienal

Compound	Carbon[a]	Element	6-31G	6-31+G	6-31++G	6-31G*	6-31G**	6-311G*	6-311G**	Exp.[b]
Acrolein	C1	σ_{iso}	212.0	213.6	211.9	196.0	194.7	197.2	196.9	193.2
		σ_{11}	75.8	75.0	73.4	91.6	89.5	87.5	85.8	
		σ_{22}	196.4	212.4	210.8	197.1	197.5	194.9	197.8	
		σ_{33}	353.7	353.5	351.5	299.4	297.1	309.3	306.9	
		σ_{anis}	217.6	209.8	209.4	155.0	153.6	168.1	165.1	
	C2	σ_{iso}	143.7	149.8	148.0	135.6	135.2	141.5	141.5	141.7
		σ_{11}	29.0	36.9	34.9	34.6	33.1	39.4	36.5	
		σ_{22}	126.5	133.4	131.7	118.6	118.0	123.3	124.1	
		σ_{33}	275.7	279.2	277.4	253.8	254.6	261.7	263.8	
		σ_{anis}	197.9	194.0	194.0	177.2	179.0	180.3	183.5	
	C3	σ_{iso}	141.3	143.1	141.5	137.6	136.9	140.4	141.5	136.2
		σ_{11}	8.7	11.7	10.4	12.1	11.5	13.9	11.9	
		σ_{22}	134.7	135.7	134.5	130.9	130.0	130.8	133.9	
		σ_{33}	280.5	281.6	279.7	269.7	269.1	276.5	278.6	
		σ_{anis}	208.8	207.8	207.2	198.2	198.4	204.2	205.7	
Crotonaldehyde	C1	σ_{iso}	211.3	212.7	211.0	195.5	194.3	196.8	196.6	192.1
		σ_{11}	76.1	75.2	73.6	91.9	89.7	87.9	86.0	
		σ_{22}	206.7	212.6	211.1	196.6	197.1	194.7	198.1	
		σ_{33}	351.0	350.2	348.4	297.9	295.9	307.8	305.7	
		σ_{anis}	209.6	206.2	206.0	153.6	152.4	166.5	163.7	
	C2	σ_{iso}	140.9	146.5	144.9	133.4	132.6	138.7	137.9	137.8
		σ_{11}	38.9	47.1	45.5	43.2	42.0	47.5	44.9	
		σ_{22}	119.6	126.9	125.4	111.2	110.4	116.1	116.3	
		σ_{33}	264.1	265.5	263.9	245.8	245.4	252.4	252.4	
		σ_{anis}	184.8	178.5	178.5	168.6	169.2	170.6	171.8	
	C3	σ_{iso}	153.3	156.5	154.9	151.4	150.8	158.6	157.9	151.9
		σ_{11}	12.1	15.5	14.1	18.2	172	23.3	20.1	
		σ_{22}	157.8	162.1	160.7	153.8	153.4	159.4	159.9	
		σ_{33}	290.0	292.0	290.1	282.1	281.8	293.2	293.6	
		σ_{anis}	205.1	203.1	202.7	196.0	196.5	201.9	203.6	
	Me	σ_{iso}	15.0	16.8	16.0	14.5	14.3	16.7	16.1	19.9
		σ_{11}	−5.4	−6.0	−5.6	−5.6	−4.7	−0.4	−1.2	
		σ_{22}	23.3	27.0	25.8	22.4	21.5	20.9	20.7	

		σ_{33}	27.0	29.3	28.0	26.8	26.2	29.6	28.9	
		σ_{anis}	18.1	18.8	17.9	18.4	17.8	19.3	19.2	
Hexa-2,4-dienal	C1	σ_{iso}	211.7	213.0	211.4	195.8	194.6	197.2	197.0	192.5
		σ_{11}	75.4	74.6	73.0	91.2	89.0	86.9	85.0	
		σ_{22}	207.7	213.5	211.9	196.9	197.6	195.3	198.9	
		σ_{33}	352.0	351.0	349.2	299.2	297.2	309.3	307.2	
		σ_{anis}	210.5	207.0	206.7	155.2	153.9	168.2	198.9	
	C2	σ_{iso}	136.1	140.5	138.9	129.1	128.5	132.1	131.3	132.9
		σ_{11}	39.1	46.6	45.2	43.8	42.5	47.2	44.3	
		σ_{22}	123.7	129.5	127.9	114.5	113.7	137.4	117.7	
		σ_{33}	245.6	245.3	243.5	229.1	228.6	231.7	231.9	
		σ_{anis}	164.1	157.3	157.0	150.0	150.5	139.4	150.8	
	C3	σ_{iso}	156.2	159.8	158.2	153.6	152.7	158.9	158.3	151.8
		σ_{11}	33.1	37.3	35.7	36.5	35.2	37.4	34.4	
		σ_{22}	155.3	159.9	158.4	150.3	149.7	156.0	156.9	
		σ_{33}	280.1	282.2	280.5	273.9	273.3	283.4	283.5	
		σ_{anis}	185.8	183.6	183.4	180.5	180.8	186.7	187.8	
	C4	σ_{iso}	137.9	141.2	139.6	131.7	130.7	136.7	135.6	133.3
		σ_{11}	34.9	39.5	38.0	38.1	36.9	40.4	37.5	
		σ_{22}	114.4	118.4	116.9	108.9	107.9	113.0	113.0	
		σ_{33}	264.4	265.6	263.9	247.9	247.4	256.8	256.4	
		σ_{anis}	189.7	186.7	186.5	174.4	175.0	180.1	181.1	
	C5	σ_{iso}	145.2	147.8	146.3	140.5	140.0	146.8	145.9	142.2
		σ_{11}	20.5	23.9	22.7	27.1	26.1	32.9	29.7	
		σ_{22}	139.7	142.2	140.8	134.5	134.0	138.3	138.6	
		σ_{33}	275.4	277.3	275.3	260.0	259.9	269.3	269.5	
		σ_{anis}	195.3	194.3	193.6	179.2	179.9	183.7	185.4	
	Me	σ_{iso}	15.1	17.1	16.3	14.4	14.2	16.7	16.1	20.4
		σ_{11}	−6.1	−6.5	−6.5	−6.3	−5.5	−1.2	−2.1	
		σ_{22}	24.6	28.5	27.2	23.5	22.8	22.3	22.0	
		σ_{33}	27.0	29.3	28.1	26.0	25.4	29.0	28.4	
		σ_{anis}	17.8	18.3	17.8	17.4	16.7	−18.5	18.4	
	RMS error[c]		9.8	11.5	10.2	3.7	3.8	4.2	4.1	

[a]For numbering of atoms, see Figure 1.
[b]Taken from Reference 18.
[c]RMS: Root mean square.

TABLE 7. ^{13}C shielding of methane (ppm)

Calc.[a]	
6-31G//6-31G	222.1
6-31+G//6-31G	224.5
6-31++G//6-31G	222.9
6-31G*//6-31G	213.5
6-31G**//6-31G	210.8
6-311G*//6-31G	202.5
6-311G**//6-31G	198.4
Exp.[b]	−2.1[c]
	−7.0[d]

[a] Absolute value.
[b] Relative to tetramethylsilane.
[c] Taken from Reference 17.
[d] Taken from Reference 18.

By applying polarization functions, *ab initio* shielding calculations for some polyenals and their Schiff bases reproduce the experimental values well even on the carbonyl and the imine carbons using the LORG theory without including correlation effects. In addition, there is a trend that the calculation with polarization functions yields smaller anisotropies of chemical shieldings than those without polarization functions.

Recently Inoue and coworkers[19] also reported *ab initio* study of ^{13}C shieldings for linear π-conjugated systems. A photoreceptive protein such as rhodopsin (Rh) or bacteriorhodopsin (bR) possesses a retinal isomer bound to a lysine residue via the protonated Schiff base linkage. Rh exists in the rod cell of the retina of vertebrate and possesses 11-*cis*-retinal (Figure 2), which is isomerized into the all-*trans* form by the absorption of photons, finally leading to signal transduction.

On the other hand, bR, which exists in the purple membrane (PM) of *Halobacterium halobium*, functions as a light-driven proton pump through a photocycle including the conversion of all-*trans* retinal into the 13-*cis* isomer. In both pigments, the conformation of retinal closely relates to the biological function, especially to the regulation of their absorption maxima. For example, in bR_{568}, the C6−C7 bond is likely to be planar s-*trans*, which essentially contributes to the fact that this pigment absorbs yellow-green light. The observation of ^{13}C NMR chemical shifts for the chromophore provides a good insight not only into its conformation but also into the interaction of the chromophore with the surrounding protein matrix. The solid-state NMR technique has been applied to Rh, bR and their photo-intermediates. Consequently, it was revealed that the chemical shifts for the chromophore are significantly different from those for the free protonated retinal Schiff base. As for bR, the chemical shifts of C5 and C8 are displaced significantly downfield and upfield, respectively, relative to those of model compounds.

Figure 2 shows the 10 diene derivatives examined in the work: (*E*,*E*)-2,4-hexadiene (HEX), (*E*,*E*)-3-methyl-2,4-hexadiene (3MET), (*E*,*Z*)-2,4-hexadiene (1CIS), (*E*,*Z*)-3-methyl-2,4-hexadiene (1C3M), (*E*)-2-methyl-2,4-hexadiene (4MET), (*E*)-2,3-dimethyl-2,4-hexadiene (34DME), (*E*,*E*)-3-*tert*-butyl-2,4-hexadiene (3TBU), (*E*)-2-methyl-3-*tert*-butyl-2,4-hexadiene (3TB4M), (*E*,*E*)-2,4-hexadienal (HEXAL) and (*E*,*Z*)-3-methyl-2,4-hexadienal (1C3MAL). These compounds are selected as minimal analogues of partial structures of 11-*cis*-retinal. The numbering of the carbon atoms and the abbreviations (in parentheses) of these dienes are not the IUPAC numbering, but given in order to easily compare the chemical shifts of corresponding carbons between different compounds.

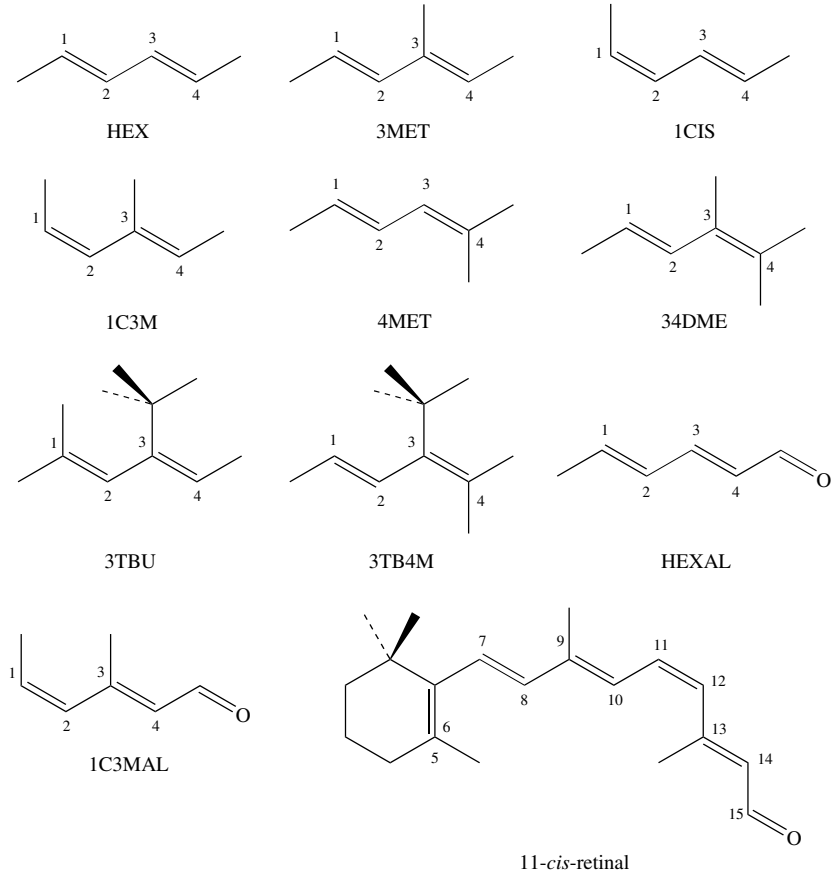


FIGURE 2. Molecular structures of the linear π-conjugated compounds studied

The *ab initio* shielding calculations are carried out in order to investigate the conformation dependence of ^{13}C chemical shifts for conjugated compounds such as the chromophore of a visual pigment Rh. First, the calculations are applied systematically to 10 diene derivatives in order to obtain basic and universal relationships between their conformation and the shieldings of unsaturated carbons. It is indicated that the conjugated carbons are classified into two types according to the profiles of the conformation dependence of the shieldings. The shieldings of the carbons composing the rotating bond exhibit complicated angular dependence. There is strong evidence that the behavior of such carbon shieldings can be understood by considering the effect of π-orbital modification, a new concept introduced in the work. On the other hand, the shieldings of the other carbons essentially follow well-known effects including the steric and charge density effects. One of the most important findings is that the steric effects are reflected predominantly on the σ_{11} component, and the effects that originated in electronic perturbation are on the σ_{22} and σ_{33} terms. This classification is hardly affected even when both types of effects act simultaneously during a conformational change. It is indicated that these basic data

for the dienes are available for interpretation of the conformational dependence of ^{13}C shieldings for more complicated compounds like retinal. Finally, by combining the data for the direct *ab initio* shielding calculations of 11-*cis*-retinal and for those of the dienes, they successfully determine the preferred conformation around the C12−C13 bond of the chromophore in Rh. It is concluded that the chromophore takes s-*trans* conformation around this bond.

III. RECENT APPLICATIONS

A. Solution NMR

1. Linear conjugated dienes

Tsuboi and coworkers[20] reported a stereoselective synthesis of 3,5-alkadienic ester obtained from 2,4-dienoic isomers and their NMR data.

The treatment of (2*E*,4*Z*)-2,4-alkadienoic esters **(7)** with lithium diisopropylamide (LDA) at −80 °C gave the (3*E*,5*E*)-isomers **(8)** with 81−98% stereoselectivity. In contrast, the treatment of (2*E*,4*E*)-isomers **(9)** under the same conditions gave the (3*E*,5*Z*)-isomers **(10)** with 72−80% stereoselectivity. ^{13}C NMR data on 3,5-dienoates are given in Tables 8a and 8b. The stereoselectivity decreased slightly as the substituent became larger. The geometry of the rearrangement products was determined by ^1H NMR spectral data with the aid of a shift reagent $Eu(dpm)_3$ and a proton decoupling technique. For example, both *J*(H3H4) and *J*(H5H6) in ethyl(3*E*,5*E*)-3,5-decadienoate **(8c)** were 15 Hz, which shows a *trans* geometry. The coupling constants of ethyl (3*E*,5*Z*)-3,5-decadienoate were *J*(H3H4) = 15.4 Hz and *J*(H5H6) = 10.8 Hz. The ^{13}C NMR spectra of compounds prepared in this work were measured and tentatively assigned as shown in Table 9.

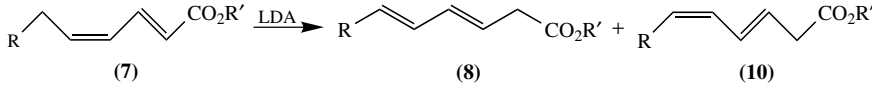
In general, signals of *cis* olefinic carbons of **10** appeared at a higher field than those of *trans*,*trans*-olefins **8** as a result of a steric effect[21]. These data afford an additional support for the structural assignment of **8** and **10**.

Bushby and Jarecki[22] reported a preparation of precursors to conformationally constrained 8π non-Kekule polyenes and their NMR data.

A synthesis is described for the *Z* and *E* isomers of 2-(2′-butylallylidene)-6,7-diazabicyclo[3.2.2]nona-3,6-diene **11** and **12**, which are potential precursors to conformationally constrained 8π non-Kekule polyenes.

Their ^1H NMR spectra were assigned with the help of two-dimensional NMR (COSY) experiments and the stereochemistry of the exocyclic double bonds through NOE experiments as detailed in Table 10.

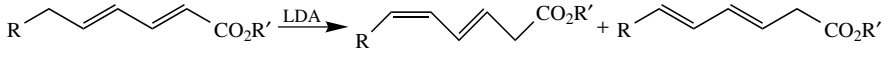
TABLE 8a. Transformation of (2*E*,4*Z*)-2,4-alkadienoates **7** to the (3*E*,5*E*)-isomers **8**



(7) **(8)** **(10)**

No.	**7** R	**7** R′	Yields of products (%) **7**	**8**	**10**	Stereoselectivity **8/10** (%)
a	C_2H_5	CH_3	2	77	3	96
b	n-C_3H_5	CH_3	0	56	1	98
c	n-C_4H_9	C_2H_5	0	87	10	90
d	n-C_7H_{15}	C_2H_5	0	68	12	85
e	n-C_8H_{17}	CH_3	23	62	15	81

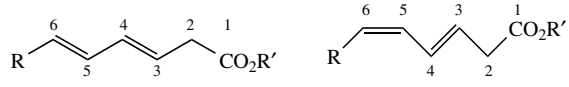
TABLE 8b. Transformation of (2*E*,4*E*)-2,4-alkadienoates **9** to the (3*E*,5*Z*)-isomers **10**



(9) **(10)** **(8)**

	9		Yields of products (%)		Stereoselctivity
No.	R	R′	**10**	**8**	**10/8** (%)
a	C_2H_5	CH_3	51	13	80
b	n-C_3H_7	CH_3	66	22	75
c	n-C_4H_9	C_2H_5	72	28	72
d	n-C_8H_{17}	CH_3	75	19	80

TABLE 9. ^{13}CNMR data of (3*E*,5*E*)-3,5-alkadienoates **8** and (3*E*,5*Z*)-3,5-alkadienoates **10**



(8) **(10)**

Compd	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}
8a	171.9	38.0	122.4	134.2	128.4	136.4	25.6	13.5						
8b	172.1	37.9	122.3	134.7	129.7	134.2	34.7	22.4	13.7					
8c	171.8	38.2	122.5	134.8	129.6	134.1	29.1	31.4	22.3	14.0				
8d	172.1	37.8	122.2	134.4	129.4	134.1	18.3	29.5[a]	29.3[a]	28.5[a]	28.5[a]	31.9	22.7	14.1
10a	171.9	38.2	124.6	134.0	127.2	129.3	21.2	14.3						
10b	172.1	38.1	124.5	132.1	127.9	129.3	29.8	22.8	13.7					
10c	171.8	38.2	123.9	132.4	126.9	128.0	28.3	31.7	22.3	14.0				
10d	172.0	38.1	124.5	132.4	127.7	129.8	27.8	29.3[a]	29.3[a]	29.6[a]	29.6[a]	31.9	22.7	14.1

[a]May be exchangeable.

Roth and coworkers[23] reported NMR data of the orthogonal butadiene (*Z*,*Z*)-3,4-dimethylhexa-2,4-diene. (*Z*,*Z*)-**13** having the planes of the double bonds at a dihedral angle not far from 90°. This diene serves as the model for 'conjugated' diene lacking π-electron delocalization and for the transition state for interconversion of antiperiplanar (*trans*) and synperiplanar (*cis* or *gauche*) butadiene.

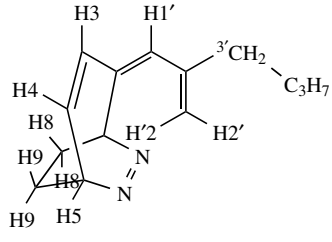
From the ^{1}H NMR and ^{13}C NMR spectra reported in Table 11, it is immediately apparent which isomer has the nonsymmetrical (*E*,*Z*) configuration.

Two features in the ^{1}H spectra are distinctive: rotation of an (*E*) double bond out of the plane shifts the vinyl proton from 5.58 ppm in (*E*,*E*)-**13** to 5.20 ppm in (*E*,*Z*)-**13**; replacement of a (*Z*) double bond in nonplanar (*Z*,*Z*)-**13** by an (*E*) double bond in nonplanar (*E*,*Z*)-**13** causes the (*Z*)-C1 CH_3 group to be shifted downfield from 1.45 to 1.56 ppm.

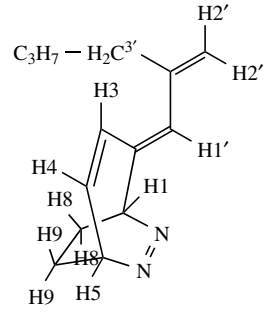
In the ^{13}C spectra, assignment of C1(4) and C2(3) rests not only on the larger intensity of the former but also on multiplicities found with the INEPT pulse sequence. (*E*)- and (*Z*)-methyl groups are distinguished in C2(3) CH_3.

Despite identical values of the angle between the planes containing the two double bonds found by electron diffraction in (*E*,*Z*)-**13** and (*Z*,*Z*)-**13**, only the latter fails to react with sulfur dioxide or maleic anhydride. Apparently, the second α,δ-dimethyl repulsion

TABLE 10. ^{1}H NMR assignments for compounds **11** and **12**

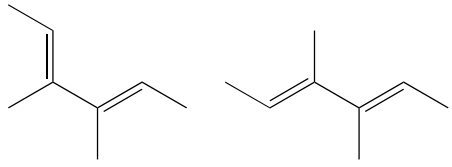


(11) *Z*-isomer

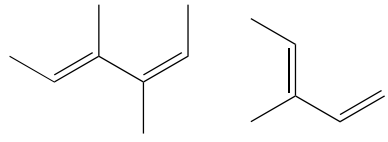


(12) *E*-isomer

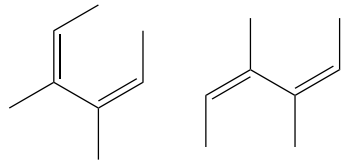
Position	$\delta(CDCl_3)$	COSY	NOE	Position	$\delta(CDCl_3)$	COSY	NOE
1	6.21	8/9	2′	1/5	5.43	4, 8/9	1′
3	5.96	4		3	6.50	4	
4	5.75	3, 5		4	5.78	1/5, 3	
5	5.45	8/9		8/9	1.5, 1.8	1/5	
8/9	1.85, 1.70	5, 1					
1′	5.90	2′		1′	5.98	2′	1
2′	5.2, 5.1	1′,3′	1	2′	5.05, 4.84	1′,3′	
3′	2.0	2′		3′	2.1	2′	



(*E*,*E*-**13**)



(*E*,*Z*-**13**)



(*Z*,*Z*-**13**)

TABLE 11. ^{1}H and ^{13}C NMR spectra of the 1,2,3,4-tetramethylbutadienes[a]

Group[a]	(*E*,*E*)-**13**	(*E*,*Z*)-**13**	(*Z*,*Z*)-**13**
		^{1}H NMR (270 MHz, $CDCl_3$)[b,c]	
C1 CH_3	1.71 (d, *J*6.6)	1.56 (dq, *J*6.6, 1.3)	1.45 (dq, *J*6.6, 1.3)
C4 CH_3		1.65 (d, *J*6.9)	
C2 CH_3	1.76 (s)	1.66 (s)	1.71 (dq, *J*1.3, 1.4)
C3 CH_3		1.73 (dq, *J*1.3)	
C1(4)	5.58 (q, *J*6.6)	5.20 (m)	5.26 (qq, *J*6.6, 1.4)
		^{13}C NMR (67.8 MHz, $CDCl_3$)	
C2(3)	137.1 (0.21)[d]	140.7 (0.15)	136.6 (0.21)
		135.8 (0.12)	
C1(4)	119.1 (1.00)	121.1 (0.83)	119.6 (0.52)
		118.9 (1.00)	
C2(3) CH_3		23.3 (1.00)	22.1 (1.00)
	14.0(0.62)	15.1 (0.47)	
C1(4) CH_3		14.5 (0.66)	1.41 (0.67)
	13.5 (0.75)	13.3 (0.48)	

[a]Names and numbering are based on butadiene for covenience.
[b]Ppm relative to TMS.
[c]Splittings (*J*) in hertz.
[d]Values in parentheses are relative intensities.

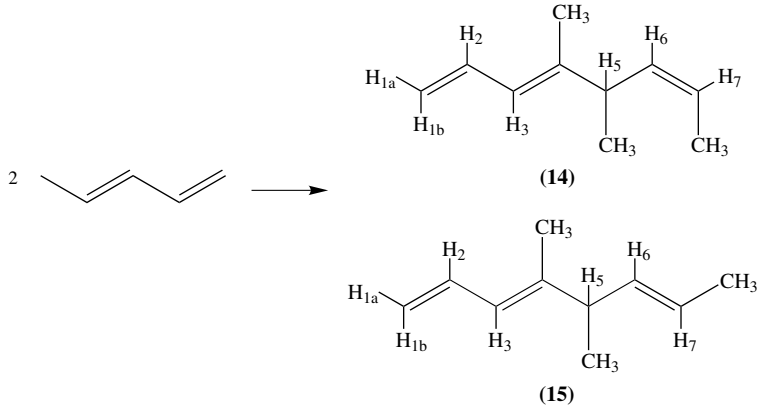
in (*Z*,*Z*)-**13** makes attainment of a planar *cis* conformation sufficiently less favorable so that the transition state for a Diels–Alder reaction is no longer within reach.

Denis and coworkers[24] reported a linear dimerization of conjugated dienes catalyzed by Ni(0)-aminophosphinite systems and their NMR data. This reaction occurs at a rather low temperature with high turnover numbers, especially with butadiene and piperylene. The reaction with butadiene gives the 1,3,6-octatriene isomers, which are further isomerized to the conjugated 2,4,6-octatrienes. With isoprene, a competitive cyclodimerization reaction occurs, but the linear dimers are obtained regioselectively by a tail-to-tail linkage. Piperylene gives rise only to head-to-head products **14** and **15**, without forming cyclodimers, which are optically active. The ee values were *ca* 90% and 35% for **14** and **15**, respectively (Scheme 1).

The LIS (Lanthanide Induced Shift) NMR technique is useful for such analysis[25] and the separation of olefin enantiomers such as limonene, α-camphene and β-pinene has been performed upon addition of silver salts such as Ag(fod)* or Ag(hfc)** to the commonly used lanthanide chiral salts such as Ln(tfc***)$_3$ or Ln(hfc)$_3$, where *fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctanedione, **hfc = heptafluoro-3-butyrylcamphorato and ***tfc = trifluoroacetylcamphorato.

Table 12 gives the chemical shifts of the olefinic protons in compound **15** in the presence of different shift reagents. Upon using the racemic **15** and that obtained with (D)-2′-Ph_2POCH(Ph)CH(Me)ND(Me)(EPHOSNH) [Ephedrine PHOSphine NH] as ligand, an enantiomeric shift is observed in the 5.3–5.6 ppm region where resonance of the three protons (H3, H6 and H7) occurs. Splitting occurs on the H6, and upon integration of the signals the ee of this *E*,*E* isomer can be estimated as $35 \pm 5\%$ (Figure 3).

The same procedure was used to analyze the *E*,*Z* isomer **14**. The higher optical rotation obtained with this compound ($-143°$) could suggest a higher optical yield. Indeed, integration of the same signals in the spectrum using Eu(tfc)$_3$ and Ag(fod) gave an optical yield of more than 90%.



SCHEME 1

TABLE 12. Olefinic protons chemical shifts of **15** in the presence of LIS reagents (*vs* TMS)

Complex (0.1 M)	H1a	H1b	H2	H3	H5	H6	H7
None	5.00	5.12	6.58	5.89	2.77	5.40	5.40
$Eu(tfc)_3$	5.00	5.12	6.58	5.89	2.77	5.40	5.40
Ag(fod)	4.96	5.10	6.82	5.96	2.9	5.60	5.60
$Eu(tfc)_3$ + Ag(fod)	4.32	4.45	6.60	5.50	2.7	5.4–5.5	

Chen and coworkers[26] reported the structures of spiral hexatrienes and the NMR data.

Steric crowding in the *cis* isomer of Mini-3 (**16**), a chain shortened triene analog of β-carotene, and hexakis (2,2′,4,4′,6,6′-trifluoromethyl)stilbene (**17**) forces the polyene chromophores to adopt a spiral conformation. Some of the associated unusual spectroscopic properties (UV-VIS and NMR) of these compounds and a rare 1,7-H shift process were described.

The unusual conformation is also in agreement with the dynamic NMR behavior exhibited by compounds **16** and **17**. For **16**, the geminal dimethyl singlet (0.98 ppm) in its room temperature ^{1}H NMR spectrum (in toluene-d_8, 500 MHz spectra) splits into two singlets ($\Delta\delta = 68.8$ Hz) upon cooling indicating that the two methyl groups are now nonequivalent, as indicated in structures **16′** and **16″**. The coalescence temperature ($T_c = -69\,^\circ$C), and the calculated $\Delta G^{\neq}$ values (9.9 kcal mol^{-1}) based on the equation[27]:

$$\Delta G^{\neq} = 4.57\ T_c[9.97 + \log T_c/(\Delta\nu \text{ values} + 6J)^{-1/2}],$$

(J being zero for both **16** and **17**) are, somewhat surprisingly, lower than those of the 7-*cis* retinoids (coalescence temperatures usually near 0 °C)[28].

The ^{19}F NMR spectra (in THF-d_8, 283 MHz) of compound **17** also exhibits dynamic NMR behavior; of **17′** and **17″**. At room temperature, two singlets ($\delta - 60.97$ and -65.05 ppm) of 2 : 1 relative intensities were observed corresponding to the *o*- and *p*-CF_3's. At lower temperatures, the major peak split into two singlets ($\Delta\delta = 136$ Hz) with the coalescence temperature being $-90\,^\circ$C, giving $\Delta G^{\ddagger} = 9.3$ kcal mol^{-1}. The higher field peak is most likely due to that of the inward CF_3 group of **17″**, now frozen in a direction above the plane of second phenyl ring. The activation parameters

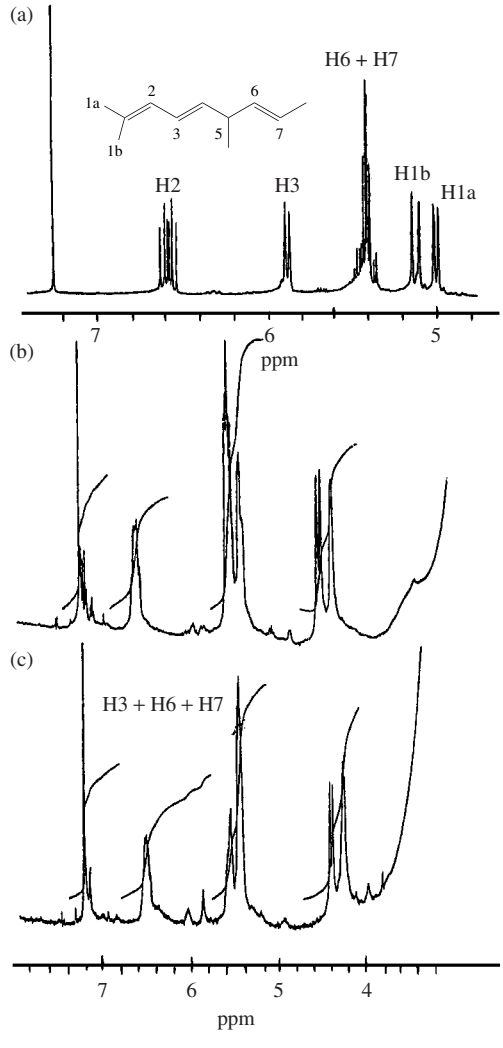
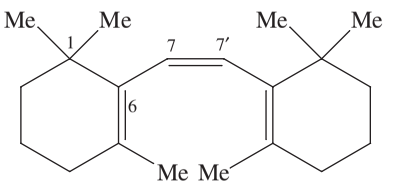


FIGURE 3. 400 MHz proton NMR spectrum of **15** in $CDCl_3$ (olefinic protons) with (a) no shift reagent, (b) racemic **15** with $Eu(tfc)_3$ and Ag(fod), (c) **15** produced from piperylene with $Ni(COD)_2$ and D-EPHOSNH, with $Eu(tfc)_3$ and Ag(fod). Reproduced by permission of Elsevier Sequoia S.A. from Reference 24

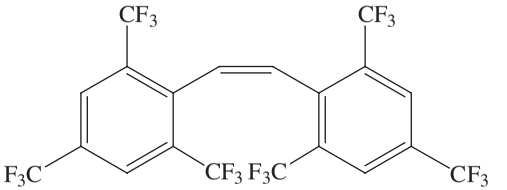
($\Delta H^{\ddagger} = 4.4$ kcal mol^{-1}, $\Delta S^{\ddagger} = -19.8$ eu) are similar to those of **16**, suggesting that a concerted motion is also involved in the equilibration process.

Taskinen[29] reported a ^{17}O NMR study of p$-\pi$ conjugation in methoxybutadienes and related compounds.

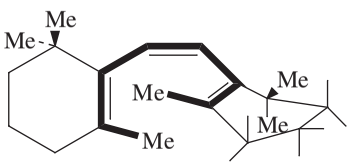
The ^{17}O NMR spectra of some monomethoxy and dimethoxy derivatives of buta-1,3-diene, hexa-2,4-diene, cyclohexa-1,3-diene and cyclohexa-1,4-diene were recorded in $CDCl_3$. The $\delta(^{17}O)$ values show that in 2-methoxybuta-1,3-diene the efficiency of p$-\pi$



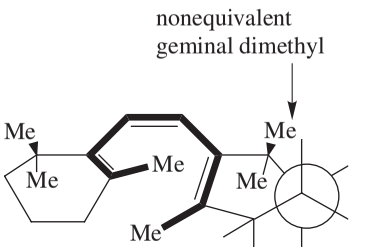
(16)



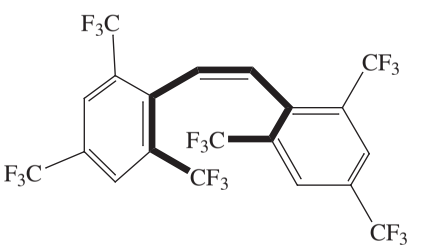
(17)



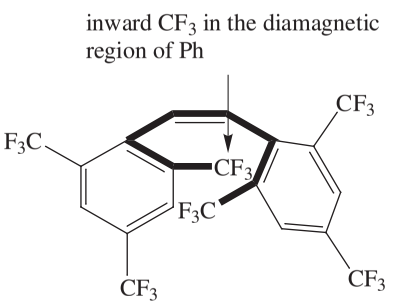
(16′)



(16″)



(17′)



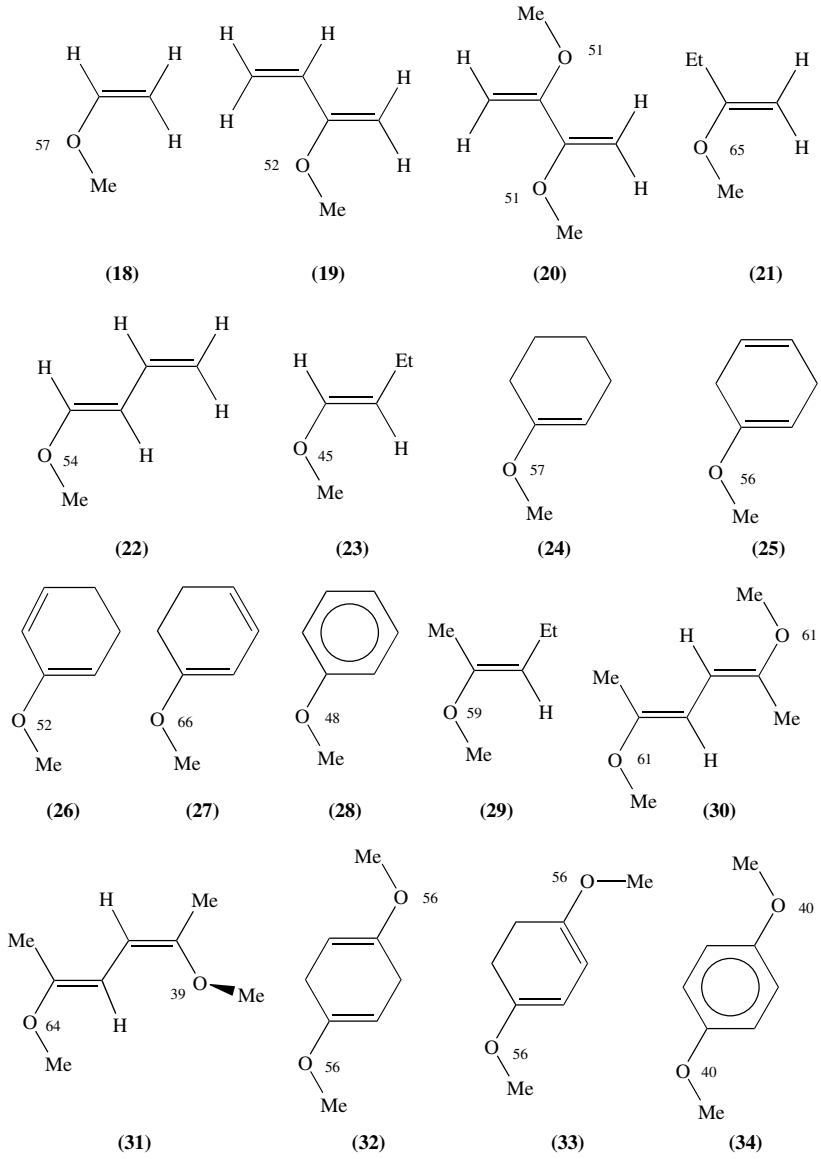
(17″)

conjugation in the −O−C=C moiety is significantly lowered by cross-conjugation of the C=C bond with the other olefinic linkage. In the related system of 2-methoxycyclohexa-1,3-diene, however, the corresponding effect is much smaller, apparently because of weak conjugative $\pi-\pi$ interaction in the olefinic system. On the other hand, the strength of the $p-\pi$ conjugation appears to be the same in the −O−C=C−C=C moieties of both 1-methoxycyclohexa-1,3-diene and 1-methoxycyclohexa-1,4-diene. Moreover, as a transmitter of substituent effects, the unsaturated system of cyclohexa-1,3-diene is comparable to that of the benzene nucleus. The $\delta(^{17}O)$ values, relative to external water, are given in Scheme 2, which shows that when the α-H atom of **18** is replaced with either a vinyl group **(19)** or a MeO-substituted vinyl group **(20)**, a decrease of 5–6 ppm in $\delta(^{17}O)$ is observed. For comparison, an Et-substituent in the α-position **(21)** causes an 8 ppm increase in $\delta(^{17}O)$. Thus there is a difference of 13 ppm in $\delta(^{17}O)$ between **21** and **19**, which suggests the $p-\pi$ conjugation to be less efficient in the latter compound. As it seems likely that the MeO group of **19** can readily adopt the planar s-*cis* conformation, the reduction in $p-\pi$ conjugation is likely to arise from electronic rather than steric factors.

As expected, $\delta(^{17}O)$ of **24** is not significantly affected by the introduction of another C=C linkage into a nonconjugated position in the six-membered ring (**25**; $\delta = 56$ ppm), or when the oxygen is at the center rather than at the terminus of the conjugated system (**26**; $\delta = 52$ ppm). However, the presence of an −O−C=C−C=C system in **27** increases $\delta(^{17}O)$ by 9 ppm, with the shift value of **24** as a reference. This agrees with the 9 ppm difference in chemical shift between the respective open-chain compounds **22** and **23**. The buta-1,3-diene skeleton of **22** is known to assume the planar s-*trans* conformation with a normal buta-1,3-diene stability while the 1,3-diene moiety of **27** behaves like that of the parent cyclohexa-1,3-diene, i.e. devoid of conjugative stabilization. Thus the ^{17}O NMR data suggest that in an −O−C=C−C=C system the oxygen chemical shift, and hence the strength of $p-\pi$ conjugation, do not essentially depend on whether or not there is any actual conjugative $\pi-\pi$ interaction between the two C=C bonds.

The $\delta(^{17}O)$ data in Scheme 2 show that replacement of the Et group of **23** by a vinyl substituent **(22)** leads to an increase of 9 ppm in $\delta(^{17}O)$. On the other hand, if the Et group of **29** is replaced with a MeO- and Me-substituted vinyl group (leading to **30**), the increase in $\delta(^{17}O)$ is only 2 ppm. Clearly, in the latter case the smaller effect of substitution must be due to the combined electron-releasing power of the MeO and Me groups at the end of the 1,3-diene system of **30**, which opposes the electron transfer due to the similar groups at the other end of the conjugated system. In **31**, however, one of the MeO groups is forced by steric reasons to assume a nonplanar *gauche* conformation about the $O-C(sp^2)$ bond, which leads to reduced $p-\pi$ conjugation between this MeO group and the adjacent C=C bond. The shift of the *gauche* MeO group is decreased by 22 ppm, whereas that of the other MeO group is increased by 3 ppm as a result of the weaker electron transfer to the 1,3-diene system by the *gauche* MeO group. It is noteworthy that the shift difference of 25 ppm between the two O atoms of **31** is in line with $\delta(^{17}O)$ data observed previously for some related pairs of geometrical isomers, such as the 2-methoxybut-2-enes, for which the shift difference is also 25 ppm[30]. A comparison of the $\delta(^{17}O)$ values of **27** and **33** (66 and 56 ppm, respectively) shows that introduction of an additional MeO group at the other end of the −O−C=C−C=C system of **27** decreases the oxygen chemical shift by 10 ppm, making it comparable to that of **32**, in which the C=C bonds are isolated.

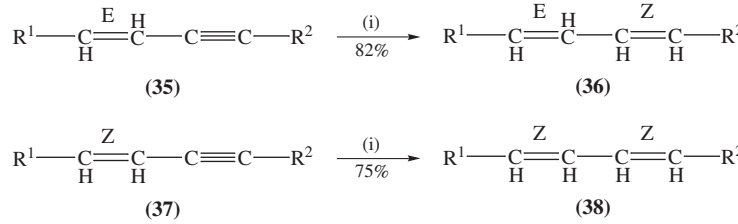
Similarly, $\delta(^{17}O)$ of **34** is 8 ppm lower than that of **28**. Accordingly, although the 1,3-diene system of **33** does not possess the nature and thermochemical stability of ordinary conjugated 1,3-dienes, substituent effects are transmitted at least as efficiently through this system as they are transmitted through the aromatic system of **34**.



SCHEME 2. ^{17}O NMR chemical shift values (ppm) in $CDCl_3$ solution for compounds **18**–**34**

Lie and coworkers[31] reported the synthesis and NMR properties of all geometrical isomers of conjugated linoleic acids. Pure geometric isomers of conjugated linoleic acid (CLA) were prepared from castor oil as the primary starting material. Methyl octadeca-9*Z*,11*E*-dienoate **(36)** and methyl octadeca-9*Z*,11*Z*-dienoate **(38)** were obtained by zinc reduction of methyl santalbate (**35**, methyl octadec-11*E*-en-9-ynoate) and methyl

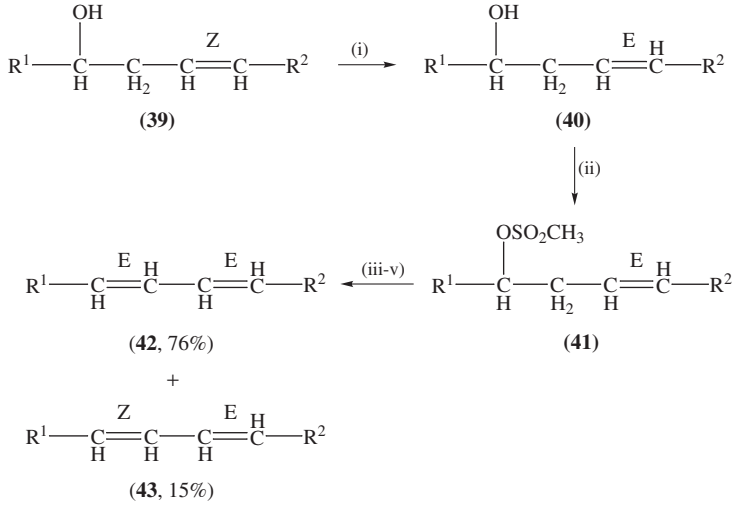
octadec-11*Z*-en-9-ynoate **(37)**, respectively, as the key intermediates. Methyl octadeca-9*E*,11*E*-dienoate **(42)** and methyl octadeca-9*E*,11*Z*-dienoate **(43)** were prepared by demesylation of the mesyloxy derivative **(41)** of methyl ricinelaidate (**40**, methyl 12-hydroxyoctadec-9*E*-enoate) which was obtained in turn from the *Z*-isomer **39** (Scheme 3).



(35) **(36)** **(37)** **(38)**

$R^1 = CH_3(CH_2)_5$; $R^2 = (CH_2)_7COOCH_3$

Reagents and conditions: (i) zinc, *n*-propanol, reflux, 10 h.



(39) **(40)** **(41)** (**42**, 76%) + (**43**, 15%)

$R^1 = CH_3(CH_2)_5$; $R^2 = (CH_2)_7COOCH_3$

Reagents and conditions:
(i) *p*-toluenesulfonic acid, dioxane, reflux, 1 h;
(ii) methanesulfonyl chloride, triethylamine, dichloromethane;
(iii) 1,8-diazabicyclo[5.4.0]undec-7-ene, dimethyl sulfoxide, reflux, 12 h;
(iv) crystallization from ethanol and urea fractionation of mother liquid;
(v) BF_3–methanol, reflux.

SCHEME 3

A study of the NMR spectra was carried out, and the shifts of the olefinic carbon atoms of 18 : 2 (9*Z*,11*E*) **(36)** and (9*E*,11*Z*) **(43)** were readily identified by a combination of incredible natural abundance double quantum transfer experiment (INADEQUATE),

heteronuclear multiple bond correlation and $^{1}H-^{13}C$ correlation spectroscopy techniques. Doubts remain in the absolute identification of the individual olefinic carbon atoms of the (9*Z*,11*Z*) **(38)** and (9*E*,11*E*) **(42)**, expect for the fact that the shifts of the 'inner' (C10 and C11) and 'outer' (C9 and C12) olefinic carbon atoms of the conjugated diene system are distinguishable.

In order to assign the chemical shifts of the carbon atoms of the conjugated diene system of each CLA isomer, it was necessary to conduct INADEQUATE, HMBC (heteronuclear multiple bond correlation) and two-dimensional $^{1}H-^{13}C$ correlation spectroscopy (COSY) techniques on the carbon signals of the diene system of the *E*,*Z*-isomers. The results of these experiments for the CLA isomers are summarized in Table 13.

The *E*,*Z*-, *Z*,*E*-, *E*,*E*- and *Z*,*Z*-isomers can be characterized in sufficient detail by a combination of NMR techniques.

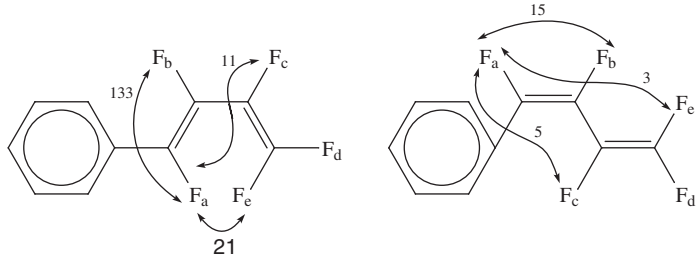
Shtarev and coworkers[32] established the structures of substituted F-polyenes on the basis of *J*(FF) coupling constants. 1-Aryl-1,3-butadienes-F_5 **44** (Figure 4) and α,ω-diaryl-F_6-polyenes **45**, **46** (Figure 5) were formed as mixtures of *E* and *Z* isomers, where *E* isomers predominated, as established on the basis of ^{19}F NMR chemical shifts, *J*(FF) coupling constants and integration of the assigned signals. There are significant differences in coupling constants between the F_a and F_b, or the F_a and F_e nuclei, due to the specific configurations and conformation of the individual isomers. The long-range coupling $^{5}J(a-e) = 20-22$ Hz in (*E*)-**44** is relatively large, although smaller than ^{5}J(F1F4) and $^{5}J(F3F6) = 29.7-32.6$ Hz for the case of the diaryl systems **45** and **46**, apparently due to a significant contribution of the cisoid conformation (Figure 6).

The assumed out-of-plane s-cisoid conformations with the dihedral angles $\phi = 5-23^{\circ}$ and $\theta = 47-49^{\circ}$, which were found in structurally similar systems and confirmed by X-ray and other spectral characteristics, are supported by relatively large ^{5}J(F1F4) and ^{5}J(F3F6)

TABLE 13. ^{13}C NMR chemical shift values of conjugated linoleic acid isomers

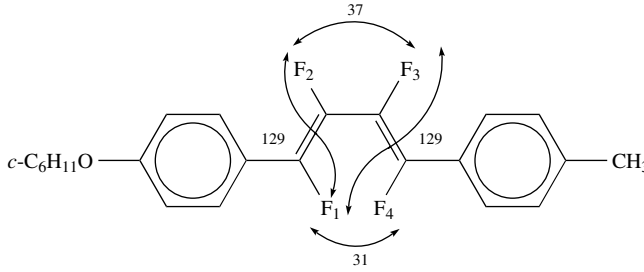
Carbon nucleus	Isomer			
	(9*Z*,11*E*) **(36)**	(9*E*,11*Z*) **(43)**	(9*E*,11*E*) **(42)**	(9*Z*,11*Z*) **(38)**
C1	174.32	174.34	174.22	174.27
C2	34.1	34.1	34.09	34.1
C3	24.95	24.95	24.95	24.97
C4	29.06	28.97	29.04	29.14
C5/C6/C7	29.12–29.67	29.13–29.45	29.14–29.77	29.11–29.60
C8	27.66	32.86	32.61a[a]	27.46
C9	129.89	134.51	132.16b[a]	131.87d[a]
C10	128.71	125.72	130.37c[a]	123.58e[a]
C11	125.58	128.57	130.51c′[a]	123.72e′[a]
C12	134.76	130.17	132.43b′[a]	132.14d′[a]
C13	32.92	27.72	32.68a′[a]	27.54
C14	29.41	29.73	29.4	29.68
C15	28.95	28.97	28.97	29.04
C16	31.77	31.77	31.82	31.81
C17	22.65	22.65	22.68	22.69
C18	14.12	14.12	14.13	14.13
$COOCH_3$	51.44	51.45	51.39	51.42

[a]The assignments a and a′, b and b′, c and c′, d and d′, e and e′ can be interchanged

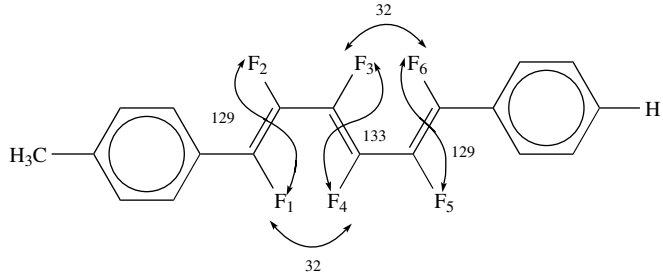


(*E*-**44**) (*Z*-**44**)

FIGURE 4. Selected *J*(FF) for *E*- and *Z*-**44**. Reprinted with permission from Reference 32. Copyright (1997) American Chemical Society



(45)



(46)

FIGURE 5. Selected *J*(FF) for (*E*,*E*)-**45** and (*E*,*E*,*E*)-**46**. Reprinted with permission from Reference 32. Copyright (1997) American Chemical Society

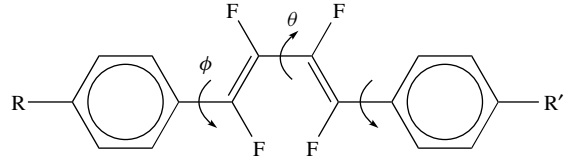
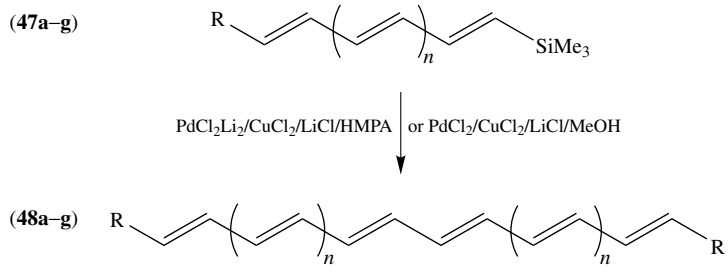


FIGURE 6. Geometry of an (all-*E*)-α,ω-diaryl-F_4-polyene. Reprinted with permission from Reference 32. Copyright (1997) American Chemical Society

coupling constants observed in the ^{19}F NMR spectra. Their magnitude is apparently due to through-space interaction, as shown for **45** and **46** in Figure 5.

Babudri and coworkers[33] reported a highly stereoselective synthesis of conjugated polyenes and their NMR data. They reported a new method for the synthesis of conjugated polyenes containing up to eight double bonds with all-*E* configuration based upon a homocoupling reaction of dienyl-, trienyl- or tetraenylsilanes, promoted by $PdCl_2$ in methanol in the presence of LiCl and $CuCl_2$.

Configurational and conformational assignments were made rigorously on the basis of NMR spectra. By applying a similar procedure to more complex systems, they prepared the series of polyenylsilanes **47a–g** and investigated their transformation into longer polyenes **48a–g** (Scheme 4). The configuration of compounds **48a–f** was determined by ^1H NMR spectroscopy. The analysis of the ^1H NMR spectrum of compound **48a** was straightforward.



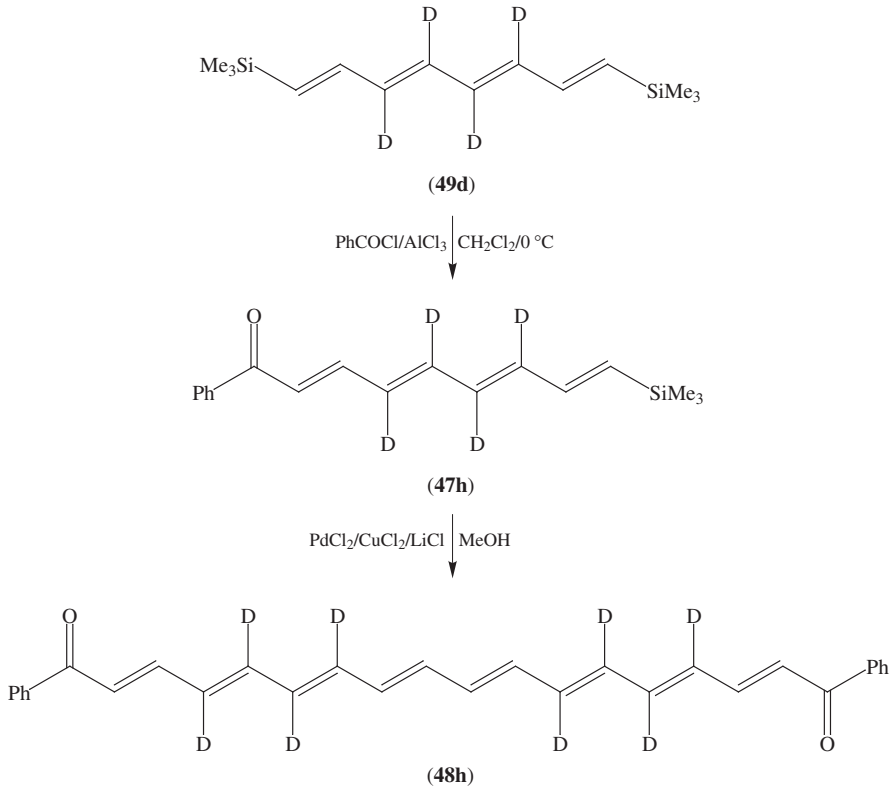
(47a)	R = PhCO	$n = 0$	**(48a)**
(47b)	R = PhCO	$n = 1$	**(48b)**
(47c)	R = $PhCH_2CO$	$n = 1$	**(48c)**
(47d)	R = 4-$CH_3C_6H_4CH_2CO$	$n = 1$	**(48d)**
(47e)	R = 4-*n*-$C_{10}H_{21}C_6H_4CH_2CO$	$n = 1$	**(48e)**
(47f)	R = PhCO	$n = 2$	**(48f)**
(47g)	R = Ph	$n = 0$	**(48g)**

SCHEME 4

For compounds **48b–f** the complexity and the extensive overlap of resonance signals limit the amount of information that can be obtained from single resonance spectra. H1/H1′ protons give distinct doublet in all the compounds examined and H2/H2′, H3/H3′, H4/H4′ resonances were assigned by homonuclear decoupling experiments. H1/H1′ and H2/H2′ were in all cases obtained directly from ^1H single resonance spectra. For the hydrogen atoms bonded to the central carbon atoms, NMR parameters could not be extracted by direct inspection of the spectra, because of second-order effects and extensive overlap of the resonance signals. Even in COSY spectra, cross-peaks originated from second-order effects precluded the possibility of obtaining vicinal coupling constants $^3J(HH)$ reliable enough to assign the configuration at the central double bonds of the polyenic chain. Least-squares analysis of the spectra was the only way to obtain chemical shifts and $^3J(HH)$ values which permitted the required configurations to be determined unambiguously.

The eight central protons H3/H3′, H4/H4′, H5/H5′ and H6/H6′ of the polyenic chains in compounds **48b–e** were analyzed as an AA′BB′CC′DD′ spin system. The resonances of H3/H3′, H5/H5′ and H6/H6′ are located in a narrow range (50 Hz), and spin-tickling

experiments were necessary for a correct assignment of the experimental frequencies to the calculated transitions. COSY spectra were helpful in estimating transitions and the proton chemical shift values used to start the iterative analysis. For compound **48f**, decoupling of H4/H4′ allowed the H3/H3′ and H5/H5′ resonances to be localized; these resonances strongly overlap with H6/H6′, H7/H7′ and H8/H8′ resonances. Since the signals arising from these 10 protons are located in a range of 90 Hz, it was not possible to carry out the spectral analysis of the spin system H5/H5′, H6/H6′, H7/H7′ and H8/H8′. The stereochemistry of the fragment C7–C8–C8′–C7′ was determined for the partially and selectively deuteriated octaene **48h**, prepared from the tetradeuteriated **49d** as shown in Scheme 5.



SCHEME 5

The ^{1}H NMR spectrum of the four central protons of **48h** was analyzed as an AA′BB′ spin system. The coupling constants between H7/H7′ and the deuterium nuclei on C6/C6′ (*ca* 2 Hz) were taken into account as first-order perturbations. In all cases coupling constants over four (−0.58 to −0.87 Hz) and five (+0.32 to +0.69 Hz) bonds were also considered in performing the spectral analysis. Chemical shifts and vicinal coupling constants for **48a–f** are reported in Table 14.

Vicinal coupling constants across double bonds are in the range 14.2–15.3 Hz, thus indicating the all-*E* configuration of the conjugated system. The ^3J(HH) values across

TABLE 14. ^{1}H NMR chemical shifts[a] and vicinal coupling constants[b] for polyenes **48a–f**

Compd	H1	H2	H3	H4	H5	H6	H7	H8
48a	7.07 (14.82)	7.48 (10.74)	6.65 (14.99)	6.76 (11.23)				
48b	6.99 (14.89)	7.48 (11.40)	6.53 (14.80)	6.69 (10.16)	6.43 (14.12)	6.48 (11.95)		
48c	6.23 (15.23)	7.25 (11.39)	6.33 (14.74)	6.65 (10.65)	6.38 (15.12)	6.46 (10.79)		
48d	6.21 (15.28)	7.25 (11.42)	6.33 (14.69)	6.64 (11.19)	6.38 (14.09)	6.45 (11.85)		
48e	6.22 (15.23)	7.26 (11.34)	6.34 (14.78)	6.65 (11.0)	6.38 (14.19)	6.45 (11.09)		
48f	6.97 (14.9)	7.47 (11.5)	6.49 (14.7)	6.72 (11.0)	6.42 (15.0)	6.48 (10.0)	6.43 (14.83)	6.40 (11.40)

[a] ^{1}H NMR chemical shifts are listed in ppm vs TMS in $CDCl_3$.

[b] Vicinal coupling constants of each proton with the following one in the polyenic chain are reported in parentheses (in Hz).

single carbon–carbon bonds, which are in the range 10.0–11.8, suggest the occurrence of a nearly planar arrangement of the polyenic chains. However, on this basis a distinction between s-*trans* or s-*cis* conformation was not possible. The conformation of **48a** was fully determined by ^{13}C NMR and 2D NOESY spectra. The 2D NOESY spectrum shows correlation peaks of significant intensities between the pairs of protons H1/H1′–H3/H3′ and H2/H2′–H4/H4′. This suggests an s-*trans* (a) conformation of the polyenic chain. Such a conformation is confirmed also by the ^{3}J(CH) values between C1/C1′ and H3/H3′ of 3.8 Hz, and between C2/C2′ and H4/H4′ of 5.0 Hz.

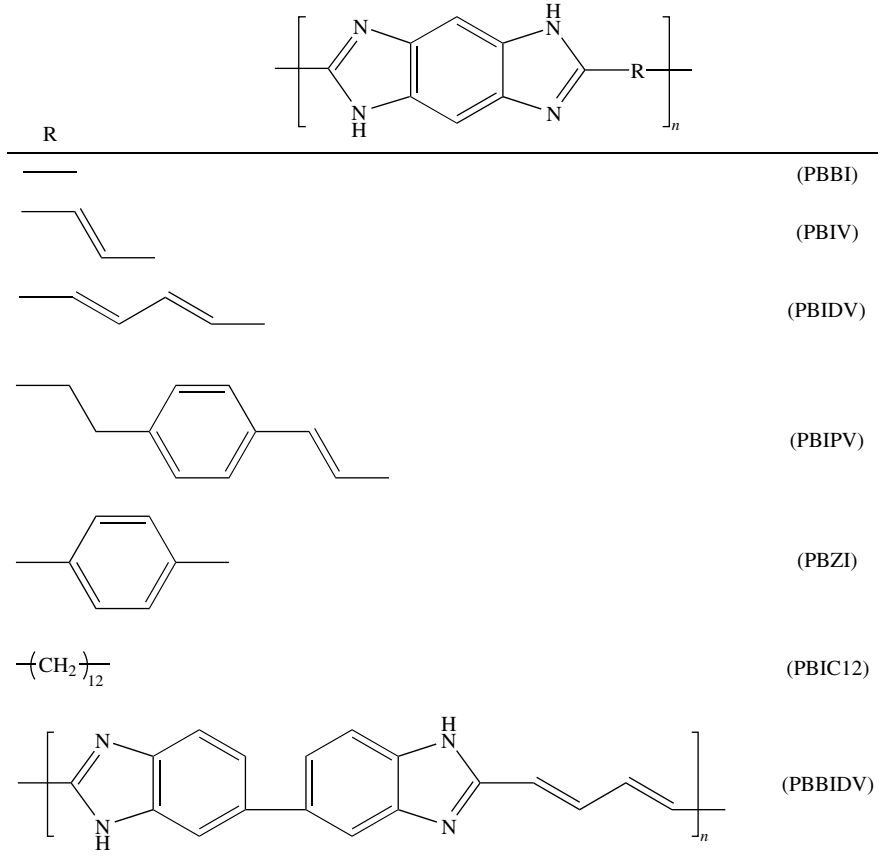
2. Polymers containing polyenes

Osaheni and Jenekhe[34] reported a synthesis of conjugated rigid-rod polymers and their NMR data. The conjugated rigid-rod polymers have interesting photoconductive, light-emitting and third-order nonlinear optical properties that have some potential for applications in optoelectronics and photonics.

New conjugated rigid-rod poly(benzobis(imidazole))s incorporating varying lengths of *trans*-polyene segments and 1,4-phenylenebis(vinylene) linkages have been synthesized and characterized by ^{1}H NMR spectra. The synthesis, characterization, thin film processing and optical properties of the conjugated poly(benzobis(imidazole))s shown in Scheme 6 were reported.

The series of polymers includes the parent poly(benzobis(imidazole)) (PBBI), poly (benzobis(imidazole)vinylene) (PBIV), poly(benzobis(imidazole)divinylene) (PBIDV), poly(benzobis(imidazole)-1,4-phenylenebis(vinylene)) (PBIPV) and poly(benzimidazole-divinylene) (PBBIDV). The new nonconjugated polymer poly(benzobis(imidazole)(dodecamethylene) (PBIC12) as well as the previously reported poly(*p*-phenylenebenzobis (imidazole)) (PBZI) were also synthesized for the purposes of comparative studies. The ^{1}H NMR spectrum of PBIDV in deuteriated nitromethane containing aluminum trichloride, shown in Figure 7, exemplifies the results.

The assignment of the resonances is also shown in Figure 7, in agreement with the proposed structure, including the *trans*,*trans*-divinylidene conformation. However, the integration of the amine (N–H) protons of the ring was not very accurate due to the rapid



SCHEME 6

proton exchange. The N−H proton resonance in the conjugated poly(benzobisimidazole)s was at 9.0–9.2 ppm whereas the resonance of this proton in the nonconjugated PBIC12 was at 6.9 ppm.

The ^{1}H NMR spectra were all in good agreement with the proposed structures of the polymers in Figure 7.

Jin and coworkers[35] reported a synthesis and characterization of new thermotropic side-chain liquid crystal polymers containing 1,6-heptadiyne backbone. Poly(1,6-heptadiyne) derivatives with side-group liquid crystalline mesogens are prepared by ring-forming metathesis polymerization with transition metal catalysts. $MoCl_5$-based catalyst systems are more effective for the polymerization of 1,6-heptadiyne monomers with various mesogenic groups than are WCl_6-based catalyst systems. The resulting polymers exhibit good solubility in common organic solvents such as chloroform and THF. The ^{1}H and ^{13}C NMR spectra of the resulting polymers indicate that side-chain liquid crystal polymers with a 1,6-heptadiyne backbone possess a polyene structure, presumably with cyclic recurring units in the polymer backbone. Thermal behaviors, morphology and electrical conductivities are investigated by using differential scanning calorimetry and cross-polarized optical

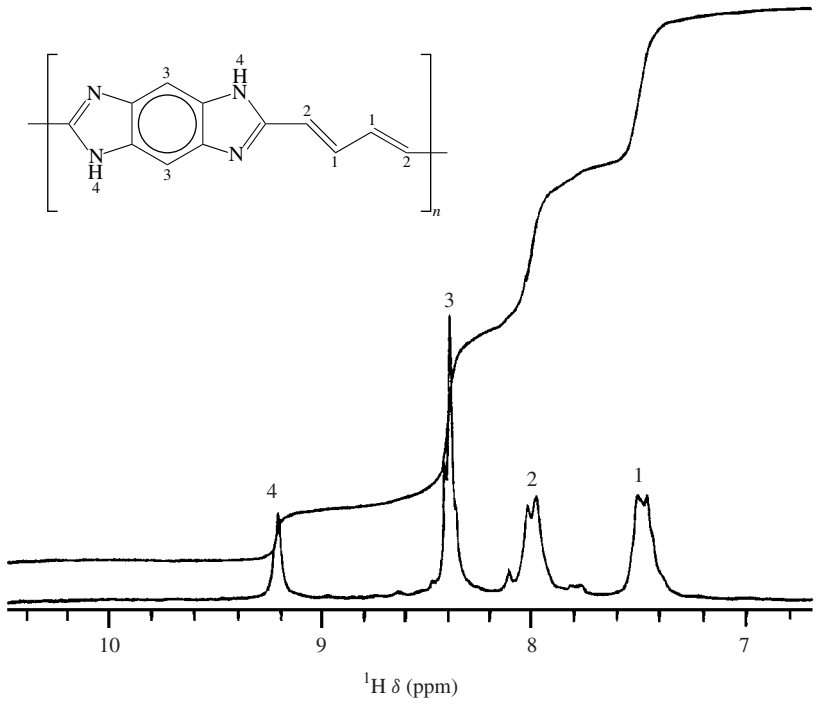


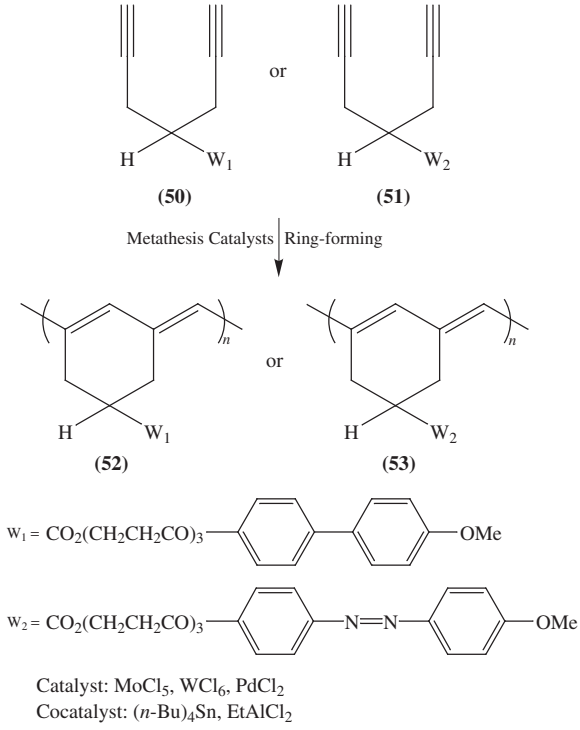
FIGURE 7. ^{1}H NMR spectrum of PBIDV in $CD_3NO_2/AlCl_3$ and its assignment. Reprinted with permission from Reference 34. Copyright (1995) American Chemical Society

microscopy. Compounds **50** and **52** displayed enantiotropic liquid crystallinity showing reversible phase transition. Compounds **51** and **53** displayed no mesophase. The electrical conductivities of the film-type polymers are in the 10^{-4} to 10^{-2} S/cm range.

The polymerization of the monomers **50** and **51** with ring-forming metathesis catalysts give **52** and **53**. The polymerization of **50** was carried out with transition metal catalysts; with $MoCl_5$ as catalyst and $(n\text{-Bu})_4Sn$ as a cocatalyst, the yield of **52** was quantitative (Scheme 7).

Careful ^{1}H and ^{13}C NMR analyses were carried out for both monomers and polymers in order to prove the chemical structures of the polymers. The ^{1}H NMR spectra of **50** and **52** are shown in Figure 8. As polymerization proceeded, an acetylenic proton peak at 2.0–2.2 ppm disappeared, while a new vinylic proton peak appeared broadly in the 6.8–7.2 ppm range. Since the new peak is weaker than those for the aromatic biphenyl rings and the two peaks are superimposed, it is hard to separate them clearly. The broad peaks at 2.6 and 3.4 ppm are assignable to the methylene protons and methine proton in the ring, respectively.

Figure 9 exhibits the ^{13}C NMR spectra of **50** and **52**. The monomer has acetylenic carbon peaks at 70 and 82 ppm, but **52** does not show these peaks. Instead, the olefinic carbon peaks of the **52** backbone appear at 123 and 141 ppm, although the value for the quaternary carbon is very weak. The peak of the methylene carbon adjacent to the polymer backbone is shifted from 20 to 43 ppm on polymerization.



SCHEME 7

3. Antibiotic polyenes

Ghirlando and coworkers[36] reported interactions between a protonated retinal Schiff base and various counterions using two-dimensional NOE NMR. Bacteriorhodopsin (bR) is the protein pigment (a constituent of the purple membrane) of *Halobacterium halobium*. Its role is to convert light energy directly into a gradient of hydrogen ion concentration across the membrane, which is subsequently used, via a chemiosmotic mechanism, to synthesize adenosine-5′-triphosphate. bR consists of a chromophore, all-*trans*-retinal, covalently bound to the polypeptide backbone through a protonated Schiff base link to the ε-amino group of a lysine. The protonated *n*-butylamine Schiff base of all-*trans*-retinal in methanol absorbs at 440 nm, whereas in bR, in its light-adapted form, it has an absorption maximum of 570 nm. This absorption maxima difference between the chromophore in the natural pigment and in methanol is defined as the opsin shift[37]. A better understanding of the mechanism through which the protein shifts the absorption maximum to longer wavelengths, in addition to accounting for the absorption maxima in various visual pigments ranging from 440 to 625 nm, is of great interest.

At present the opsin shift in bR is interpreted as a result of a combination of different factors: (i) weaker hydrogen bonding in the pigment between the positively charged nitrogen and its counterion relative to the hydrogen bonding existing in methanol solution, (ii) s-*trans* ring-chain planarity and (iii) interaction of the retinal chromophore with a nonconjugated dipole introduced by the protein.

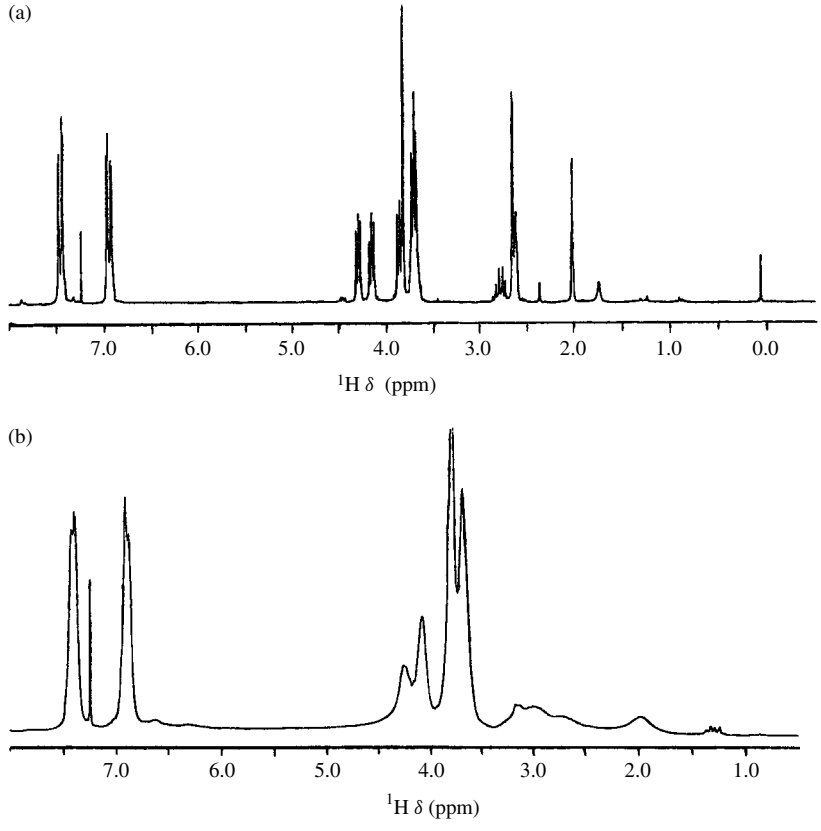
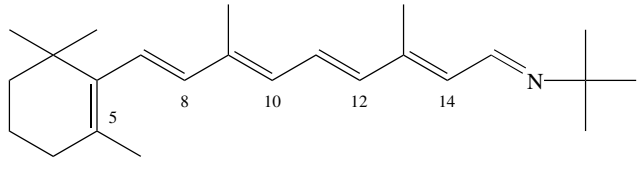


FIGURE 8. ^{1}H NMR spectrum of (a): **50** and (b): **52** in $CDCl_3$. Reproduced by permission of Marcel Dekker, Inc. from Reference 35

The importance of the interaction between the protonated retinal Schiff base and its counterion for determining the absorption maxima was pointed out by Blatz and Mohler[38], who first noticed a correlation between the type of counterion used and the change in the wavelength of the absorption maximum in aprotic solvents. Excess of trifluoroacetic acid, in methylene chloride as a solvent, introduced a red shift due to the weakening of the electrostatic interaction between the positively charged nitrogen and its counterion. It is therefore important to determine directly the actual spatial location of the counterion along the polyene chain of the all-*trans* protonated retinal Schiff base in solution. The structure of a retinal Schiff base of *t*-butylamine is given below.



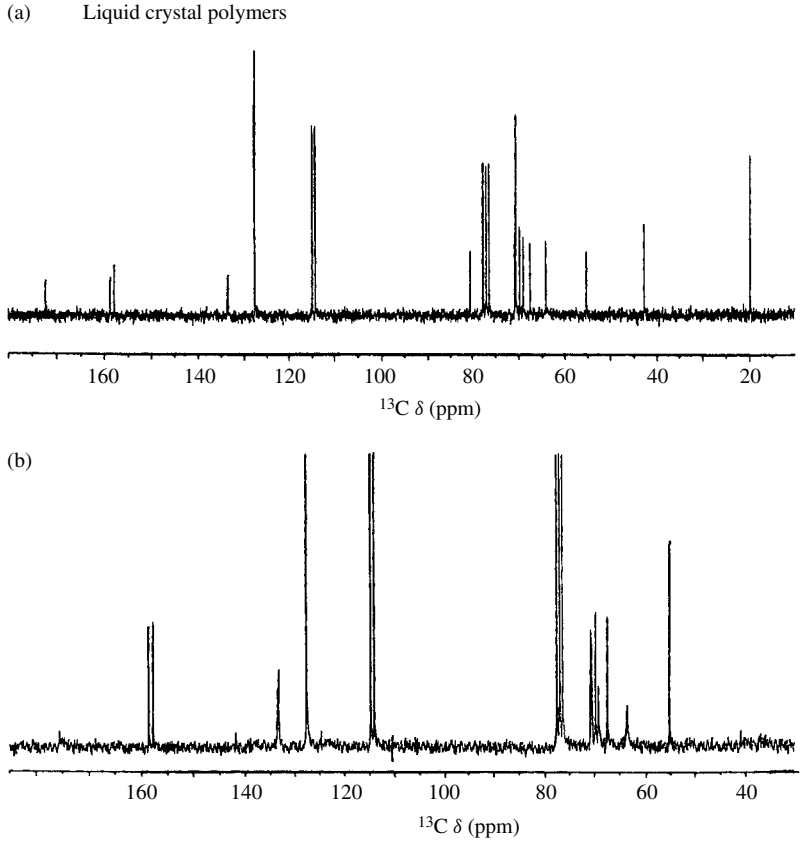


FIGURE 9. ^{13}C NMR spectrum of (a): **50** and (b): **52** in $CDCl_3$. Reproduced by permission of Marcel Dekker, Inc. from Reference 35

Blatz and Mohler[38] have performed 2D NOE NMR experiments on the protonated *t*-butylamine Schiff base of all-*trans*-retinal using different counterions, each carrying at least one nonexchangeable proton. The study has indicated that a proton on the counterion molecule is spatially close, in aprotic solvents, to the protons of the chromophore near the positively charged nitrogen. It has also shown that the ion-pair formation is relaxed in either the presence of excess carboxylic acid (the counterion) or when using methanol as a solvent.

Experiments were performed at 5 °C in order to arrest the *cis–trans* isomerization of the protonated Schiff base. Spectra with one equivalent of acid and different mixing times showed one NOE cross-peak between H15 of the retinal molecule and the proton on the counterion, as shown for a mixing time of 0.4 s in Figure 10. The strong chemical shift dependence of the H15 resonance on the concentration of the acid dictated the use of less than one equivalent of the protonating formic acid, and therefore an incomplete protonation (>80%) of the retinal, in order to avoid an overlap between the formate and the H15 peaks in the spectrum. This should not affect the observed result since an average chemical shift, between those of H15 of the retinal in its nonprotonated and protonated

states, was observed, suggesting a fast exchange. Electrostatic considerations imply that the formate counterion will only interact with the charged protonated retinal Schiff base molecules.

The discrepancy between the intensities of the signals of the formyl proton and of H15 (Figure 10) arises from the large difference in the relaxation times of the two molecules. This has a more pronounced effect on the observed intensity in the 2D NMR projection than in the normal NMR spectrum.

Using two-dimensional NMR spectroscopy, the spatial location of various carboxylate anions relative to the polyene chain of the protonated Schiff base of all-*trans*-retinal was determined. The observed intermolecular NOE cross-peaks between a proton on the counterion and a proton near the nitrogen atom indicate the existence of ion-pair formation between the protonated retinal Schiff base and various counterions in chloroform. The results suggest that the most likely site of the carboxylate group of the counterion is in the immediate vicinity of the positively charged nitrogen atom of the retinal Schiff base.

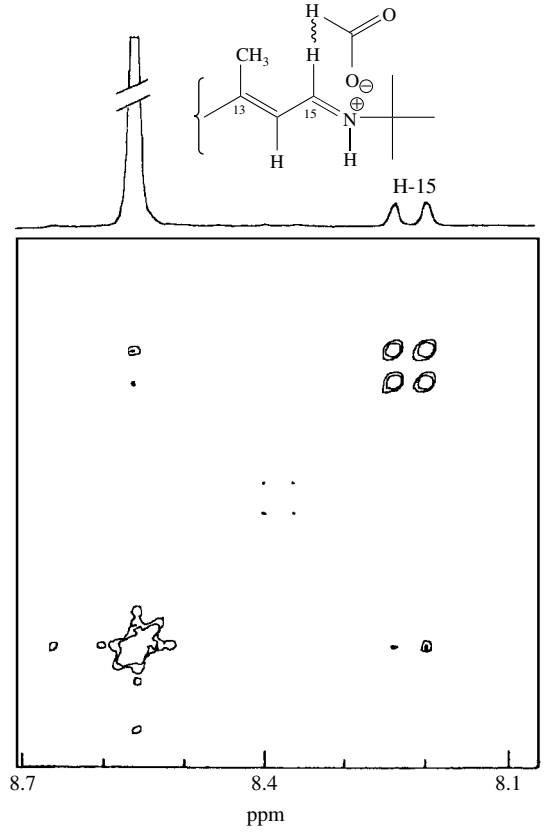


FIGURE 10. Contour plot of two-dimensional nuclear Overhauser effect ^{1}H NMR (NOESY) of the protonated Schiff base of all-*trans*-retinal, in chloroform, with formate as the counterion. The intermolecular NOE cross-peak observed between H15 of the retinal and the counterion proton, at a mixing time of 0.4 s, is shown. Top trace: f_2 projection of the 2D NOE spectrum. Reproduced by permission of John Wiley & Sons from Reference 36

Li and coworkers[39] reported the production of new polyene antibiotics. Ethyl (*Z*)-16-phenylhexadeca-9-enoate **(56)**, an analog of ethyl oleate **(55)**, was synthesized and added to cultures of *Streptomyces cellulosae* ATC C12625, which normally produce fungichromin **(54)** as the principal polyene antibiotic (Figure 11). These cultures showed drastic reduction of fungichromin biosynthesis but afforded four new polyene antibiotics with a truncated four-carbon side chain which are designated as isochainin **(58)** [an isomer of chainin **(57)**], 14-hydroxyisochainin **(59)**, 1′-hydroxyisochainin **(60)** and 1′,14-dihydroxyisochainin **(61)**. The close correspondence of ^{13}C NMR chemical shifts between these compounds and fungichromin and the coproduction of compounds **58–61** and fungichromin **(54)** suggest that the stereochemistry at every site is exactly analogous (Table 15).

Recently, the absolute stereochemistry of pentamycin, an antibiotic from *Streptomyces pentaticus* with the same gross structure as fungichromin **(54)**, has been reported as being either **62a** or **62b**. Elucidation of the stereochemical relationship between pentamycin **(62)**

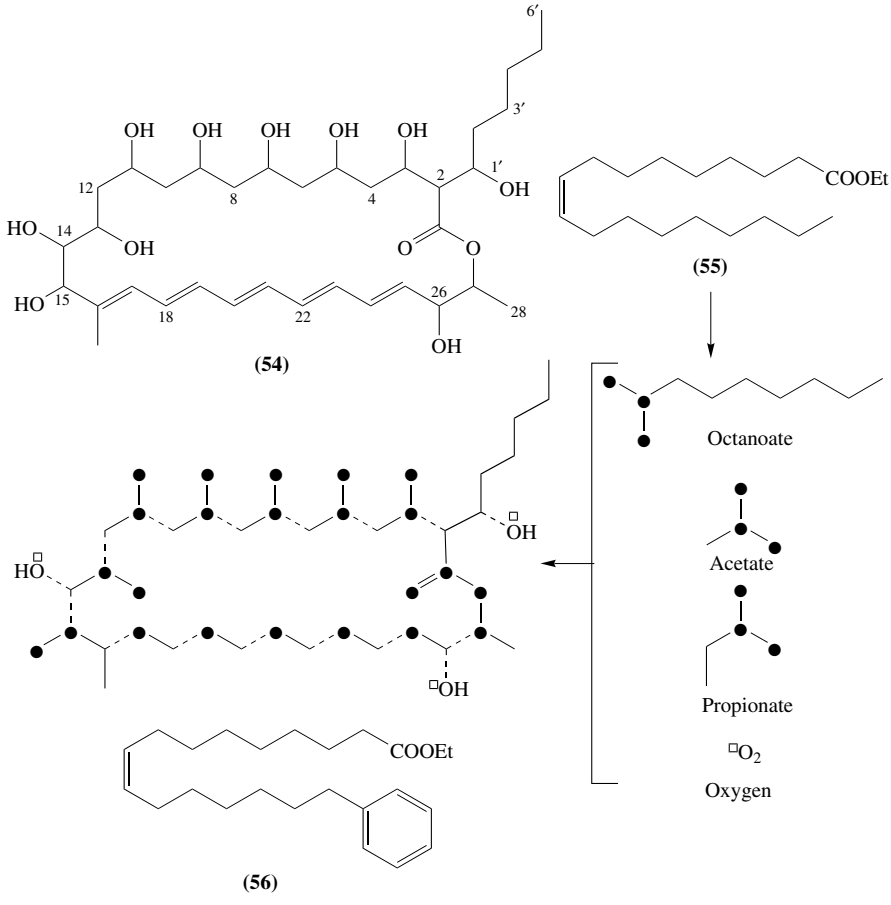


FIGURE 11. Biosynthetic origin of fungichromic **(54)** and structure of oleate analog **(56)**. Reproduced by permission of Japan Antibiotics Research Association from Reference 39

TABLE 15. ^{13}C chemical shifts (δ) for fungichromin **(54)**, isochainin **(58)**, 14-hydroxyisochainin **(59)**, 1′-hydroxyisochainin **(60)** and 1′,14′-dihydroisochainin **(61)**[a]

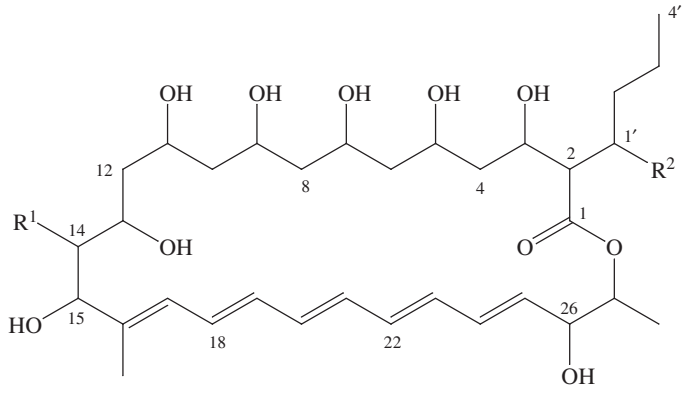
Carbon	**54**	**58**	**59**	**60**	**61**
29	11.74	11.45	11.80	11.08	11.70
6′	14.38	—	—	—	—
28	17.96	18.29	18.30	17.95	17.91
5′	23.65	—	—	—	—
3′	26.01	23.60	23.61	19.51	19.52
4′	32.88	14.21	14.25	14.23	14.23
2′	36.22	29.87	30.18	38.36	38.40
12	39.58	42.52	39.50	41.58	39.54
4	41.38	42.70	42.33	42.86	41.34
10	44.34	44.20	44.15	44.18	44.36
6	45.17	44.91	44.83	45.17	45.21
8	45.33	45.11	45.16	45.26	45.36
2	60.35	54.26	54.40	60.31	60.46
13	70.34	67.50	70.26	67.47	70.38
11	71.45	71.00	71.35	71.12	71.46
1′	72.59	30.60	30.57	72.28	72.21
26	73.25	73.15	73.44	73.15	73.30
3	73.41	73.29	73.55	73.60	73.30
7	73.92	73.38	73.56	73.65	73.90
5	74.08	73.55	73.64	73.65	74.08
9	74.20	74.24	74.02	73.91	74.17
27	75.25	74.47	74.58	75.10	75.25
14	78.31	45.21	78.20	45.29	78.32
15	80.43	75.63	80.32	75.83	80.50
18	129.06	128.04	129.25	128.35	129.05
17	129.91	129.57	129.79	129.31	129.93
24	131.97	132.43	131.99	132.25	132.03
22	133.66	133.62	133.74	133.82	133.67
20	134.13	134.15	133.96	134.12	134.13
23	134.21	134.19	134.32	134.12	134.17
25	134.28	134.44	134.37	134.28	134.27
21	134.81	134.57	134.45	134.59	134.85
19	135.36	134.68	135.18	134.96	135.41
16	138.55	140.64	138.71	140.34	138.53
1	172.98	175.43	175.37	173.02	173.01

[a] 100.6 MHz ^{13}C NMR spectrum in methanol-d_4 with solvent reference at 49.00 ppm.

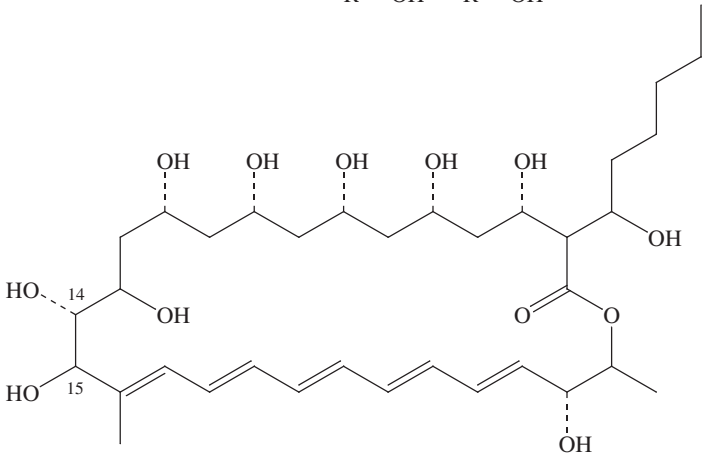
and fungichromin **(54)** should allow stereochemical assignment of isochainin **(58)** and its hydroxylated derivatives **59–61** with reasonable confidence.

Sowinski and coworkers[40] reported a structure of vacidin A **(63)**, an aromatic heptaene macrolide antibiotic. The constitution of vacidin A, a representative of the aromatic heptaene macrolide antibiotics, was established on the basis of ^{13}C and $^{1}H-^{1}H$ double quantum filtered correlated spectroscopy, rotating frame nuclear Overhauser effect spectroscopy, *J*-resolved ^{1}H as well as $^{1}H-^{13}C$ correlation NMR spectra. The geometry of the polyene chromophore was determined as 22*E*, 24*E*, 26*E*, 28*Z*, 30*Z*, 32*E*, 34*E*.

The ^{13}C NMR spectrum of **64**, an amide of **63**, showed sixty-two carbon signals of which partial assignments, shown in Table 16, were made based upon distortionless enhancement by polarization transfer(DEPT), $^{1}H-^{13}C$ correlation experiments and literature data describing ^{13}C NMR analysis of polyene macrolides.



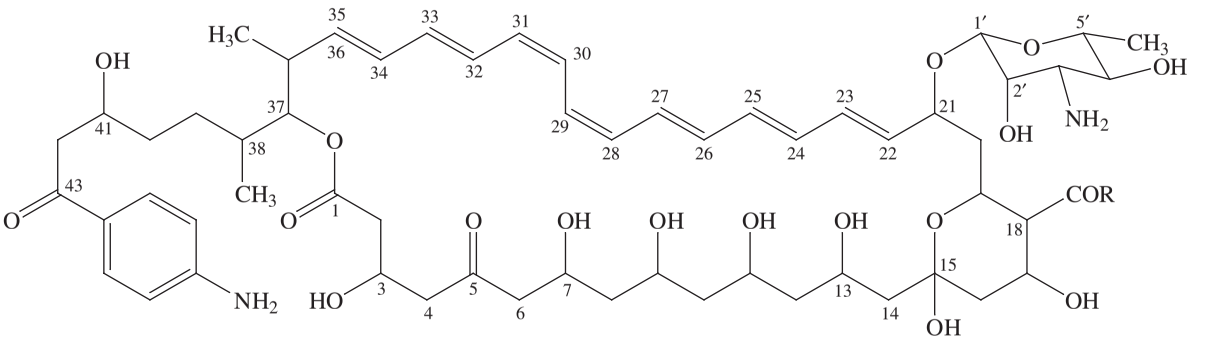
Chainin	**(57)**	$R^1 = H$	$R^2 = H$
Isochainin	**(58)**	$R^1 = H$	$R^2 = H$
	(59)	$R^1 = OH$	$R^2 = H$
	(60)	$R^1 = H$	$R^2 = OH$
	(61)	$R^1 = OH$	$R^2 = OH$



(62a) 14-OH is in a dashed line and 15-OH in a full bond
(62b) 14-OH is in a full line and 15-OH in a dashed bond

The data from ^{1}H NMR studies of **63**, which included double quantum filtered phase sensitive correlated spectroscopy (DQF-COSY) and rotating frame nuclear Overhauser effect spectroscopy (ROESY) experiments (Figure 12), are collected in Table 17.

The latter, in contrast to nuclear Overhauser enhancement and exchange spectroscopy (NOESY), always feature positive NOEs (negative cross-peaks with respect to diagonal), eliminating known problems of NOEs vanishing or spin diffusion, depending on correlation time, when high field spectrometers are used for measurements of medium-size compounds.



vacidin A (**63**) R = OH
vacidin A methoxycarbonylmethylamide (**64**) R = $NHCH_2COOCH_3$

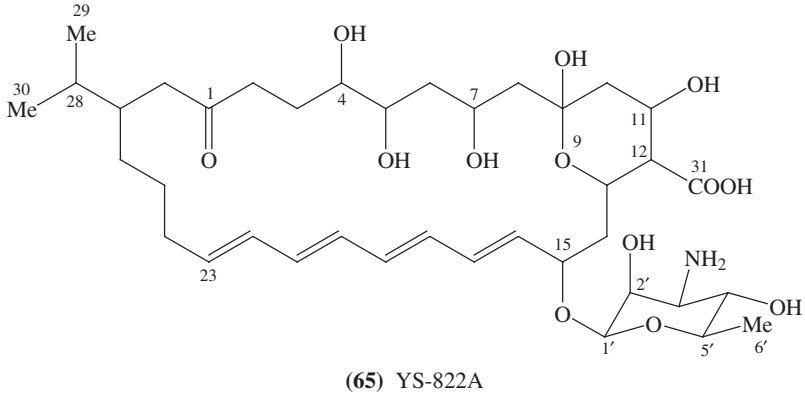
TABLE 16. ^{13}C NMR data for vacidin A methoxycarbonylmethylamide **(64)**

Description	No. of carbon atoms	δ (ppm)	Description	No. of carbon atoms	δ (ppm)
CH_3	4	13.5, 16.7, 18.6, 52.4	C27		128.58
CH_2	13	31–52	C28		130.91
CH:			C29		125.53
$CHCH_3$	2	34.3, 40.4	C30 (C24)		125.28
$CHNH_2$	1	57.9	C31		130.84
CHCONHR	1	59.3	C32		128.62
CHOR	13	64–79	C33 (C23)		134.42
Acetal	1	97.7	C34		133.67
CH Ar	4	113.7, 131.6	C35		137.88
=CH–			Nonprotonated:		
(olefinic)[a]:C22		113.67	Hemiketal	1	98.2
C23 (C33)		130.00	C Ar	2	127.0, 171.2
C24 (C30)		134.80	COXR	3	171.8, 174.6, 174.7
C25		133.10	C=O	2	198.1, 208.9
C26		135.64			

[a]Assignment by H, C-COSY. Interchangeable assignments are shown in parentheses.

The coupling constants listed in Table 17 were assigned on the basis of the 1D ^1H NMR spectrum of **63**, but for a few cases the analysis of phase structure of the cross-peaks in the DQF-COSY spectrum was carried out to attribute correct values to the appropriate protons. Also, the analysis of the NOE effects yields the same results (Figure 13).

Hirota and coworkers[41] reported a planar structure of new polyene macrolide antibiotic YS-822A **(65)**, which they isolated. ^1H and ^{13}C NMR spectra of **65** showed a number of broad and overlapping signals, but the $^1H-^1H$ and $^{13}C-^1H$ COSY spectra implied the existence of a mycosamine moiety and several other partial structures. The connectivity of these partial structures was established by extensive 2D NMR experiments, including homonuclear Hartmann–Hahn and heteronuclear multiple-bond connectivity measurements, which led to the determination of the gross planar structure of **65**.



(65) YS-822A

Although 1D ^1H and ^{13}C NMR spectra of **65** in DMSO-d_6 showed a number of broad and overlapping signals, the $^{13}C-^1H$ COSY spectrum afforded the assignment

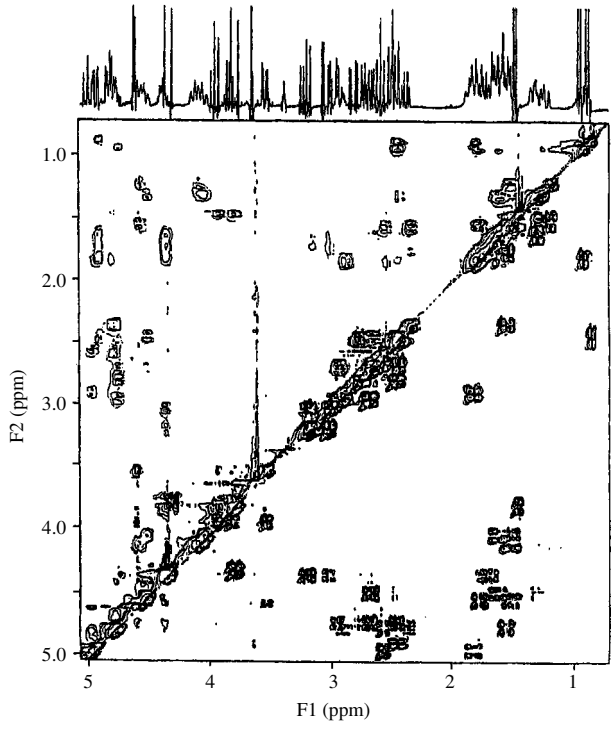


FIGURE 12. Spectra of vacidin A methoxycarbonylmethylamide **64**. Spectral region 0.72–5.06 ppm of 300 MHz ROESY (upper triangle) and DQF-COSY (lower triangle) spectra of VacGlyOMe (15 mg ml^{-1}, pyridine-d_5-methanol-d_4, 9 : 1) combined along the diagonal. Reproduced by permission of Japan Antibiotics Research Association from Reference 40

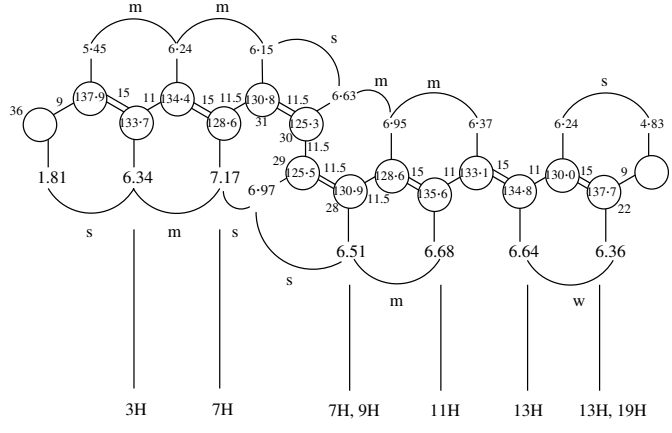


FIGURE 13. Polyene part of vacidin A. NOE's, J(HH) and ^{1}H, and ^{13}C chemical shifts. Reproduced by permission of Japan Antibiotics Research Association from Reference 40

TABLE 17. ^{1}H NMR data for the vacidin A and NOE effects[a]

No. of proton	δ (ppm)	J(HH) (Hz) (coupling partner)	NOE to protons (intensity)
2a	2.80	15.1 (2b), 3.7 (3)	3 (m)
2b	2.45	15.1 (2a), 9.3 (3)	3 (w)
3	4.78	9.3 (2b), 8.1 (4b), 5.6 (4a), 3.7 (2a)	38-CH_3 (w), 2a (m), 4a (m), 4b (m), 2b (w), 34 (m)
4a	2.96	17.5 (4b), 5.6 (3)	3 (m), 4b (s)
4b	2.68	17.5 (4a), 8.1 (3)	3 (m), 4a (s)
6a	2.68	16.8 (6b), 9.6 (7)	6b (s), 8a (w)
6b	2.44	16.8 (6a), ~2 (7)	6a (s), 8b (w), 7 (m)
7	4.54	9.6 (6a), 9.6 (8a), ~2 (6b), ~2 (8b)	8b (m), 6b (m), 9 (s), 28(m), 29(m)
8a	1.62	~ 13 (8b), 9.6 (7), 10.0 (9)	6a (w)
8b	1.30	~ 13 (8a), ~2 (7), ~2 (9)	7 (m), [c](m), 6b (w)
9	4.06	10.0 (8a), 10.0 (10a), ~2 (8b), ~2 (10b)	[10b or 8b] [c](m), 7 (s), 28 (m)
10a	1.51	~13 (10b), 10.0 (9), 10.3 (11)	
10b	1.27	~13 (10a), ~2 (9), ~2 (11)	[c](m), [d](m)
11	4.11	10.3 (10a), 10.3 (12a), ~2 (10b), ~2 (12b)	[12b or 10b] [d](m), 13 (s), 26 (m)
12a	1.51	10.3 (11), 10.5 (13), 13.5 (12b),	
12b	1.21	~2 (11), ~2 (13), 13.5 (12a)	13 (m), [d](m)
13	4.59	10.5 (12a), 10.5 (14a)[b], 2 (12b), 2 (14b)[b]	12b (m), 14b (w), 11 (s), 23 (w), 22 (m), 24 (m)
14a	1.78	10.5 (13)	16a (w)
14b	1.54	2 (13)	13 (m)
16a	2.35	12.2 (16b), 4.7 (17)	16b (m), 14a (w), 17 (m)
16b	1.56	12.2 (16a), 10.3 (17)	18 (m), 16a (m)
17	4.82	10.3 (16b), 10.3 (18)	16a (m), 18 (m), 19 (m)
18	2.56	10.3 (17), 10.1 (19)	16b (m), 20b (w), 19 (m), 17(m)
19	5.00	10.1 (18), 10.1 (20b)[b]	18 (m), 20 (m), 2′ (m), 1′ (m), 17 (m), 23 (w), 22 (m)
20a	2.90	~9 (21)	20b (m), 21 (w), 19 (m), 1′ (m)
20b	1.82	10.1 (19)	18 (w), 21 (w), 20 (m)
21	4.83	9 (22), ~9 (20a)[b]	20a (w), 20b (w), 1′ (s), 23 (s), 22 (m)
22	6.36	9 (21), 15 (23)	19 (m), 21 (m), 24 (w), 13 (m)
23	6.24	11 (24), 15 (22)	19 (w), 21 (s), 13 (w), [24 or 30 or none] [e](w)
24	6.64	11 (25), 15 (23)	13 (m), 22 (w), [e](w)
25	6.37	11 (26), 15 (24)	27 (m)
26	6.68	11 (25), 15 (27)	11 (m), 28 (m)
27	6.95	11.5 (28), 15(26)	30 (m), 25 (m)
28	6.51	11.5 (27), 11.5 (29)	7 (m), 9(m), 26 (m), 29 (s)
29	6.97	11.5 (28), 11.5 (30)	7 (m), 28 (s), 32 (s)
30	6.63	11.5 (29), 11.5 (31)	31 (s), 27 (m), [33 or 23 or none] [e](w)
31	6.15	11.5 (30), 11.5 (32)	33 (m), 30 (s)
32	7.17	11.5 (31), 15 (33)	34 (m), 33 (w), 29 (s)
33	6.24	11 (34), 15 (32)	35 (m), 31 (m), 32 (w), [e](w)
34	6.34	11 (33), 15 (35)	35 (m), 3 (m), 36 (s), 32 (m)

(*continued overleaf*)

TABLE 17. (*continued*)

No. of proton	δ (ppm)	J(HH) (Hz) (coupling partner)	NOE to protons (intensity)
35	5.45	9 (36), 15 (34)	36-CH_3 (m),37 (m), 33 (m), 34 (m)
36	1.81	9 (35), 9.8 (37)	38-CH_3 (m), 36-CH_3 (m), 38(w),37 (m), 34 (s)
37	4.94	9.8 (36), 2.2 (38)	36-CH_3 (m), 38 (m), [40 or 39] [f] (m), 36 (m), 35 (m)
38	1.81	6.7 (39)[g], 2.2 (37)[g]	36-CH_3 (m), 38-CH_3 (m), 36 (w), 37 (m)
39a	1.61		[f] (m)
39b			
40a	1.70		[f] (m)
40b			
41	4.37	8.1 (42a), 4.2 (42b)	40a/b (m), 42a (m), 42b (m)
42a	3.20	15.6 (42b), 8.1 (41)	41 (m), 42b (s)
42b	3.02	15.6 (42a), 4.2 (41)	41 (m), 42a (s)
36-CH_3	0.87	6.6 (36)	35 (w), 37 (m), 38 (m), 36 (m)
38-CH_3	0.94	6.8 (38)	3 (w), 38 (m), [39 or 40] [f] (m), 36 (m)
1′	5.14	~0 (2′)	20a (m), 3′ (s), 5′ (s), 2′ (s), 21 (s), 19 (m)
2′	4.63	3.3 (3′), 0 (1′)	3′ (s), 1′ (s), 19 (m)
3′	3.55	9.7 (4′), 3.3 (3′)	1′ (s), 2′ (s)
4′	3.97	9.7 (3′), 9.7 (5′)	6′ (m)
5′	3.82	9.7 (4′), 5.9 (6′)	6′ (m), 1′ (s)
6′	1.45	5.9 (5′)	4′ (m), 5′ (m)
Aromatic	6.81	8.6	
protons	7.95	8.6	
Glycine methyl ester protons			
OCH_3	3.66 (s)		
CH_2	3.81/4.35	17.6	

[a] NOE scale: 100% for CH_2CO; 10–20% (w), 20–75% (m), 75–200% (s).

[b] The correct values of coupling constants were attributed to the appropriate protons by the analysis of antiphase structures of cross-peaks in DQF-COSY spectrum.

[c] H10a and H8b have nearly the same chemical shifts. NOE between (H10b or/and H8b) and H9.

[d] H12b and H10b have nearly the same chemical shifts. NOE between (H12b or/and H10b) and 11-H.

[e] The pairs H23, H33 and H24, H30 have nearly the same chemical shifts. NOE between (H23 or H33) and (H24 or H30).

[f] H39 and H40 have nearly the same chemical shifts. NOE between (H39 or/and H40) and H37.

[g] Values from ^{1}H NMR spectrum in 35% DMSO-d_6 in methanol-d_4.

of directly bonded carbons and protons (see Table 18), and the ^{1}H–^{1}H COSY (see Figure 14) spectrum implied the existence of several partial structures (A, B, C, D and E) as shown in Figure 15). The presence of mycosamine moiety (a partial structure A) was deduced from ^{1}H–^{1}H COSY correlation peaks [H1′(δ4.55)/H2′(δ3.80), H2′/H3′(δ2.92), H3′/H4′(δ3.22), H4′/H5′(δ3.32), and H5′/Me6′(δ1.17)], and comparison of its ^{1}H and ^{13}C chemical shifts. One side of the all-*trans*-tetraene moiety, the presence of which was predicted from the UV spectrum and was confirmed by these NMR spectra, was

TABLE 18. ^{13}C and ^{1}H NMR data for YS-882A **(65)**

Carbon	^{13}C	^{1}H	Carbon	^{13}C	^{1}H
1	173.2 s		20	131.8 d	6.28
2	30.7 t	2.38, 2.52	21	131.5 d	6.15
3	28.1 t	1.65, 1.75	22	130.9 d	5.95
4	72.2 d	3.20	23	133.4 d	5.73
5	72.7 d	3.55	24	29.8 t	1.98, 2.10
6	38.9 t	1.42, 1.58	25	24.4 t	1.20, 1.48
7	67.4 d	4.31	26	29.8 t	1.45, 1.55
8	45.8 t	1.55, 1.61	27	76.0 d	4.78
9	97.0 s		28	31.4 d	1.75
10	44.3 t	1.10, 1.85	29	17.7 q	0.84 (3H, d, $J = 7$ Hz)
11	65.6 d	4.00	30	18.5 q	0.86 (3H, d, $J = 7$ Hz)
12	58.8 d	1.82	31	177.5 s	
13	65.2 d	4.20	1′	95.4 d	4.55
14	36.1 t	1.45, 2.18	2′	67.8 d	3.80
15	74.0 d	4.40	3′	56.2 d	2.92
16	136.2 d	6.05	4′	69.6 d	3.22
17	128.3 d	6.12	5′	72.4 d	3.32
18	132.9 d	6.35	6′	17.9 q	1.17 (3H, d, $J = 6$ Hz)
19	131.2 d	6.20			

attached with a methylene (δ_C 29.8 t, δ_H 1.98 and 2.10), which was in turn connected with a methylene (δ_{C2} 4.4 t, δ_H 1.20 and 1.48). The other side of the tetraene moiety was connected with a methine (δ_{C7} 4.0 d, δ_H 4.40; adjacent to an oxygen), and it was probable from the $^{1}H-^{1}H$ COSY spectrum that this methine was connected with a unit consisting of two methylenes and three methines to compose a partial structure B. The partial structures C and D were also deduced from $^{1}H-^{1}H$ COSY correlations, even though there were several severely overlapping signals; for example there were 11 proton signals between δ_H 1.4 and 1.8. The ambiguity and the poor reliability of the assignments and proposed partial structures C and D were dissolved by homonuclear Hartmann–Hahn (HOHAHA) and heteronuclear multiple-bond connectivity (HMBC) spectra. HOHAHA and HMBC measurements not only confirmed the deductions above but also connected all the remaining fragments and quaternary carbons (Figure 16). That is, the distinct correlation peaks of a carbonyl carbon (C1; δ173.2) with H2 (δ2.38 and 2.52) and H27 (δ4.78) appeared on the HMBC spectrum, which established the connection between partial structures C and D through an ester group. In the HOHAHA spectrum, a methine proton at δ4.78 (H27) showed correlation peaks with protons at δ1.98 and 2.10 (H24) through 1.45 and 1.55 (H26), and 1.20 and 1.48 (H25), and two methyl protons at δ0.84 and 0.86 through 1.75 (H28), which not only confirmed the partial structure D but also established the connection between D and B. Correlation peaks between C15 (δ74.0) and H1′ (δ4.55) and between C31 (δ177.5) and H12 (δ1.82) on the HMBC spectrum supported the partial structure E.

YS-822A had nine degrees of unsaturation, all of which have already been assigned to four double bonds, two carbonyls (a lactone and a carboxylic acid) and three rings. Consequently, all the oxygen functional groups at C should be hydroxyls. Thus, the planar structure of YS-822A was determined as **65**.

Gebhard and coworkers[42] reported a synthesis and spectroscopy of chemically modified spheroidenes. The structure and numbering of the system is shown in **66**. The syntheses and spectroscopic properties of the all-*E* isomers of 11′,12′-dihydrospheroidene **(67)**,

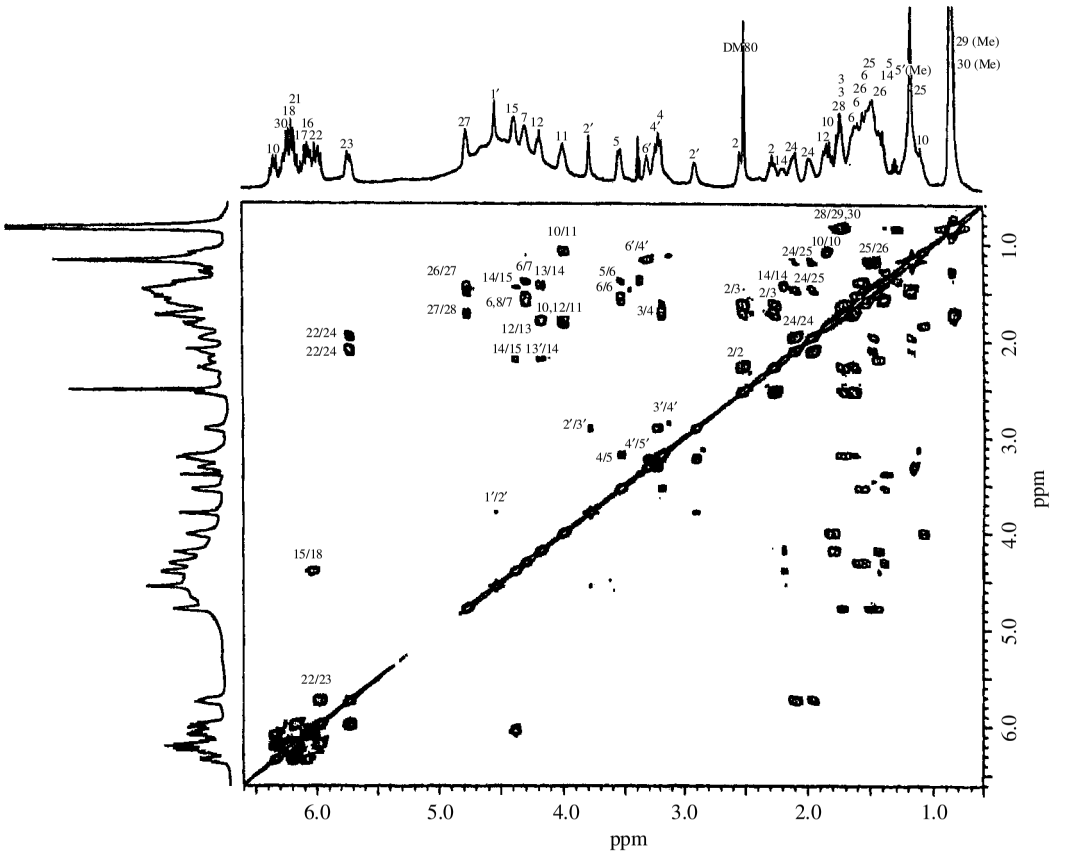


FIGURE 14. $^{1}H-^{1}H$ COSY spectrum of YS-822A **(65)** in DMSO-d_6(300 K). Reproduced by permission of Japan Antibiotics Research Association from Reference 41

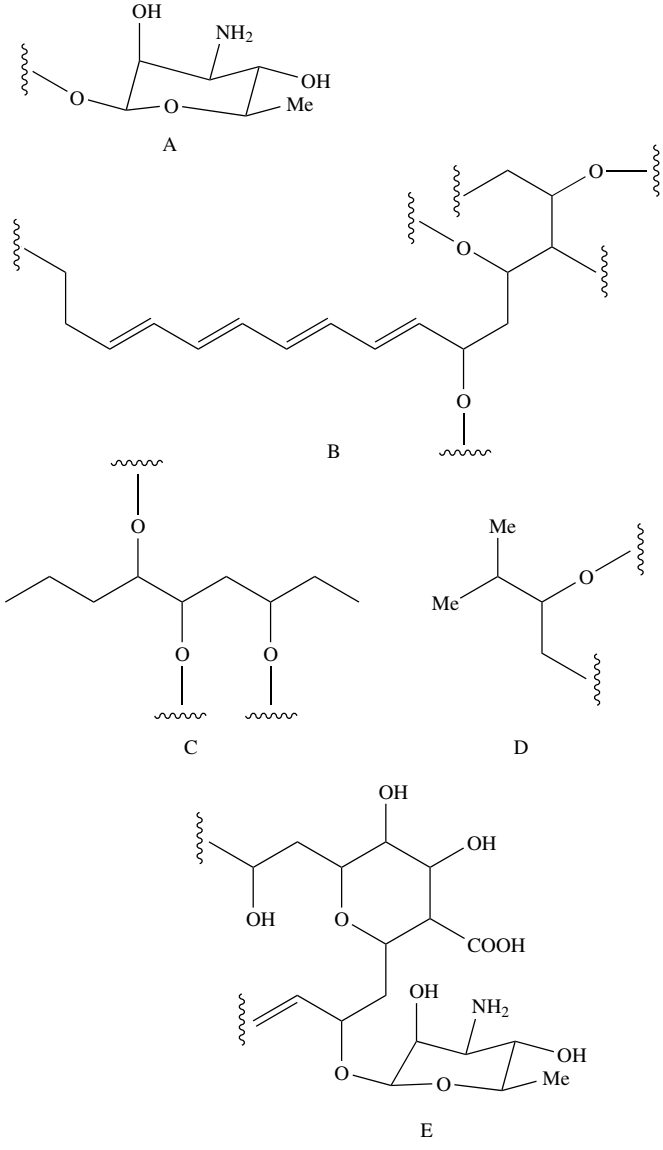


FIGURE 15. Partial structures of YS-822A **(65)**. Reproduced by permission of Japan Antibiotics Research Association from Reference 41

3,4,11′,12′-tetrahydrospheroidene **(68)**, 3,4-dihydrospheroidene **(69)**, 3,4,5,6-tetrahydrospheroidene **(70)**, 3,4,7,8-tetrahydrospheroidene **(71)** and 15,15′-didehydrospheroidene **(72)** are described.

Spheroidenes **67**–**71** have the same overall shape as native all-*trans* spheroidene **(66)**, which is the carotenoid bound in the photosynthetic reaction center of *Rhodobacter*

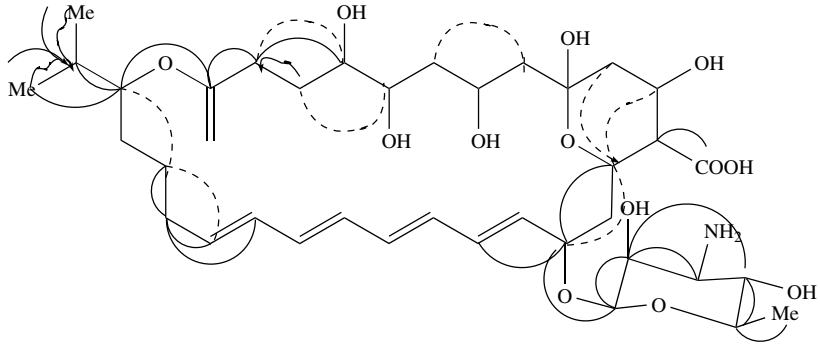


FIGURE 16. Results of HMBC and $^{1}H-^{1}H$ HOHAHA measurements of YS-822A in DMSO-d_6(300 K). Solid arrows denote correlation peaks between carbons (tail) and protons (head) in the HMBC spectrum. Dotted lines indicate $^{1}H-^{1}H$ HOHAHA correlations after removal of $^{1}H-^{1}H$ COSY ones. Reproduced by permission of Japan Antibiotics Research Association from Reference 41

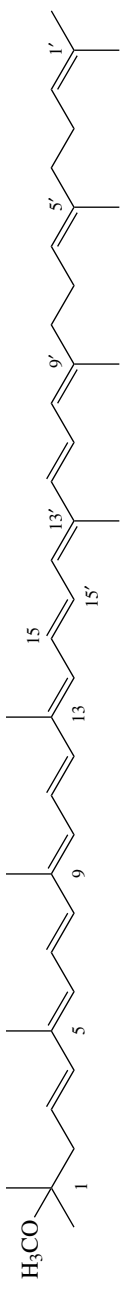
sphaeroides. They have instead polyene chromophores of nine **(69)**, eight **(67, 70)** or seven **(68, 71)** conjugated double bonds. In **72**, the central double bond is substituted by a triple bond. A detailed analysis of the ^{1}H and ^{13}C NMR spectra of **66**–**72** has been achieved by mutual comparison.

The 300 MHz ^{1}H NMR spectra of the all-*E* isomers of **67**–**72** were measured in $CDCl_3$. The signals were assigned using the COSY technique. The chemical shift values and the values of the coupling constants are completely in agreement with their all-*trans* structures and are summarized in Tables 19 and 20, respectively, together with the values for **66** which are included for comparison.

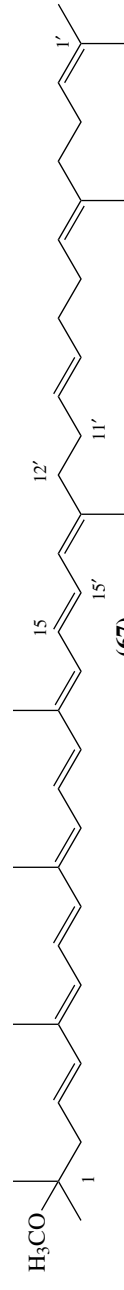
As can be seen from Table 19, the saturation between C11′ and C12′ in **67** causes an upfield shift of H14′ (*ca* 0.2 ppm) and of H15 and H15′ (*ca* 0.1 ppm) compared with **66**. The remaining polyene protons in **67** are only slightly affected. Similar features are observed upon comparison of the chemical shift values of the protons of the polyene chains of **68**, **69**, **70** and **71** with those of **66**. Thus, saturation of a double bond in a polyene chain generally leads to an upfield shift of *ca* 0.2 ppm for the protons connected to the γ- and the δ-carbons; the upfield shift of the remaining polyene protons is generally less than 0.05 ppm. Comparison of the chemical shift values of **72** with those of **66** shows that the introduction of the 15,15′-triple bond in **72** leads to an upfield shift of the signals of H14 and H14′ (*ca* 0.5 ppm), whereas the chemical shift values of the other polyene protons are only slightly affected.

In the ^{1}H-noise-decoupled 75 MHz ^{13}C NMR spectra of the all-*trans* isomers of **67**–**70** and **72**, the expected 40 different signals are present. In the spectrum of 3,4,7,8-tetrahydrospheroidene **(71)**, only 29 separated signals are observed due to the almost perfect twofold symmetry of the C7–C7′ part of the molecule. The signals of the proton-bearing carbon atoms were assigned using the attached proton test (ATP) and the $^{13}C-^{1}H$ correlated technique. The signals of the quaternary carbon atoms were assigned by comparison with the spectrum of **66** and by using chemical shift increments. The ^{13}C chemical shift values of **67**–**72** are completely in agreement with the all-*E* structures of **67**–**72** and are collected with their assignments in Table 21. For comparison, the chemical shift values of **66** and the chemical shift differences between **67**–**72** and **66** are also given.

In the spectrum of **67**, the signals of C11′ and C12′ (changed to sp^3 hybridization from sp^2) are shifted to the high-field part of the spectrum, i.e. the saturation of the 11′, 12′



(66)



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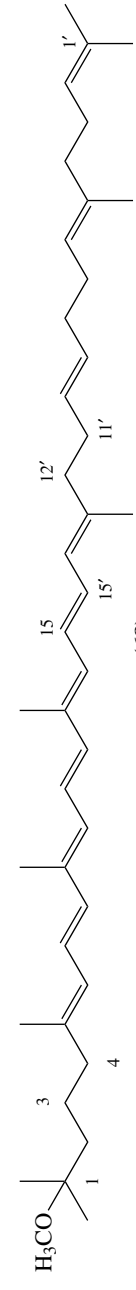


(68)

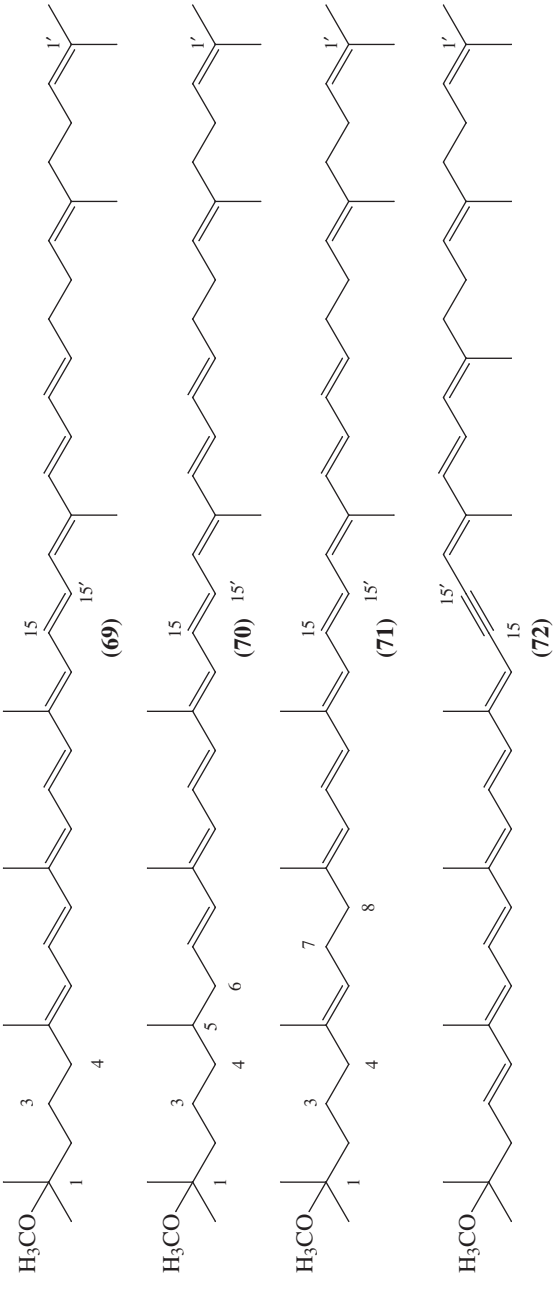

H3CO
1
3
4
15
15′
1′
(69)
H3CO
1
3
4
5
6
15
15′
1′
(70)
H3CO
1
3
4
7
8
15
15′
1′
(71)
H3CO
1
15′
15
1′
(72)

TABLE 19. ^{1}H NMR chemical shift values (ppm) of all-*E* **66–72**[a]

H	**66**	**67**	**68**	**69**	**70**	**71**	**72**
2	2.32	2.32	1.45	1.45	1.30	1.40	2.32
3	5.72	5.71	1.45	1.45	1.30	1.40	5.73
4	6.16	6.15	2.10	2.10	1.15/1.3	1.95	6.16
5	—	—	—	—	1.54	—	—
6	6.11	6.10	5.96 (−0.15)	5.95 (−0.16)	1.95/2.1	5.12	6.10
7	6.60	6.58	6.47 (−0.13)	6.50 (−0.10)	5.69 (+0.09)	2.10	6.63
8	6.35	6.34	6.24 (−0.09)	6.24 (−0.09)	6.12 (−0.23)	2.10	6.33
10	6.22	6.21	6.17	6.18	6.09 (−0.13)	5.95 (−0.27)	6.19
11	6.63	6.59	6.59	6.62	6.59	6.48 (−0.15)	6.38 (+0.07)
12	6.37	6.35	6.34	6.35	6.33	6.24 (−0.13)	6.38
14	6.26	6.21	6.19 (−0.07)	6.27	6.23	6.19 (−0.07)	5.72 (−0.54)
15	6.61	6.49 (−0.12)	6.49 (−0.12)	6.61	6.60	6.59	—
15′	6.62	6.49 (−0.13)	6.49 (−0.13)	6.61	6.60	6.59	—
14′	6.20	5.98 (−0.22)	5.96 (−0.24)	6.22	6.19	6.19	5.68 (−0.52)
12′	6.23	2.12	2.12	6.25	6.24	6.24	6.25
11′	6.50	2.05	2.06	6.48	6.50	6.48	6.57 (+0.07)
10′	5.95	5.10	5.10	5.95	5.95	5.95	5.93
8′	2.12	2.05	2.05	2.10	2.15	2.10	2.05
7′	2.05	2.05	2.05	2.10	2.05	2.10	2.05
6′	5.12	5.10	5.10	5.10	5.12	5.12	5.12
4′	2.05	2.05	2.05	2.10	2.05	2.10	2.05
3′	2.05	2.05	2.05	2.10	2.05	2.10	2.05
2′	5.10	5.10	5.10	5.10	5.10	5.10	5.10
1-(CH_3)	1.16	1.15	1.14	1.14	1.14	1.13	1.16
5-CH_3	1.93	1.92	1.81 (−0.12)	1.81 (−0.12)	0.88	1.61 (−0.32)	1.93
9-CH_3	1.98	1.97	1.96	1.96	1.91 (−0.07)	1.82 (−0.16)	1.99
13-CH_3	1.95	1.93	1.94	1.96	1.94	1.94	2.10 (+0.15)
13′-CH_3	1.97	1.80 (−0.17)	1.81 (−0.16)	1.95	1.95	1.94	2.09 (+0.12)
9′-CH_3	1.82	1.60 (−0.22)	1.60 (−0.22)	1.82	1.82	1.82	1.83
5′-CH_3	1.61	1.60	1.60	1.60	1.61	1.61	1.62
1′-CH_3(*E*)	1.68	1.68	1.68	1.68	1.68	1.68	1.68
1′-CH_3(*Z*)	1.60	1.60	1.60	1.60	1.60	1.60	1.61
OCH_3	3.25	3.25	3.17	3.17	3.17	3.16	3.23

[a]In parentheses relevant chemical shift differences from **66** of more than ±0.05 ppm are given.

TABLE 20. Values of the $^1H-^1H$ coupling constants as obtained from the spectra of **66–72** (*, obtained by spectral simulation; nd, not determined, due to overlap of signals)

^3J(HH)	**66**	**67**	**68**	**69**	**70**	**71**	**72**
H2H1	7.5	7.4	—	—	—	—	7.4
H3H4	15.5	15.6	—	—	—	—	15.8
H6H7	11.9	11.3	10.9	11.3	6.3	—	11.3
H7H8	15.0	14.9	15.2	15.0	15.3	—	15.0
H10H11	11.3	11.3	11.3	11.7	11.2	10.9	11.3
H11H12	14.8	14.8	15.0	14.9	15.5	15.1	14.9
H14H15*	10.7	11.0	11.0	nd	11.5	11.5	—
H15H15′*	14.0	14.6	14.6	nd	14.5	14.5	—
H15′H14′*	11.0	11.0	11.0	nd	11.5	11.5	—
H13′H11′	15.0	—	—	15.2	15.1	15.1	15.1
^4J (HH)							
H14′H15*	nd	−1.1	−1.1	nd	−0.9	−0.9	—
H14H15′*	nd	−1.1	−1.1	nd	−0.9	−0.9	—

bond in **67** shows a pronounced effect on the carbon atoms of the polyene chain compared with **66**. C13′ is shifted downfield by 3.7 ppm and an upfield shift of 5.6 ppm is observed for C14′. The chemical shift values of the carbon atoms 10, 12, 14, 15′ are not affected, while an upfield shift is observed for C9 (0.4 ppm), C11 (0.5 ppm), C13 (0.6 ppm) and C15 (2.2 ppm). The 11′, 12′ single bond in **67** also affects the chemical shift of the 13′-CH_3 group: it is located 4.2 ppm downfield from the 13′-CH_3 group in **66**. As can be seen in Table 21, similar effects are observed for the chemical shifts of the polyene carbons 3, 4, 5 and 6 upon saturation of the 3, 4 bond, the 5, 6 bond and the 7, 8 bond, respectively. This effect, which has previously been noted for short polyenes, can be generalized as follows: removal of a double bond in a polyene chain leads to a downfield shift of *ca* 4 ppm of the signal of the α-carbon atom. An upfield shift is observed for the chemical shift of the β, δ and ζ olefinic carbon atoms (decreasing with increasing distance), while the chemical shift values of the γ, ϵ and η carbon atoms changed only slightly.

In the ^1H noise-decoupled 75.5 MHz ^{13}C NMR spectrum of **72**, the signals of the sp-hybridized carbon atoms C15 and C15′ are found at 98.3 and 97.3 ppm. This is in the expected region for substituted alkynes and the chemical shifts agree very well with those of other didehydrocarotenoids. As can be seen in Table 21, the 15,15′-triple bond leads to an upfield shift of *ca* 22 ppm for the directly connected C14 and C14′. The chemical shifts of the other carbon atoms of the polyene chain are also affected: a downfield shift is observed for the odd carbon atoms and a (slight) upfield shift for the even carbon atoms, both decreasing with increasing distance from the central part.

Hand and coworkers[43] reported an effect of electron-donating and electron-withdrawing substituents on ^1H and ^{13}C NMR chemical shifts of novel 7′-aryl-substituted 7′-apo-β-carotenes. Their synthesis, where aryl(Ar) is C_6F_5, 4-$O_2NC_6H_4$, 4-$(MeO_2C)C_6H_4$, 2,4,6-$Me_3C_6H_2$, Ph and 4-$MeOC_6H_4$ **(73a–f)**, was described. NMR chemical shifts of all H- and C-nuclei are presented, together with specific examples of the spectra. In contrast to ^1H chemical shifts which, except for HC8′ and HC7′, did not differ greatly from those of β,β-carotene, considerable variations in ^{13}C chemical shifts were observed.

In **73a–f**, 13 of the 14 olefinic protons give rise to ^1H NMR signals within 0.50 ppm of each other; in the spectrum of **73d** all olefinic signals fall within this range. Thus, even at relatively high frequency (360 MHz), extensive overlap occurs (Figures 17–20).

TABLE 21. ^{13}C NMR chemical shift values (ppm) of all-*E* **66–72**[a]

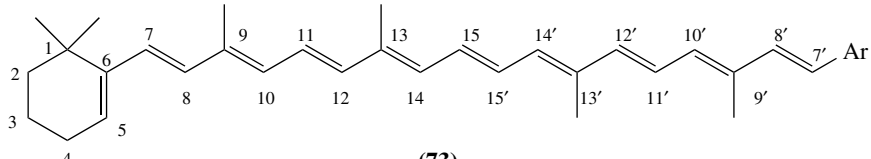
C	**66**	**67**	**68**	**69**	**70**	**71**	**72**
1	75.0	75.0	74.5	74.5	74.6	74.6	75.0
2	43.7	43.7	39.3	39.3	40.0	39.2	43.7
3	125.3	125.2	22.1	22.1	21.3	22.1	125.6 (+0.3)
4	137.5	137.5	40.5	40.5	37.2	40.1	137.5
5	135.2	135.0	139.2 (+4.0)	139.4 (+4.2)	33.5	135.4	135.7 (+0.5)
6	130.6	130.6	125.8 (−4.8)	125.7 (−4.9)	40.7	124.0	130.4
7	124.6	124.4	124.4	124.6	128.8 (+4.2)	26.7	125.3 (+0.7)
8	137.5	137.5	135.4 (−2.1)	135.4 (−2.1)	136.1 (−1.4)	40.2	137.5
9	135.9	135.5 (−0.4)	135.4 (−0.5)	136.0	135.4 (−0.5)	139.5 (+3.6)	137.2 (+1.3)
10	132.6	132.6	131.5 (−1.1)	131.6 (−1.0)	130.1 (−2.5)	125.8 (−6.8)	131.8 (−0.8)
11	124.9	124.4 (−0.5)	124.4 (−0.5)	124.9	124.8	124.9	127.0 (+2.1)
12	138.0	138.1	137.5 (−0.5)	137.4 (−0.6)	137.1 (−0.9)	135.3 (−2.7)	135.6 (−2.4)
13	136.1	135.5 (−0.6)	135.5 (−0.6)	136.1	136.1	136.1	146.3 (+10.3)[b]
14	133.0	132.8	132.5 (−0.5)	132.6 (−0.4)	132.3 (−0.7)	131.4 (−2.6)	111.0 (−22.0)
15	129.4	127.3 (−2.1)	127.3 (2.1)	129.5	129.4	129.5	98.3
15′	130.3	130.3	130.1	130.1	130.0 (−0.3)	129.5 (−0.8)	97.3
14′	131.4	125.8 (−5.6)	125.8 (−5.6)	131.4	131.4	131.4	109.6 (−22.7)
13′	136.6	140.3 (+3.7)	140.2 (+3.6)	136.5	136.4	136.1 (−0.5)	146.3 (+9.8)[b]
12′	135.2	40.2	40.2	135.3	135.3	135.3	133.0 (−2.2)
11′	125.1	26.5	26.5	125.0	125.0	124.9	127.3 (+2.2)
10′	125.8	124.1	124.2	125.8	125.8	125.8	125.3 (−0.5)
9′	139.7	134.9	134.9	139.7	139.6	139.5	141.5 (+1.8)
8′	40.2	39.7	39.7	40.2	40.2	40.2	40.2
7′	26.7	26.7	26.7	26.7	26.7	26.7	26.7
6′	123.9	123.7	123.8	123.8	123.8	123.9	123.7
5′	135.3	135.0	135.0	135.4	135.4	135.4	135.5
4′	39.7	39.7	39.7	39.7	39.7	39.7	39.7
3′	26.6	26.6	26.6	26.6	26.6	26.6	26.5
2′	124.3	124.3	124.4	124.3	124.3	124.3	124.3
1′	131.3	131.2	131.2	131.3	131.3	131.3	131.3
1-$(CH_3)_2$	24.9	24.9	25.0	25.0	25.0	25.0	24.9
5-CH_3	13.0	13.0	16.9 (+3.9)	16.8	19.6 (+6.6)	15.9	13.0

(*continued overleaf*)

TABLE 21. (*continued*)

C	**66**	**67**	**68**	**69**	**70**	**71**	**72**
9-CH_3	12.9	12.8	12.8	12.8	13.0	17.0 (+4.1)	12.9
13-CH_3	12.8	12.6	12.7	12.9	12.8	12.8	15.3
13′-CH_3	12.7	16.9 (+4.2)	16.8 (+4.1)	12.8	12.8	12.8	15.3
9′-CH_3	17.0	16.0	16.0	17.0	17.0	17.0	17.1
5′-CH_3	16.0	16.0	16.0	16.0	16.0	16.0	16.0
1′-CH_3 (*E*)	25.7	25.7	25.7	25.7	25.7	25.7	17.7
1′-CH_3 (*Z*)	17.7	17.6	17.7	17.7	17.7	17.7	25.7
OCH_3	49.3	49.3	49.1	49.1	49.1	49.1	49.3

[a] In parentheses relevant chemical shift differences from **66** of more than ±0.03 ppm are given.
[b] Might be interchanged.



(73)

(a) Ar = C_6F_5, **(b)** Ar = 4-$O_2NC_6H_4$, **(c)** Ar = 4-($MeO_2CC_6H_4$), **(d)** Ar = 2,4,6-$Me_3C_6H_2$, **(e)** Ar = Ph, **(f)** Ar = 4-$MeOC_6H_4$

The spectrum of the ester **73c** is similar to that of the unsubstituted phenyl compound **73e** (both not shown). It is noted that the chemical shift of the HC8′ reflects the electron-withdrawing properties of the substituents. A combination of 1D and 2D techniques is used to establish the assignments shown, and the chemical shift changes as compared to β,β-carotene are listed in Tables 22 and 23.

Chemical shifts of compounds **73a**, **73d** and **73f** were deduced as described for **73b**. Comparison of the data reveals certain trends that were then utilized in the analyses of the spectra of **73c** and **73e**, for which HMBC spectra were not determined. First, apparent first-order coupling constants of corresponding protons are similar; approximate values are: J(7, 8; 7′, 8′), *ca* 16; J(10, 11; 10′, 11′), *ca* 10–12; J(11, 12; 11′, 12′), *ca* 15; J(14, 15; 14′, 15′), *ca* 10; and J(15, 15′), *ca* 14 Hz. Except for J(7, 8), the coupling constants J(11, 12; 11′, 12′) are considerably larger than the others, so that the doublets due to HC12, HC12′, and HC10′ can be identified, even in regions of overlap. Second, for the paired doublets of HC7′/HC8′ in compounds **73a**, **73b**, **73f** the chemical shift of HC8′ is greater than that of HC7′. Third, for a given pair with nonprimed and corresponding primed C-nuclei,δ (no n-primed) > δ(primed) for odd-numbered C-nuclei, whereas the opposite is true for even-numbered C-nuclei. That is, those atoms that bear a formal positive charge in the resonance structures, i.e. $-[-C(\beta)^{\delta+} = C(\alpha)-]_n-Ar^{\delta-}$, are deshielded; the others are shielded. Fourth, compared with β,β-carotene, C_β atoms are in general deshielded (Table 23), while C_α nuclei are shielded. Both effects decrease in a regular, albeit nonlinear manner similar to the shift changes reported for apo-β-carotenals. Exceptions are the chemical shifts of C7′ and C8′, which are subject to anisotropy effects

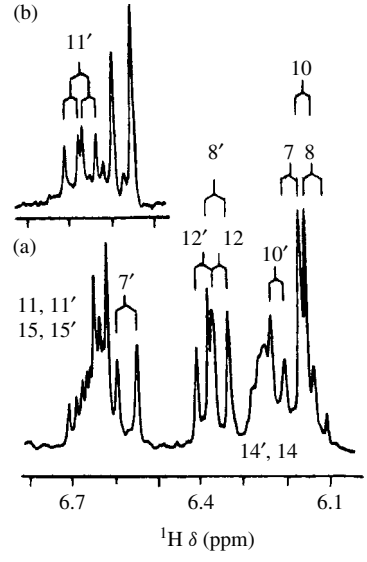


FIGURE 17. ^{1}H NMR spectra of **73d** (*ca* 25 mg ml^{-1} $CDCl_3$): (a) olefinic region and (b) NOE difference spectrum (irradiation at 2.06 ppm). Reproduced by permission of Neue Schweizerische Chemische Gesellschaft from Reference 43

(of the Ar substituent) that differ from those in β,β-carotene. The fact that all substituents, whether electron-donating or electron-withdrawing in the classical sense, cause shifts in the same direction suggests that in the polyene chain C electron densities are similar. Correlations of ^{13}C chemical shifts and electron densities (AM1 calculation) in these compounds was investigated.

^{1}H NMR data of a minor isomer of **73e** are consistent with the (7′Z)-structure that is expected on chemical grounds. Thus, the observed highfield shift of one CH_3 signal (1.70 vs 2.05 ppm) is expected if Me-C9′ lies above the plane of the Ph ring.

Further, the doublets due to HC7′ and HC8′ in the (*E*)-isomer (6.57 and 6.90 ppm) are shifted upfield (6.43 and 6.27 ppm) in the (*Z*)-isomer, as is observed in the spectra of other (*E*/*Z*)-isomers.

Yamagishi and coworkers[44] reported a structure determination of rumbrin **74**, a new cytoprotective substance. Its structure was elucidated by NMR spectral analysis and was found to possess a novel skeleton containing α-pyrone, tetraene and pyrrole moieties.

The ^{1}H NMR spectrum of **74** (Figure 21) showed 14 signals, which were attributed to two singlet CH_3(δ_H 1.92 and 2.05), one OCH_3(δ_H 3.95), one imine (δ_H 11.44) and 10 olefinic methine protons. The ^{13}C NMR spectrum of **74** showed signals for 20 carbons. The distortionless enhancement by polarization transfer (DEPT) experiment assigned them to 3 methyl, 10 sp^2 methine and 7 quaternary carbons including one ester carbonyl carbon (C18) and two-oxygenated sp^2 carbons (C14 and C16). The ^{1}H–^{1}H COSY spectrum established a tetraene structure composed of C6–C12 with *E* geometrical configurations for the C6–C7, C8–C9 and C10–C11 double bonds, which are apparent from the coupling constants [$J(6, 7) = 15.0$ Hz, $J(8, 9) = 14.5$ Hz and $J(10, 11) = 14.0$ Hz]. HMBC experiment on **74** showed long-range couplings of 19-CH to C13 (δ_C 124.8) and C14 (δ_C 159.1), 21CH_3 to C16 (δ_C 165.7), C17 (δ_C 100.3) and C18 (δ_C 163.4), 20-OCH_3 to

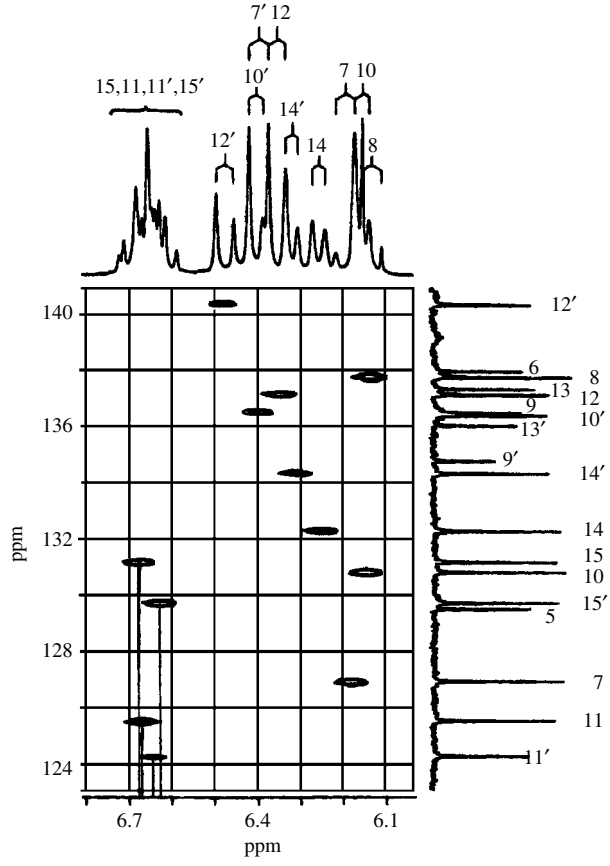


FIGURE 18. Selected portion of a HETCOR plot of **73a** (13 mg ml^{-1} $CDCl_3$). Projections along the axes are 1D spectra obtained at 360 MHz for ^{1}H and 90 MHz for ^{13}C. The spectra contain additional olefinic signals at 141.76(C(8′)), 110.81(C(7′)) and 7.18 (d, H−C(8′)) ppm. Reproduced by permission of Neue Schweizerische Chemische Gesellschaft from Reference 43

C16 and H15 to C13, C14 and C17. These correlations established the connectivities of C13−C18. Taking into consideration the number of oxygen atoms contained in **74** and the chemical shifts of C14 and C18, one oxygen atom must be inserted between C14 and C18. Thus, the existence of an α-pyrone unit in **74** was confirmed, as shown in Figure 22.

The HMBC experiment also showed long-range couplings of 19-CH_3 to C12 (δ_C 134.7), C13 (δ_C 124.8) and C14. Thus, the tetraene and the α-pyrone units are linked through C13 (Figure 22). The diagnostic ^{13}C chemical shift for C19 (δ_C 21.1) and NOE between H12 and 19-CH_3 defined the configuration of the C12−C13 double bond as *Z*.

In the ^{1}H−^{1}H COSY spectrum, cross peaks were observed among the two methine protons H2 (δ_H 6.90, $J = 2.6$, 3.0 Hz) and H3 (δ_H 6.13, $J = 2.3$, 3.0 Hz) and an imine proton (δ_H 11.44, $J = 2.3$, 2.6 Hz). In addition, long-range couplings were observed from H3 to C2 (δ_C 120.2) and C4 (δ_C 111.5), H2 to C3 (δ_C 109.0), C4 and C5 (δ_C 125.9), H6 to C4 and H7 to C5 in the HMBC experiment. These couplings indicated the presence

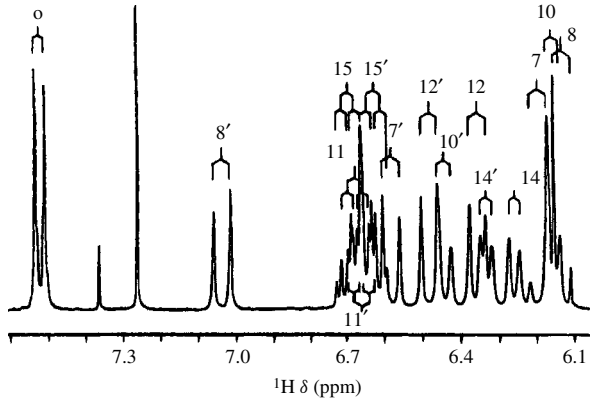


FIGURE 19. Selected portion of the ^{1}H NMR spectrum of **73b** (18 mg ml^{-1} $CDCl_3$). The d due to H−C(3′) and H−C(5′) (8.17 ppm) is not shown. Reproduced by permission of Neue Schweizerische Chemische Gesellschaft from Reference 43

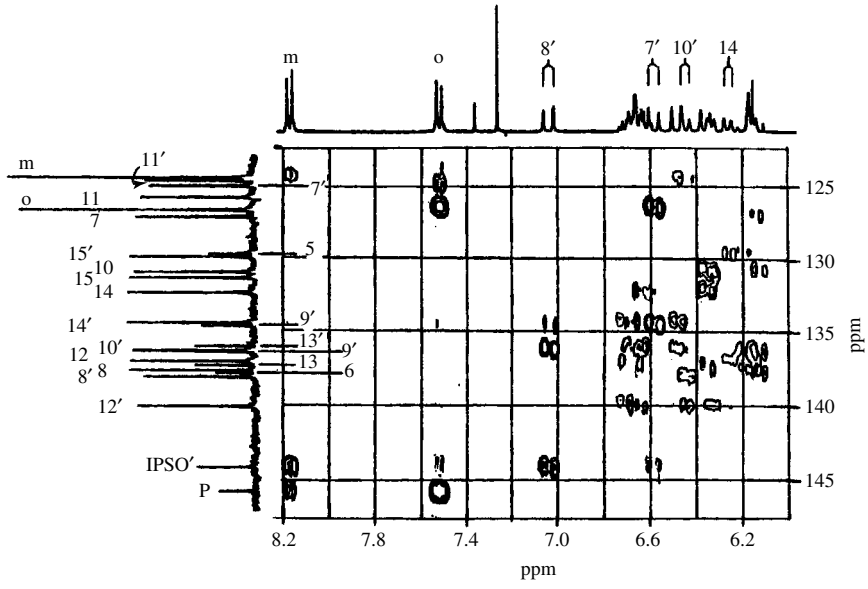


FIGURE 20. Contour plot of a selected portion of the ^{13}C, ^{1}H HMBC spectrum of **73b** (20 mg ml^{-1} $CDCl_3$). Projections along the axes are 1D spectra obtained at 360 MHz for ^{1}H and 90 MHz for ^{13}C. Reproduced by permission of Neue Schweizerische Chemische Gesellschaft from Reference 43

of a 2,3-disubstituted pyrrole ring consisting of C2–C5, and the linkage to the tetraene unit at C5. Therefore, attachment of the chlorine atom to the quaternary carbon C4 was deduced (Figure 22). Based on all these findings, the total structure of **74** was established to be (1*Z*, 3*E*, 5*E*, 7*E*)-6-(8-(3-chloro-^{1}H-pyrrol-2-yl)-1,3,5,7-octatetraenyl)-4-methoxy-3-methyl-2*H*-pyran-2-one.

TABLE 22. ^{1}H NMR chemical shift differences (ppm) of olefinic protons of (all-*E*)-7′-aryl-7′-*apo*-*β*-carotens and *β*,*β*-carotene[a]

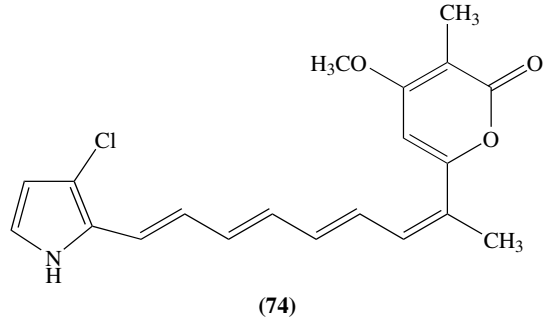
Hydrogen	**73a**	**73b**	**73c**	**73d**	**73e**	**73f**
HC15	0.05	0.07	0.03	−0.01	0.00	0.00
HC14′	0.06	0.07	0.05	0.00	0.01	−0.01
HC12′	0.11	0.12	0.08	0.02	0.06	0.03
HC11′	−0.01	0.00	0.00	0.01	0.00	0.01
HC10′	0.24	0.28	0.22	0.05	0.17	0.14
HC8′	1.04	0.90	0.84	0.21	0.76	0.63
HC7′	0.19	0.38	0.38	0.37	0.37	0.34

[a]In the symmetrical *β*,*β*-carotene, *δ* values of primed and nonprimed atoms are identical. Other chemical shifts of **73a–d** were the same (±0.01 ppm) as those reported for *β*,*β*-carotene, except for Me-C(9′): **73a,** 2.03; **73b,** 2.05; **73c,** 2.04; **73d,** 2.06; **73e,** 2.05; **73f,** 2.03; *β*,*β*-carotene, 1.98 ppm.

TABLE 23. ^{13}C NMR chemical shift differences (ppm) of compounds **73a–f** (all-*E*) and *β*,*β*-carotene[a]

Carbon	**73a**	**73b**	**73c**	**73d**	**73e**	**73f**
C7′	−15.93	−2.01	−0.69	−1.10	+0.61	+0.22
C9′	−1.30	−1.45	−1.03	−0.48	−0.61	−0.36
C11′	−0.86	−0.74	−0.48	−0.32	−0.25	−0.10
C13′	−0.50	−0.48	−0.34	−0.19	−0.18	−0.07
C15′	−0.38	−0.38	−0.26	−0.15	−0.16	−0.10
C14	−0.22	−0.23	−0.14	−0.07	−0.09	−0.04
C12	−0.22	−0.25	−0.17	−0.09	−0.13	−0.09
C10	−0.11	−0.13	−0.09	−0.05	−0.07	−0.05
C8	−0.09	−0.12	−0.08	−0.05	−0.07	−0.06
C6	−0.14	−0.17	−0.14	−0.09	−0.15	−0.14
C5	0.10	0.11	0.07	0.00	0.04	+0.02
C7	0.16	0.17	0.09	−0.04	0.00	−0.04
C9	0.41	0.37	0.23	0.04	0.11	0.05
C11	0.40	0.43	0.26	0.04	0.10	0.02
C13	0.80	0.85	0.55	0.15	0.27	0.13
C15	1.07	1.11	0.74	0.21	0.34	0.14
C14′	1.83	1.91	1.30	0.41	0.69	0.39
C12′	3.00	2.90	1.96	0.67	0.99	0.45
C10′	5.48	5.44	3.95	1.24	2.33	1.37
C8′	3.94	0.34	−1.66	0.71	−4.17	−6.09

[a]Negative values indicate upfield shifts, compared to those of *β*,*β*-carotene, except that values of C9 and C13 are interchanged.



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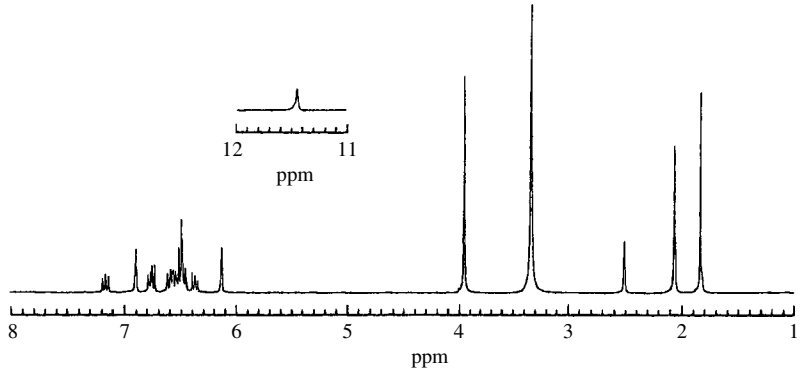


FIGURE 21. The 500 MHz ^{1}H NMR spectrum of rumbrin in DMSO-d_6. Reproduced by permission of Japan Antibiotics Research Association from Reference 44

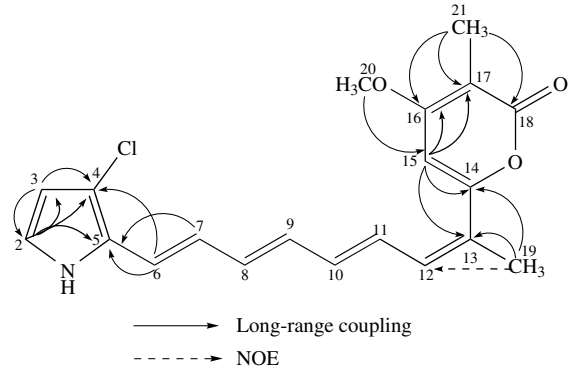


FIGURE 22. ^{1}H–^{13}C long-range couplings and NOE of rumbrin (**74**). Reproduced by permission of Japan Antibiotics Research Association from Reference 44

In the ^{1}H–^{13}C COSY spectrum, the olefinic carbon signals could not be unambiguously assigned because of the overlapping of their proton signals. Therefore, these carbons were assigned and the structure of **74** was confirmed using ^1J(CC) information[44]. The biosynthetic origin of the polyene and α-pyrone units was expected to be mainly acetate. Thus, an incorporation experiment with [1,2-$^{13}C_2$]acetate was carried out with a culture of *A. umbrium* n13. By adding 1 g of sodium [1,2-$^{13}C_2$]acetate 48 hours after the beginning of a 1-liter culture, 4 mg of labeled **74** were obtained. A 2D INADEQUATE experiment using this sample confirmed the structure of **74** and the assignments of all sp^2 carbons (Figure 23). The complete carbon and proton assignment is given in Table 24.

Chatterjee and coworkers[45] recently reported the taxonomy, production, isolation, structure elucidation and biological properties of a new antibacterial antibiotic alisamycin (**75**), a new member of the manumycin group of antibiotics obtained by the fermentation of *Streptomyces actuosus*.

Table 25 summarizes the ^{1}H and ^{13}C NMR spectra of **75**. The proton resonances were analyzed by double quantum filtered H–H shift-correlated COSY spectrum and

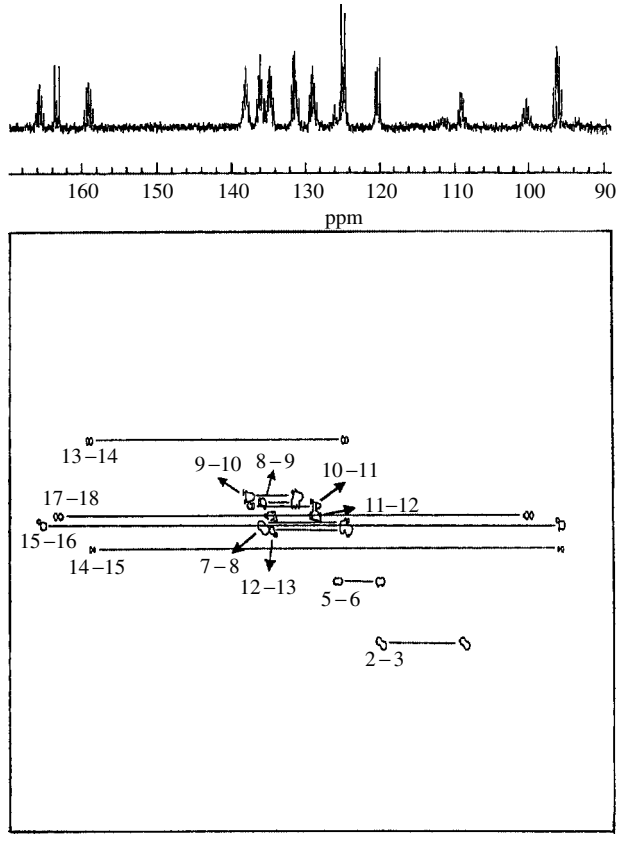


FIGURE 23. 2D INADEQUATE spectrum of [1,2-$^{13}C_2$]acetate labeled rumbrin. Reproduced by permission of Japan Antibiotics Research Association from Reference 44

the carbon resonances were assigned by a proton-detected CH shift-correlated multiple quantum coherence (HMQC) NMR experiment. The spectral properties showed strong similarities to those reported for the manumycin group of antibiotics. From the COSY spectrum recorded in $CDCl_3$, four spin systems could be extracted including a conjugated diene moiety attached to a methine multiplet (H6′, δ2.10) being part of a cyclohexane unit, one isolated triene moiety, three signals from the 5-epoxycyclohex-2-enone and two strongly coupled signals representing four protons.

In $CDCl_3$, **75** also revealed the presence of four D_2O exchangeable singlets at δ13.52, 7.58, 7.54 and 3.25 corresponding to one enolic hydroxyl, two amides and a hydroxy proton, respectively. On addition of DMSO-d_6 as co-solvent, the first three signals underwent large downfield shifts to δ14.00, 9.60 and 8.45, respectively, and the fourth one was not observed. The amide singlet at δ7.54 showed COSY correlation to H2′ (δ5.84) and also to the H3 (δ7.40) which, in turn, showed coupling ($J = 2.6$ Hz) to the epoxy proton H5. All these observations were suggestive of a carboxamide group linking the diene unit to the epoxycyclohexenone. A full confirmation was obtained by a proton-detected long-range CH shift correlation (HMBC)NMR experiment (Table 25). Thus this amide proton

TABLE 24. The 500-MHz ^{1}H NMR and 125-MHz ^{13}C NMR spectral data for rumbrin in DMSO-d_6[a]

Position	δ_H	δ_C
1-NH	11.44 (dd 2.3, 2.6)	
2	6.90 (dd 2.6, 3.0)	120.2(d)
3	6.13 (dd 2.3, 3.0)	109.0(d)
4		111.5(s)
5		125.9(s)
6	6.49 (d 15.0)	120.2(d)
7	6.75 (dd 11.0, 15.0)	124.8(d)
8	6.59 (dd 11.0, 14.5)	135.9(d)
9	6.37 (dd 11.3, 14.5)	131.3(d)
10	6.54 (dd 11.3, 14.0)	137.9(d)
11	7.16 (dd 12.5, 14.0)	128.9(d)
12	6.47 (d 12.5)	134.7(d)
13		124.8(s)
14		159.1(s)
15	6.50 (s)	96.2(d)
16		165.7(s)
17		100.3(s)
18		163.4(s)
19	2.05 (s)	21.1(q)
20	3.95 (s)	56.6(q)
21	1.92 (s)	8.5(q)

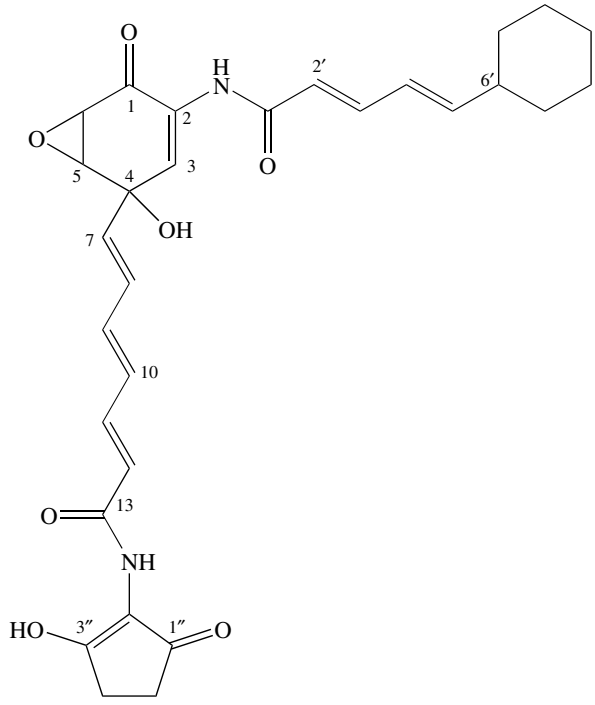
[a]Coupling constants in J(Hz) are given in parentheses.

showed ^3J(CH) correlation to C3 (δ126.36), C1 (δ188.63); and ^2J(CH) correlation to C1′ (δ165.16), and could thereby be assigned to the 2-NH proton. The more downfield amide proton showed an exchange cross peak with the enolic proton in the NOESY spectrum and it also showed long-range COSY correlation with the H11 proton (δ7.32).

In the HMBC spectrum this NH proton exhibited ^3J(CH) correlation to the C3″ (δ174.15) and ^2J(CH) interaction to the C13 (δ165.48) carbonyl, the latter in turn showing ^2J(CH) interaction with H12(δ6.05). Thus it became clear that a carboxamide group linked the conjugated triene and the cyclopentenone unit. A ^2J(CH) coupling of the triene terminus H7 to C4 (δ_H/δ_C 5.86/71.20) established the point of attachment of the triene unit to C4. An observed NOE interaction between the H7 and H5 lent further support to this attachment and was suggestive of proximal orientation of the *trans*-Δ^7 bond to the epoxy unit in the most preferred conformation. The absolute configuration at C4 was not established.

The double bond geometries were determined by coupling constant measurements as well as NOE studies. Large coupling constant values (14–15 Hz) observed for H12 and H2′ established *E*-configuration of the corresponding double bonds. The olefinic protons H8/H9 and H4′/H5′ are isochronous, appearing at δ6.58 and 6.12, respectively, and their coupling constant values could not be measured by simple analysis of the ^{1}H NMR spectrum (Figure 24).

The problem of strong coupling could be resolved by simulating all the olefinic signals with the LAOCOON program and the best fitting values were taken. These values confirmed *E*-configuration for all the five disubstituted double bonds of **75**. Most of the olefinic protons also exhibited long-range couplings (Table 25). The *E*-configurations of the double bonds were further corroborated by the NOE network (Figure 24) as revealed



(75)

in a phase-sensitive 2D NOESY spectrum (300 MHz, $CDCl_3-DMSO\text{-}d_6$, 500 ms mixing time with 4% random variation).

Imai and coworkers[46] reported a structural study of lagunamycin **(76)**, a novel 5-lipoxygenase inhibitor which is isolated from the culture filtrate of *Streptomyces sp.* AA0310 and showed inhibitory activity against 5-lipoxygenases and antibacterial activity against Gram-positive bacteria. The structure of **76** has been elucidated to be 6-diazo-4-[(*E*)-4,6-dimethyl-2-hepten-2-yl]-3-methyl-2,5,7,8-tetraoxoquinoline by a combination of chemical degradations and NMR studies.

The ^{13}C and ^{1}H NMR data are summarized in Table 26. All one-bond $^{1}H-^{13}C$ connectivities were determined by a $^{13}C-^{1}H$ COSY experiment. $^{1}H-^{1}H$ COSY, NOESY and long-range $^{13}C-^{1}H$ COSY experiments indicated a partial structure of $C_{13}H_{21}NO$ containing an amide as depicted in Figure 25. The geometry of the double bond (2′,3′) was established as *E* by measurement of the $^{3}J(CH)$ value (8.3 Hz) between C1′ and H3′ in a nondecoupled ^{13}C NMR spectrum.

The lower field ^{13}C NMR signals of **76** suggested a substituted pyridone (δ116.3 s, 130.0 s, 138.6 s, 151.4 s and 161.3 s) and a 2-diazo-3-oxo-1,4-benzoquinone (δ87.5 s, 168.8 s, 172.5 s and 173.6 s) moiety by comparison with the reported values of diazaquinomycin A and 2-diazo-3-oxo-1,4-naphthoquinone, respectively. Similar stabilities of 1- and 2-diazo-3-oxo-1,4-naphthoquinone under acidic conditions indicated the presence of a diazo group in **76**. By combining these results, the structure of **76** was assigned.

Seto and coworkers[47] reported a study on viridenomycin **(77)**, a novel 24-membered macrocyclic polyene lactam antibiotic. A new antitumor antibiotic, designated AL081,

TABLE 25. ^{13}C (67.5 MHz) and (400 MHz) ^{1}H NMR spectral data of alisamicin **(75)** ($CDCl_3$, 303 K)[a]

Position	δ_C[b]	^{1}H		
		δ	HMBC partner	
		(multiplicity, J in Hz)	^{2}J(CH)	^{3}J(CH)
1	188.63	—		
2	128.08	—		
3	126.36	7.40 (d, 2.6)	C2	C1
4	71.20	—		
5	57.41	3.70 (dd, 2.6, 3.6)	C4	C7
6	52.93	3.65 (d, 3.6)	C1, C5	C2
7	136.29	5.86 (dd, 14.5, 0.3)		C3, C9
8	131.58	6.58 (dd, 11.3, 14.5)		
9	139.52	6.58 (dd, 14.8, 11.3)		
10	131.74	6.42 (ddd, 11.2, 14.8, 0.3)		
11	143.45	7.32 (dd, 11.2, 14.7)		C13
12	121.59	6.05 (d, 14.7)	C13	C10
13	165.48	—		
1′	165.16	—		
2′	120.95	5.84 (d, 14.8)	C1′	
3′	144.16	7.22 (ddm, 14.8, 10.5)		
4′	125.52	6.12 (dd, 10.5, 15.5)	C3′	
5′	150.76	6.12 (m)		C3′
6′	41.13	2.10 (m)		
7′, 11′	32.25	1.76 (m) (eq), 1.13, (m) (ax)		
8′, 10′	25.80	1.73 (m) (eq), 1.28 (m) (ax)		
9′	26.00	1.67 (m) (eq), 1.18 (m) (ax)		
1″	197.39	—		
2″	115.01	—		
3″	174.15	—		
4″	32.14	2.61 (m)		
5″	25.65	2.53 (m)		
3″-OH	—	13.52 (s)		
4-OH	—	3.25 (s)		
2-NH	—	7.54 (s)	C1′	C1, C3
13-NH	—	7.58 (s)	C13	C3″

[a]The ^{1}H and ^{13}C chemical shifts are in ppm from $(CH_3)_4Si$ and $CDCl_3$ as internal standards, respectively.

[b]The carbon multiplicities were determined by DEPT-135 experiment.

was obtained from the culture filtrate of an actinomycete identified as *Streptomyces gannmycius*, and found to be identical with **77** by direct comparison.

The structure was determined by NMR spectral analysis including a variety of two-dimensional NMR techniques. The 500-MHz ^{1}H NMR spectrum of **77** taken in $CDCl_3$ (Figure 26) revealed the presence of 5 aromatic protons, 15 olefinic protons, a methoxy (δ3.65), an allylic methyl (δ2.14) and a tertiary methyl group (δ1.33). The ^{13}C NMR spectrum showed signals due to all 34 carbons, which were assigned to 7 quaternary carbons, 23 methines, 1 methylene and 3 methyls by DEPT experiments. The ^{13}C and ^{1}H NMR spectral data are summarized in Table 27.

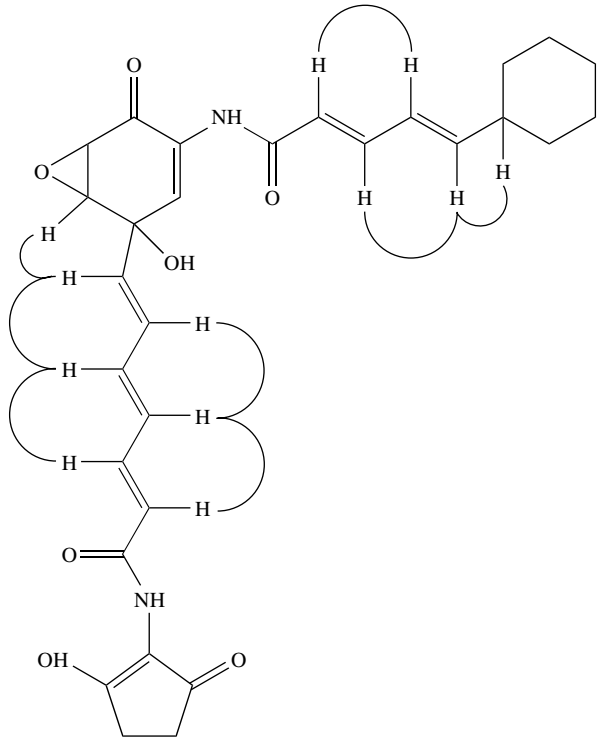
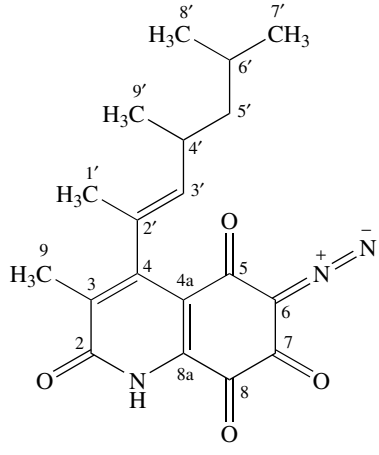


FIGURE 24. NOE network of alisamycin **(75)**. Reproduced by permission of Japan Antibiotics Research Association from Reference 45



(76)

TABLE 26. ^{13}C and ^{1}H NMR spectra of lagunamycin **(76)** in $CDCl_3$

Atom	^{13}C	^{1}H
1		9.60 (1H, s)
2	161.3 (s)	
3	130.0 (s)	
4	151.4 (s)	
4a	116.3 (s)	
5	173.6 (s)	
6	87.5 (s)	
7	168.8 (s)	
8	172.5 (s)	
8a	138.6 (s)	
9	14.0 (q)	2.18 (3H, s)
1′	16.8 (q)	1.90 (3H, d, $J = 1.3$)
2′	137.4 (s)	
3′	135.0 (d)	4.86 (1H, dq, $J = 9.4, 1.3$)
4′	30.4 (d)	2.68 (1H, m)
5′	46.6 (t)	1.19 (2H, m)
6′	25.9 (d)	1.61 (1H, m)
7′	22.4 (q)	0.93 (3H, d, $J = 6.4$)
8′	23.2 (q)	1.93 (3H, d, $J = 6.4$)
9′	20.4 (q)	1.01 (3H, d, $J = 6.6$)

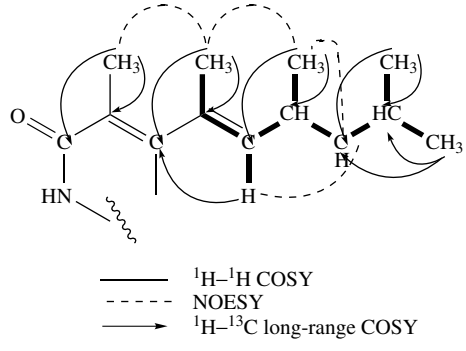
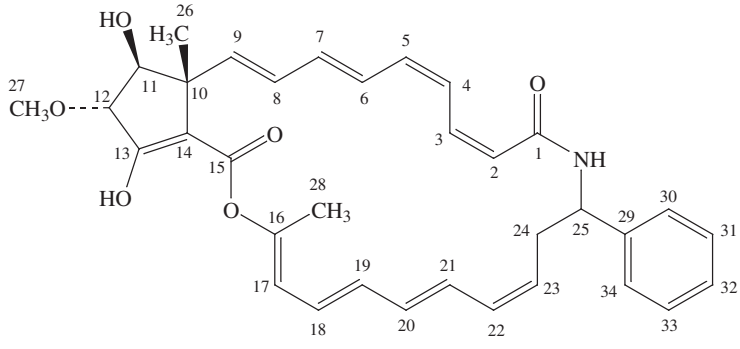


FIGURE 25. A partial structure of lagunamycin **(76)** as revealed by $^{1}H-^{1}H$ COSY, NOESY and $^{1}H-^{13}C$ long-range COSY experiments. Reproduced by permission of Japan Antibiotics Research Association from Reference 46

All one-bond $^{1}H-^{13}C$ connectivities were established by a heteronuclear multiple-quantum coherence (HMQC) experiment. Partial structures including a tetraene system, a phenyl group and a diol moiety as shown in Figure 27A were determined by a $^{1}H-^{1}H$ COSY experiment.

The remaining olefinic methine (C21), which could not be assigned due to overlapping of three olefinic protons (H20, H21 and H22) at δ6.22, was assumed to form another tetraene system together with C16–C20, C22 and C23 from their chemical shifts. $^{1}H-^{13}C$ long-range couplings in the heteronuclear multiple-bond correlation (HMBC) spectrum confirmed this tetraene moiety. As shown in Figure 27B, long-range couplings



(77)

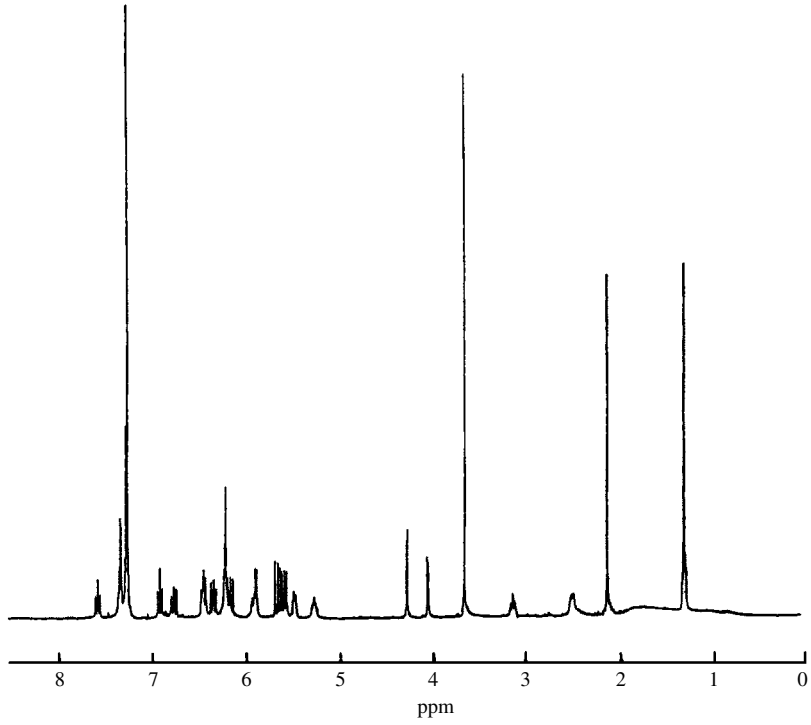


FIGURE 26. The 500-MHz ^{1}H NMR spectrum of viridenomycin **(77)** in $CDCl_3$. Reproduced by permission of Japan Antibiotics Research Association from Reference 47

were observed between H20 (or H21) and the carbon at δ133.7, and H24 and the carbon at δ133.7. Therefore carbon signals at δ134.3, 128.1 and 133.7 were assigned to C20, C21 and C22, respectively.

The connectivities of the partial structures thus obtained were elucidated by observation of the $^1H-^{13}C$ long-range correlations from H2, H3 and NH25 to a carbonyl carbon (C1,

TABLE 27. ^{13}C and ^{1}H NMR assignments for viridenomycin **(76)** in $CDCl_3$

No.	δ_C[a]	δ_H	(J, Hz)[a]
1	166.2 s		
2	120.8 d	5.59	(d, 11.5)
3	134.9 d	6.92	(t, 11.5)
4	124.6 d	7.57	(t, 11.5)
5	135.8 d	6.45	(t, 11.5)
6	126.3 d	6.77	(dd, 15.0, 11.5)
7	136.3 d	6.46	(dd, 15.0, 10.5)
8	131.4 d	6.34	(dd, 15.0, 10.5)
9	141.7 d	5.68	(d, 15.0)
10	46.8 s		
11	83.4 d	4.06	(d, 6.5)
12	85.3 d	4.29	(d, 6.5)
13	171.1 s		
14	105.9 s		
15	167.1 s		
16	147.7 s		
17	119.1 d	5.63	(d, 11.5)
18	126.3 d	6.17	(dd, 14.5, 11.5)
19	133.7 d	5.91	(dd, 14.5, 10.0)
20	134.3 d	6.22	(br s)
21	128.1 d	6.22	(br s)
22	133.7 d	6.22	(br s)
23	125.7 d	5.28	(ddd, 11.0, 10.0, 6.5)
24	33.7 t	3.12	(ddd, 13.5, 10.0, 4.5)
		2.50	(ddd, 13.5, 6.5, 3.5)
25	51.5 d	5.49	(ddd, 9.5, 4.5, 3.5)
25-NH		5.90	(d, 9.5)
26	17.0 q	1.33	(s)
27	59.1 q	3.65	(s)
28	15.9 q	2.14	(s)
29	139.5 s		
30, 34	126.3 d	7.28	(d, 7.0)
31, 33	128.5 d	7.34	(t, 7.0)
32	127.3 d	7.28	(d, 7.0)

[a] s, singlet; d, doublet; t, triplet; q, quartet.

δ166.2), and from H30 and H34 to a methine carbon (C25, δ51.5), thereby showing that the tetraene moiety consisting of C2 to C9 was attached to C25 through an amide linkage, and the phenyl group is connected to C25.

The remaining functional groups including a tertiary methyl, a methoxy, a diol moiety and three quaternary carbons were assembled as shown in Figure 27C by analysis of the HMBC spectral data, which revealed the $^{1}H-^{13}C$ long-range couplings from the tertiary methyl (H26) to C9, C10, C11 and C14, from the oxymethine (H12) to C13 and C14, and from the methoxy (H27) to C12. These correlations established a cyclopentene ring structure (C10–C14) substituted with a methoxy group at C12 and a tetraene moiety at C9. The only remaining carbon (C15) was assignable to an ester from its chemical shift (δ167.1) and an IR absorption at 1700 cm^{-1}. In order to explain the chemical shifts of C13 (δ171.1) and C14 (δ105.9), and a positive ferric chloride reaction for viridenomycin, C13 and C14 must form an enol group conjugated to the ester carbonyl (C15). The ester linkage between C15 and C16 was determined by the chemical shift of C16

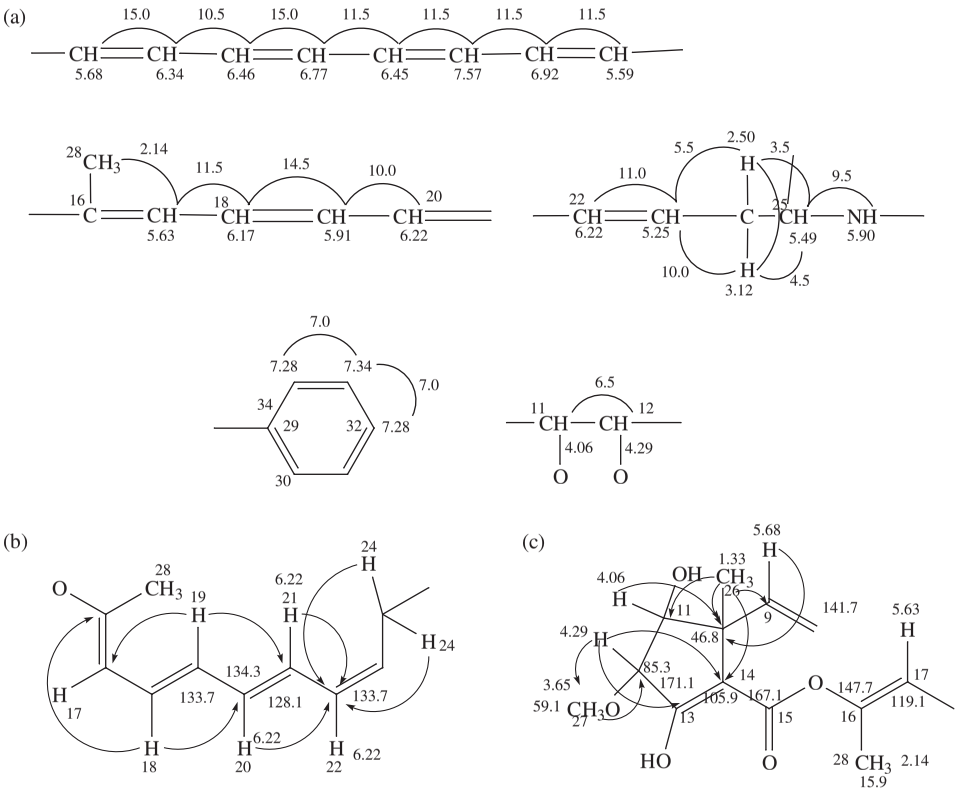


FIGURE 27. Partial structures of viridenomycin. (a): Data from $^{1}H-^{1}H$ COSY experiment; (b), (c): The solid line arrows indicate $^{1}H-^{13}C$ long-range coupling detected by HMBC

(δ147.7) and long-range couplings from the allylic methyl (H28) to only two carbons, C16 and C17.

Six of the eight geometries of the two tetraene systems were established to be 2*Z*,4*Z*,6*E*, 8*E*,18*E* and 22*Z* by the coupling constants $J(23) = 11.5$ Hz, $J(45) = 11.5$ Hz, $J(67) = 15.0$ Hz, $J(1819) = 14.5$ Hz and $J(2223) = 11.0$ Hz. An upfield chemical shift of C-28 (δ15.9) and no NOE between H17 and H28 showed the *E* configuration for C16. The remaining stereochemistry at C20 proved to be 20*E* by the chemical shifts of C19 (δ133.7) and C22 (δ133.7) observed at a low-field region free from the γ effects in comparison with C21 (δ128.1) and C23 (δ125.7). NOEs observed from H26 to H12 but not to H11 indicated that the relative configuration of the cyclopentene ring was as shown in Figure 27B. The stereochemistry at C25 remains to be determined.

Thus, the structure of viridenomycin was established except for the absolute configuration. This antibiotic is partially related to hitachimycin, which is a 19-membered lactam antibiotic possessing a phenyl group and a cyclopentene ring, but devoid of the tetraene systems and ester linkage.

Colmenares and coworkers[48] reported a ^{19}F NMR study of rhodopsin analogs. ^{19}F NMR spectra of 11-*cis* and 9-*cis* isomers of six fluorinated rhodopsin analogs with the label(s) located at the vinylic positions of the polyene chain (8F, 10F, 12F, 14F, 8,12F_2, 10,14F_2) are reported along with their UV-Vis and CD spectra. The regiospecific F chemical shift data are analyzed in terms of chromophore changes and local perturbation resulting from specific interactions with the protein. Two analogs (11-*cis*-12-F and 11-*cis*-8-F) and also 9,11-di-*cis*-12-F display FOS (fluorine opsin shift) values uniquely different from others. *Ab initio* ^{19}F NMR chemical shielding calculations of model structures provide support to the assumption that a strong protein perturbation to the 12F position prevails in the binding cavity and that the F8 shift is sensitive to variation of the nearby dihedral angle(s). Possible causes for the broad line width of the F signals of these membrane proteins are discussed.

Freshly reconstituted and concentrated pigment analogs were used for ^{19}F NMR studies for recording the 'before photoirradiation' and 'after irradiation' spectra. Representative spectra of the 8-F and 14-F monofluoro analogs are shown in Figures 28 and 29. The signal that disappears upon photobleaching is identified as that of the pigment analog, the new signal that appears upon irradiation of the photobleaching product, stereochemistry identified by their F shifts and the HPLC retention time and UV data of the extracted retinal analog. Chemical shifts are listed in Table 28.

The fluorine chemical shift is very sensitive to changes in the environment. In this study, the F shift of each fluorinated pigment (a protonated Schiff base PSB) is compared to that of the solution value of the corresponding free PSB. The difference in their ^{19}F NMR chemical shifts represents the change imposed by the local environment (the protein binding cavity) on the F probe. This value is now termed the ^{19}F NMR opsin shift (FOS). The FOS values for the 9-*cis* as well as the 11-*cis* pigments are listed in Table 28. They have a mean value of 6.6 ppm with 95% of them distributed between 4.6 and 8.6 ppm. Only three FOS values are exceptional, falling outside this range: those of 9,11-di-*cis*-12-F (-2.1 ppm), 11-*cis*-8-F (13.1 ppm) and 11-*cis*-12-F (13.2 ppm) and, to a lesser degree, also those for the disubstituted 11-*cis*-8,12-F_2 (11.8, 11.7 ppm). The trends are evident in the plot of FOS values vs the F position along the chromophore chain shown in Figure 30.

Li and coworkers[49] reported a molecular motion of β-carotene and a carotenoporphyrin dyad (composed of a porphyrin, a trimethylene bridge and a carotenoid polyene) in solution. Internal rotational motions in carotenoid polyenes and porphyrins are of interest because they can mediate energy and electron transfer between these two moieties when the pigments are joined by covalent bonds. Such internal motions can affect the performance of synthetic model systems which mimic photosynthetic antenna function,

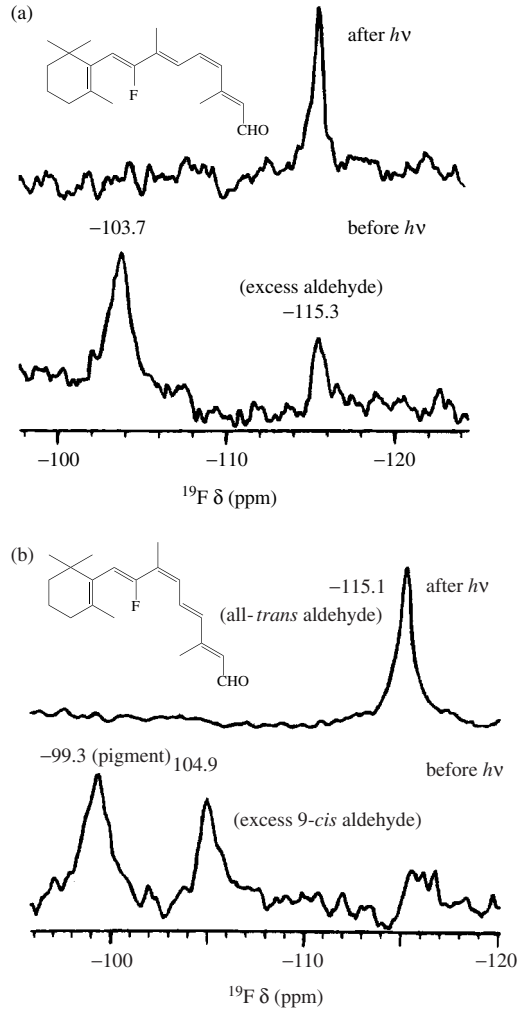


FIGURE 28. 283-MHz ^{19}F NMR spectra of isomers of 8-F-rhodopsin in CHAPS before (lower) and after photoirradiation (upper): (a) 11-*cis* (pulse delay, D5 = 5.0 s, number of acquisitions, NA = 5200, line broadening, LB = 80 Hz); (b) 9-*cis* (D5 = 50 ms, NA = 160000, LB = 80 Hz). Disappearance of the excess 9-*cis* aldehyde was due to repeated formation and bleaching of pigment during the irradiation process. Reprinted with permission from Reference 48. Copyright (1996) American Chemical Society

photoprotection and photoinduced electron transfer. Analysis of ^{13}C NMR spin-lattice relaxation times (T_1) yields information concerning both overall tumbling of molecules in solution and internal rotations about single bonds. Relaxation time and nuclear Overhauser effect data have been obtained for β-carotene **(78)** and the related molecules, squalene **(82)** and carotenoporphyrin **(80)** which is a zinc *meso*-tetraphenylporphyrin **(79)** covalently linked to a carotenoid polyene through a trimethylene bridge. Squalane **(81)**

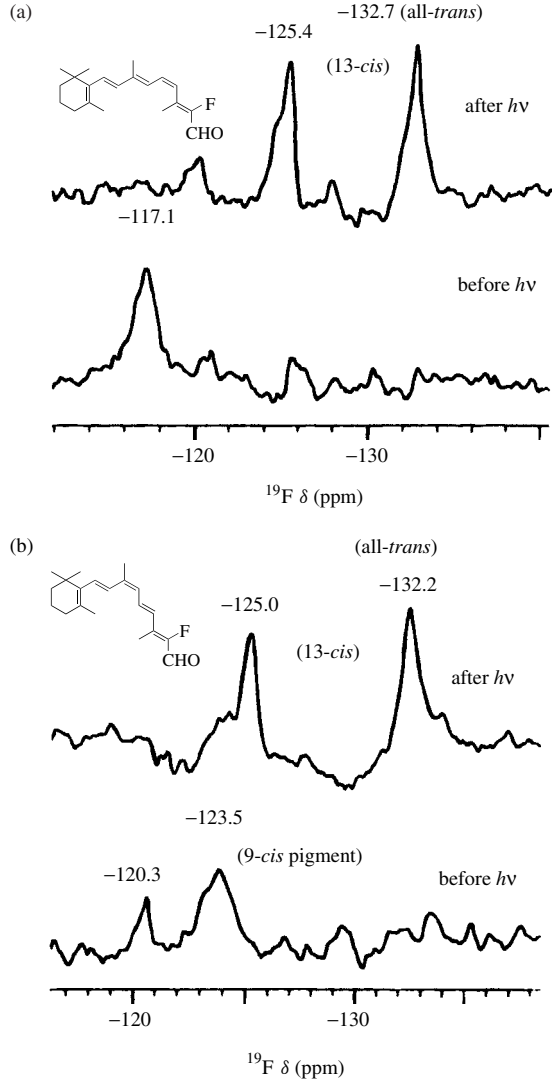


FIGURE 29. 283-MHz ^{19}F NMR spectra of 14-F-rhodopsin in CHAPS before and after photoirradiation: (a) 11-*cis* (D5 = 50 ms, NA = 196136, LB = 80 Hz); (b) 9-*cis* (D5 = 50 ms, NA = 200000, LB = 80 Hz). The 13-*cis* isomer was from dark isomerization. Reprinted with permission from Reference 48. Copyright (1996) American Chemical Society

and squalene **(82)**, which lack conjugated double bonds, behave essentially as limp string, with internal rotations at least as rapid as overall isotropic tumbling motions. In contrast, β-carotene reorients as a rigid rod, with internal motions which are too slow to affect relaxation times. Modeling it as an anisotropic rotor yields a rotational diffusion coefficient for motion about the major axis, which is 14 times larger than that for rotation

TABLE 28. ^{19}F NMR chemical shifts of retinylidene PSBs, (protonated schiff bases), rhodopsin pigments and corresponding ^{19}F NMR opsin shifts

Analog	PSB (CD_2Cl_2)	Pigment (CHAPS)[c]	F NMR OS[a]
11-*cis*-8-F	−116.8	−103.7	13.1
11-*cis*-10-F	−112.2[b]	−107.4	4.8
11-*cis*-12-F	−107.8[b]	−94.6	13.2
11-*cis*-14-F	−125.5	−117.1	8.4
11-*cis*-8, 12-F_2	−117.0	−105.2	11.8
	−104.6	−92.9	11.7
11-*cis*-10, 14-F_2	−115.3	−111.8	3.5
	−122.7	−117.6	5.1
9-*cis*-8-F	−105.9	−99.3	6.6
9-*cis*-10-F	−119.7[b]	−115.3	4.4
9-*cis*-12-F	−120.9	−114.3	6.6
9-*cis*-14-F	−131.4	−123.5	7.9
9-*cis*-10, 14-F_2	−119.1	−115.4	3.7
	−128.8	−121.2	7.6
9, 11-di-*cis*-12-F	−108.7	−110.8	−2.1
9-*cis*-9-CF_3	−64.6	−60.2	4.4

[a] ^{19}F NMR opsin shift = (column 3 − column 2) in δ (ppm).

[b] In $CDCl_3$.

[c] CHAPS = A membrane protein solubilizing agent: *N*,*N*-Dimethyl-*N*-(3-sulfopropyl)-3-{[(3α, 5β, 7α, 12α)-3,7,12-trihydroxy-24-oxocholan-24-yl]amino}-1-propanaminium inner salts.

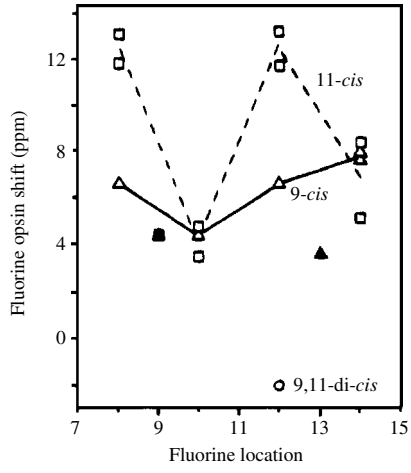
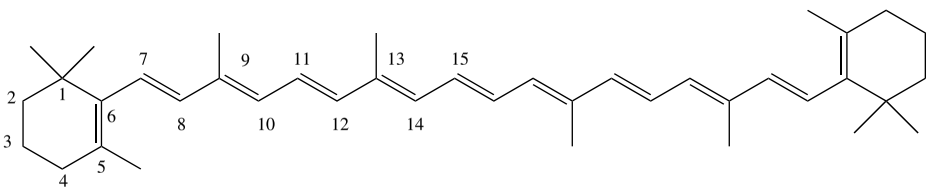
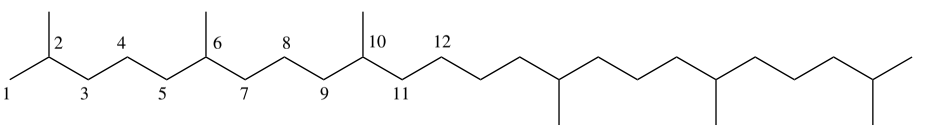


FIGURE 30. Plot of FOS (ppm) for vinyl-F labels at several locations on the chain of the retinyl chromophore in the (□) 11-*cis*, dashed line, (△) 9-*cis*, solid line, and (○) 9,11-di-*cis* configurations. Where appropriate, the averaged FOS values from mono- and dilabeled analogs were used for connecting lines. Solid symbols are for CF_3. Reprinted with permission from Reference 48. Copyright (1996) American Chemical Society

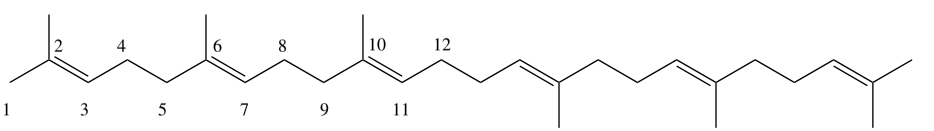
about axes perpendicular to that axis. The porphyrin reorients more nearly isotropically and features internal librational motions about the single bonds to the phenyl groups. The relaxation time data for the carotenoporphyrin are consistent with internal motions similar to those of a medieval military flail, consisting of a rigid, rod-like carotenoid



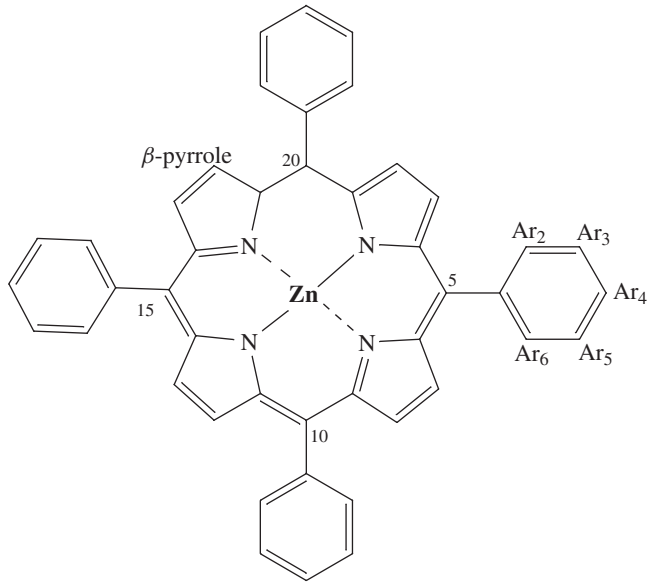
β-Carotene **(78)**



Squalane **(81)**



Squalene **(82)**



Zinc *meso*-tetraphenylporphyrin **(79)**

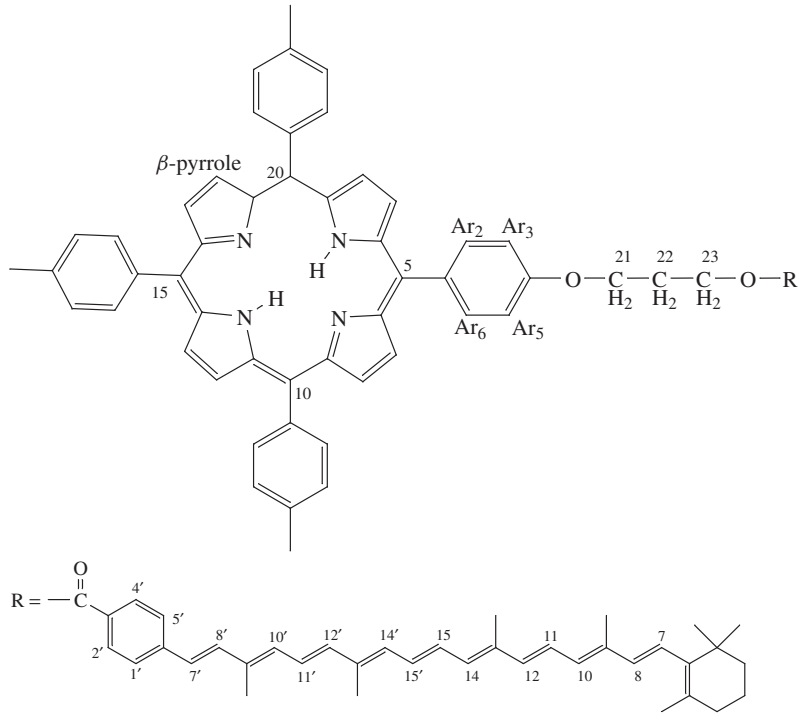
and ball-like porphyrin linked by a flexible chain of single bonds. Internal reorientation about this linkage is approximately 100 times faster than triplet-triplet energy transfer from the porphyrin to the carotenoid, which is mediated by such motions. The chemical shift assignments for the carbon nuclei of interest are given in Tables 29–32.

The assignments have been achieved using COSY, NOESY, ROESY, HMQC and HMBC experiments.

Spin–lattice relaxation time-T_1 and nuclear Overhauser effect $(1 + \eta)$ for relevant carbon nuclei of **78–82** were determined in deoxygenated $CDCl_3$ at 297 ± 2 K. Three magnetic field strengths (7.0, 9.4, and 11.7 T) were employed. For T_1 measurements the inversion recovery technique was used, e.g. for **78** (Figure 31), whereas NOE values were determined by a gated decoupling method. Results for squalane **(81)** and squalene **(82)** appear in Table 29, whereas those for **78–80** are given in Tables 30–32, respectively. The reported T_1 values are averages of at least three separate determinations and are reproducible to within 5%. The NOE values are less reliable (15%), due in part to a less than optimal signal-to-noise ratio.

The T_1 and NOE results for the monoprotonated carbon atoms of the β-carotene backbone of **78** at three magnetic field strengths are given in Table 30. An obvious difference from the results for **81** and **82** is that the T_1 values do not increase dramatically as one moves along the carbon chain away from the center of mass. In fact, the T_1 values for carbons 10, 11, 12, 14 and 15 are identical, within experimental error, while those for carbons 7 and 8 at the end of the chain are only slightly longer. This result indicates that the overall tumbling of the β-carotene molecule about its center of mass is substantially faster than internal rotations about the carbon–carbon bonds in the backbone, so that internal motions no longer affect relaxation significantly. The molecule behaves essentially as a rigid rotor.

Given the fact that β-carotene behaves essentially as a rigid rotor, the linear geometry of the molecule as shown by X-ray studies suggests that it should not tumble



Carotenoporphyrin **(80)**

isotropically. Indeed, to a first approximation, it might be expected to rotate more like an ellipsoid of rotation, with a major axis lying more or less along the conjugated carbon backbone. The field dependence of the T_1 and NOE data shown in Table 30 is consistent with this interpretation. In the first place, it will be noted that the NOE values are not maximal (2.99) and that they decrease with increasing magnetic field. At first glance, this might be taken to mean that a second relaxation mechanism, which becomes more important at higher fields, is contributing. The most likely candidate is chemical shift anisotropy. The chemical shift anisotropy relaxation rate is proportional to the square of the spectrometer magnetic field strength, and the mechanism should therefore be more effective at the higher fields. However, it can be seen in Table 30 that the spin–lattice relaxation times increase with magnetic field. Relaxation is becoming less effective rather than more effective. Any additional relaxation mechanism coming into play at higher field strengths could only decrease relaxation times. Thus chemical shift anisotropy, and indeed any other mechanism competing with dipole–dipole relaxation, may be ruled out.

An alternative explanation, consistent with the data, is that dipole–dipole relaxation dominates for β-carotene, but that molecular reorientation is anisotropic and occurs in a time range where the NOE is less than the maximum of 2.99 that is found in the 'extreme narrowing' region. For a rigid isotropic rotor, the correlation times are such that $\omega^2\tau_c^2 \ll 1$ and T_1 will be independent of magnetic field strength and the NOE will be full (2.99). For the field strengths used in this study, this extreme narrowing region includes diffusion coefficient values greater than about 5×10^9 s^{-1}. For smaller values

TABLE 29. ^{13}C NMR chemical shift values (δ), observed and calculated[a] spin–lattice relaxation times (T_1) and observed nuclear Overhauser effects (NOE) for squalane **(81)** and squalene **(82)** in $CDCl_3$ solution at 11.7 *T*

Carbon	**81**				**82**			
	δ (ppm)[b]	obsd T_1 (s)	calcd T_1 (s)	obsd NOE $(1+\eta)$	δ (ppm)	obsd T_1 (s)	calcd T_1 (s)	obsd NOE $(1+\eta)$
2	28.05	4.85	3.70	2.83				
3	39.47	2.50	1.76	2.09	124.46	4.31	3.99	2.85
4	24.88	1.75	1.66	2.54	26.81	1.85	1.83	3.13
	24.89							
5	37.39	1.33	1.57	2.69	39.75	1.62	1.73	3.05
6	32.86	1.86	2.96	2.76				
7	37.48	1.24	1.39	2.81	124.32	2.26	3.05	2.85
	37.52							
8	24.56	1.02	1.30	2.85	26.69	1.14	1.36	3.13
9	37.50	1.03	1.21	2.69	39.77	1.17	1.27	3.05
	37.55							
10	32.86	1.83	2.23	2.76				
11	37.20	0.88	1.03	2.75	124.35	1.77	2.15	2.85
	37.21							
	37.29							
	37.30							
12	27.52	0.91	0.91	2.78	28.30	0.90	0.90	3.17
	27.53							
	27.54							

[a]The rotational diffusion coefficients used to calculate the various T_1 values are discussed in the text.

[b]As discussed in the text, this sample is a mixture of stereoisomers and, as a result, resonances for some carbons appear as clusters of closely spaced peaks with chemical shift values as listed in this column. The reported experimental T_1 and NOE values are averages for these clusters.

TABLE 30. ^{13}C NMR chemical shift values (δ), spin–lattice relaxation times (T_1) and nuclear Overhauser effects (NOE) for β-carotene **(78)** in $CDCl_3$ at various magnetic field strengths

Carbon	δ (ppm)	7.0 T		9.4 T		11.7 T	
		T_1 (s)	NOE $(1+\eta)$	T_1 (s)	NOE $(1+\eta)$	T_1 (s)	NOE $(1+\eta)$
7	126.67	0.58	2.55	0.67	2.46	0.71	2.25
8	137.28	0.59	2.48	0.66	2.49	0.70	2.34
10	130.85	0.54	2.49	0.61	2.38	0.67	2.29
11	125.05	0.51	2.46	0.57	2.43	0.61	2.18
12	137.25	0.52	2.54	0.60	2.53	0.65	2.30
14	132.43	0.54	2.53	0.59	2.42	0.63	2.37
15	130.00	0.51	2.69	0.57	2.44	0.59	2.38

of the diffusion coefficient, T_1 will increase with increasing magnetic field strength, and NOE will decrease until it reaches a limiting minimum value.

Rochet and Lancelin[50] reported revised ^1H and ^{13}C NMR assignments of the polyene antibiotic Filipin III **(83)**. This macrolide which was isolated from *Streptomyces filipinensis* was reinvestigated in DMSO-d_6 solution using homonuclear and heteronuclear correlation spectroscopy. In addition to several corrections to previous ^1H NMR

TABLE 31. ^{13}C NMR chemical shift values (δ), observed and calculated spin–lattice relaxation times (T_1) and observed nuclear Overhauser effects (NOE) for zinc *meso*-tetraphenylporphyrin **(79)** in $CDCl_3$ solution at 9.4 *T*

Carbon	δ (ppm)	Obsd T_1 (s)	Calcd T_1 (s)	NOE $(1+\eta)$
β-pyrrole	131.99	0.40	0.40	2.85
Ar 2, 6	134.45	0.64	0.64	2.72
Ar 3, 5	126.55	0.63	0.64	3.10
Ar 4	127.49	0.41	0.40	2.61

TABLE 32. ^{13}C NMR chemical shift values (δ) and observed and calculated[a] spin–lattice relaxation times (T_1) for carotenoporphyrin **(80)** in $CDCl_3$ solution at 11.7 *T*

Carbon	δ (ppm)	Obsd T_1 (s)	Calcd T_1 (s)
β-pyrrole	130.6–130.8[b]	0.30	0.30
5-Ar 2, 6	135.59	0.31	0.32
5-Ar 3, 5	112.70	0.32	0.32
10, 15, 20-Ar 2, 6	134.51	0.37	0.38
10, 15, 20-Ar 3, 5	127.39	0.38	0.38
21	64.78	0.26	0.26
22	29.02	0.44	0.44
23	61.89	0.24	0.24
1′, 5′	126.09	0.37	0.41
2′, 4′	130.06	0.34	0.41
12′	139.26	0.44	0.41
8	137.74	0.52	0.41
12	137.14	0.45	0.41
8′	136.20	0.40	0.41
10′	134.78	0.42	0.41
14′	133.74	0.40	0.41
14	132.31	0.38	0.41
10	130.82	0.40	0.41
15	130.78	0.32	0.41
15′	129.79	0.36	0.41
7	126.83	0.54	0.41
7′	126.09	0.37	0.41
11	125.36	0.40	0.41
11′	124.58	0.39	0.41

[a]The rotational diffusion coefficients used to calculate the variations in T_1 values are discussed in the text.
[b]As discussed in the text, the β-pyrrole resonances for this molecule appeared as a broad singlet. The reported T_1 value is therefore an average for all β-pyrrole resonances.

assignments (Figure 32), the nine exchangeable hydroxylic protons were structure-specifically assigned together with ^{13}C NMR lines using proton-detected HSQC spectroscopy (Table 33). The magnitudes of the ^3J(HH) indicated a probable constrained geometry of the macrocyclic lactone.

4. Metal bound polyenes

Yasuda and coworkers[51] reported a route to niobocene-allyl compounds by hydrometalation of conjugated dienes with niobium hydrido-olefin complexes, $NbH(C_5H_5)_2$(olefin),

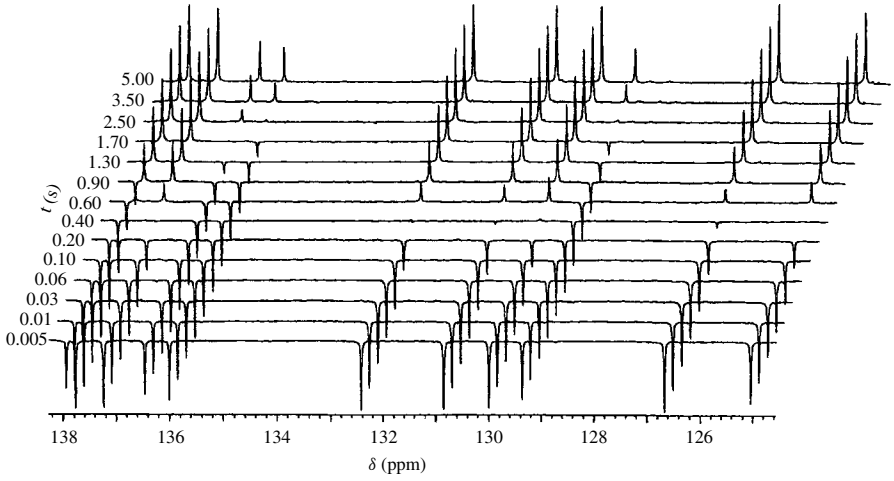
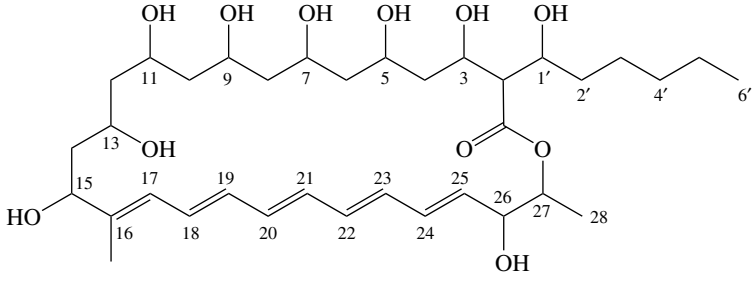


FIGURE 31. Typical data set for measurement of the spin–lattice relaxation times of the sp^2-hybridized carbon atoms of β-carotene at 11.7 T. The chemical shift values are shown across the bottom of the figure. The t-value for each spectrum is the delay time in the inversion-recovery pulse sequence. Reprinted with permission from Reference 49. Copyright (1995) American Chemical Society



(83)

which readily react with conjugated dienes such as butadiene, isoprene and pentadiene, to give $Nb(C_5H_5)_2(\eta^3$-allyl) derivatives of *syn* or *syn*,*syn* geometry, in 80%–90% yields with high regioselectivity. All the complexes were isolated as crystals and their structures were determined by NMR spectroscopy (equations 1 and 2).

The coordinated ethylene is readily expelled at 25 °C by the attack of a conjugated diene and the hydride is transferred to the sterically less crowded diene terminus. Thus the niobium hydrido-olefin complexes serve as convenient reagents for the preparation of 1,2- or 1,3-dialkyl-substituted allylniobium compounds starting from butadiene, (*E*,*E*)- and (*E*,*Z*)-2,4-hexadiene, (*E*)- and (*Z*)-1,3-pentadiene (equation 1), 3-methyl-1,3-pentadiene and isoprene (equation 2). All the allyl niobium compounds synthesized were isolated as air-sensitive pale-yellow crystals by crystallization from hexane.

All of the allylniobium compounds are monomeric, as revealed by the mass spectroscopic analysis, and always exist in the thermodynamically more favored *syn*- or

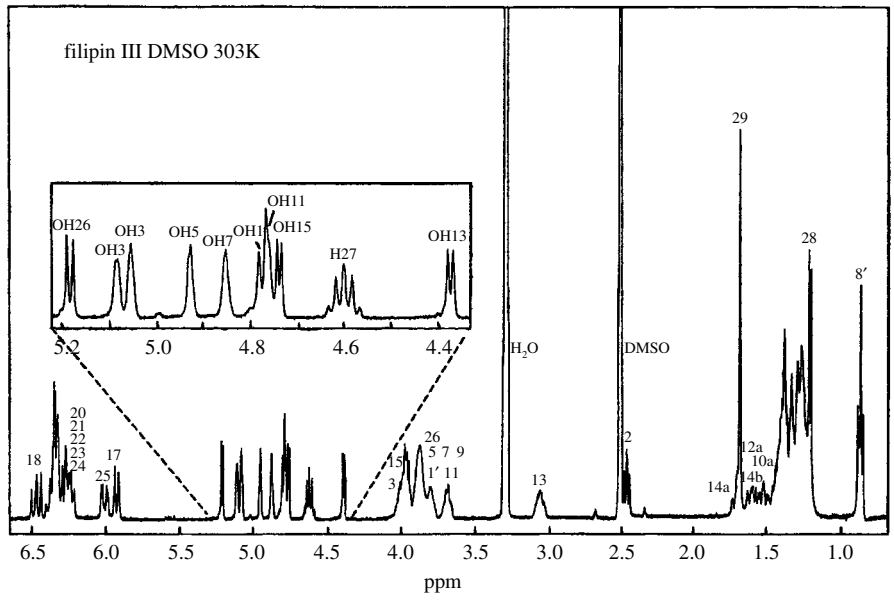
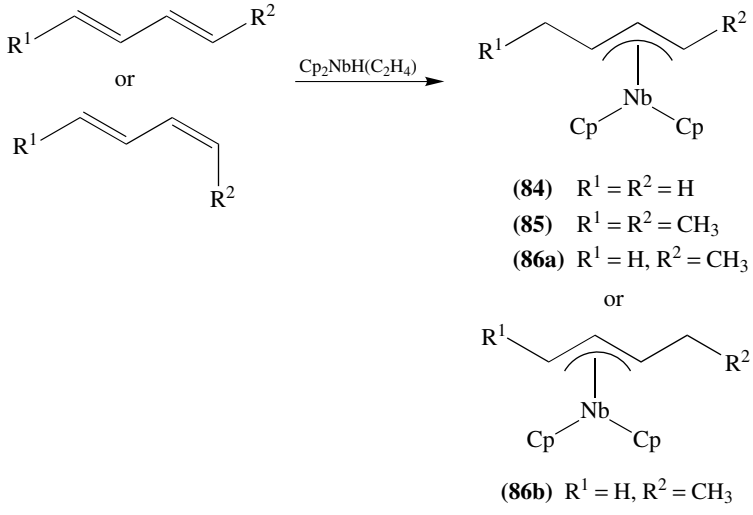


FIGURE 32. ^{1}H NMR spectrum of filipin III, 3 mM in DMSO-d_6, recorded at 400 MHz and 25 °C. The expanded region contains nine hydroxylic proton resonances that fully exchange with deuterium oxide and correspond to the nine hydroxyl groups of filipin III. No apodization functions were applied prior to the Fourier transformation. Reproduced by permission of John Wiley & Sons from Reference 50

syn,*syn*-allyl structure as deduced from one or more ^{1}H NMR parameters, such as J(H1R2) and/or J(R2H3) of 13.5–14.2 Hz (Table 34).

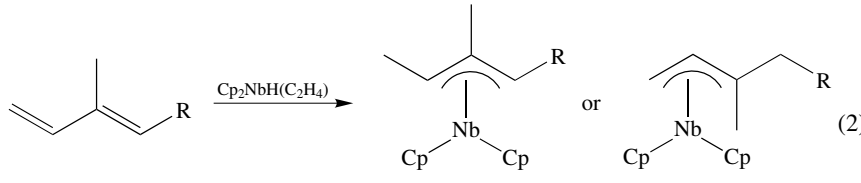


(1)

TABLE 33. ^{1}H and ^{13}C chemical shifts (ppm) of filipin III in DMSO-d_6 solution at 303 K.[a]

Position	$\delta^{1}H$	$\delta^{13}C$
2	2.44	58.1
3	3.98, 5.08 (OH)	69.9
4	1.36, 1.36	40.0
5	3.87, 4.93 (OH)	69.4
6	1.30, 1.30	43.4
7	3.85, 5.85 (OH)	69.4
8	1.30, 1.38	43.4
9	3.84, 5.06 (OH)	69.9
10	1.26, 1.36	42.3
11	3.77, 4.76 (OH)	68.3
12	1.28, 1.58	44.3
13	3.04, 4.37 (OH)	64.7
14	1.49, 1.68	42.4
15	3.94, 4.74 (OH)	71.0
17	5.91	125.4
18	6.44	127.7
19	6.22	131.0
20	6.30	128.8*
21	6.30	131.0*
22	6.30	132.0*
23	6.30	132.7*
24	6.30	132.8*
25	5.98	134.8
26	3.94, 5.19 (OH)	73.0
27	4.60	72.6
28	1.18	17.0
29	1.67	10.0
1′	3.66, 4.77 (OH)	69.5
2′	1.25, 1.34	33.6
3′	1.18, 1.22	30.6
4′	1.24, 1.42	24.0
5′	1.23	21.3
6′	0.83	12.9

[a] Asterisked resonances can be interchanged. Quaternary C-1 and C-16 are not assigned.



(2)

(87a) R = H **(87b)**

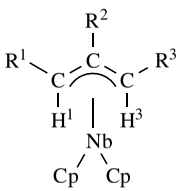
(88a) R = CH_3 **(88b)**

Lehn and coworkers[52] reported the synthesis, crystal structure and dinuclear copper(I) complexes of tris-carotenoid macrobicyclic ligands. The macrobicycles **89** and **90** were obtained in good yields in a one-step macrobicyclisation condensation between the tripode $N(CH_2CH_2NH_2)_3$ and the polyolefinic dialdehydes **93** and **94**.

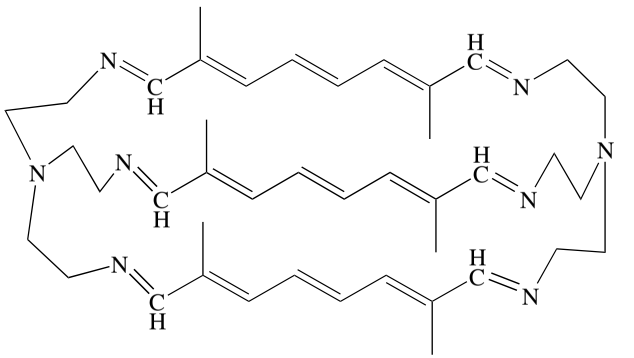
TABLE 34. ^{1}H NMR parameters for niobocene-allyl compounds[a]

$Cp_2Nb(R^1CH^1CR^2CH^3R^3)$			Chemical shifts (δ, ppm)						Coupling constants (Hz)[c]				
R^1	R^2	R^3	ν (H1)	ν (R1)	ν (R2)	ν (H3)	ν (R3)	ν (Cp)	$J(H^1, R^1)$	$J(H^1, R^2)$	$J(R^1, R^2)$	$J(R^2, H^3)$	$J(H^3, R^3)$
H	H	CH_3 **(84)**	0.51	2.65	2.29	1.46	2.01	4.54 4.14	−4.4	13.6	9.5	11.5	5.6
CH_3	H	C_2H_5 **(85)**	1.17	1.95	2.33	1.61	2.28 1.33	4.48 4.11	5.5	13.8		13.7	5.7
CH_3	H	CH_3 **(86a)**	1.17	1.97	2.34	1.17	1.97	4.50 4.15	5.5	13.9		13.9	5.5
CH_3	CH_3	CH_3 **(87a)**	0.97	1.88	152	0.97	1.88	4.53 4.04	5.8				5.8
H	CH_3	CH_3 **(88a)**	0.62	2.73	1.59		1.89	4.54 4.09	−5.0				5.5
H	H	H[b]	0.75	2.95	2.18	0.75	2.95	4.53 4.08	−4.5	14.9	9.5	14.9	−4.5
H	CH_3	H[b]	0.86	2.90	1.60	0.86	1.60	4.49 4.10	−4.8				−4.8

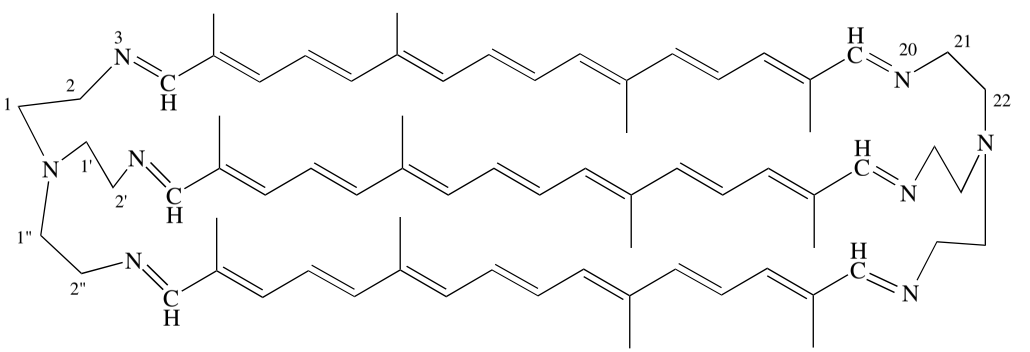
Numbering scheme



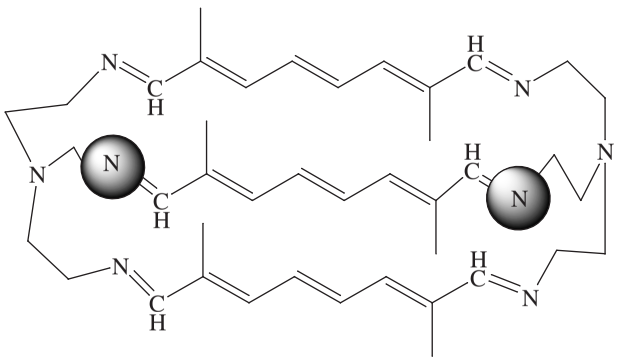
[a]Parameters were determined by the computer simulation of the 100 MHz NMR spectra (C_6D_6 at 30 °C). Chemical shifts are expressed in ppm downfield from TMS with calibration with C_6H_6 assumed to be at 7.2 ppm as internal standard.
[b]Prepared by reaction of Cp_2NbCl_2 with allylmagnesium bromide.
[c]J(H1H3) and J(H1R3) (R = H) are in the ranges −0.5 to −0.9 and −0.1 to −0.2 Hz, respectively.



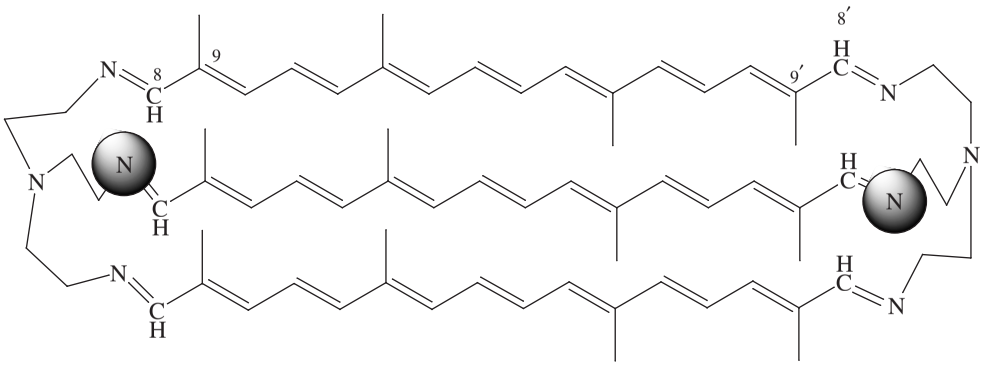
(89)



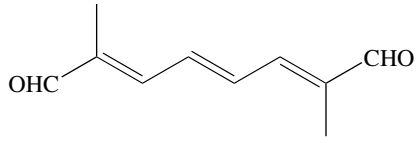
(90) (arbitrary numbering)



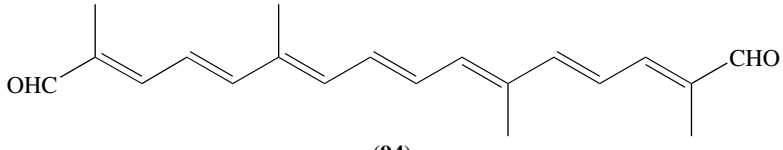
(91)



(92) (carotenoid numbering)



(93)



(94)

89 and **90** form dinuclear cryptates by complexation of two Cu(I) ions. The crystal structure of the tris-carotenoid **90** confirms that it contains three parallel polyolefinic strands. These substances may formally be considered as prototypes of molecular 'cables' formed by three electron-conducting molecular wires. The ^{1}H NMR spectra of the free ligands **89** and **90** and of their complexes **91** and **92** (the darkened circle represents the Cu atom) show notable differences (Figures 33 and 34).

In particular, the CH_2CH_2 unit of the free ligands **89** and **90** presents signals of the ABCD type, all four protons being different; this indicates an unsymmetrical structure which is also sufficiently rigid so as not to undergo conformational averaging by a twisting motion around the *N*,*N*-bridgehead axis. This agrees with the conformation found in the crystal structure when it is motionally frozen on the NMR time scale. High-temperature NMR measurements of **89** in $C_2D_2Cl_4$ indeed show coalescence of the four CH_2CH_2 signals at 2.33 and 2.92 ppm and at 3.23 ppm into two broad resonances at *ca* 2.7 and 3.5 ppm, respectively, with a coalescence temperature of *ca* 340 K. The corresponding free energy of activation $\Delta G_c^{\neq}$ is calculated to be *ca* 16 kcal mol^{-1}.

In contrast, the CH_2CH_2 resonances of the corresponding complexes **91** and **92** are of A_2X_2 type indicating a highly symmetrical averaging by rapid torsional oscillation around the *N*,*N*-bridgehead axis. The olefinic protons display a compression of signals into a narrower ppm range, and the CH=N signal undergoes a downfield shift of *ca* 0.5 ppm on complexation.

In comparison, both the free ligand and the dinuclear Cu(I) cryptate of an analogous macrobicyclic structure possessing a diphenylmethane group as a central unit display only two resonances for the CH_2CH_2 fragment, as is the case here only for the complexes **91** and **92**. This points to the special conformation features of the free macrobicycles **89** and **90**.

B. Solid State NMR

1. ^{13}*C CP/MAS NMR*

Polydiacetylenes are obtained as single crystals by topochemical solid-state polymerization of the monomer single crystal. These compounds have received considerable attention because of their one-dimensionally π-conjugated structure. Their unique π-electron structures, and therefore superior third-order nonlinear optical properties, have been extensively investigated.

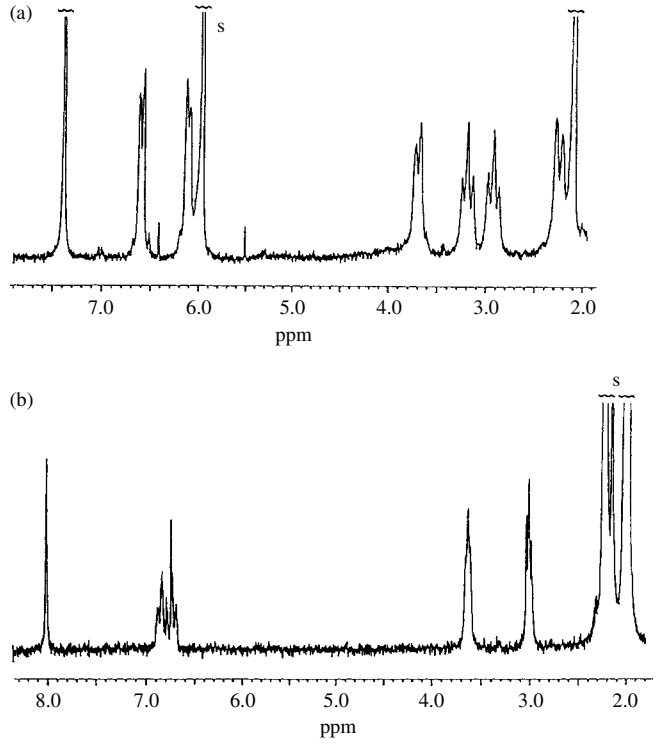


FIGURE 33. ^{1}H NMR spectra (200 MHz): (a) of cryptand **89** in $C_2D_2Cl_4$ and (b) of its dinuclear Cu^1 complex **91** in CD_3CN (s = solvent). Reproduced by permission of Neue Schweizerische Chemische Gesellschaft from Reference 52

Hayamizu and coworkers[53] reported the polymerization of the octatetrayne monomer 15,17,19,21-hexatriacontatetrayne (HTY) **(95)** to the polydiacetylene **96** with butadiynyl substituents (R = H) as presented in Figure 35 as an example.

It was found that solid-state polymerization of these monomers always proceeds by 1,4-addition. Furthermore, polydiacetylene **96** could be thermally reacted and the structure of the final polymer was proposed to be that of the ladder polymer **97** where the repeating unit is 1,6-didehydro[10]annulene **(98)**, i.e. two conjugated polydiacetylenes. However, the annulene **98** is expected to be unstable. In fact, its cycloaromatization reaction to the 1,5-dehydronaphthalene diradical **99** was recently reported. The instability is considered to be due to in-plane repulsion of the face to face π-orbitals at sp-hybridized carbon in the annulene ring. Thus, the final structure of the polymers from octatetrayne derivatives after the thermal reaction may be either a planar cycloaromatized polymer and/or a three-dimensional polymer, which would be obtained if the polymerization proceeded in a different direction from that of the same column of the polymer side chain. To obtain the ladder polymer where two polydiacetylenes are conjugated in each repeating unit, it is necessary to keep the polydiacetylene backbones separated by conjugated divalent groups.

In this study, a dodecahexayne derivative with long alkyl substituents, i.e. 15,17,19,21, 23,25-tetracontahexayne (THY), was also synthesized as an extension of the study of the octatetrayne system. Its solid-state polymerization behavior was investigated using

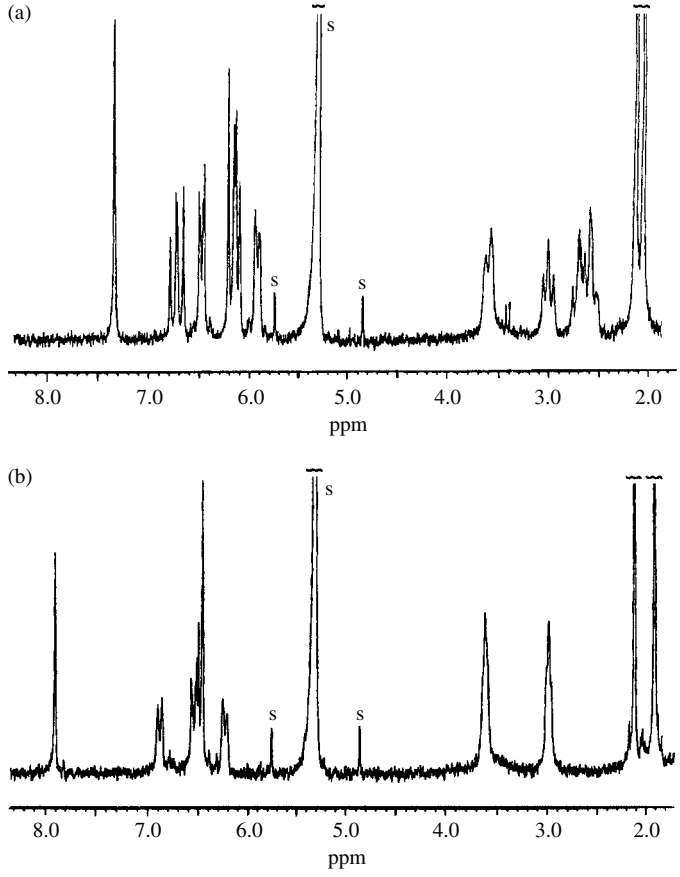


FIGURE 34. ^{1}H NMR spectra (200 MHz): (a) of cryptand **90** and (b) of its dinuclear Cu^{1} complex **92** in $C_2D_2Cl_4$. (s = solvent). Reproduced by permission of Neue Schweizerische Chemische Gesellschaft from Reference 52

IR and visible near-IR absorption, NMR, ESR and X-ray diffraction. It was emphasized that solid-state high-resolution ^{13}C NMR spectroscopy is a powerful tool for the structure analysis of polydiacetylenes. THY is particularly attractive because of its potential for forming the polydiacetylene ladder polymer.

The ^{13}C CP/MAS NMR spectrum taken 30 min after recrystallization of THY is shown in Figure 36A, and the ^{13}C chemical shift values of this spectrum together with those of the THY monomer in $CDCl_3$ solution are summarized in Table 35.

The assignment of the monomer solution spectrum was performed by using an NMR spectral database system (SDBS-NMR)[54]. The signals of the six acetylene carbons from 60.34 to 81.91 ppm in the solution spectrum indicated the monomer structure of a dodecahexyne derivative substituted symmetrically by alkyl groups. Since the spectral patterns in Figure 36A are almost the same as those of the monomer, only a small extent of polymerization had occurred during the 30 min after recrystallization. The signal at about

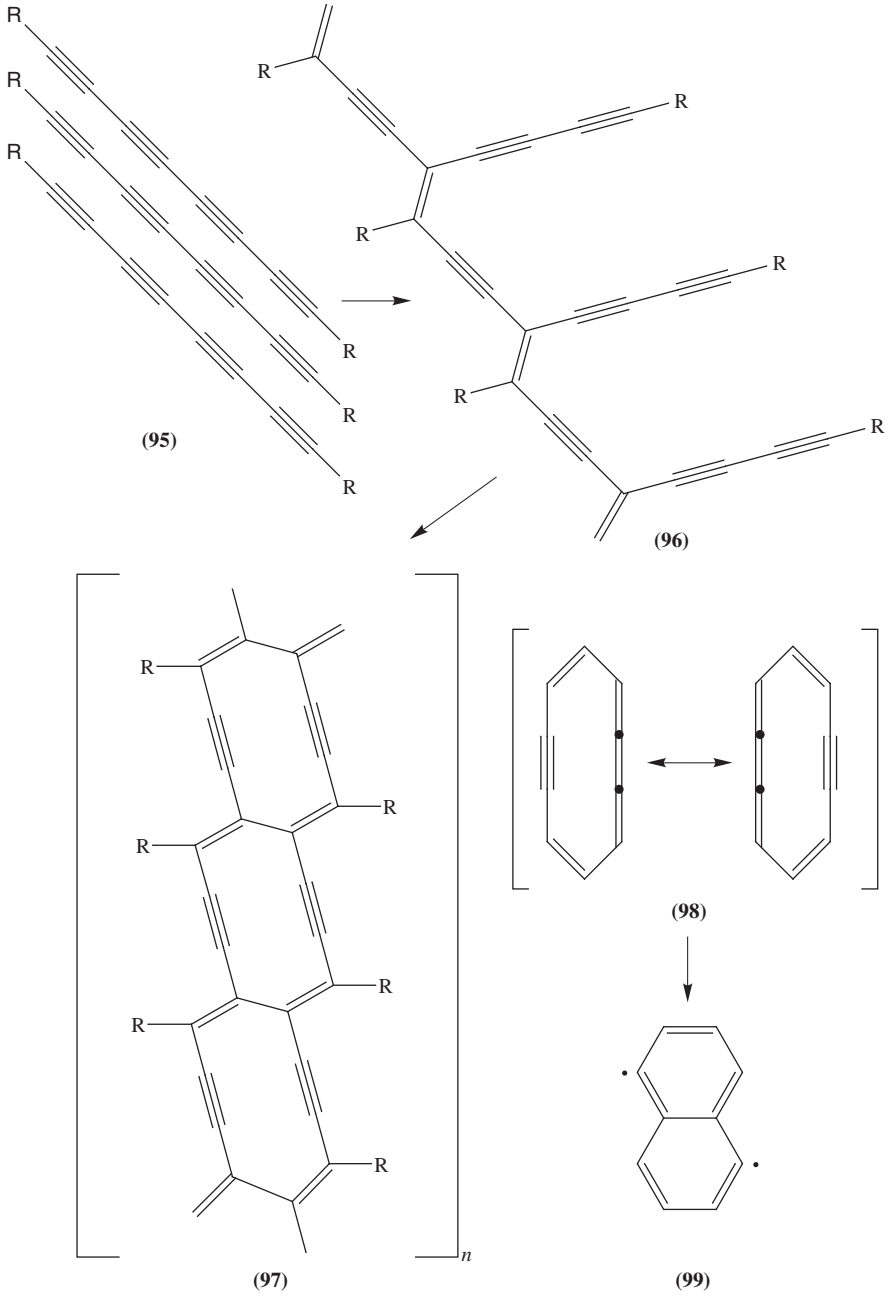


FIGURE 35. Polymerization schemes of octatetrayne derivatives and cycloaromatization of 1,6-didehydro[10]annulene (**98**). Reprinted with permission from Reference 53. Copyright (1994) American Chemical Society

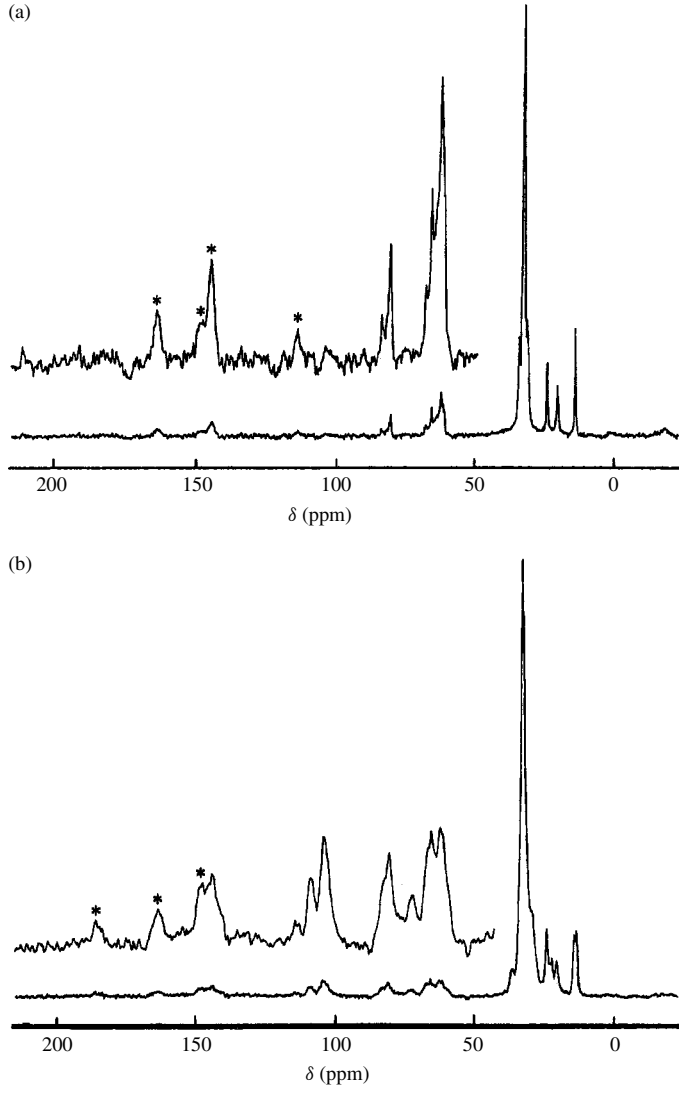


FIGURE 36. (a) ^{13}C CP/MAS spectrum of THY 30 min after recrystallization. Asterisks indicate spinning sidebands. The signals can be assigned to the THY monomer. (b) The spectrum after 22 h. The signals can be assigned to structure **100** shown in Figure 37. Reprinted with permission from Reference 53. Copyright (1994) American Chemical Society

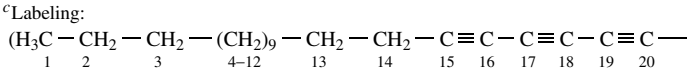
82 ppm is assigned to the acetylene carbons at position 15 next to the alkyl chain, which splits into two peaks with a separation of 3.3 ppm. Similarly, the signal of the acetylene carbons at position 16 splits with a smaller separation of 2.2 ppm.

Although the signals of other acetylene carbons are split, they overlap in a very small range between 62 and 64 ppm and are too complicated to be distinguished from each other.

TABLE 35. ^{13}C chemical shifts of the THY monomer in solution and THY in the solid state after 30 min

In solution[a] (δ_{sn})	In the solid state[b] (δ_{sd})	$\delta_{sd} - \delta_{sn}$	Assignment[c]
81.91	85.2	3.3	15
	81.9	0	
	69.2	3.6	16
65.61	67.0	1.4	
62.70	62–64[d]	1–2	17
62.36	d		18
61.46	d		19
60.34	d		20
31.92	35.4	3.5	3
28.82–29.64[e]	33.8[f]	4	4–12
27.83	32.5	4.7	13
22.69	25.6	2.9	2
19.52	21.8	2.3	14
14.14	15.4	1.3	1

[a] $CDCl_3$ solution.
[b] CP/MAS.
[c] Labeling:

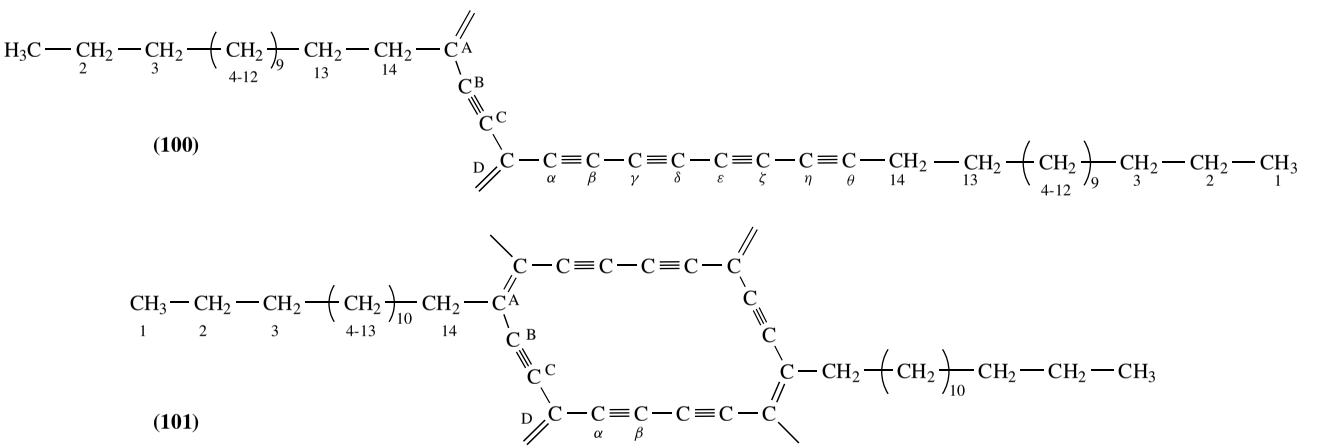


[d] Overlap each other.
[e] Separated seven peaks for nine carbons.
[f] Many peaks overlap.

The splitting of the resonances from carbons in the same position is due to polymorphism of the monomer in the solid state. A similar ^{13}C signal splitting was found in monomers of octatetrayne derivatives containing urethane groups. It was not observed, however, in the corresponding alkyl-substituted octatetrayne monomer of HTY (**95**). In the THY monomer spectrum, the ^{13}C chemical shifts in the solid state (δ_{sd}) move to the low-field side from those in solution (δ_{sn}), and these differences ($\delta_{sd} - \delta_{sn}$) are shown in Table 35. Large low-field shifts are generally observed when the packing of alkyl chains is tight. In the case of the corresponding alkyl-substituted octatetrayne derivative of HTY, a signal of the carbons originating from the mobile chains was observed as a sharp line with a ^{13}C chemical shift similar to that found in the solution spectrum. Since the THY monomer did not show such mobile carbon signals, it is suggested that the stacking of the alkyl chains of the THY monomer is more rigid than in the HTY monomer.

After about 3 h, additional peaks at 146, 111 and 106 ppm appeared and their intensities gradually increased. These three peaks were assigned to the unsaturated carbons in the asymmetrically-substituted polydiacetylene backbone with acetylene substituents. A ^{13}C spectrum obtained after 22 h, when those three peaks were clearly observed, is shown in Figure 36B.

The structure of the polymer in the first step of polymerization is presented in Figure 37. The symbols defining the carbons are given in this figure. In the spectrum in Figure 36B, the peak at 73 ppm was assigned to the acetylene carbon (α) of the side chain. These assignments were based on the ^{13}C spectra of the polymer obtained from HTY. Spectral changes also occurred in the alkyl carbon region. The peak at 38 ppm was assigned to the methylene carbon ($14'$) next to the olefin carbon in the polymer backbone. The intensity of the signal increased gradually concomitantly with those of the peaks for the polymer-backbone carbons. Simultaneously, the peak of the methylene carbon attached



(100)

(101)

FIGURE 37. Proposed polymer structures from THY obtained by solid-state polymerization at ambient temperature without irradiation. Reprinted with permission from Reference 53. Copyright (1994) American Chemical Society

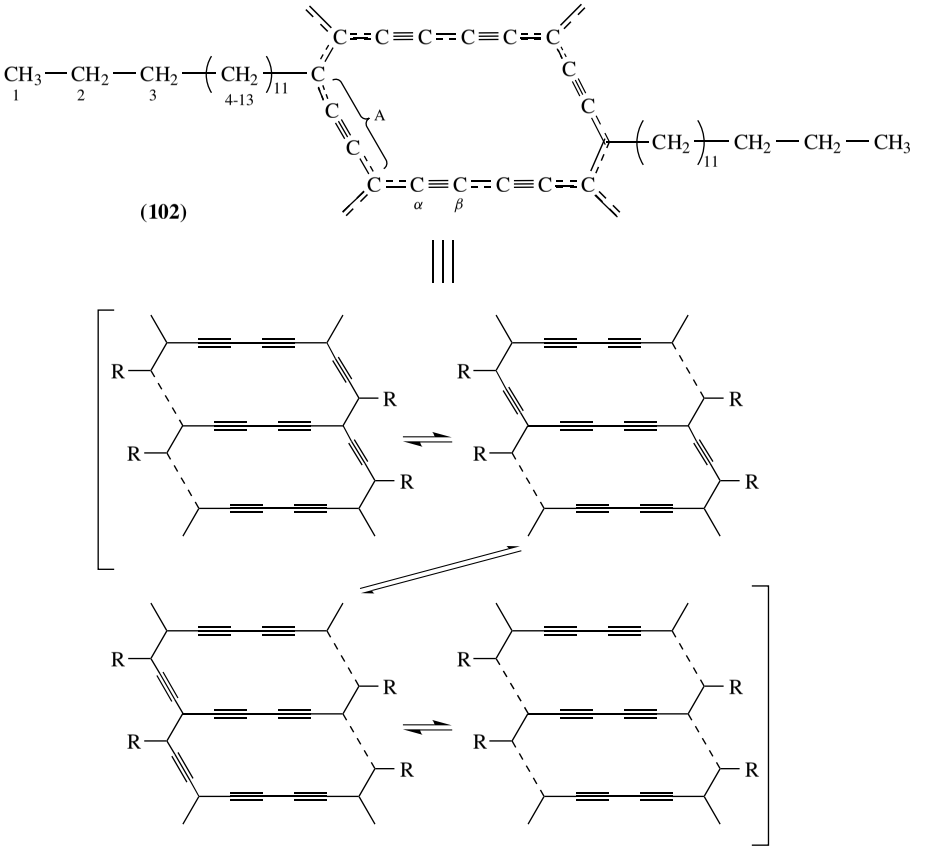


FIGURE 37. (*continued*)

to the acetylene moiety at 22 ppm decreased in intensity, and the relative intensities of the two peaks at 22 and 38 ppm became almost the same, as shown in Figure 36(b). The methyl carbon signal at 15.4 ppm came to have a shoulder on the higher field side and eventually separated to form a new peak at 14.6 ppm. After 22 h, the relative intensities of these two methyl carbon peaks became almost equivalent.

At this stage the main part of the crystals had changed from that of the monomer to **100** by the 1,4-addition. The ^{13}C chemical shifts of **100** are summarized in Table 36 together with those of the polydiacetylene with butadiynyl substituents (**96**) obtained from HTY.

The only difference between **100** and **96** is the acetylene carbon numbers in the side chains, i.e. six for **100** and four for **96**. However, the alkyl signals of **100** have a more complicated pattern than those of **96**. The signal positions of alkyl carbons attached to the acetylene side chain are assumed to be near those of the monomer, and those attached directly to the backbone may move to the higher field near those of the monomer in solution. The alkyl carbons bound to the polymer backbone and the acetylene group in **96** may be in similar situations since the ^{13}C peaks of the alkyl chain carbons in **96** do not split.

The ^{13}C spectral pattern for both the alkyl and the unsaturated carbon signals changed continuously. The ^{13}C spectrum measured after 56 h is shown in Figure 38(a).

The terminal methyl and methylene signals for the $-CH_2-CH_3$ moiety have become single lines, and the decreasing signals adjacent to the acetylene carbon around 22 ppm have disappeared, while the intensities of the signals at about 38 ppm from the newly formed methylene groups have increased. At the same time, the signal intensities of the main chain acetylene and olefin carbons in the region of 100–150 ppm have increased

TABLE 36. ^{13}C chemical shifts (CP/MAS) of **100** from THY and **96** from HTY

100	**96**	Assignment[a]
146	146.3	A
111.0	110.2	D
105.7	105	B, C
84		θ
82.1	80.7	β
73.2	72.6	α
67.0		ζ
67.0		η
65		ε
63.6	65.4	γ
63.6	88.7	δ
37.7	37.3	14′
35.2	[b]	3
33.8[c]	33.7[c], 31.3[c,d]	4–12
32.5	[b]	13
25.4	24.4	2
23.5		
21.9	22.3	14
15.4	14.8	1
14.6		

[a] For labeling of **100** see Figure 37.
[b] Broad signal,
[c] Many overlapping peaks.
[d] Mobile methylene carbons.

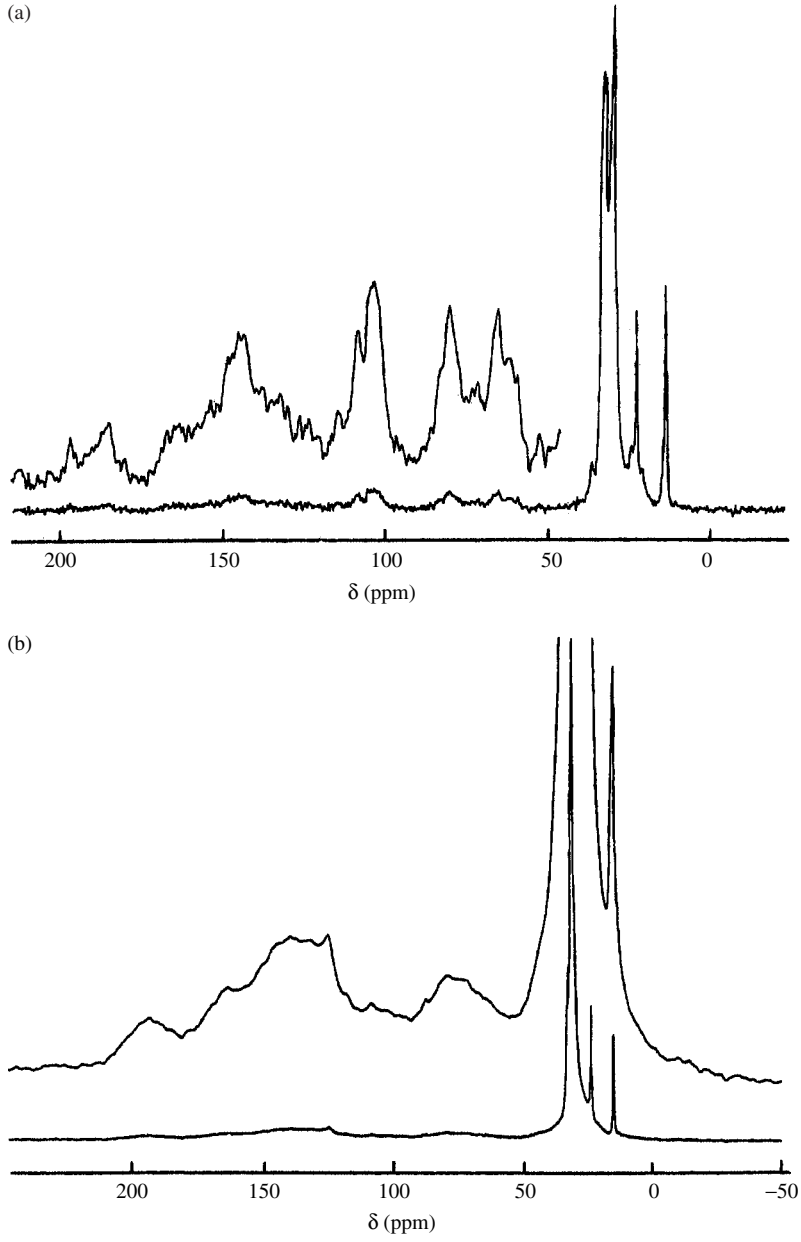


FIGURE 38. (a) ^{13}C CP/MAS spectrum of THY after 56 h. The proposed structure from this spectrum is the ladder polymer **101** shown in Figure 37. (b) The spectrum after 11 days. The proposed structure from this spectrum is the ladder polymer **102** shown in Figure 37. Reprinted with permission from Reference 53. Copyright (1994) American Chemical Society

relative to those of the side chain acetylene carbons (60–95 ppm), and signal patterns in the region for the unsaturated carbons became simpler than in the spectrum in Figure 36(b). The spectra measured successively during these periods indicate that the second step of polymerization occurred at the ξ- and θ-positions of **100** in the 1,4-polymerization scheme to produce a new ladder polymer **(101)**, as presented in Figure 37 (the symbols defining the carbons are also indicated). Such a ladder-type structure with an extended π-electron system was also supported by the absorption in the >900 nm region described above. The ^{13}C chemical shifts of **101** are summarized in Table 37.

Since polymer **101** has a symmetrical structure, the number of nonequivalent carbons in the conjugated system was expected to be five with an intensity ratio of 1 : 1 : 2 : 1 : 1, which corresponds to the carbon positions A : D : B + C : β : α. The ^{13}C chemical shift values are also expected to remain similar to those of **100**. Subsequently, five peaks were observed at 147, 110, 105, 82 and 67 ppm having relative intensities of 1 : 1 : 2 : 1 : 1, as shown in Figure 38. The signals at 82 and 67 ppm were assigned to the ladder carbons at the β- and α-positions of the polydiacetylene chains, respectively. The three different methylene peaks from 30 to 34 ppm were assigned to the long chain carbons 3–13 in different stacked states in the solid state. In Figure 38, broad signals were observed around 120–170 and 190 ppm, and their intensity gradually increased. The rate of spectral change slowed down at this stage.

After 11 days, the alkyl carbon signals became simpler and only four peaks were observed, as shown in Figure 38(b). In this spectrum, the backbone acetylene and olefin carbon signals (100–150 ppm) were observed. The integrated intensity of the ladder carbon signals between 60 and 90 ppm accounted for 30% of the signals for unsaturated carbons (60–220 ppm).

Since the starting monomer of THY is a hydrocarbon and the reactions took place spontaneously in the solid state, the resulting polymer should be a hydrocarbon. No oxidation was confirmed from the IR spectra. The most likely chemical structures giving signals in the region >180 ppm are allenes. It was assumed[54] that the predominant structures of the final polymer are allene-type ladder polymers **102**, as shown in Figure 37. There are few ^{13}C shift data to examine for these allene structures. It has been confirmed that the solid-state ^{13}C shifts of tetraphenylbutatriene agree well with the solution data for the α- and β-cumulene carbons to the phenyl groups, which are at 124.1 and 152.9 ppm,

TABLE 37. ^{13}C chemical shifts (CP/MAS) of **101**

101	Assignment[a]
147	A
110	D
107	B, C
82	β
67	α
37[b]	14
33.8[c], 30.6[c,d]	4–13
32.5	3
23.4	2
14.5	1

[a]For labeling of structure **101** see Figure 37.
[b]Broad signal.
[c]Many overlapping peaks.
[d]Mobile methylene carbons.

respectively. The effect of the number of double bonds has been studied in solution, and the carbons at the β-position from the substituents in the allenes having an even number of double bonds with an odd number of sp-carbons give peaks between 180 and 210 ppm. From comparison with the data of 2,4-dimethyl-2,3-pentadiene and tetraphenylpropadiene, the ^{13}C chemical shift values of the α- and β-carbons of the methyl derivative shift about 20 and 10 ppm to a lower field, respectively. Although model compounds for the proposed structure of **102** could not be found and the substituent effects on the ^{13}C chemical shifts for longer allene systems are uncertain, the ^{13}C chemical shift values observed in Figure 38(a) seem reasonable.

The ^{13}C NMR spectra were measured regularly over 6 months (190 days) and the polymer structure became almost stable after this period. After 6 months, the relative intensities in the unsaturated carbon region were independent of CP time. The alkyl signal positions became constant after 11 days (Figure 38(b)). However, their line width gradually broadened to double the width after 6 months.

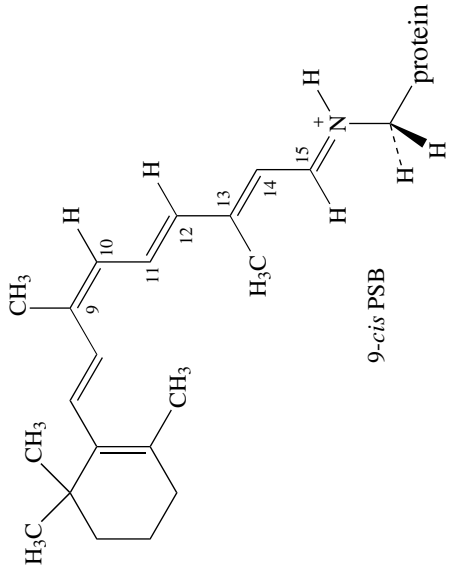
Smith and coworkers[55] reported a solid-state NMR study of the mechanism of the opsin shift in the visual pigment rhodopsin. They have presented solid-state NMR spectra of rhodopsin and isorhodopsin regenerated with retinal containing ^{13}C labels at each position along the conjugated chain of the chromophore. Comparison of the $^{13}C^*$ chemical shifts observed in the pigment with the corresponding chemical shifts of retinal PSB model compounds allowed them to examine the mechanism of the opsin shift in these pigments.

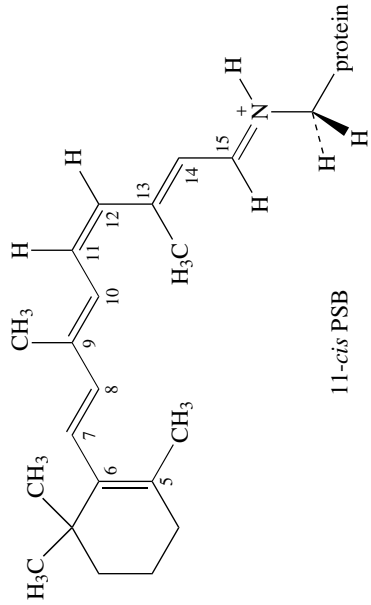
The chemical shifts for $^{13}C5$, $^{13}C6$, $^{13}C14$ and $^{13}C15$ correspond closely to the chemical shifts observed in the 9-*cis* and 11-*cis* PSB model compounds (shown below), while differences in chemical shifts are observed for C8 through C13, with the largest differences in both pigments localized at C13. These data provide support for the model of the opsin shift, which relies on a protein perturbation in the vicinity of C13. Concurrently, the results argue that the factors regulating the absorption wavelength in another well-studied retinal protein, bacteriorhodopsin, namely protein perturbations near the β-ionone ring (C5-$\cdots$C7), a 6-s-*trans* single bond and a weak hydrogen-bonding interaction with the Schiff base counterion, are not important in rhodopsin and isorhodopsin. Finally, in isorhodopsin a substantial shift is observed at C7, and only a small shift is present at C12. Taken together with resonance Raman results, these observations suggest that 9-*cis*- and 11-*cis*-retinals reside differently in the opsin binding pocket, in line with their significantly different opsin shifts (*ca* 1000 cm^{-1} less for isorhodopsin).

The general strategy for establishing the sites of protein–chromophore interactions in rhodopsin involves introduction of selective ^{13}C labels at each position along the length of the retinal chromophore.

Differences in the ^{13}C chemical shifts between rhodopsin and retinal PSB model compounds reveal the regions of the chromophore where changes occur in the retinal's structure or environment. Figure 39 presents several solid-state ^{13}C NMR spectra of rhodopsin that illustrate the resolution and sensitivity which can be obtained by using MAS methods.

In these spectra, the protein has been regenerated with retinal specifically ^{13}C labeled at positions 11, 12 and 13, and in each case the retinal resonance exhibits a sharp centerband at the isotropic chemical shift and is flanked by rotational sidebands. Other lines in the spectrum are the natural-abundance ^{13}C resonances of the protein carbonyls (*ca* 175 ppm) and aliphatic carbons (0–100 ppm). Contributions from the Ammonyx-LO detergent in these spectra are seen in the different intensities in the 0–100 ppm region. Ammonyx-LO does not exhibit NMR resonances above 100 ppm. Spectra of the 9-*cis* pigment isorhodopsin are similar. Table 38 summarizes the isotropic chemical shifts from the solid-state NMR spectra of rhodopsin regenerated with retinal ^{13}C labeled at each position along


protein
H
N
+
H
H
H
15
14
13
12
11
10
9
H
H
H
CH3
H3C
CH3
CH3
H3C
9-cis PSB


protein
H
N
+
H
H
H
15
14
13
12
11
10
9
8
7
6
5
H
H
H
CH3
H3C
CH3
CH3
H3C
11-cis PSB

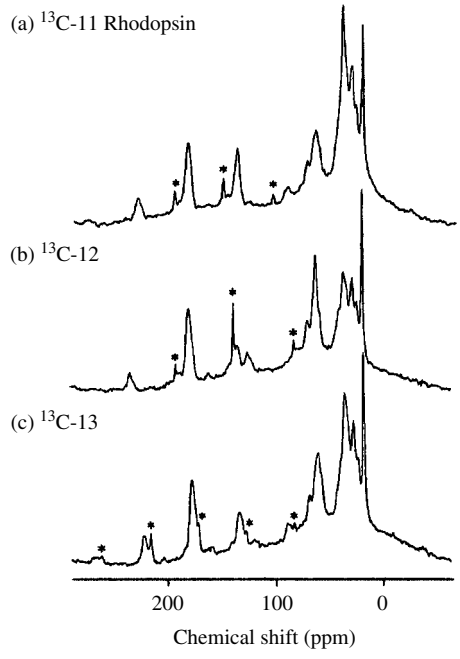


FIGURE 39. MAS ^{13}C NMR spectra of (a) ^{13}C-11, (b) ^{13}C-12 and (c) ^{13}C-13 rhodopsin. Centerbands and rotational sidebands of the retinal resonances are marked with asterisks. Reprinted with permission from Reference 55. Copyright (1990) American Chemical Society

TABLE 38. ^{13}C chemical shifts (ppm)[a] for rhodopsin and 11-*cis* PSB model compounds

Position	Rhodopsin	11-*cis*-PSB	
		Cl^{-}[b], *n*-propyl[c]	ClO_4^{-}[b], *t*-butyl[c]
5	130.3	131.7	132.0
6	137.7	137.2	137.5
7	132.3	132.3	132.2
8	139.2	137.2	137.0
9	148.5	146.6	146.8
10	127.8	126.4	127.7
11	141.6	137.5	139.1
12	132.1	129.0	129.4
13	168.9	162.7	166.0
14	121.2	121.3	119.5
15	165.4	163.9	160.0
19	12.0	12.5	12.5
20	168.8	18.8	18.0

[a]Chemical shifts are referenced to TMS.
[b]Designates the counterion to the PSB.
[c]Amine used to form the Schiff base.

the conjugated polyene chain. These data are compared with chemical shifts from two 11-*cis* PSB salts which differ in the amine and acid used to form the protonated Schiff base. The λ_{max} for the all-*trans*-retinal PSB perchlorate salt is at *ca* 470 nm in CCl_4 compared to *ca* 440 nm for the chloride salt. Thus, the bulky ClO_4^- counterion and *t*-butyl group may be inducing a weaker hydrogen bond at the Schiff base.

The differences in chemical shift observed between rhodopsin and the 11-*cis* PSB chloride salt are plotted in Figure 40. The shifts of ^{13}C5 through ^{13}C7, ^{13}C14 and ^{13}C15 in rhodopsin are close to their values in the 11-*cis* PSB model compound, while larger shift differences are observed at ^{13}C11 (4.1 ppm), ^{13}C12 (3.1 ppm) and ^{13}C13 (6.2 ppm).

Table 39 summarizes the isotropic chemical shifts from the ^{13}C NMR spectra of isorhodopsin along with chemical shift data from the 9-*cis* PSB chloride salt. The difference in chemical shifts between isorhodopsin and the 9-*cis* PSB are qualitatively similar to the differences observed between rhodopsin and the 11-*cis* PSB with the exception of C7, where a 4.3 ppm chemical shift difference is observed, and C12, where the difference, amounting to about 3 ppm in rhodopsin, has now vanished.

Some possible explanations for these differences in isorhodopsin are considered below. In both rhodopsin and isorhodopsin, the largest chemical shift difference is observed at C13. Recently, an analysis of the solid-state NMR spectrum of ^{13}C12 rhodopsin suggested that both the isotropic chemical shift and individual shift tensor elements shifted relatively to their values in bR[56]. These results were interpreted as indicating a strong protein interaction at C12. The authors have reexamined these shifts and found that, although the isotropic chemical shift moves slightly in comparison to the PSB model compounds (129 → 132 ppm), the principal values of the chemical shift tensor are largely unperturbed ($\sigma_{11} = 58$ ppm, $\sigma_{22} = 133$ ppm, $\sigma_{33} = 212$ ppm). This is illustrated in Figure 41, where difference spectra between labeled and unlabeled rhodopsin highlight the retinal resonance, and are compared with simulations using the shift tensor values obtained from the all-*trans* PSB model compound (Figure 41b) and from the previous ^{13}C12 rhodopsin spectra of Mollevanger and coworkers[56] (Figure 41c). In these spectra, the centerband (at the isotropic chemical shift) is at *ca* 130 ppm and is flanked by rotational sidebands spaced at the spinning frequency. The relative intensities of the centerbands and sidebands determine

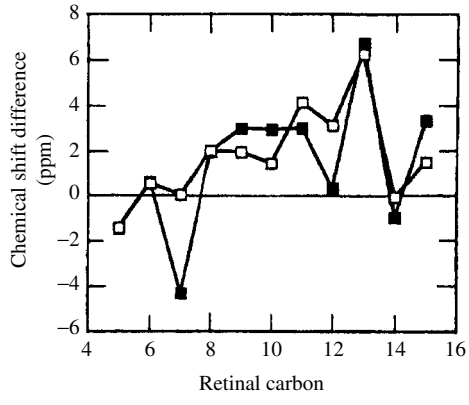


FIGURE 40. Plot of the differences in chemical shift observed between rhodopsin and the 11-*cis*-retinal PSB chloride salt (open squares), and between isorhodopsin and the 9-*cis*-retinal PSB chloride salt (closed squares), for retinal carbons along the polyene chain. Reprinted with permission from Reference 55. Copyright (1990) American Chemical Society

TABLE 39. ^{13}C chemical shifts (ppm)[a] for isorhodopsin and the 9-*cis* PSB *n*-butylammonum chloride salt

	Isorhodopsin	9-*cis* PSB
5	130.5	132.0
6	137.0	136.4
7	128.2	132.5[b]
8	131.1	129.2
9	147.5	144.5
10	130.8	127.9
11	139.3	136.3
12	133.9	133.6[b]
13	169.2	162.5
14	119.0	120.0
15	166.5	163.2
19	19.8	20.9
20	13.6	14.3

[a]All chemical shifts are referenced to TMS.
[b]The assignments of the C7 and C12 resonances in the 9-*cis* PSB may be reversed since on-resonance decoupling affects both resonances.

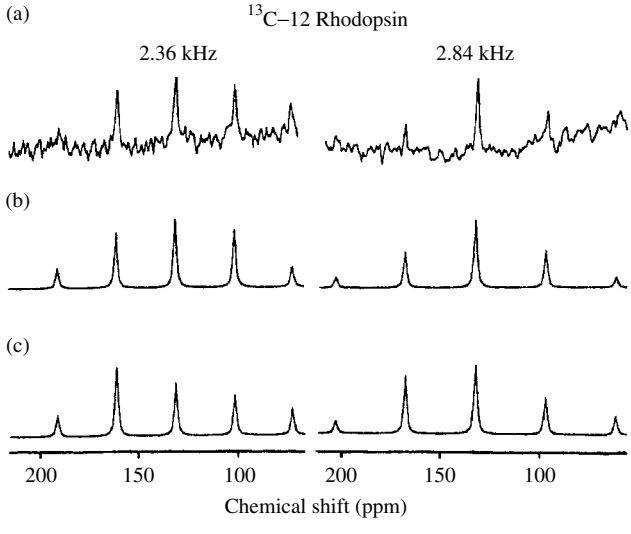


FIGURE 41. Solid-state NMR spectra of the ^{13}C-12 retinal resonance in rhodopsin (a) obtained by taking the difference between ^{13}C-12 rhodopsin and unlabeled rhodopsin spectra. Spectra were obtained at two spinning speeds, 2.36 kHz (left) and 2.84 kHz (right), and are compared with simulations (b and c) based on different chemical shift tensors. The simulations in (b) are for a chemical shift tensor having the principal tensor elements of the all-*trans* PSB chloride salt ($\sigma_{11} = 58$, $\sigma_{22} = 133$, $\sigma_{33} = 212$), while the simulations in (c) use the shift tensor values ($\sigma_{11} = 41$, $\sigma_{22} = 149$, $\sigma_{33} = 209$) obtained for $^{13}C12$ rhodopsin by Mollevanger and coworkers[56]. Reprinted with permission from Reference 55. Copyright (1990) American Chemical Society

the chemical shift tensor. Comparison of the intensity of the first sideband with the centerband intensity clearly shows the difference between the two simulations.

The experimental data closely resemble the simulation based on the all-*trans* PSB values. The discrepancy between the two solid-state NMR studies on rhodopsin arises in part from a difference, in signal-to-noise ratio and in part from possible problems associated with a fatty acid resonance which overlaps with the centerband in the previous study. The simulations illustrate the sensitivity of the sideband intensities to changes in the chemical shift tensor, as well as the quality of data necessary to accurately determine the shift tensor values.

2. ^2H static NMR

Ulrich and coworkers[57] reported a distorted structure analysis of the retinal chromophore in bacteriorhodopsin resolved by ^2H NMR. Measuring the orientations of its individual methyl groups reveals structural details about the geometry of the retinal chromophore in the binding pocket of bacteriorhodopsin. Solid-state ^2H NMR measurements were performed on macroscopically oriented samples of purple membrane patches, containing retina specifically deuterium-labeled at one of the three methyl groups along the polyene chain (C18, C19, C20). The deuterium quadrupole splitting of each 'zero-tilt' spectrum is used to calculate the orientation of the corresponding $C-CD_3$ bond vector with respect to the membrane normal; however, two possible solutions may arise. These ambiguities in angle could be resolved by recording a tilt series of spectra at different sample inclinations to the magnetic field and analyzing the resulting complex line shapes with the aid of computer simulations. The angles for the C18, C19 and C20 group are found to be $37 \pm 1^\circ$, $40 \pm 1^\circ$ and $32 \pm 1^\circ$, respectively. These highly accurate values imply that the polyene chain of the retinal chromophore is not straight but rather has an in-plane curvature and possibly an out-of-plane twist. Together with the angles of the remaining methyl groups on the cyclohexene ring that have been measured previously, an overall picture has thus emerged of the intramolecular conformation and the three-dimensional orientation of retinal within bacteriorhodopsin. The deduced geometry confirms and refines the known structural information on the chromophore, suggesting that this ^2H NMR strategy may serve as a valuable tool for other membrane proteins.

Immobilized proteins in uniaxially oriented membrane samples give rise to highly characteristic ^2H NMR spectra, when labeled at one specific position such as an individual methyl group. The deuterium quadrupole splitting and the spectral line shapes contain information about the bond vector that can be used for the structure determination[58]. Note that, due to the rapid spinning of the methyl group in the otherwise immobilized sample, the orientation of the three deuterium atoms are time-averaged and the effective bond vector corresponds to the methyl-rotor axis. Generally, there exists a simple relationship between the spectral quadrupole splitting $\Delta\nu Q$ and the angle θ of a $C-CD_3$ bond vector with respect to the magnetic field direction (equation 3):

$$\Delta\nu Q = 40(3\cos^2\theta - 1) \quad \text{(kHz)} \tag{3}$$

The scaling factor of 40 kHz was independently determined at $-60\,^\circ C$ from the powder spectrum of a random dispersion of a deuteriated PM sample[59]. This value was furthermore confirmed in the simulations of the ^2H NMR tilt series for each of the three labeled methyl groups, according to the total spectral width and line-shape arguments discussed by Ulrich and Watts[58].

Simple ^2H NMR spectra that can be readily interpreted are observed when the uniaxially oriented sample is aligned with its normal parallel to the spectrometer magnetic field

direction ('zero-tilt' spectrum). These spectra consist of a pair of resonances, separated by a certain quadrupole splitting which is determined by the orientation of the methyl group on the protein. In this experimental geometry, all the labeled bond vectors make the same angle θ with the sample normal and therefore also with the spectrometer field direction. All deuteriomethyl groups thus contribute the same quadrupole splitting $\Delta\nu Q$ to the overall spectral line shape. In practice, when the alignment of the membrane fragments in the sample plane is less than perfect, the mosaic spread of the sample gives rise to a certain degree of spectral line broadening.

From the quadrupole splitting in the zero-tilt spectrum of a single labeled methyl group, it should be straightforward to calculate the angle of that group relative to the membrane normal, using equation 3. However, only the absolute value and not the sign of the quadrupole splitting is measured from the spectrum, and positive and negative splittings cannot be discriminated.

Therefore, two solutions to equation 3 are obtained whenever $\Delta\nu Q < 40$ kHz, which corresponds to the range of angles between 35° and 90°. To resolve this ambiguity, Ulrich and Watts[58] have recently developed a strategy by which the value of the angle θ can be extracted uniquely from a series of measurements of the oriented sample at different inclinations to the spectrometer field. The line shapes of such a tilt series are considerably more complex than the simple zero-tilt spectrum described above, because the bond vectors are distributed over a range of different angles. Consider a cone of methyl group bond vectors being progressively tilted with respect to the reference direction of the spectrometer field. Depending on the cone opening angle θ, at any particular alignment relative to the field, the bond vectors assume a discrete range of angles. They all contribute their respective quadrupole splitting to the overall spectral line shape, which can be computed by summing up these overlapping contributions weighted by their corresponding probability density. A full tilt series can thus be analyzed quantitatively with the aid of computer simulations, or qualitatively by eye, revealing both the value and the sign of the quadrupole splitting, from which the angle is unambiguously defined between 0° and 90° with respect to the membrane normal.

The ^{2}H NMR spectra from three different bR samples (dark adapted) are shown in Figure 42, where the retinal is selectively deuteriated in the C18, C19 or C20 methyl group, respectively. The uniaxially oriented PM patches were measured with the membrane normal parallel to the spectrometer magnetic field, at −60 °C. Measurements at room temperature gave essentially the same spectra but with a poorer signal-to-noise ratio, and the line shapes were obscured by an isotropic resonance from the residual deuterium in the water. In each of the zero-tilt spectra in Figure 42, two broad resonances are seen with a respective quadrupole splitting (absolute value) of 36 kHz (for C18), 30 kHz (for C19) and 46 kHz (for C20). The initial step in the analysis consists of calculating the corresponding value(s) for θ from equation 3. In the case of the C20-labeled retinal with a (46 ± 1)-kHz splitting, the angle between the $C-CD_3$ vector and the membrane normal is found to be $\theta = 32 \pm 1°$. This solution is unambiguous, because the quadrupole splitting is larger than 40 kHz and must therefore be positive. The other two quadrupole splittings of 36 and 30 kHz from the C18 and C19 deuteriomethyl groups, on the other hand, each gives rise to two possible bond angles, depending on the sign of the splitting, which is not known. That is, with a measured $\Delta\nu Q$ of 36 kHz, a bond angle of $\theta = 37°$ or 73° is calculated for the C18 group, and a $\Delta\nu Q$ of 30 kHz for C19 gives $\theta = 40°$ or 73°, for positive or negative splitting, respectively. The correct bond angle can be distinguished by measuring a tilt series of ^{2}H NMR spectra, as illustrated in Figure 43.

The experimental data from the C19 deuteriomethyl group are given in the middle column, at seven different sample inclinations (α, angle between sample normal and spectrometer field direction) from 0° to 90° in the spectrometer. For comparison, the line shapes predicted by computer simulation are shown on either side of the experimental

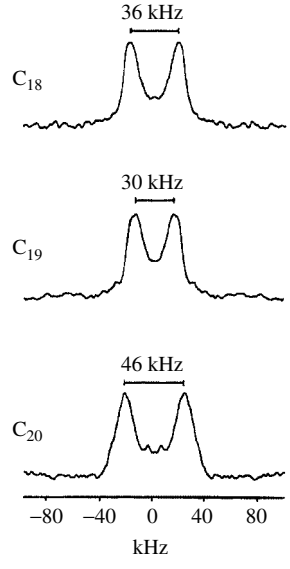


FIGURE 42. ^{2}H NMR spectra from three different bR samples containing retinals with the individually deuterium-labeled methyl groups C18, C19 and C20. Reprinted with permission from Reference 57. Copyright (1994) American Chemical Society

tilt series, with the simulation for $\theta = 40^\circ$ in the left-hand column and for $\theta = 73^\circ$ in the right-hand column. Note that only the zero-tilt simulations at $\alpha = 0^\circ$ in the top row are indistinguishable, regardless of the sign of the 30 kHz quadrupole splitting, which is positive in the left column ($\theta = 40^\circ$) and negative in the right column ($\theta = 73^\circ$).

Across the whole tilt series in Figure 43, a close resemblance is seen between the experimental spectra in the middle column with the simulated line shapes on the left ($\theta = 40^\circ$) but not with those on the right ($\theta = 73^\circ$). Therefore, the angle θ is uniquely identified to be $40 \pm 1^\circ$ for the deuteriated C19 group on retinal. A similar analysis for the C18 group ($\Delta\nu Q = 36$ kHz) yields an angle of $37 \pm 1^\circ$, and the other possible value of 79° is rejected. The experimental spectra of that tilt series plus those of C20 ($\Delta\nu Q = 46$ kHz, $\theta = 32^\circ$, see above) are shown in Figure 44, together with the superimposed best-fit line shape simulations.

The analysis of a full tilt series of ^{2}H NMR spectra not only allows the determination of the unique bond angle for a deuteriated methyl group, but also provides an internal check for the consistency of the spectral interpretation. In particular, simulations provide a means for the analysis of line-broadening effects, which arise from the sample mosaic spread as well as the intrinsic line width of the nuclear transition and instrumental factors. When line shapes are fitted to a full tilt series of spectra in a concerted manner and are also compared with the powder spectrum of an unoriented sample, the different contributions can be discerned. In that way an intrinsic line width of around 2 kHz is found for the spectra shown here, together with a mosaic spread between $\pm 8^\circ$ and $\pm 10^\circ$ for the three samples.

From the good fit to the experimental spectra it is thus evident that one characteristic angle θ describes the whole tilt series and that the underlying cone model for the bond vectors is consistent. The accuracy of the angles determined is estimated to be within

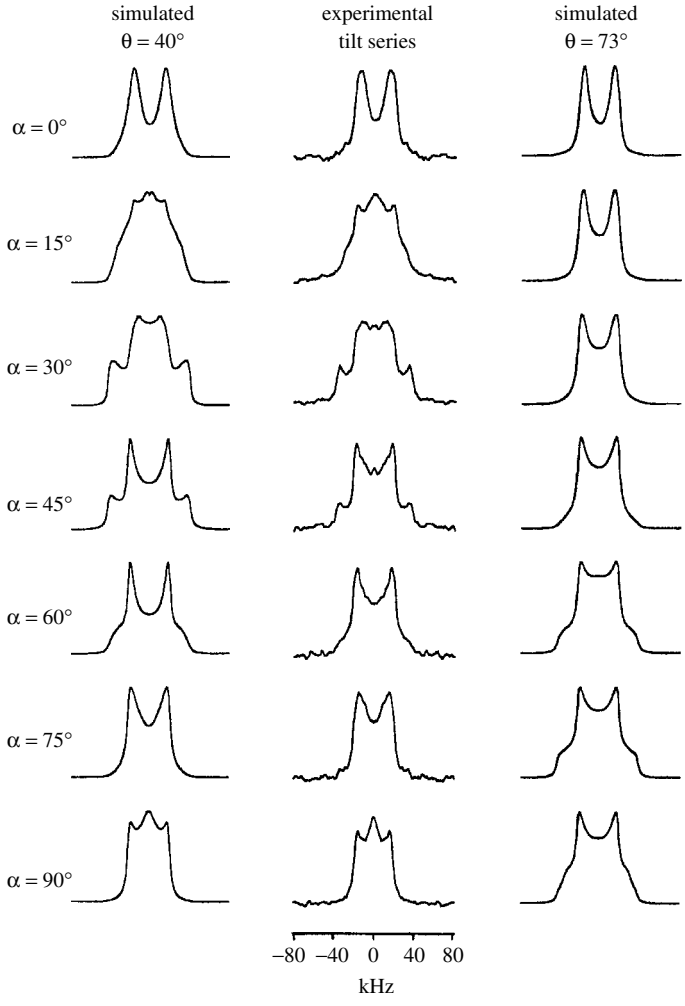


FIGURE 43. Tilt series of ^{2}H NMR spectra from the C19 deuteriomethyl group of retinal in oriented purple membranes, recorded at seven different inclinations (α) of the sample normal relative to the spectrometer field. Both the experimental data (middle column) and the two simulated series (outer columns) are characterized by an absolute quadrupole splitting of 30 kHz in the zero-tilt spectrum ($\alpha = 0^\circ$, top row). The simulations on the left are based on a methyl group angle of $\theta = 40^\circ$ which corresponds to a positive splitting, while the simulations on the right are based on $\theta = 73^\circ$ with a negative quadrupole splitting. Reprinted with permission from Reference 57. Copyright (1994) American Chemical Society

$\pm 1^\circ$, since the range around 45° is particularly sensitive as is seen from equation 3. A small change of 1° in θ would lead to a significant change in the quadrupole splitting of around 2 kHz in the zero-tilt spectrum. When the labeled segment is undergoing any small oscillations with a correlation time of less than $1/\Delta\nu Q$, *ca* 10^{-5} s, the angle obtained represents the time-averaged orientation of the methyl group.

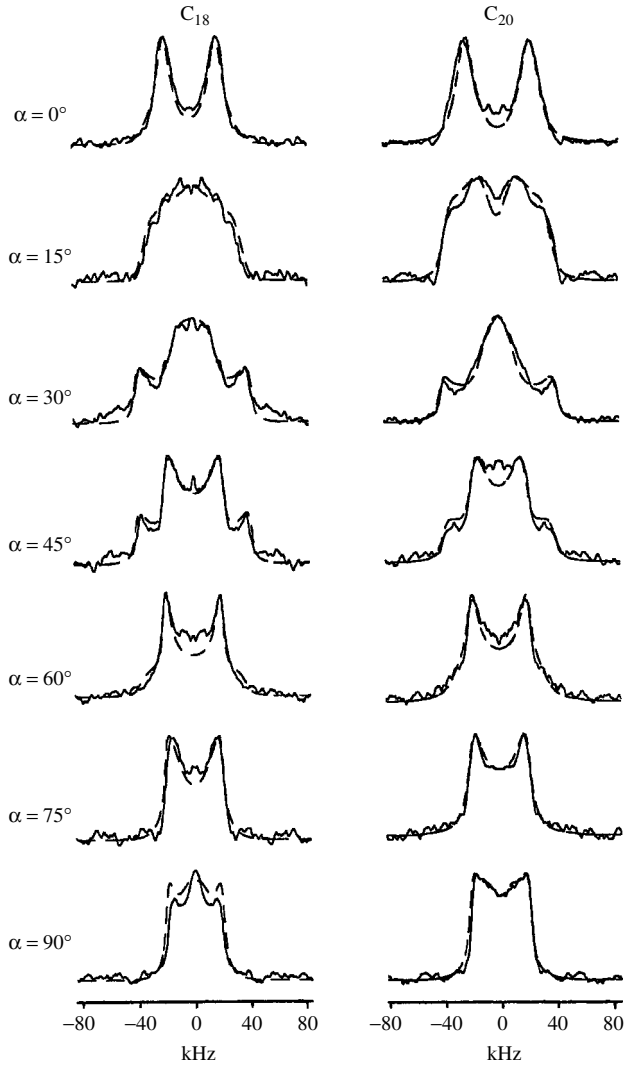


FIGURE 44. Tilt series of ^{2}H NMR spectra from the deuteriomethyl groups C18 (left column) and C20 (right column) of retinal in oriented purple membranes, at seven different sample inclination (α) in the spectrometer field. The line-shape simulations are superimposed over the experimental spectra in order to illustrate the good line fit obtained by the prediction method. Reprinted with permission from Reference 57. Copyright (1994) American Chemical Society

Figure 45 illustrates how all the different methyl group orientations with respect to the membrane normal N are accommodated in space by the proposed structure of retinal within bR. This picture is clear from the measured values of θ, which are indicated as labels to the individual methyl groups. The roughly parallel orientations of the two methyl groups, C18 ($\theta = 37°$) and C19 ($\theta = 40°$), demonstrate that retinal must have a

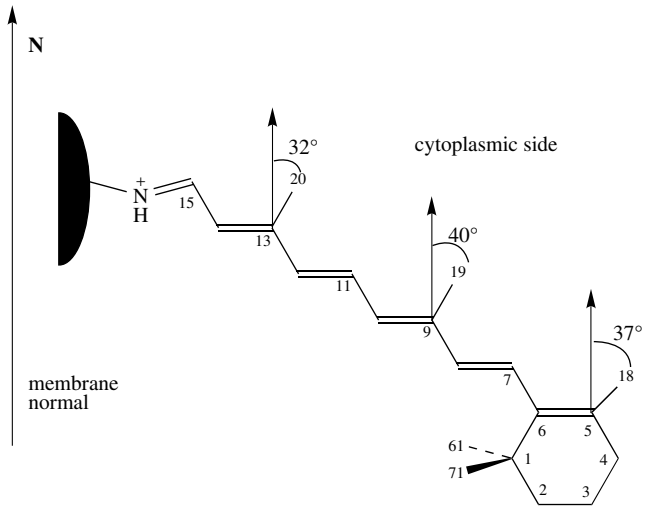


FIGURE 45. Orientation and conformation of retinal in bR, constructed from the individual methyl group orientations that have been determined by solid-state ^{2}H NMR. The angles θ of the C−CD_3 bond vectors with respect to the membrane normal (N) were evaluated for C_{18} (37°), C_{19} (40°) and C_{20} (32°) from the zero-tilt spectra shown in Figure 44 and with the aid of line-shape simulation of the tilt series in Figure 42 and 43. Reprinted with permission from Reference 57. Copyright (1994) American Chemical Society

6*s-trans* rather than a 6*s-cis* conformation when bound to bacteriorhodopsin. That is, a 180° rotation around the C6−C7 bond, which has a substantially lower energy barrier compared to the other single bonds of the conjugated system, would produce a structure that is incompatible with the measured angles. This conclusion confirms previous solid-state NMR studies that have proposed a 6*s-trans* chromophore from comparison with crystalline model compounds. By focussing on the specific angles of the three methyl groups, C18, C19 and C20, along the polyene chain, it is apparent that the chromophore backbone cannot be perfectly straight.

In an undistorted system of conjugated double bonds, the three methyl groups would be expected to be exactly parallel; however, in this case their individual orientations are not the same with respect to the membrane. In particular, the two neighboring methyl groups, C19 ($\theta = 40°$) and C20 ($\theta = 32°$), show that the carbon framework of the polyene chain must be distorted by an in-plane curvature and possibly an out-of-plane twist. The fact that the two methyl groups, C18 ($\theta = 37°$) and C19 ($\theta = 40°$), are not entirely parallel may be partially attributed to the additional rotational flexibility around the C6−C7 bond. It thus appears that the observed in-plane curvature, and possibly an out-of-plane twist, relieve the steric crowding of the three methyl groups (C18, C19 and C20) along the retinal chain, as well as the interference of the *gem*-dimethyl groups (C16 and C17) on the ring with the proton on C8. A more refined picture of the chromophore in terms of the individual bond and torsion angles could be obtained by computer modeling of the molecular framework to the set of geometrical constraints, i.e. to the measured methyl group orientations. However, since the in-plane and out-of-plane distortional modes are interdependent, it is not possible to quantify the contribution of each, and a family of plausible retinal structures which are compatible with the ^{2}H NMR results would emerge.

Ulrich and coworkers[59] reported the orientation and conformation of the cyclohexene ring of retinal in bacteriorhodopsin of the purple membrane of *Halobacterium halobium* by solid-state ^{2}H NMR spectroscopy, through the determination of individual chemical bond vectors (Figure 46). The chromophore ([2,4,4,16,16,16,17,17,17,18,18-^{2}H11] retinal) was specifically deuterium-labeled on the cyclohexene ring and incorporated into the protein. A uniaxially oriented sample of purple membrane patches was prepared and measured at a series of inclinations relative to the spectrometer field. Computer simulations were applied in the analysis of the ^{2}H NMR spectrum line shapes. From the deuterium quadrupole splittings, the specific orientations of the three labeled methyl groups on the cyclohexene ring could be calculated. The two adjacent methyl groups (on C1) of the retinal were found to be approximately horizontal to the membrane and make respective angles of $94^\circ \pm 2^\circ$ and $75^\circ \pm 2^\circ$ with the membrane normal. The third group (on C5) points toward the cytoplasmic side with an angle of $46^\circ \pm 3^\circ$. These intramolecular constraints indicate that the cyclohexene ring lies approximately perpendicular to the membrane surface and that it has a 6*s-trans* conformation. From the estimated angle of the tilt of the chromophore long axis, it is concluded that the polyene chain is slightly curved downward to the extracellular side of the membrane (Figure 47).

Figure 48 shows representative experimental ^{2}H NMR spectra from the labeled retinal in bR in a dark-adapted PM sample. The line shape simulations that were generated in the data analysis are superimposed on the experimental spectra. The powder pattern [Figure 48(a)] serves as a general reference for the tilt series of spectra recorded at various sample inclinations [Figure 48(b)], because it defines the accessible frequency region over which the spectral intensity can occur. The oriented sample was measured at every 22.5° between 0° and 90°, of which three inclinations are represented in Figure 48(b) with $\alpha = 0^\circ$, 45° and 90°.

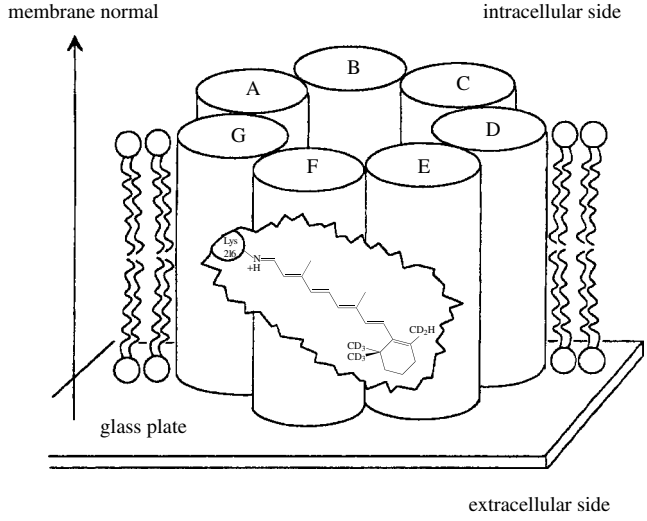


FIGURE 46. Retinal chromophore in bR is attached via a protonated Schiff base to Lys-216 on helix G and is tilted toward the extracellular side. To determine its detailed structure, retinal was selectively deuteriated on the three methyl groups on the cyclohexene ring and incorporated into bR from *H. Halobium*. Reprinted with permission from Reference 60. Copyright (1997) American Chemical Society

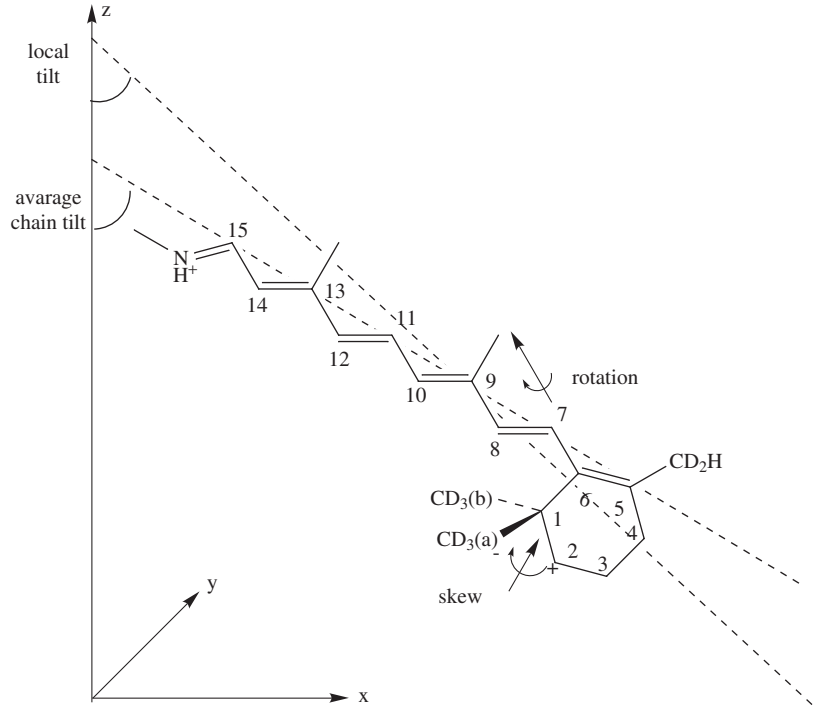


FIGURE 47. Three-dimensional structure of the cyclohexene ring of retinal in bR as determined by ^{2}H NMR, relative to the membrane surface in the $x-y$ plane. Analysis of the orientations of the three deuterium labeled methyl groups on the puckered ring (skew around C1–C6) indicates that the chromophore has a 6*s-trans* conformation around the C6–C7 bond. Reprinted with permission from Reference 60. Copyright (1997) American Chemical Society

With the sample aligned horizontally in the magnet, further spectra were recorded over a range of temperatures from 30° down to −120 °C. Representative line shapes are compared in Figure 48 for 21 °C (c) and −60 °C (b). The signal-to-noise ratio improves dramatically with decreasing temperature, and therefore the spectral analysis was based on the set of data acquired at −60 °C. The central resonance line which appears at temperatures above 0 °C is due to HDO. Two components appear to be resolved at 21 °C, but they are found to broaden and merge to give the unresolved line shape at −60 °C. A possible interpretation of this observation could be that some small local fluctuations within the puckered cyclohexene ring are frozen out in a slight glassy disorder, which is commonly found in crystalline retinal derivatives. Nevertheless, the overall line shape does not change significantly over the whole range of temperatures examined, and therefore the structure of the chromophore appears to remain relatively unaffected by freezing.

The characteristic shape of the ^{2}H NMR powder pattern [Figure 48(a)] indicates that the dynamics of the rotating methyl groups is within the fast-motional limit at temperatures down to −120 °C. This assumption is further supported by the increasing signal-to-noise ratio with decreasing temperature, since no loss, but rather a gain, in intensity is observed on cooling. It is also clear that the cyclohexene ring does not undergo significant librational

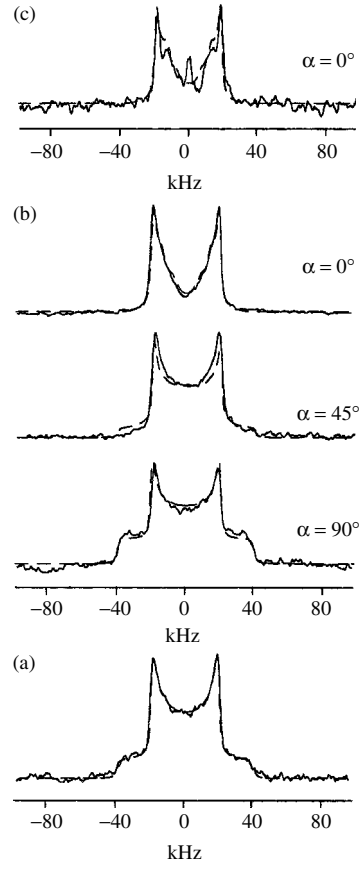


FIGURE 48. Representative ^{2}H NMR spectra (full lines) of dark-adapted bR (90 mg) containing deuteriated retinal, with line shape simulations (dashed lines) superimposed. Both the powder spectrum (a) from randomly oriented PM patches and the tilt series (b) over sample inclinations, $\alpha = 0^\circ$, 45° and 90°, were recorded at $-60\,^\circ$C (number of scans, 1.7×10^5, for $\alpha = 0^\circ$). Spectrum (c) was measured at $21\,^\circ$C with $\alpha = 0^\circ$ (number of scans, 3×10^5). Reprinted with permission from Reference 60. Copyright (1997) American Chemical Society

motion within its binding pocket, since the ^{2}H NMR spectra are not time-averaged by this type of random oscillation (with a correlation time $\tau_c < 10^{-6}$ s). The polyene chain of the chromophore has been shown to be completely immobilized on the time scale of $10^{-9}-10^{-2}$ s, indicating the absence of any rotational freedom.

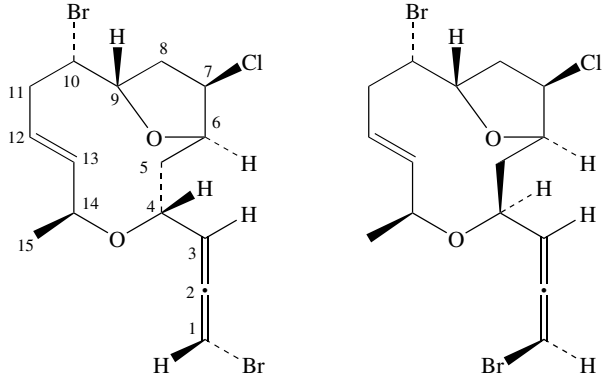
With a horizontally oriented sample ($\alpha = 0^\circ$), the spectrum of the labeled bR in Figure 48(b) should display three quadrupole splittings corresponding to the three labeled methyl groups on the retinal. It is apparent, however, that the expected three pairs of resonances are not resolved because of spectral overlap of the broadened lines. A computer simulation approach was used to analyze the spectral line shapes despite the overlap, but much qualitative information about the cyclohexene ring can be gained by simple inspection of the experimental data in Figure 48.

IV. SPECIAL TOPICS

A. Allenes

Allenes form a unique class of compounds which are dienes (or polyenes), but simultaneously they are the parent compounds for the interesting family of cumulenes. The NMR investigation of these compounds is interesting in view of their unique electronic and structural properties.

A new C15 bromoallene[60], dactylallene **(103)**, was isolated from the digestive gland of the anaspidean mollusc *Aplysia dactylomela*. The structure was established by using mainly one- and two-dimensional NMR techniques, whereas the absolute stereochemistry was determined by X-ray diffractometric analysis. Ichthyotoxicity and antifeedant activity suggests a defensive role of **103** against predators. The structure of **103** is given below together with that of its steroisomer **104**.



(103) **(104)**

The ^{1}H NMR spectrum displayed signals attributable to a secondary methyl at δ1.33 (H15, d, $J = 7.0$ Hz), six deshielded methines at δ4.00 (H-6), δ4.19 (H-4), δ4.38 (H-7), δ4.42 (H-14), δ4.48 (H-10), δ4.73 (H-9) and three methylenes at δ1.59 (H-5a, ddd, $J = 14.0$, 10.7 and 1.9 Hz) and δ1.69 (H-5b, m), δ2.40 (H-8a, m), and δ2.43 (H-8b, m), δ2.43 (H-11a, m) and δ2.89 (H-11b, m), strongly suggesting a nonterpenoid structure containing heteroatoms.

The presence of a bromoallene function was indicated both by two long-range coupled methine signals in the ^{1}H NMR spectrum at δ6.01 (H1, dd, $J = 5.8$ Hz and 1.7 Hz) and δ5.35 (H3, dd, $J = 5.8$ and 6.0 Hz) and by the resonances in the ^{13}C NMR spectrum at δ73.66 (C1), δ103.62 (C3) and δ200.99 (C2) (Table 40).

However, dactylallene **(103)** differs from **104** mainly in the chemical shifts of C14 (δ70.54 in **103**, δ61.26 in **104**), C4 (δ64.68 in **103**, δ76.34 in **104**) and C15 (δ14.05 in **103**, δ21.19 in **104**), suggesting a different relative stereochemistry for C4 or C14. However, the difference between the δ values for C4 and C14 in **103** and **104** is too large to be justified only by a different relative stereochemistry at the chiral center C4 or C14; it is most likely that these assignments in **104** should be reversed. In addition, the sign of $[\alpha]_D$ of **103**, opposite to that of **104**, indicated a different absolute stereochemistry of the allene residue, which could be predicted as S according to the Lowe–Brewster's rule[61].

Barretta and coworkers[62] reported an assignment of the absolute configuration of chiral allenes, which is usually a difficult task. The problem has been solved by suitable chemical

TABLE 40. ^{1}H and ^{13}C NMR data[a,b] for dactylallene **(103)**

Position	$\delta^{1}H$	m	J(Hz)	$\delta^{13}C$	m[c]	Long-range connectivities[d]
1	6.01	dd	5.8 and 1.7	73.66	d	H3
2				200.99	s	H1, H3, H4
3	5.35	dd	5.8 and 6.0	103.62	d	H1, H4, H5a
4	4.19	m		64.68	d	H1, H3, H5a, H14
5	1.59	ddd	14.0, 10.7, 1.9	37.05	t	H4
	1.69					
6	4.00	m		76.69	d	H5b, H7, H8, H9
7	4.38	m		62.51	d	H6, H8
8	2.40	m		38.61	t	
	2.43					
9	4.73	m		78.26	d	H7, H11
10	4.48	m		49.96	d	H8, H11
11	2.43	m		37.84	t	H9
	2.89					
12	5.79	m		128.23	d	H11, H14, H15
13	5.72	m		128.23	d	H11, H14, H15
14	4.42	m		70.54	d	H4, H12, H13, H15
15	1.33	d	7.0	14.05	q	

[a]Bruker AMX 500 MHz, $CDCl_3$; δ values are reported in ppm referred to $CHCl_3$ (δ_H 7.26) and to $CDCl_3$ (δ_C 77.0).
[b]Assignments determined by $^{1}H^{13}C$HETCOR, $^{1}H^{1}H$COSY, $^{1}H-^{1}H$ decoupling experiments.
[c]Determine by DEPT sequence.
[d]By HMBC (J = 10 Hz).

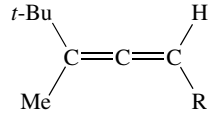
correlations of allenes with centrodisymmetric molecules of known absolute configuration or by developing semiempirical rules, which relate the absolute configuration to the sign of the rotatory power or CD bands.

An alternative approach is provided by NMR spectroscopy. Separate NMR signals can be in principle obtained for stable or short-lived diastereomeric derivatives of the enantiomeric mixtures, the intensities of which are correlated with the enantiomeric composition and their relative stereochemistry to the absolute configuration. For this reason, great effort has been continually devoted to the development of new chiral auxiliaries for NMR spectroscopy. The majority of these are dedicated to the chiral assay of molecules having polar functional groups.

Recently, it was found that the commercially available heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (permethylated β-cyclodextrin, TRIMEB), induced nonequivalence in the ^{1}H NMR spectra, in CD_3OD, of enantiomeric mixtures of trisubstituted allenes devoid of polar functional groups, thus affording a simple and general way to determinations of their enantiomeric purity[63].

The authors reported that a consistent correlation exists between the absolute configuration of the trisubstituted allenes **105a–e** and the permethylated β-cyclodextrin induced shifts of their proton signals. Hence the use of TRIMEB as chiral auxiliary for the rapid and reliable NMR determination of their absolute configuration was proposed. The enantiomeric purities of the samples have been determined by analyzing the ^{1}H NMR spectra of their mixtures with permethylated β-cyclodextrin (with TRIMEB/allene molar ratios of 1–2) in CD_3OD solutions. In all cases TRIMEB distinguished between the two enantiomers of each of the allenes **105a–e**. The corresponding spectral regions relative to the resonances of the allene protons of the substrates in the presence of the cyclodextrin are reported in Figure 49. The bromoallene (*R*)-**105a** showed the major signal at 6.10 ppm, at

higher field than the minor signal corresponding to the (*S*)-allene at 6.14 ppm. The allenes **105b–e**, having (*S*)-absolute configuration, generated from the bromoallene **105a**, showed a major signal (at 6.12, 6.13, 7.02 and 6.09 ppm for **105b**, **105c**, **105d** and **105e**, respectively), which was at lower field than the minor signal due to the (*R*)-allene (at 6.09 ppm for **105b–c**, 6.95 ppm for **105d** and 6.06 ppm for **105e**). For the (*R*)-allenes **105b–e**, it has been also verified that the allene absorption of the (*R*)-enantiomers resonates at higher field with respect to the same signal of the (*S*)-enantiomer. It is noteworthy that the same kind of correlation between the sense of nonequivalence, i.e., the relative position of the absorption of one enantiomer with respect to the other, and the absolute configuration has been found for the alkyl protons: all the proton signals due to the (*S*)-enantiomer are lower field shifted with respect to the corresponding signals due to the (*R*)-enantiomer (Table 41).



(**105**)

(**a**) R = Br
(**b**) R = Ph
(**c**) R = *p*-FC_6H_4
(**d**) R = α-Naph
(**e**) R = *p*-$MeOC_6H_4$

In conclusion, the most important result is that the use of permethylated cyclodextrin as chiral solvating agent for NMR spectroscopy not only affords a simple and practical way for the determination of the stereochemical purities of trisubstituted allenes, but also allows one to simultaneously determine their absolute configuration. Indeed, TRIMEB induced only positive complexation shifts of all the allene protons, which are greater for the (*S*)-enantiomer than for the (*R*)-enantiomer, independent of the structure of the allene. This empirical correlation seems to be reliable since it has been satisfied by a large number of trisubstituted allenes.

The method is undoubtedly very attractive from the practical point of view: it only requires the acquisition of a routine NMR spectrum for the suitable allene/TRIMEB mixture.

With the aid of ^{13}C NMR, ^{6}Li NMR and ^{1}H HOESY (heteronuclear Overhauser effect spectroscopy) NMR of α-lithiomethoxyallene **(106)** and 1-lithio-1-ethoxy-3-*t*-butylallene **(107)** as well as by *ab initio* model calculations on monomeric and dimeric α-lithiohydroxyallene, Schleyer and coworkers[64] proved that **106** and **107** are dimeric in THF (**106** forms a tetramer in diethyl ether) with a nonclassical 1,3-bridged structure. The ^{13}C NMR spectrum of allenyllithium in THF is also in agreement with the allenic-type structure: the chemical shift of C2 (196.4 ppm) resembles that of neutral allene (212.6 ppm), rather than C2 of propyne (82.4 ppm).

The structures of **106** and **107** were also investigated in ether and THF solutions by using IR and NMR methods. Compound **107** was synthesized in order to avoid problems with the rapid rearrangement at $> -20\,^{\circ}C$ of **106** to an alkynyllithium derivative. The lithiomethoxyallene had to be synthesized at *ca* $-78\,^{\circ}C$ in THF or diethyl ether and it was measured *in situ* without isolation of the metalated product. Its NMR data are given in Table 42.

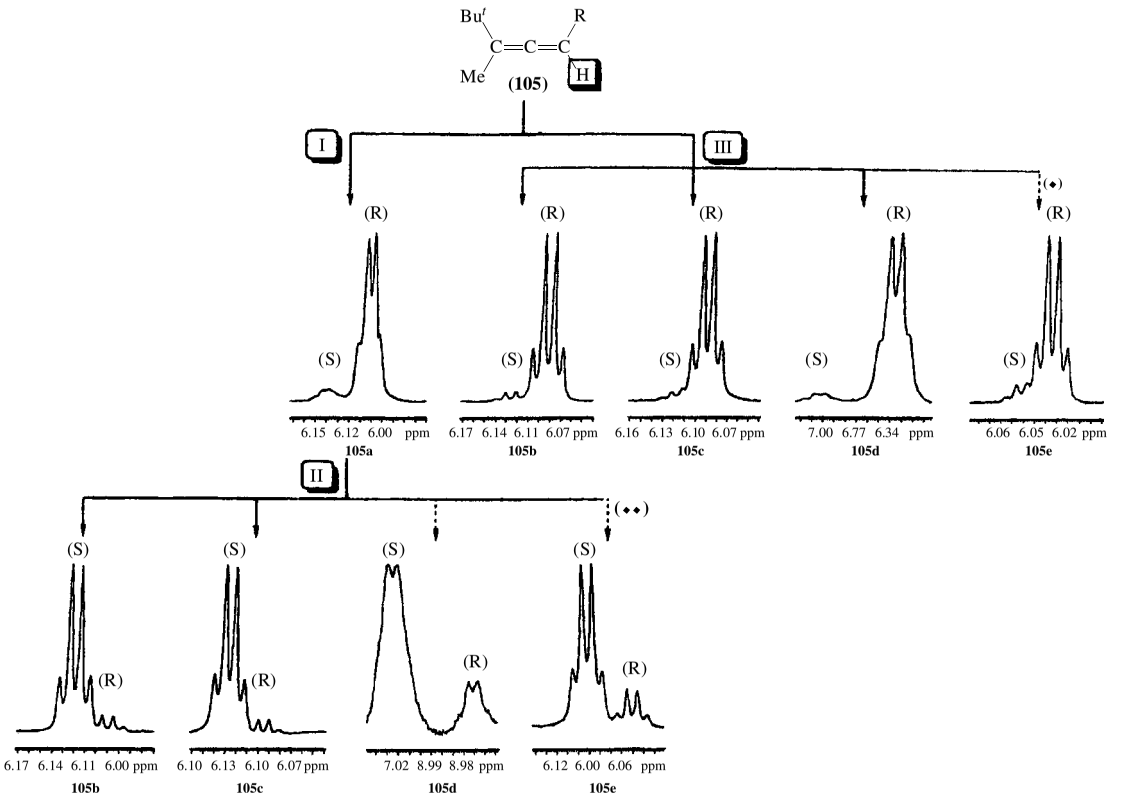
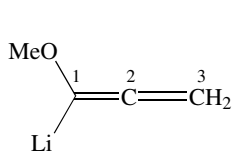


FIGURE 49. ^{1}H NMR (300 MHz, CD_3OD) spectra of samples of allenes **105a–e** obtained by starting from (*S*)-**105** (ee 89%): Spectral regions corresponding to the allene proton absorptions for mixtures TRIMEB/allene (molar ratio 1 : 1 for **105a–c, e** and 2 : 1 for **105d**), at −20 °C for **105a–c, e** and at −40 °C for **105d**. (♦) (*R*)-**105e** was obtained by starting from a sample of (*S*)-**105** with lower enantiomeric purity (81%). (♦♦) (*S*)-**105d–e** were obtained by starting from a sample of **105a** with lower enantiomeric purity (64%). Reprinted with permission from Reference 62. Copyright (1995) American Chemical Society

TABLE 41. Complexation shifts ($\Delta\delta^a$, 300 MHz, CD_3OD) induced by TRIMEB on the two enantiomers of allenes **105a–e**

Allene	$\Delta\delta_S$			$\Delta\delta_R$				Molar
	H	Me	*t*-Bu	H	Me	*t*-Bu	T(°C)	ratio
105a	9.88	3.48	3.30	7.69	2.38	2.93	25	1 : 1
	40.55	11.16	8.20	29.88	7.93	6.55	−20	1 : 1
105b	7.05	5.14	4.12	5.43	4.18	3.68	25	1 : 1
	23.83	12.52	10.27	15.59	9.22	7.89	−20	1 : 1
105c	4.86	1.72	1.62	2.21	0.47	0.59	25	1 : 1
	22.75	9.02	7.78	11.58	5.01	4.49	−20	1 : 1
105d	9.15	4.40	4.40	5.67	2.20	2.57	25	1 : 2
	67.41	21.70	25.35	42.05	10.99	14.55	−40	1 : 2
105e	8.23	4.03	3.66	3.94	1.83	1.47	25	1 : 1
	26.85	11.88	10.50	10.14	5.42	4.64	−20	1 : 1

[a] $\Delta\delta = \delta_{mixture} - \delta_{free}$, Hz.



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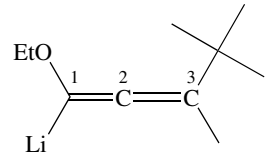

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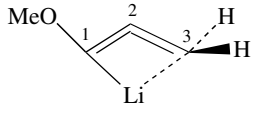
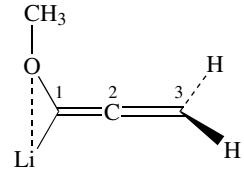


(108)



(109)

In **106**, the ^{13}C signal of C1 is shifted *ca* 30 ppm downfield and the C3 signal is shifted *ca* 20 ppm upfield compared with the parent compound. The essentially unchanged C2 signal at *ca* 195 ppm proves an allenic structure for **106** both in THF and in diethyl ether. The C1 ^{13}C signal of a ^6Li-labeled lithiomethoxyallene exhibits scalar $^{13}C^6Li$ coupling, a quintuplet [$^1J(^{13}C^6Li) = 6.0$ Hz] at −100 °C in THF indicates a dimer and a septuplet [$^1J(^{13}C^6Li) = 4.5$ Hz] at −93° in diethyl ether indicates a tetrameric aggregate (Figure 50).

In addition, the C3–H coupling constant (from a gated decoupling NMR experiment) of 161.8 Hz in **106** compared with 162 Hz in allenyllithium vs 167.5 Hz in methoxyallene and 168 Hz in allene is also in agreement with an allenic structure. However, neither the C–H coupling constant nor the NMR chemical shifts distinguish between the alternatives that **106** has a nonclassical 1,3-bridged structure **108** (M = Li) or an *O*-coordinated allenic structure **(109)**. Hence the ^6Li, ^1H-HOESY NMR technique which can be used to detect close proximities (*ca* < 3.5 Å) between ^1H and ^6Li nuclei was applied. The HOESY spectrum of α-lithiomethoxyallene in THF solution (in which **106** is dimeric) is shown

TABLE 42. NMR data (δ in ppm) of α-lithiomethoxyallene (**106**) and 1-lithio-1-ethoxy-3-*tert*-butylallene (**109**) and their neutral parent compounds

		C1	C2	C3	C4	C5	OCH_2/OCH_3	OCH_2CH_3
Methoxyallene	^{1}H NMR (26 °C,$CDCl_3$)	6.77 (t, 6.1 Hz)		5.48 (d, 6.1 Hz)			3.41 (s)	
Methoxyallene	^{13}C NMR (26 °C,$CDCl_3$)	122.8	201.1	91.2			55.8	
106	^{1}H NMR (−86 °C, 0.71 M in THF-d_4)			3.81 (s)			3.31 (s)	
106	^{13}C NMR (−100 °C, 0.82 M in THF-d_4)	154.1	194.1	67.0			57.7	
106	^{13}C NMR (−93 °C, 1.26 M in Et_2O)	150.4	195.4	69.8			56.7	
1-Ethoxy-3-*tert*-butylallene	^{1}H NMR (25 °C, $CDCl_3$)	6.7 (d, 6 Hz)		5.8 (d, 6 Hz)		1.1 (s)	3.6 (q, 6 Hz)	1.3 (t, 6 Hz)
1-Ethoxy-3-*tert*-butylallene	^{13}C NMR (25 °C, acetone-d_6)	122.5	190.1	117.1	32.9	29.2	63.4	14.3
107-$TMEDA_{0.5}$	^{1}H NMR (−30 °C, 0.44 M in THF-d_4)			4.34 (s)		0.95 (s)	3.59 (q, 6.0 Hz)	1.14 (t, 6.0 Hz)
107-$TMEDA_{0.5}$	^{13}C NMR (−30 °C, 0.44 M in THF-d_4)	159.3	188.1	96.8	32.7	31.6	64.6	16.1
107	^{13}C NMR (−92 °C, 1.20 M in THF, ext. acetone-d_6)	157.9 158.0	186.5 186.4	95.4	31.8	30.5	63.7 63.6	14.6

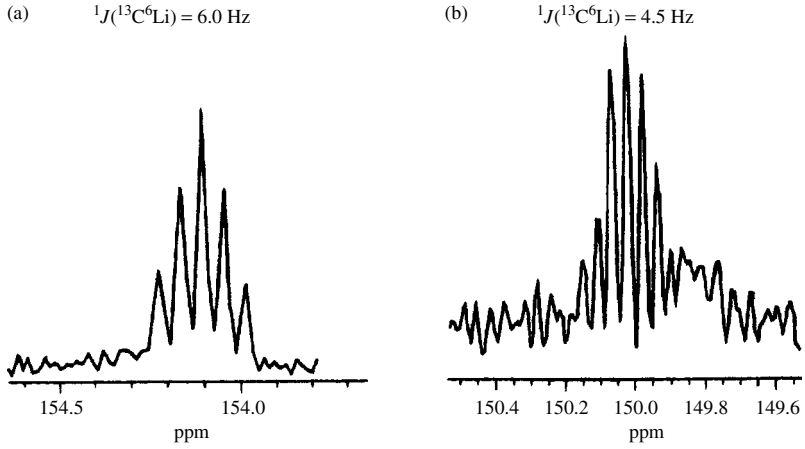


FIGURE 50. C1 ^{13}C NMR signal of ^6Li-labeled α-lithiomethoxyallene **(106)** in THF-d_8 at $-100\,^\circ C$ and (b) in diethyl ether at $-93\,^\circ C$. Reprinted with permission from Reference 64. Copyright (1993) American Chemical Society

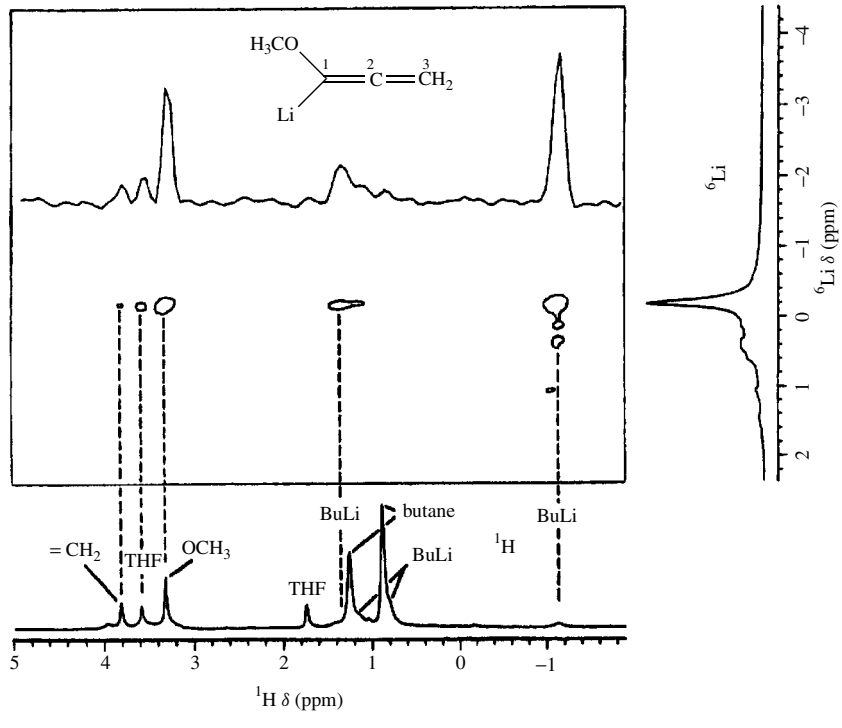


FIGURE 51. ^6Li ^1H-HOESY spectrum of ^6Li-labeled α-lithiomethoxyallene **(106)** (0.71 M) in THF-d_8 at $6\,^\circ C$. Mixing time 2.0 s. Reprinted with permission from Reference 64. Copyright (1993) American Chemical Society

in Figure 51. Besides cross peaks between the Li signal and the protons of excessive *n*-BuLi and of THF, there are two cross peaks involving the lithioallene: one to the methoxy protons at 3.31 ppm and one to the CH_2 protons of the allenic moiety at 3.81 ppm.

In analogy to **106**, significant changes in the ^{13}C NMR spectrum of **107** in THF are only observed for C1 and C3 compared with the neutral parent compound. The C1 ^{13}C signal of a ^{6}Li-labeled compound **107** is split into a six-line multiplet (Figure 52).

This is interpreted as the superposition of two quintuplets [$^{1}J(^{13}C^{6}Li) = 6.5$ Hz] which are separated by *ca* 6.5 Hz.

Since **107** is chiral, the two quintuplets are assigned to a pair of enantiomeric dimers (*RR*-dimer and *SS*-dimer) and to the diastereomeric *meso* form of a dimer (*RS*-dimer). Because both diastereomeric dimers of **107** are formed in approximately equal amounts, the difference in the chemical shift of C1 of both diastereomers is approximately equal to the coupling constant, and a six-line multiplet results. In addition, two equally intense singlets are observed for each C2 and OCH_2 carbon atoms of the two diastereomers. A ^{6}Li ^{1}H-HOESY spectrum of 8-$TMEDA_{0.5}$ in THF (Figure 53; TMEDA = tetramethylethylenediamine) shows ^{6}Li cross peaks to all protons of the lithioallene and the TMEDA molecules. Again, the cross peak due to the H3 proton at 4.34 ppm indicates a 1,3-bridged structure for **107**.

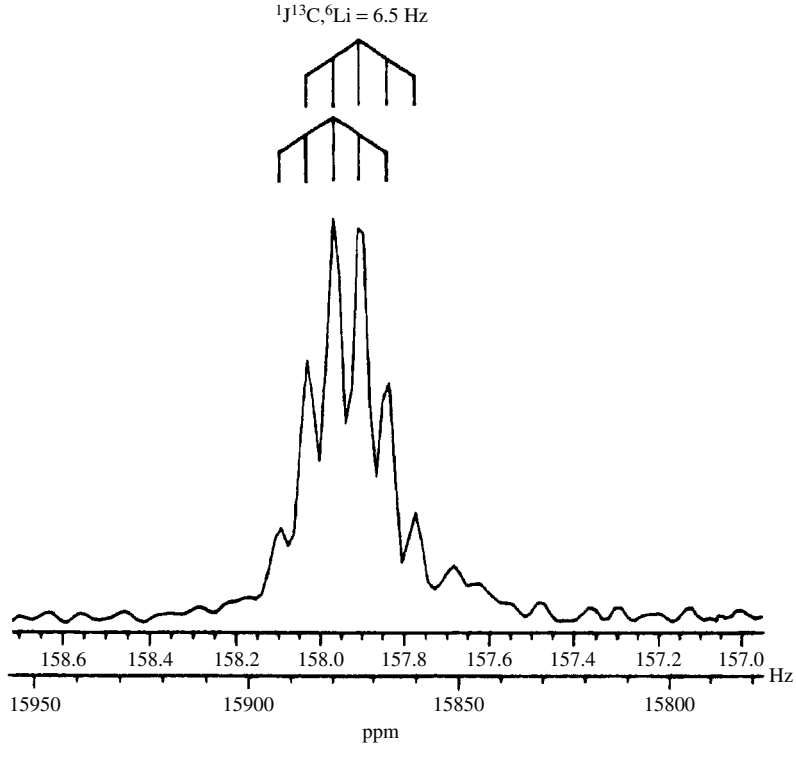


FIGURE 52. C1 ^{13}C NMR signal of ^{6}Li-labeled 1-lithio-1-ethoxy-*t*-butylallene **(107)** in THF-d_8 at -92 °C. Reprinted with permission from Reference 64. Copyright (1994) American Chemical Society

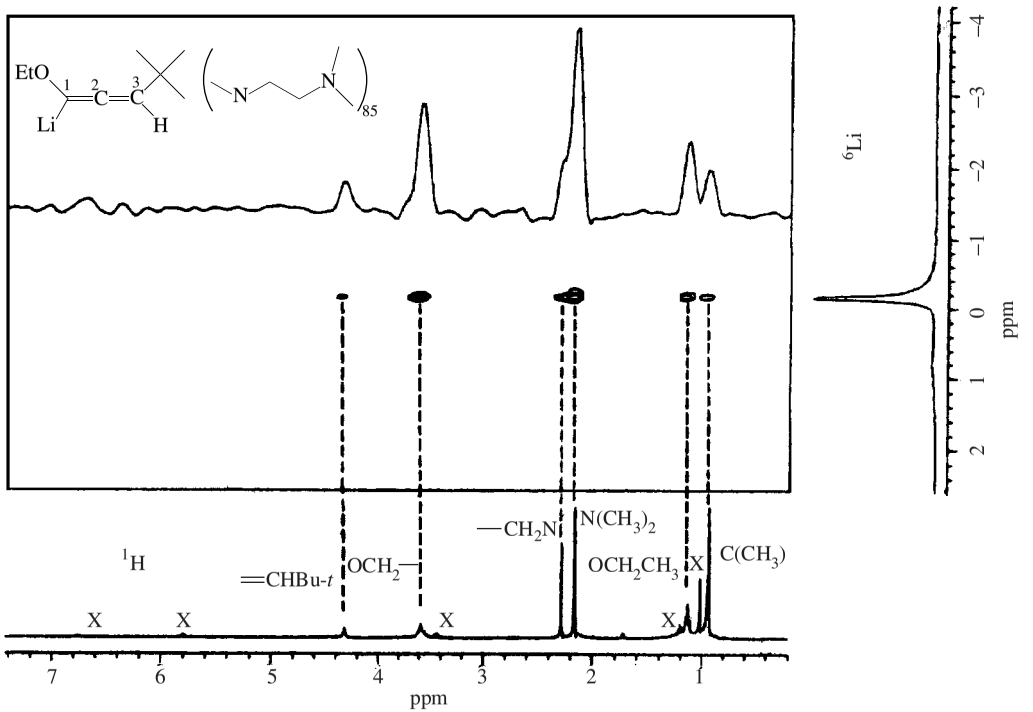
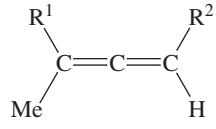


FIGURE 53. ^{6}Li ^{1}H -HOESY spectrum of ^{6}Li-labeled 1-lithio-1-ethoxy-*t*-butylallene (**107**). TMEDA$_{0.5}$ in THF-d$_8$ at −60 °C. X denotes signals of the allene. Mixing time 2.0 s. Reprinted with permission from Reference 64. Copyright (1993) American Chemical Society

Barretta and coworkers[63] reported a direct determination of the enantiomeric purity of chiral trisubstituted allenes by using permethylated cyclodextrin as a chiral solvating agent. They found that the heptakis β-cyclodextrin TRIMEB discussed above can be successfully used as a chiral solvating agent (CSA) for the NMR determination of the enantiomeric purity of trisubstituted allenes **110a–f**. An accurate analysis of the experimental conditions (molar ratio allene/TRIMEB, temperature and solvent) required to optimize the enantioseparation has been carried out. The ^{1}H NMR spectra of TRIMEB, allenes **110a–f**, and the mixtures TRIMEB/allene have been recorded at 300 MHz in CD_3OD as solvent.



(110)

(**a**) $R^1 = t$-Bu, R^2 = Br

(**b**) R^1 = Et, R^2 = Br

(**c**) R^1 = Pr, R^2 = Br

(**d**) $R^1 = t$-Bu, R^2 = Ph

(**e**) R^1 = Et, R^2 = Ph

(**f**) $R^1 = R^2 = t$-Bu

The proton spectrum of the permethylated cyclodextrin at room temperature is completely restricted to the region between 3.0 and 4.0 ppm, with the exclusion of the sharp doublet centered at 5.14 ppm. The free allene **110a** shows a well-recognizable singlet at 1.09 ppm, due to the absorption of the t-butyl group, and a doublet ($J = 2.2$ Hz) centered at 1.82 ppm, corresponding to the resonance of the methyl group; in the low-field spectral region, only the quartet centered at 6.01 ppm is present, arising from the proton directly bound to the allene moiety. Similarly, allenes **110b–f** show resonances between 0.9 and 2.2 ppm due to the methyl, the alkyl protons R^1 (and R^2 for **110f)** and a well-resolved signal, near 6.0 ppm for **110b–e** and near 5.0 ppm for **110f** which is due to the allene proton. In the case of allenes **110d** and **110e**, absorptions between 7.0 and 7.7 ppm are observed, arising from the phenyl protons. Therefore, the absorptions of the allenes and cyclodextrin fall in distinct spectral regions and mutual interference is not observed in the spectra.

By comparing the spectra of the racemic allenes **110a–f** in the free state and in the presence of the cyclodextrin, it has been observed that TRIMEB produced duplication of almost all signals of allene. As an example, the well-resolved quartet of the allene proton of free **110a** (at 6.01 ppm at 25 °C in CD_3OD, Figure 54a) gives two partially superimposed quartets centered at 6.04 and 6.03 ppm (Figure 54b, $\Delta\delta = 3.9$ Hz) in the presence of equimolar amounts of TRIMEB. These two absorptions correspond in position to those obtained starting from each enantiomer of allene, respectively, at same allene/TRIMEB molar ratio, total concentration and temperature (Figure 54c,d).

Consequently, the splitting observed is due to the fact that TRIMEB induces nonequivalence in the proton nuclei of the two enantiomers of the allenes, thus enabling one to determine the enantiomeric purities by using a chiral solvating agent. In all cases examined the extent of the nonequivalence, i.e. the difference of the proton chemical shifts of the two enantiomers in the presence of TRIMEB, can be increased by increasing the

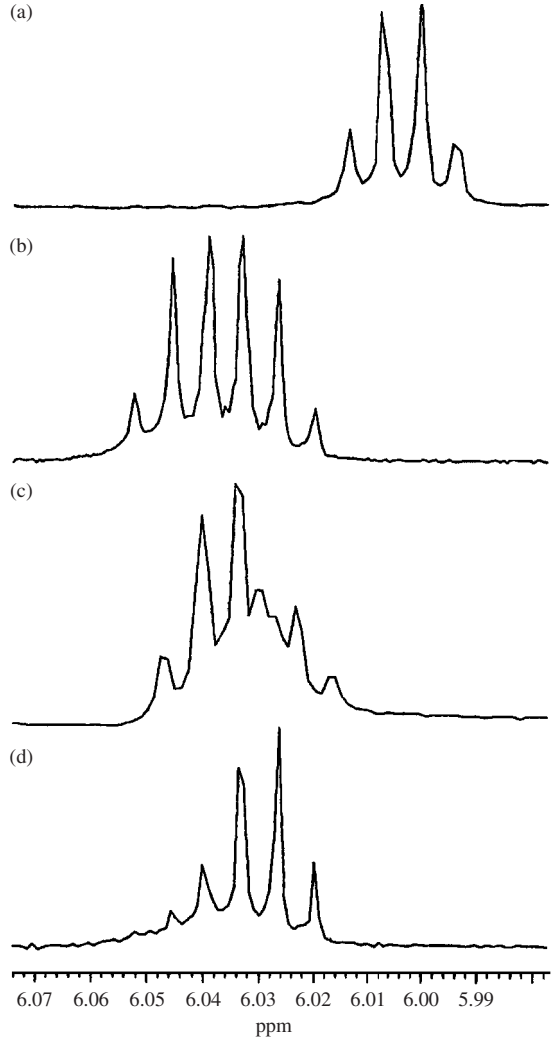


FIGURE 54. ^{1}H NMR spectra (300 MHz, CD_3OD), ppm referred to TMS as external standard, 25 °C) of (a) free compound **110a** (40 mM), (b) equimolar mixture of (*R*,*S*)-**110a**/TRIMEB, (c) equimolar mixture as in (b) starting from a sample of **110a** enriched in the (+)-(*S*)-enantiomer and (d) equimolar mixture as in (b) starting from a sample of enantiomerically pure (−)-(*R*)-**110a**. Reprinted with permission from Reference 63. Copyright (1994) American Chemical Society

TRIMEB/allene molar ratio. Data relative to the allene proton of **110a–f** are summarized in Table 43.

As shown in Figure 55 for the allene proton of **110a**, the nonequivalence increases from 3.9 Hz (Figure 55a) in an equimolar solution to 7.0 Hz (Figure 55b) by adding an additional equivalent of TRIMEB and to 10.9 Hz (Figure 55c) in the presence of 3 equivalents of the cyclodextrin, giving rise to two completely separated signals.

TABLE 43. Unequivalence ($\Delta\delta^a$ at 300 MHz, CD_3OD) induced in the allene proton of trisubstituted allene (40 mM) in the presence of TRIMEB, as a function of the temperature and of the allene/TRIMEB molar ratio

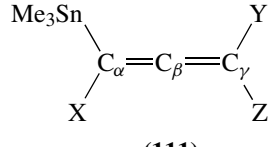
Allene	25 °C		−40 °C
	molar ratio 1 : 1	molar ratio 1 : 2	molar ratio 1 : 1
110a	3.9	7.0	18.1
110b	1.8	2.0	7.4
110c	1.1	4.2	5.9
110d	3.3	7.0	23.4
110e	2.9	3.3	11.7
110f	0.5	2.9	4.9

[a] $\Delta\delta$ = difference between the proton chemical shifts (Hz) of the two enantiomers in the presence of TRIMEB.

The use of CD_3OD as a solvent also allowed one to affect the nonequivalence by temperature variations: the absorptions of the allene proton of **110a** in the two enantiomers are separated by 11.9 Hz at −20 °C (Figure 56a) and by 18.1 Hz at −40 °C (Figure 56b). The possibility of increasing the nonequivalence by decreasing the temperature instead of increasing the CSA/allene molar ratio represents a double advantage: the measurement requires a minor amount of TRIMEB, thus becoming less expensive, and better results are obtained taking into account that the non-equivalence is very sensitive to temperature variations.

On the basis of the results above it can be concluded that, at least for the allenes investigated, the complete separation of the two allene absorptions can be achieved both by varying the molar ratio and by lowering the temperature, and hence the enantiomeric composition can be accurately determined by comparing the areas of the two absorptions by integration.

A series of stannylallene derivatives **(111)** was studied by means of ^{13}C, ^{29}Si and ^{119}Sn NMR spectroscopy by Lukevics and coworkers[65]. The effects of substituents on chemical shift values and J (SSCC) in **111** are additive. A set of linear correlations between the isotope shifts (IS) and SSCC for **111** demonstrates the interrelation of these values.



(111)

X = H, $SnMe_3$, $SiMe_3$, $GeMe_3$, SC_2H_5, Br
Y = H, $SnMe_3$
Z = H, $SnMe_3$, $SiMe_3$, $GeMe_3$, SC_2H_5

The ^{13}C, ^{29}Si and ^{119}Sn NMR chemical shifts measured for stannylallenes and silylstannylallenes are presented in Tables 44 and 46; $^nJ(^{119}Sn^{13}C)$, $^nJ(^{119}Sn^{117}Sn)$, $^nJ(^{29}Si^{13}C)$ and isotope shifts (IS) are given in Tables 45 and 46.

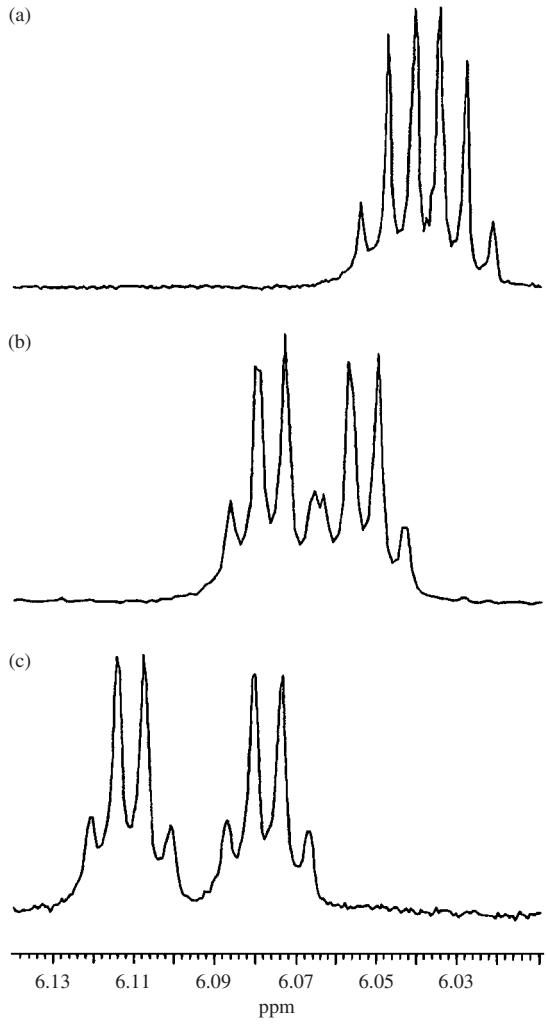


FIGURE 55. ^{1}H NMR spectra (300 MHz, CD_3OD, ppm referred to TMS as external standard, 25 °C) of (a) equimolar mixture of (*R*,*S*)-**110a**/TRIMEB, (b) 1 : 2 mixture of (*R*,*S*)-**110a**/TRIMEB and (c) 1 : 3 mixture of (*R*,*S*)-**110a**/TRIMEB. Reprinted with permission from Reference 63. Copyright (1994) American Chemical Society

Analysis of the chemical shifts of ^{13}C and ^{119}Sn for stannylallenes **111** (Table 44) shows that these values are additive and can be described by equations 4 to 6:

$$\delta(^{13}C_{\alpha,\gamma}) = 81.2 + \Sigma X_{\alpha} + \Sigma X_{\gamma} \quad (4)$$

$$\delta(^{13}C_{\beta}) = 219.0 + \Sigma X_{\beta} \quad (5)$$

$$\delta(^{119}Sn) = -21.6 + X_{\alpha} + \Sigma X_{\gamma} \quad (6)$$

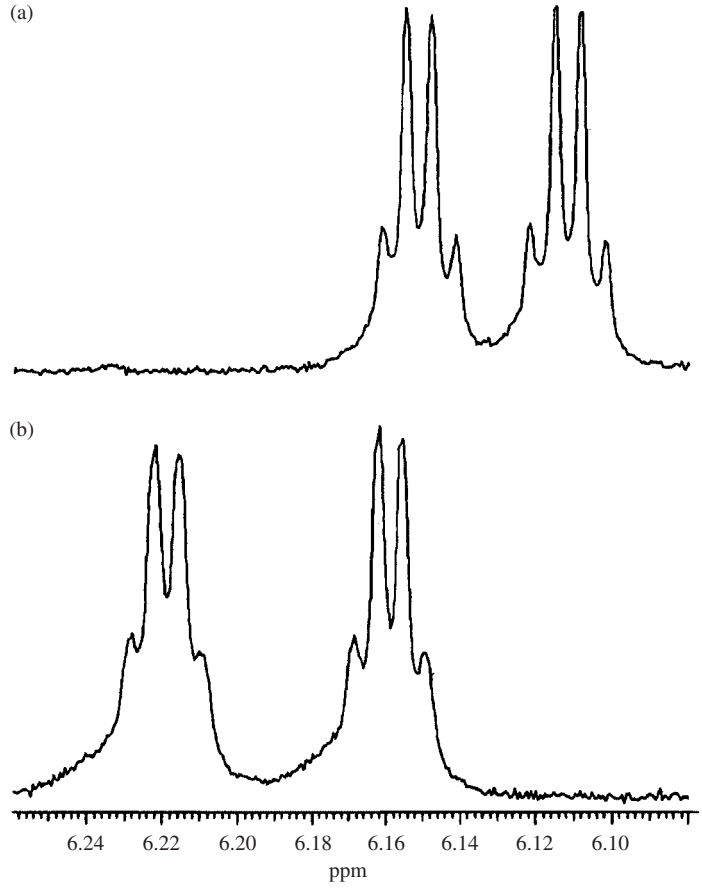
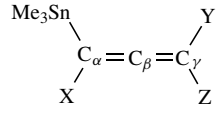


FIGURE 56. ^{1}H NMR spectra (300 MHz, CD_3OD, ppm referred to TMS as external standard) of an equimolar mixture of (*R*,*S*)-**110a**/TRIMEB recorded at (a) $-20\,^{\circ}$C and (b) $-40\,^{\circ}$C. Reprinted with permission from Reference 63. Copyright (1994) American Chemical Society

where X_α, X_β and X_γ are increments of the corresponding substituents in the α-, β- and γ-positions with regard to the nuclei under study. The calculated increments of substituents are presented in Table 47.

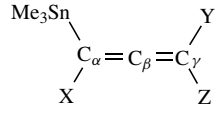
The difference between the calculated ^{13}C and ^{119}Sn CS and their experimental values for C_α, C_β and C_γ does not exceed -0.6 ppm and for ^{119}Sn CS $-$ 0.3 ppm. The relatively small values of these deviations demonstrate that the increments can be used for analytical purposes. The study of increments for ^{13}C (Table 47) provides evidence for a considerably larger influence of the MMe_3 group in the γ-position of the allene system than in the α- and β-positions. The negative sign of the γ-increment results from exponential correlation between the electronegativity of the substituent and the γ-increment value. A significant increase in the shielding of the γ-carbon nucleus (owing to the introduction of a MMe_3 group into the α-position of the allene system) is observed in the sequences CMe_3 <

TABLE 44. ^{13}C and ^{119}Sn chemical shifts δ (ppm) of stannylallenes in C_6D_6



X	Y	Z	δ	$\delta(^{13}C)$					
			(^{119}Sn)	C_α	C_β	C_γ	$SnCH_3$	XCH_3	$C_{Y,Z}$
$SnMe_3$	H	H	−9.55	75.23	205.98	53.01	−8.53	−8.53	—
	H	$SiMe_3$	−3.56	65.06	202.91	55.36	−8.35	−8.53	−0.06
	H	$GeMe_3$	−4.94	65.96	201.76	56.70	−8.38	−8.38	−0.82
	H	$SnMe_3$	−3.12	61.98	201.32	50.49	−8.38	−8.38	−9.03
	H	SC_2H_5	−5.07	79.59	204.08	65.14	−8.06	−8.06	29.86 (CH_2) 15.09 (CH_3)
	$SnMe_3$	$SiMe_3$	3.40	50.78	196.08	52.69	−8.29	−8.29	−8.23($SnMe_3$) 0.67 ($SiMe_3$)
	$SnMe_3$	$GeMe_3$	1.87	52.06	196.13	54.20	−8.27	−8.27	−8.32($SnMe_3$) 0.01 ($GeMe_3$)
	$SnMe_3$	$SnMe_3$	3.73	47.36	195.58	47.36	−8.32	−8.32	−8.32
	$SnMe_3$	SC_2H_5	−1.82	70.04	200.00	64.03	−8.06	−8.06	29.04 (CH_2) 15.41 (CH_3) −8.79 ($SnMe_3$)
$SiMe_3$	H	$SiMe_3$	−5.95	71.44	204.93	59.14	−8.15	0.32	−0.09
	H	$GeMe_3$	−7.73	71.92	203.32	60.05	−8.21	0.32	−0.85
	H	SC_2H_5	−6.08	77.92	206.13	68.63	−7.88	0.53	29.74 (CH_2) 15.21 (CH_3)
	$SnMe_3$	$SiMe_3$	0.34	56.79	197.48	56.79	−8.06	0.76	0.23 ($SnMe_3$) 0.18 ($SiMe_3$)
	$SnMe_3$	$GeMe_3$	−1.48	57.64	196.97	57.73	−8.14	0.74	−8.17 ($SnMe_3$) 0.04 ($GeMe_3$)
	$SnMe_3$	$SnMe_3$	0.02	52.69	196.08	50.78	−8.23	0.67	−8.29
	$SnMe_3$	SC_2H_5	−3.68	76.40	200.59	67.52	−7.88	0.38	−8.76($SnMe_3$) 28.81 (CH_2) 15.35 (CH_3)
$GeMe_3$	H	$SiMe_3$	−7.42	71.59	203.58	59.69	−8.26	−0.29	−0.12
	H	$GeMe_3$	−9.01	72.20	202.10	60.71	−8.32	−0.34	−0.89
	H	SC_2H_5	−8.49	78.71	204.36	69.30	−8.00	−0.35	29.30 (CH_2) 15.21 (CH_3)
	$SnMe_3$	$SiMe_3$	−0.95	57.73	197.48	57.64	−8.17	0.04	−8.14($SnMe_3$) 0.74 ($SiMe_3$)
	$SnMe_3$	$GeMe_3$	−2.61	58.60	196.45	58.06	−8.21	−0.04	—
	$SnMe_3$	$SnMe_3$	−1.03	54.20	196.13	52.06	−8.21	0.01	−8.27($SnMe_3$)
	$SnMe_3$	SC_2H_5	−3.96	77.33	199.54	68.66	−7.97	−0.15	−8.76($SnMe_3$) 28.78 (CH_2) 15.41 (CH_3)
H	$SnMe_3$	$SnMe_3$	−8.66	50.49	201.32	61.98	−9.03	—	−8.38
SC_2H_5	$SnMe_3$	$SiMe_3$	−1.88	67.52	200.59	76.40	−8.76	28.81(CH_2) 15.36(CH_2)	−7.88($SiMe_3$) 0.38 ($SiMe_3$)
	$SnMe_3$	$GeMe_3$	−3.48	68.66	199.54	77.33	−8.76	28.78(CH_2) 15.41(CH_2)	−7.97($SnMe_3$) −0.15($GeMe_3$)
	$SnMe_3$	$SnMe_3$	−2.94	64.03	200.00	70.04	−8.79	29.04(CH_2) 15.41(CH_2)	−8.06($SnMe_3$)
Br	H	H	2.98	78.51	206.98	74.96	−8.56		

TABLE 45. Coupling constants and isotope shifts of stannylallenes in C_6D_6



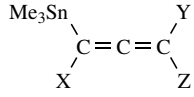
X	Y	Z	Coupling constants (Hz)				Isotope shifts (ppb)		
			SnC_α	SnC_β	SnC_γ	$^{119}Sn-^{117}Sn$	SnC_{CH_3}	$^1\Delta^{119}Sn(C_\alpha)$	$^1\Delta^{119}Sn(C_{CH_3})$
$SnMe_3$	H	H	261.7	30.5	60.6	158.5	348.2	31.8	9.0
	H	$SiMe_3$	264.4	26.3	50.1	169.1	349.4	34.3	7.1
	H	$GeMe_3$	269.9	26.8	57.1	190.9	347.6	33.8	7.7
	H	$SnMe_3$	274.1	26.0	58.9	199.4(^2J)	347.0	34.2	7.7
	H	SC_2H_5	239.8	31.2	65.1	166.5	348.1	37.5	6.6
	$SnMe_3$	$SiMe_3$	281.7	21.4	48.6	202.6(^2J) 248.6(^4J)	348.0	32.2	7.5
	$SnMe_3$	$GeMe_3$	285.1	22.7	54.5	226.2(^2J) 250.5(^4J)	345.9	31.9	9.2
	$SnMe_3$	$SnMe_3$	292.9	22.1	54.8	234.0(^2J) 254.2(^4J)	345.6	31.1	9.3
	$SnMe_3$	SC_2H_5	263.2	30.5	66.4	246.3(^2J) 202.3(^4J)	343.0	33.2	7.5
$SiMe_3$	H	$SiMe_3$	254.4	31.6	49.6	—	348.3	35.5	8.0
	H	$GeMe_3$	261.6	[a]	56.4	—	346.7	35.0	8.0
	H	SC_2H_5	233.5	36.6	64.5	—	346.5	36.5	7.4
	$SnMe_3$	$SiMe_3$	270.4	27.7	47.8	241.1(^4J)	346.0	33.3	8.3
	$SnMe_3$	$GeMe_3$	276.8	28.8	53.9	244.6(^4J)	344.6	32.7	8.5
	$SnMe_3$	$SnMe_3$	284.0	28.2	54.8	248.7(^4J)	347.2	32.2	8.6
	$SnMe_3$	SC_2H_5	257.7	28.4	65.7	199.3(^4J)	340.2	34.6	8.2
$GeMe_3$	H	$SiMe_3$	280.3	23.6	48.5	—	349.1	33.4	8.2
	H	$GeMe_3$	286.9	23.0	54.6	—	347.4	30.5	8.5
	H	SC_2H_5	258.9	26.7	62.6	—	347.6	35.6	7.1
	$SnMe_3$	$SiMe_3$	298.1	19.2	46.3	244.6(^4J)	347.0	31.7	9.2
	$SnMe_3$	$GeMe_3$	304.6	20.1	52.1	247.3(^4J)	345.7	30.7	9.3
	$SnMe_3$	$SnMe_3$	310.0	19.3	53.3	250.5(^4J)	344.9	30.0	9.7
	$SnMe_3$	SC_2H_5	283.7	26.2	61.6	198.6(^4J)	341.3	33.0	7.9
H	$SnMe_3$	$SnMe_3$	423.5	6.1	44.8	248.3(^4J)	353.5	22.4	12.1
SC_2H_5	$SnMe_3$	$SiMe_3$	410.6	352	32.2	199.3(^4J)	353.2	38.4	6.3
	$SnMe_3$	$GeMe_3$	417.0	26.2	35.1	198.6(^4J)	352.6	37.6	6.6
	$SnMe_3$	$SnMe_3$	433.7	32.1	36.4	202.3(^4J)	350.9	36.6	7.2
Br	H	H	360.8	32.5	27.4	—	371.5	26.4	1.1

[a]Not measured.

$GeMe_3 < SiMe_3 < SnMe_3$. This is corrected by the increasing σ-donating capacity of substituents in this sequence, suggesting that the negative values of the γ-increment result from the σ-donating capacity of the MMe_3 group.

Generally, inverse relationships are observed between the ^{119}Sn and ^{13}C chemical shifts of the β-carbon atom in **111** (Table 44). This indicates a conjugation between the tin atom and the allene system as a downfield shift of the $^{13}C_\beta$ signal corresponds to an upfield shift

TABLE 46. ^{29}Si NMR spectra of stannylsilylallenes and related compounds in C_6D_6



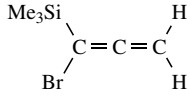
X	Y	Z	δ (^{29}Si) (ppm)	Coupling constants (Hz)			$^1\Delta^{29}Si$ (C_α) (ppm)
				$^{29}Si-C_{CH_3}$	$^{29}Si-C_\alpha$	$^{29}Si-^{119}Sn$	
$SnMe_3$	$SiMe_3$	H	−5.06	52.86	66.19	27.74	−9.1
$GeMe_3$	$SiMe_3$	H	−5.12	52.91	65.21	26.94	−9.5
$SiMe_3$	$SiMe_3$	H	−4.94	53.20	64.61	26.68	−9.6
$SiMe_3$	$SnMe_3$	$SnMe_3$	−3.59	52.75	58.69	27.56 (^4J)	−9.8
						23.81 (^2J)	
$SiMe_3$	$SnMe_3$	$GeMe_3$	−3.66	52.87	57.96	27.16 (^4J)	−10.0
						20.28 (^2J)	
$SiMe_3$	$SnMe_3$	$SiMe_3$	−3.98	53.31	57.56	18.03 (^4J)	−10.5
						20.14 (^2J)	
$SiMe_3$	H	$SiMe_3$	−3.89	52.95	55.40	18.49	−10.4
$SiMe_3$	H	$GeMe_3$	−4.01	53.06	55.58	26.26 (^4J)	−10.4
$SiMe_3$	H	SC_2H_5	−3.41	53.31	52.91		−11.1
$SiMe_3$	$SnMe_3$	SC_2H_5	−3.34	52.98	55.61		−10.3
					21.64 (^2J)		
			−0.31				

TABLE 47. Values of the calculated increments of substituents in stannylallenes **111** in C_6D_6

Measured value	Increment of group				
	$SnMe_3$	$GeMe_3$	$SiMe_3$	SC_2H_5	CMe_3
$\delta(^{13}C_\alpha)$	−2.5	+3.6	+2.6	+13.3	+28.6
$\delta(^{13}C_\beta)$	−6.1	−5.0	−4.4	−1.6	−5.6
$\delta(^{13}C_\gamma)$	14.1	−10.0	−10.8	+8.3	−3.5
$\delta(^{119}Sn)$	+12.4 (α)	+7.6 (α)	+8.7 (α)	+6.0 (α)	
	+6.6 (γ)	+4.6 (γ)	+6.3 (γ)	+3.0 (γ)	
$^1J(^{119}Sn^{13}C_\alpha)$	+130.6 (α)	−113.4 (α)	+139.4 (α)		
	+15.9 (γ)	+9.6 (γ)	+5.2 (γ)		
$^2J(^{119}Sn^{13}C_\beta)$	+16.0 (α)	+13.0 (α)	+22.1 (α)		
	−4.4 (γ)	−3.6 (γ)	−4.6 (γ)		
$^3J(^{119}Sn^{13}C_\gamma)$	+10.0 (α)	+8.0 (α)	+9.5 (α)		
	−2.1 (γ)	−4.0 (γ)	−10.7 (γ)		

of the ^{119}Sn resonance. In a series of structurally similar compounds, the relative changes in the shielding of nuclei under the influence of substituents are related to corresponding changes in the electron density of these nuclei. Therefore, one can assume that an increase in the negative charge on the tin atom results from a decrease in the charge of C_β in the $Me_3Sn-C_\alpha=C_\beta=C_\gamma$ system. This conclusion is in agreement with the correlation found earlier between the shielding of the central $^{13}C_\beta$ atom in the allene system and substituent resonance effects. Judging from the β-increments (Table 47), the π-acceptor capacity of the MMe_3 group increases in the sequence Sn < Ge < Si.

B. Solitons

Tolbert and Ogle[66] reported a ^{13}C NMR study on soliton model compounds. Although many of the qualitative aspects of charge transport in conductive polymers have their counterparts in classical organic chemistry, the concept of a mobile charge carrier ('soliton') is one of the most difficult to reconcile with the conventional understanding of resonance. According to the soliton theory, the charge carrier in reductively (or oxidatively) doped polyacetylene is a resonance-stabilized carbanion (or carbocation) of finite width with maximum charge at the center of the defect and diminishing amplitude away from the center. Charge transport is thus associated with migration of the charge density wave down the polymer chain (Figure 57).

Such migration will be isoergic only if the solitonic charge density wave has finite width relative to the unsaturation length. Although increased charge density at the center of an odd-alternant hydrocarbon anion has been a familiar aspect of the chemistry of polyenyl anions since the pioneering work of Kloosterziel and Werner[67], less widely understood is the requirement that what would ordinarily be static resonance forms become only dynamically equivalent at long chain length. Figure 57 thus represents the centers of delocalized finite domains as they migrate down the chain. The relevance of the interchain charge-transport mechanism to the overall mechanism of conductivity in bulk polymers, for which interchain charge migration ('intersoliton hopping') is apparently rate-limiting, is still the subject of controversy and is not addressed here.

In order to relate this conclusion from solid-state theoretical physics to the organic chemistry of conductive polymers, Tolbert and Ogle undertook an examination of the effect of increasing chain length on the spectral properties of polyenyl anions, using ^{13}C NMR spectroscopy. By using α, ω-diphenylpolyenyl anions (DP1, DP3, DP5, etc.), they investigated the chain length at which the properties of these anions and n-doped polyacetylene converge (Scheme 8).

Treatment of the appropriate hydrocarbon precursors DPN-H (= DP1-H, DP2-H, ...) in Me_2SO solution with potassium (methylsulfinyl)methide ('dimsyl') resulted in an immediate color formation that varied from orange to deep blue-black to colorless as the chain length increased. The higher homologues were poorly soluble and required filtration under inert atmosphere in order to obtain homogeneous solutions for NMR analysis. In the case of DP17 and higher homologues, anisotropic line broadening prevented acquisition of analyzable spectra. However, anions DP1–DP13 yield quite satisfactory ^{13}C and ^{1}H spectra for further analysis. Curiously, although DP3 exhibited both *E*,*E* and *E*,*Z* conformers

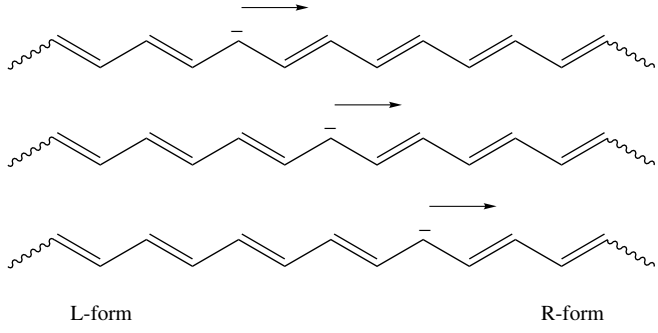
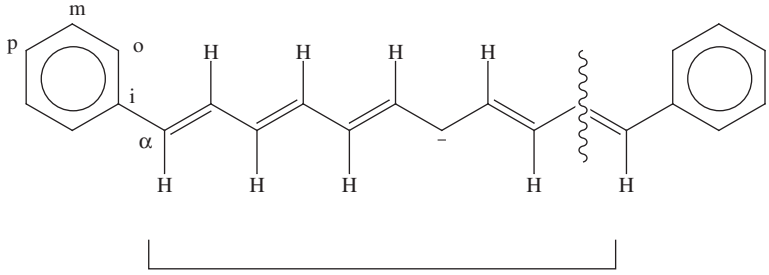


FIGURE 57. Coupled soliton modes in n-doped polyacetylene. Reprinted with permission from Reference 66. Copyright (1990) American Chemical Society



DPN, $N = 1–17$, carbon number

SCHEME 8

in accordance with literature studies in non-ion pairing solvents, the higher homologues showed little conformational diversity apart from absorbances of $<$ *ca* 5% intensity that apparently corresponded to *Z* conformers. By analogy with DP3, for which proton and carbon chemical shifts had similar frequency separation and, therefore, similar exchange kinetics, such conformers in the higher homologues should have been visible in the carbon spectra. It was concluded that the carbon chemical shifts corresponded to the single isomer represented in the proton spectra. Moreover, the coupling constants, which ranged from 11.7 Hz for central protons to 14.8 Hz for the α protons, are consistent only with the all-*trans* planar conformation in which increased bond localization at the ends of the chain leads to a higher coupling constant. The ^{13}C chemical shifts of the anions were found to be devoid of counterion effects as indicated by employing $CH_3SOCH_2^-K^+$/18-crown-6 in Me_2SO-d_6 as the base. The chemical shift of C-1 of DP1 was obtained only after addition of Me_2SO-d_6 to the deprotonated substrate, since facile protium/deuterium exchange led otherwise to line broadening and an isotope effect on the chemical shift. Similarly, DP3 underwent slow exchange with Me_2SO-d_6 to yield a deuteriated anion which exhibited an isotope effect on the C1 chemical shift. Although the assignment of ^{13}C chemical shifts for anions DP1–DP7 was straightforward by the use of two-dimensional (HETCOR) spectroscopy (Figure 58a), the higher homologues required more rigorous examination. The HETCOR of DP9 with carbon and proton assignments is shown in Figure 58a.

In particular, DP9 presented ambiguities associated with the proton assignments from which the ^{13}C assignments were derived. Thus, it was necessary to use the COSY method to assign the proton absorptions first. Homonuclear COSY NMR spectroscopy allowed unambiguous assignment of proton chemical shifts in all cases.

Figure 58(b) shows a COSY spectrum of DP9 as a representative example of ^1H chemical shifts that were readily assigned from the doublet at δ5.38 ($J = 14.4$ Hz) corresponding to the C-1 proton. Heteronuclear (HETCOR) $^{13}C–^1H$ spectroscopy allowed indirect assignment of the ^{13}C chemical shifts. The assignment of all chemical shifts and calculated charge densities for anions DP1–DP13 is presented in Table 48[68].

In all cases, the nuclei corresponding to the odd-numbered carbon atoms had upfield chemical shifts (excess charge densities) vs their even-numbered counterparts. More illustrative of this is the plot of the ^{13}C spectra of the linear odd-alternant α,ω-diphenylpolyenyl anions $[Ph(CH)_nPh^-$, $n = 1, 3, 5, 7, 9, 11, 13]$ shown in Figure 59. Linear least-squares treatment of the average charge density ρ_{av} vs ^{13}C chemical shift (see Figure 60), excluding DP1, gave excellent statistics and allowed a calculation of individual charge densities at each site from equation 7:

$$\rho C = (\delta C - 132.7)/187.3 \tag{7}$$

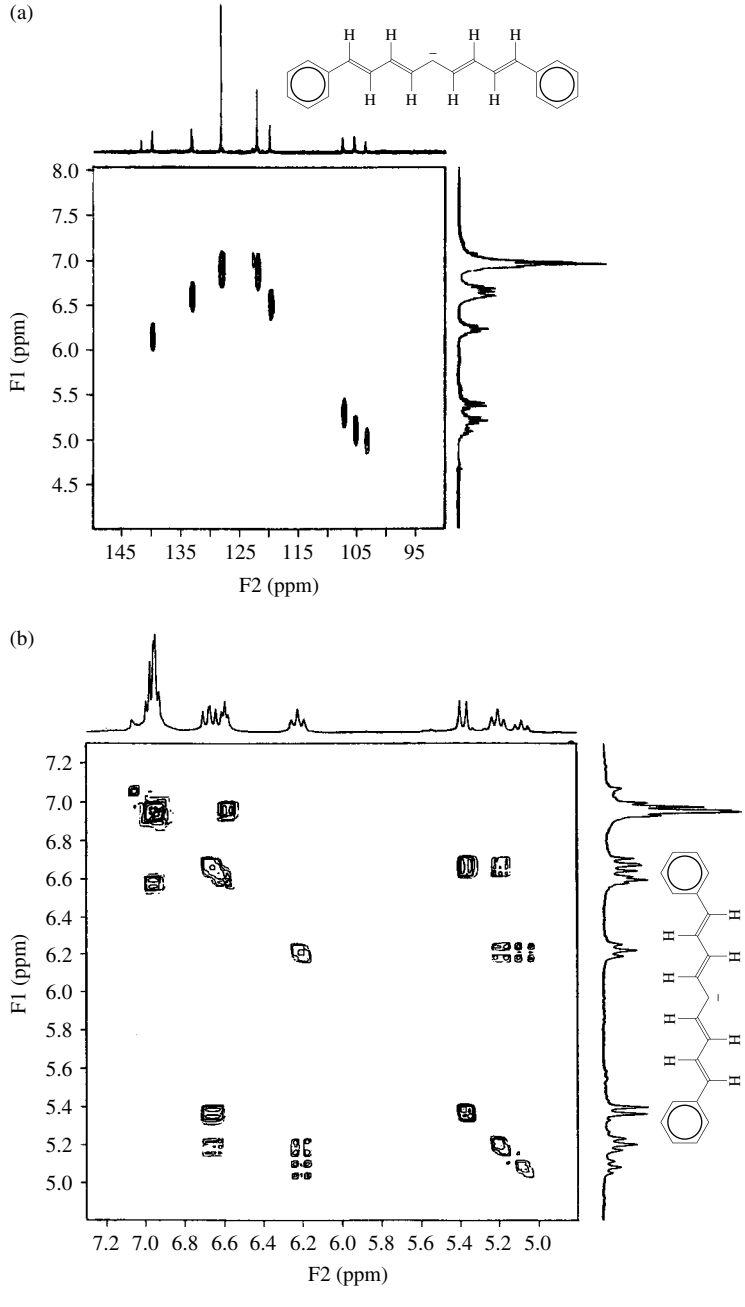


FIGURE 58. (a) HETCOR spectrum of DP9. (b) COSY spectrum of DP9. Reprinted with permission from Reference 66. Copyright (1990) American Chemical Society

TABLE 48. Chemical shift and charge densities for anions DP1 – DP13

DPN	Chemical shift δ (in ppm) and charge densities (in parentheses)										
N =	C1	C2	C3	C4	C5	C6	C7	*ipso*	*ortho*	*meta*	*para*
1	80.4							145.2	116.2	127.7	105.9
	(−0.279)							(0.067)	(−0.091)	(−0.026)	(−0.143)
3	90.2	127.9						145.4	117.5	128.1	111.3
	(−0.227)	(−0.026)						(0.068)	(−0.081)	(−0.025)	(−0.114)
5	96.5	134.6	98.2					143.9	119.4	128.0	115.0
	(−0.193)	(0.010)	(−0.184)					(0.058)	(−0.071)	(−0.025)	(−0.095)
7	102.4	133.7	101.5	140.5				142.7	120.8	128.1	117.7
	(−0.163)	(0.005)	(−0.167)	(0.042)				(0.053)	(−0.064)	(−0.025)	(−0.080)
9	107.4	133.2	105.4	139.8	103.3			141.7	121.9	128.2	119.7
	(−0.135)	(0.003)	(−0.146)	(0.038)	(−0.157)			(0.048)	(−0.058)	(−0.024)	(−0.036)
11	111.5	132.7	109.1	139.2	105.9	139.6		140.9	122.8	128.3	121.3
	(−0.113)	(0.000)	(−0.126)	(0.035)	(−0.143)	(0.037)		(0.044)	(−0.053)	(−0.023)	(−0.061)
13	114.9	132.3	112.5	138.6	108.6	139.0	107.5	140.3	123.4	128.3	122.5
	(−0.095)	(−0.002)	(−0.108)	(0.032)	(−0.129)	(0.034)	(−0.135)	(0.041)	(−0.050)	(−0.023)	(−0.054)

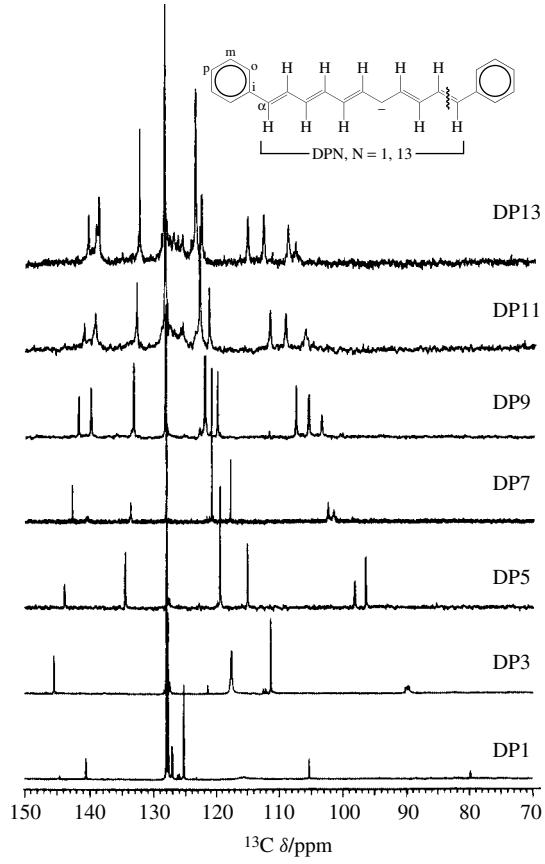


FIGURE 59. Stacked spectra of diphenylpolyenyl anions (DPN). Reprinted with permission from Reference 66. Copyright (1990) American Chemical Society

More illustrative are these results plotted in histogram form. Figure 61 indicates the results for DP13.

C. Fullerenes

The finding of fullerenes has stimulated chemists belonging to a variety of fields including those who use NMR. In this section, some examples of papers in which NMR plays an important role will be described.

Bellavia-Lund and coworkers[69] reported a nitrogen-containing fullerene carbon resonance assignment through $^{15}N-^{13}C$ coupling constants and location of the sp^3 carbon atoms of $(C_{59}N)_2$. While C_{60} shows a single line at 143 ppm in its ^{13}C NMR spectrum and is a magnetically deshielded moiety, a detailed assignment of all carbon resonances in a modified fullerene, which could have up to 60 resonances, is very difficult. However, for azafullerene **(112)**, the carbon atoms in positions α and β to the nitrogen, as well as those linking the cage to other substituents, are potentially assignable using $^{13}C-^{15}N$ coupling.

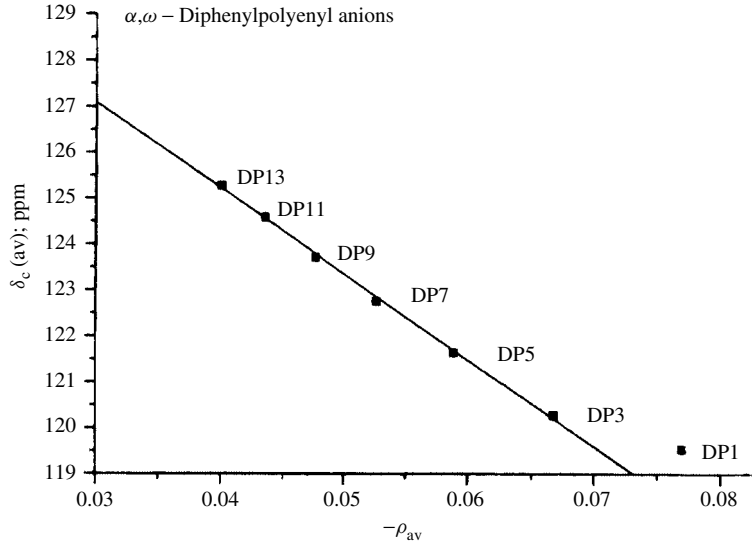


FIGURE 60. Average ^{13}C chemical shift vs average charge density (ρ_{av} for diphenylpolyenyl anions (DPN). Reprinted with permission from Reference 66. Copyright (1990) American Chemical Society

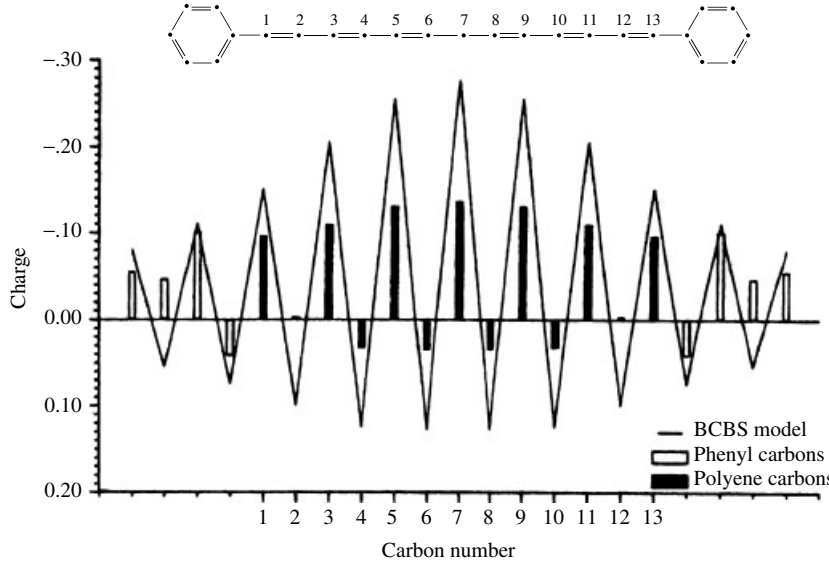


FIGURE 61. Histogram of charge density vs carbon number for DP13. Reprinted with permission from Reference 66. Copyright (1990) American Chemical Society

If such an experiment were successful, then assignment of carbons α to cage sp^3 carbons in any modified fullerene should be possible by extrapolation. The authors report that such a characterization is indeed possible for molecules $C_{59}HN$ **(113)**, $(C_{59}N)_2$ **(114)** and the recently synthesized $C_{59}(CHPh_2)N$ **(115)**. The nitrogen-coupled carbon NMR spectrum of the labeled ketolactam **112** revealed five carbons coupled to nitrogen at 80.8, 128.0, 139.7, 141.8 and 163.8 ppm, as shown for structure **112** (Figure 62). The labeled ketolactam was then converted to both **113** and **114**. The former heterofullerene showed five carbons coupled to nitrogen at 71.7, 124.3, 134.9, 147.1 and 155.3 ppm. Assignment of the sp^3-hybridized α carbon at 155.3 ppm [$^1J(CN) = 12.1$ Hz] was straightforward. Low-intensity resonances at 124.3, 134.9 and 147.1 must therefore be a result of β-coupling, where the carbon resonance at 134.9 ppm is mostly modified by the ^{15}N coupling. The carbon resonating at 147.1 ppm was shown to also be β-coupled to the proton as depicted in **113** (Figure 62). This leaves the resonances at 124.3 and 134.9 ppm to be assignable to 'b' or 'c'. If resonance arguments apply to spin–spin coupling, then the unusual bond localization *sui generis* to fullerene bonding (hexagons are cyclohexatrienes and pentagones are 5-radialenes) demands that 'c' be assigned to the 134.9 ppm resonance. This would also explain why 'b' and 'd', two carbons which are not in direct conjugation with the nitrogen, show very minor coupling.

Armed with this information, the authors examined the ^{15}N-coupled ^{13}C NMR spectrum of the dimer in order to finally locate the interdimer carbon 'a'. Only one carbon resonance was found that split at 156 ppm [$^1J(CN) = 11.6$ Hz], another that broadened was found at 138 ppm, and two more carbons were found that broadened to a lesser extent at 125.1 and 148.8 ppm.

In structure **114** (Figure 67), the assignment of one out of the two possible α sites to 'e' as well as the uncertainty in assignment of the crucial α carbon 'a' are shown.

As is well known in fullerene chemistry, it is possible that when a fullerene is a substituent it has a strong deshielding effect. If $C_{59}N$ has the same magnetic properties as C_{60}, in $(C_{59}N)_2$ **(114)**, each half of the molecule acts as a deshielding group on the other. Moreover, the interball bonding carbons 'a' are pressed against the opposite ball's nitrogen atom's lone pair, and this causes further deshielding. An additional complication is that the 'a' carbons are α to their own ball's nitrogen but β to the adjacent ball's nitrogen. This could cause further splitting and/or broadening of the signal corresponding to the α carbon 'a'. Quantum mechanical calculations at the LDF (local density functional) level reveal that the hybridization of 'a' is between sp^2 and sp^3; the C–H coupling constant in **113** also supports this theory and allows for the possible assignment of 'a' at 138 ppm. However, the magnitude of deshielding suffered by carbon 'a' was still in question.

To gain information on the chemical shift variation as a function of substituent, the labeled and unlabeled diphenylmethyl azafullerene derivative **115** was synthesized from the corresponding azafullerene dimer **114**. The ^{13}C NMR spectrum of **115** revealed the sp^3 carbon α to the nitrogen on the fullerene cage at 86.3 ppm. It seemed unreasonable that the broadened peak at 138 ppm in the spectrum of **114** could be the α carbon resonance that they had been searching for. This reasoning stems from the fact that changing the substituent from diphenylmethyl to $C_{59}N$ should not shift the 'sp^3' resonance downfield by 51.4 ppm, considering that in going from a proton in $C_{59}HN$ **(113)** to an alkyl substituent in $C_{59}(CHPh_2)N$ **(113)**, the α carbon resonance shifted by only 14.9 ppm.

An ^{15}N-coupled ^{13}C NMR spectrum of **115** showed a pattern similar to that of its precursors: splitting at 86.3 and 155.5 correspond to the sp^3-hybridized α carbon 'a' and the sp^2 α carbon 'e', respectively, as illustrated in **115**. Broadening was observed for β carbon resonances at 137.6 and to a lesser extent at 65.2, 124.7 and 148.9 ppm. The ^1H-coupled ^{13}C NMR spectrum of **115** showed that the resonance at 148.9 ppm was also

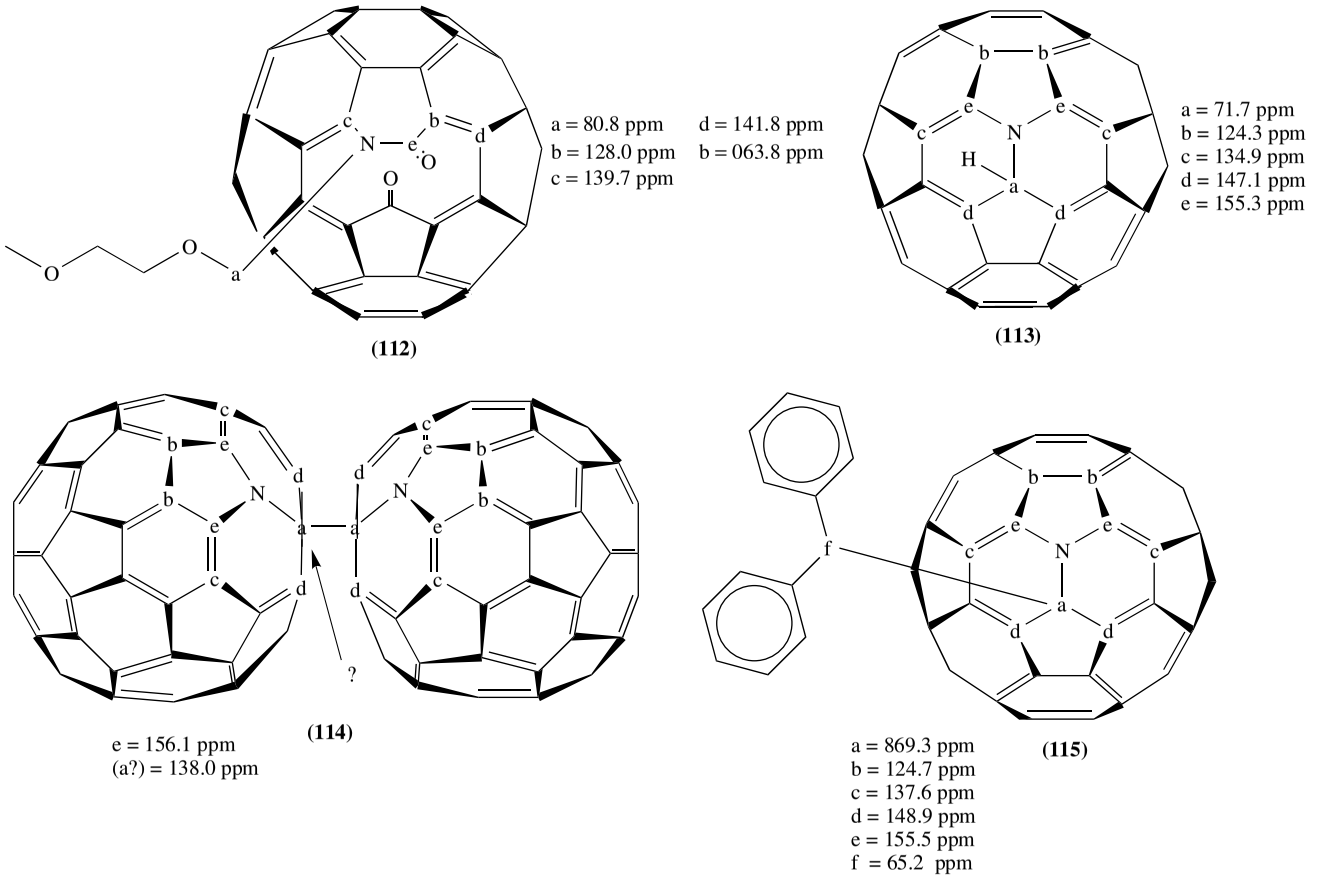


FIGURE 62. ^{13}C NMR data of azafullerenes **112–115**. Reprinted with permission from Reference 69. Copyright (1997) American Chemical Society

γ-coupled to the methine proton. The assignment of 'b' and 'c' in **115** is again based on the fact that 'c', unlike the other three β carbons, is in conjugation with nitrogen and should exhibit a stronger spin–spin interaction.

After comparison of the three derivatives, it is possible by extrapolation to assign the β carbons of **114** (Table 49). The assignments of the β carbons at 134.9 ppm for **113** and 137.6 ppm for **115** supported the notion that the 138 ppm resonance in the dimer was also due to β-coupling and strongly suggested that the sp^3 α carbon of **114** was still unassigned.

Re-evaluation of pulse delay times used to record fullerene ^{13}C NMR spectra revealed that a 16 s pulse delay, twice the value for a 'standard' detection, allowed the observation of a weak resonance in the sp^3 region at 90.4 ppm in the ^{13}C NMR spectrum of the 'unlabeled' heterofullerene **114**. Attempts were made to optimize the NMR experimental parameters for a long T_1, i.e. the variation of delay times and pulse angles. Various conditions were tried on the labeled material without success. This is probably due to the mixture of the labeled and unlabeled **114** which give too low S/N for signal detection. Table 49 summarizes the NMR results obtained and illustrates a distinct pattern of the azafullerenes.

The numbers in Table 49 indicate that as the electronegativity of R increases, the chemical shifts of the sp^3 and (for the most part) the sp^2 carbon atoms α and β to the nitrogen atom also increase. In all three cases, the pattern is reproduced and similar coupling constants are observed. The only exception appears to be carbon 'd' in **115**, which has approximately the same chemical shift as that of **114**.

Brunner, Pines and coworkers[70] reported on the enhancement of ^{13}C NMR signals in solid C_{60} and C_{70} using a laser-polarized xenon. NMR signals emanating from surface nuclei of solids may be enhanced by the transfer of spin polarization from laser-polarized noble gases via SPINOE (spin polarization induced nuclear Overhauser effect). The paper describes experiments in which the spin polarization is transferred under MAS from laser-polarized ^{129}Xe to ^{13}C, a nuclear spin with a low gyromagnetic ratio in the fullerenes C_{60} and C_{70}, which are polycrystalline materials with a low surface area. In C_{70}, a different degree of enhancement of the NMR spectrum is observed for the different atomic sites in the molecule.

Spin polarization transfer via SPINOE requires effective adsorption of laser-polarized ^{129}Xe on the sample under study. Figure 63 shows the ^{129}Xe MAS NMR spectra of laser-polarized ^{129}Xe adsorbed on fullerenes at 150 K. The spectra exhibit narrow signals at *ca* 0 ppm due to gaseous xenon and broad signals centered at 100–120 ppm (50–80 ppm wide), characteristic of adsorbed xenon. The intensity of the latter signals is 4–5 times higher for C_{70} than for C_{60}, because the specific surface of the C_{70} sample was approximately twice the specific surface of C_{60} and the mass of the C_{70} sample was 2.5 times the

TABLE 49. ^{15}N-coupled carbon atoms a–f as a function of R on the fullerene cage

	a	b	c	d	e	f
R = H **(113)**	71.7(3.5)[a]	124.3[b]	134.9[b]	147.1[b]	155.3(12.1)[a]	
R = $CHPh_2$**(115)**[c]	86.6(4.5)[a]	124.6[b]	137.6[b]	149.1[b]	155.7(11.9)[a]	65.4[b]
R = $C_{59}N$**(114)**	90.4[b]	125.1[b]	138	148.8[h]	156.1(11.6)[a]	

[a] $^{15}N-^{13}C$ coupling constant (Hz) in ODCB-d_4 (ODCB = *o*-dichlorobenzene).

[b] Broad, low intensity peak.

[c] Chemical shifts of carbons given next to the structure of **115** differ slightly from those here because they were obtained in CS_2.

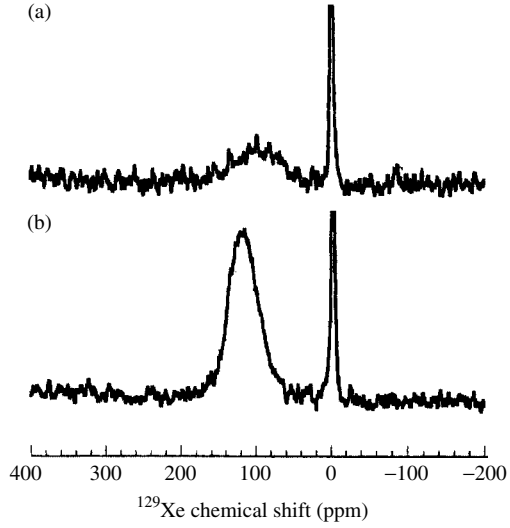


FIGURE 63. ^{129}Xe MAS NMR spectra of laser-polarized ^{129}Xe adsorbed on C_{60} (a) and C_{70} (b), measured at 150 K. Note that the sharp signals at 0 ppm due to gaseous ^{129}Xe are clipped to enlarge the scale. Reproduced by permission of Elsevier Science B. V. from Reference 70

mass of the C_{60} sample. The fractional coverage of the surface with xenon was apparently the same for both samples.

Figure 64(a) shows the ^{13}C MAS NMR spectrum of C_{60} with the characteristic single line at 144 ppm. The SPINOE spectrum shown in Figure 64(b) is obtained as the difference between the spectrum measured when the ^{129}Xe flowing into the rotor is laser-polarized and the spectrum measured when the ^{129}Xe exhibits its normal thermal equilibrium polarization. The intensity corresponds to *ca* $15 \pm 5\%$ of the intensity of the spectrum observed when the ^{129}Xe flowing through the sample is not laser-polarized (Figure 64c).

From the mean crystalline diameter of *ca* 4 μm and the diameter of a C_{60} molecule (*ca* 1 nm), one can estimate that only a fraction of *ca* 0.0015 of the C_{60} molecules is located at the surface of the particles. Assuming that effective polarization transfer only occurs for C_{60} molecules located at the surface, one concludes that the observed signal enhancement of $15 \pm 5\%$ corresponds to a polarization enhancement factor of *ca* 100 ± 30. However, it should be noted that this simple estimation neglects the influence of spin diffusion which can lead to a transport of spin polarization into the bulk, resulting in a lower surface enhancement factor.

Figure 65(a) and (b) shows the ^{13}C MAS NMR spectra of C_{70} measured at room temperature and 150 K, respectively. The signal at 147 ppm arises from ^{13}C nuclei at positions C2 and C3, whereas the nuclei located at C4 and C5 give rise to the signals at 144.5 and 130 ppm, respectively. It should be noted that the signal at 150 ppm due to ^{13}C nuclei located at C1 position is clearly resolved at room temperature, but it appears only as a 'shoulder' at 150 K since the residual linewidth of the ^{13}C MAS NMR signals of C_{70} increases on decreasing the temperature. The spectrum shown in Figure 65(b) was measured in the presence of a gas stream carrying unpolarized ^{129}Xe (i.e. laser turned off). Turning the laser light on increases the signal intensity of the carbons in the C2 and C3 positions (147 ppm) by $25 \pm 5\%$, an effect that can also be seen in the difference

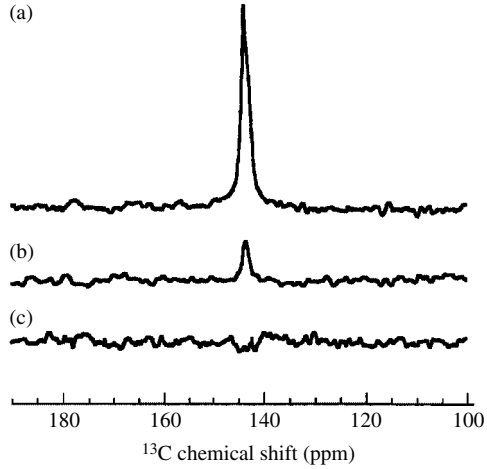


FIGURE 64. ^{13}C MAS NMR spectra of C_{60} acquired at 150 K: (a) Spectrum obtained when the gas stream is not laser-polarized (laser off). (b) Difference between the spectrum obtained when the gas stream is laser-polarized (laser on) and spectrum (A). This spectrum quantitatively represents the observed SPINOE intensity. (c) Difference between two successively recorded spectra obtained when the ^{129}Xe flowing into the rotor is not laser-polarized. This demonstrates that the difference spectrum is free of artifacts. Reproduced by permission of Elsevier Science B. V. from Reference 70

spectrum (Figure 65c and d). The intensity of the 'shoulder' at 150 ppm also increases, but a quantitative evaluation of this effect is difficult on the basis of the present data. The increase in the intensities of the signals at 144.5 and 130 ppm is within the experimental error and is not considered to be significant. Identical T_1 values of 5 ± 1 were measured for the ^{13}C nuclei located at positions C2, C3, C4 and C5 at 150 K. It is concluded, therefore, that the more intense SPINOE for ^{13}C nuclei located at C2 or C3, or at both positions, results from a higher cross-relaxation rate. A plausible explanation for this selective enhancement would be a better accessibility of xenon atoms to these sites and/or a higher heat of adsorption of xenon on these sites.

Pines and coworkers[70] showed the feasibility of spin polarization transfer by SPINOE from laser-polarized ^{129}Xe to surface ^{13}C nuclei on low surface area materials in high-resolution solid-state NMR experiments. This technique provides the basis for novel surface ^{13}C NMR investigations, e.g. of surface coatings, supported catalysts and electrode materials.

Under appropriate nonequilibrium growth conditions, carbon atoms form relatively stable hollow clusters of well-defined mass number, fullerenes. The mass production, purification and condensation of such clusters into a molecular solid are generally essential for a full experimental characterization. The initial discovery of C_{60}, for example, had to wait six years for a bulk synthesis method before detailed characterization of the molecule was possible. Gas-phase experiments have indicated the existence of a wide range of fullerene clusters, but beyond C_{60} only a few pure fullerene solids have been obtained, most notably C_{70}. Low-mass fullerenes are of particular interest because their high curvature and increased strain energy owing to adjacent pentagonal rings could lead to solids with unusual intermolecular bonding and electronic properties. Piskoti and coworkers[71] reported C_{36}, a new carbon solid by the arc-discharge method. They

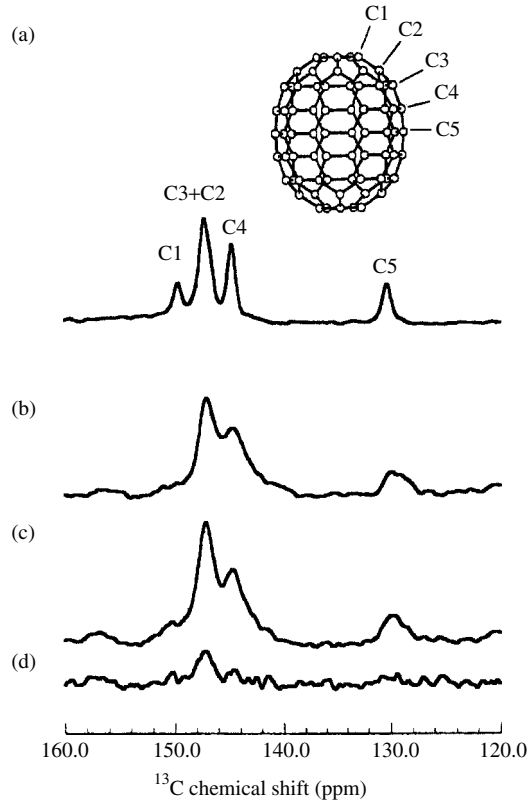


FIGURE 65. ^{13}C MAS NMR spectra of C_{70} acquired at room temperature (a) and 150 K (b–d). (b) Spectrum obtained when the ^{129}Xe flowing into the rotor is not laser-polarized. (c) Spectrum obtained when the ^{129}Xe flowing into the rotor is laser-polarized. (d) Difference between spectrum (c) and spectrum (b). Reproduced by permission of Elsevier Science B. V. from Reference 70

have developed purification methods that separate C_{36} from amorphous carbon and other fullerenes, to yield saturated solutions, thin films and polycrystalline powders of the pure solid form. Solid-state NMR measurements suggest that the molecule has D_{6h} symmetry and electron-diffraction patterns are consistent with a tightly bound molecular solid with an intermolecular spacing of 6.68Å. Large increases in the electrical conductivity of the solid on doping with alkali metals were found.

Figure 66 shows the experimental ^{13}C NMR spectrum of C_{36} powder. The experimental spectrum contains two prominent peaks, one at 146.1 ppm and another (with approximately one-half the intensity) at 135.7 ppm. The inset to Figure 66 shows the predicted molecular NMR spectra for the isolated D_{6h} and D_{2d} isomers (along with schematic structure drawings). The experimental spectrum appears inconsistent with predictions for the D_{2d} isomer. On the other hand, taking into account experimental broadening of the peaks, one would expect for the D_{6h} isomer two peaks, one near 135 ppm and another, a 'double intensity' peak at higher ppm arising from the two higher, nearly degenerate resonances. This is precisely what is observed experimentally. The smaller experimentally observed

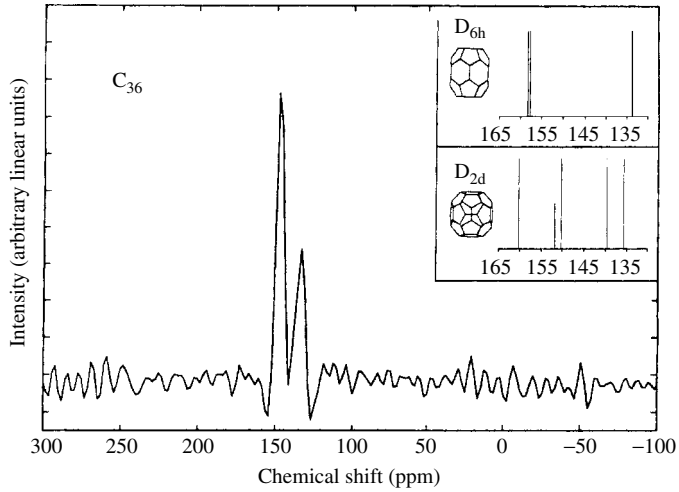


FIGURE 66. Predicted and observed NMR spectra of C_{36}. Reproduced by permission of Nature Management Offices from Reference 71

shift of the 'double intensity' peak (at 146 ppm vs the predicted 158 ppm) is accounted for by additional shielding of these reactive carbon atom sites by neighboring molecules in the solid (this shielding is not considered in the simple molecular calculations). In this way C_{36} was identified as a cage molecule having a D_{6h} symmetry.

V. REFERENCES

1. For example, J. March, *Advanced Organic Chemistry; Reactions, Mechanism and Structure*, 3rd edn., Wiley, New York, 1985, pp. 668–670.
2. For review see R. Huisgen, R. Grashey and J. Sauer, in *The Chemistry of Alkenes* (Ed. S. Patai), Chap. 11, Wiley, New York, 1964, pp. 739–953.
3. R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press, New York, 1970.
4. L. M. Jackman, F. Sondheimer, Y. Amiel, D. A. Ben-Efraim, Y. Gaoni, R. Wolovski and A. A. Bothner-By, *J. Am. Chem. Soc.*, **84**, 4307 (1962).
5. For example, V. S. Watts and J. H. Goldstein, *'Nuclear Magnetic Resonance Spectra of Alkenes'*, in *The Chemistry of Alkenes*, Vol. 2 (Ed. J. Zabicky), Chap. 1, Wiley, London, 1970, pp. 1–38.
6. (a) E. Pretsch, T. Clerc, J. Seibl and W. Simon, *Tabellen Zur Strukturaufklarug Organisher Verbindungen*, Springer-Verlag, Berlin, 1976, pp. H210–H235.
   (b) L. M. Jackman and S. Sternhell, *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd edn., Pergamon Press, Oxford, 1969, pp. 186–190.
7. H. O. Kalinowski, S. Berger and S. Braun, *Carbon-13 NMR Spectroscopy*, Wiley, New York, 1984, pp. 132–152.
8. G. C. Levy, R. L. Lichter and G. L. Nelson, *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd edn., Wiley, New York, 1980, pp. 78–91.
9. U. Fleischer and W. Kutzelnigg, *J. Chem. Phys.*, **82**, 5035 (1988).
10. K. Wokinski, J. F. Hinton and P. Pulay, *J. Am. Chem. Soc.*, **112**, 1360 (1990).
11. (a) A. E. Hansen and T. D. Bouman, *J. Chem. Phys.*, **82**, 5035 (1985).
    (b) J. C. Facelli, D. M. Grant, T. D. Bouman and A. E. Hansen, *J. Comput. Chem.*, **11**, 510 (1990).

12. M. Wada, M. Sakurai, Y. Inoue, Y. Tamura and Y. Watanabe, *Magn. Reson. Chem.*, **33**, 453 (1995).
13. T. D. Bouman and A. E. Hansen, RPAC Version 9.0 (1991).
14. M. J. Frisch, M. H. Gordon, G. W. Trucks, J. B. Foresman, H. B. Schlegel, K. Raghavachari, M. A. Robb, J. S. Binkley, C. Gonzalez, D. J. Fox, R. A. Whiteside, R. Seeger, C. F. Mellius, J. Baker, R. L. Martin, L. R. Kahn, J. J. P. Stewart, S. Topio and J. A. Pople, *Gaussian 90*, Gaussia, Pittsburgh (1990).
15. W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.
16. J. M. Foster and S. F. Boys, *Rev. Mod. Phys.*, **32**, 300 (1960).
17. J. B. Stothers, *^{13}C NMR Spectroscopy*, Academic Press, New York, 1972.
18. A. K. Jameson and C. J. Jameson, *Chem. Phys. Lett.*, **134**, 461 (1987).
19. H. Houjou, M. Sakurai, N. Asakawa, Y. Inoue and Y. Tamura, *J. Am. Chem. Soc.*, **118**, 8904 (1996).
20. S. Tsuboi, J. Sakamoto, A. Kuroda, M. Utaka and A. Takeda, *Bull. Chem. Soc. Jpn.*, **61**, 1410 (1988).
21. D. E. Dorman, M. Jautelat and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971).
22. R. J. Bushby and C. Jarecki, *Tetrahedron Lett.*, **29**, 2715 (1988).
23. W. R. Roth, H. W. Lennartz, W. von E. Doering, W. R. Dolbier, Jr. and J. C. Schmidhauser, *J. Am. Chem. Soc.*, **110**, 1883 (1988).
24. P. Denis, J. F. Croizy, A. Mortreux and F. Petit, *J. Mol. Catal.*, **68**, 159 (1991).
25. A. F. Cockerill, G. L. D. Davies, R. C. Harden and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973).
26. R. Chen, L. U. Colmenares, J. R. Thiel and R. S. H. Liu, *Tetrahedron Lett.*, **35**, 7177 (1994).
27. (a) M. L. Martin, G. J. Martin and J.-J. Delpuech, *Practical NMR Spectroscopy*, Heyden, London, 1980, pp. 339–349.
(b) M. Oki, *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, Weinheim, 1985, pp. 3–11.
28. R. S. H. Liu, J. P. Zingoni, A. Kini, M. Trammell, D. Chu, A. E. Asato and T. T. Bopp, *J. Org. Chem.*, **48**, 4817 (1983).
29. E. Taskinen, *Magn. Reson. Chem.*, **33**, 256 (1995).
30. E. Taskinen and J. Hellman, *Magn. Reson. Chem.*, **32**, 353 (1994).
31. S. F. Marcel, K. J. Lie, K. P. Mohammad and S. A. Mohammad, *Lipids*, **32**, 1041 (1997).
32. A. B. Shtarev, M. M. Kremlev and Z. Chvatal, *J. Org. Chem.*, **62**, 3040 (1997).
33. F. Babudri, A. R. Cicciomessere, G. M. Farinola, V. Fiandanese, G. Marchese, R. Musio, F. Naso and O. Sciacovelli, *J. Org. Chem.*, **62**, 3291 (1997).
34. J. A. Osaheni and S. A. Jenekhe, *Macromolecules*, **28**, 1172 (1995).
35. S. H. Jin, S. W. Kang, J. G. Park, J. C. Lee and K. S. Choi, *Pure Appl. Chem.*, **A32**, 455 (1995).
36. R. Ghirlando, E. Berman, T. Baasov and M. Sheves, *Magn. Reson. Chem.*, **25**, 21 (1987).
37. K. Nakanishi, V. B. Nair, M. Arnaboldi, K. Tsujimoto and B. Honig, *J. Am. Chem. Soc.*, **102**, 7945 (1980).
38. P. E. Blatz and J. H. Mohler, *Biochemistry*, **14**, 2304 (1975).
39. Z. Li, B. J. Rawling, P. H. Harrison and J. C. Vederas, *J. Antibiot.*, **17**, 577 (1989).
40. P. Sowinski, P. Gariboldi, A. Czerwinski and E. Borowski, *J. Antibiot.*, **17**, 1631 (1989).
41. H. Hirota, A. Itoh, J. Ido, Y. Iwamoto, E. Goshima, T. Miki, K. Hasuda and Y. Ohashi, *J. Antibiot.*, **44**, 181 (1991).
42. R. Gebhard, J. T. M. van Dijk, E. van Ouwerkert, M. V. T. J. Boza and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, **110**, 459 (1991).
43. E. S. Hand, K. A. Belmore and L. D. Kispert, *Helv. Chem. Acta*, **76**, 1928 (1993).
44. Y. Yamagishi, K. Shindo and H. Kawai, *J. Antibiot.*, **46**, 888 (1993).
45. S. Chatterjee, E. K. S. Vijayakumar, C. M. M. Franco, J. Blumbach, B. N. Ganguli, H. W. Fehlhaber and H. Kogler, *J. Antibiot.*, **46**, 1027 (1993).
46. K. Imai, Y. Nihei, M. Oka, T. Yamasaki, M. Konishi and T. Oki, *J. Antibiot.*, **46**, 1031 (1993).
47. M. Nakagawa, Y. Toda, K. Furihata, Y. Hayakawa and H. Seto, *J. Antibiot.*, **45**, 1133 (1992).
48. L. U. Colmenares, W. P. Niemczura, A. E. Asato and R. S. H. Liu, *J. Phys. Chem.*, **100**, 9175 (1996).

49. S. Li, S. L. Swindle, S. K. Smith, R. A. Nieman, A. L. Moore, T. A. Moore and D. Gust, *J. Phys. Chem.*, **99**, 3371 (1995).
50. P. Rochet and J. M. Lancelin, *Magn. Reson. Chem.*, **35**, 538 (1997).
51. H. Yasuda, T. Arai, T. Okamoto and A. Nakamura, *J. Organomet. Chem.*, **361**, 161 (1989).
52. J. M. Lehn, J. P. Vigneron, I. B. Waksman, J. Guihem and C. Pascard, *Helv. Chim. Acta*, **75**, 1069 (1992).
53. S. Okada, K. Hayamizu, H. Matsuda, A. Masaki, N. Minami and H. Nakanishi, *Macromolecules*, **27**, 6259 (1994).
54. O. Yamamoto, K. Hayamizu and M. Yanagisawa, *Anal. Sci.*, **4**, 461 (1988).
55. S. O. Smith, L. Paulings, M. E. Miley, J. Courtin, H. de Groot, J. Lugtenburg, R. A. Mathies and R. G. Griffin, *Biochemistry*, **29**, 8158 (1990).
56. L. C. P. J. Mollevanger, A. P. M. Kentegens, J. A. Pardoen, J. M. L. Courtin, W. S. Veeman, J. Lugtenburg and W. J. deGrip, *Eur. J. Biochem.*, **163**, 9 (1987).
57. A. S. Ulrich, A. Watts, I. Wallat and M. P. Heyn, *Biochemistry*, **33**, 5370 (1994).
58. A. S. Ulrich and A. Watts, *Solid State Nucl. Magn. Reson.*, **2**, 21 (1993).
59. A. S. Ulrich, M. P. Heyn and A. Watts, *Biochemistry*, **31**, 10390 (1992).
60. M. L. Ciavatta, M. Gavanin, R. Puliti, G. Cimino, E. Martinez, J. Ortea and C. A. Mattia, *Tetrahedron*, **53**, 17343 (1997).
61. E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, pp. 1119–1190.
62. G. U. Barretta, F. Balzano, A. M. Caporusso, A. Iodice and P. Salvadori, *J. Org. Chem.*, **60**, 2227 (1995).
63. G. U. Barretta, F. Balzano, A. M. Caporusso and P. Salvadori, *J. Org. Chem.*, **59**, 836 (1994).
64. C. Lambert, P. v. R. Schleyer and E. U. Wurthwein, *J. Org. Chem.*, **58**, 6377 (1993).
65. E. Liepins, I. Birgele, E. Lukevics, E. T. Bogoradovsky and V. S. Zavgorodny, *J. Organomet. Chem.*, **402**, 43 (1991).
66. L. M. Tolbert and M. E. Ogle, *J. Am. Chem. Soc.*, **112**, 9519 (1990).
67. H. Kloosterziel and M. A. Werner, *Recl. Trav. Chim. Pays-Bas*, **94**, 124 (1975).
68. L. M. Tolbert and M. E. Ogle, *J. Am. Chem. Soc.*, **111**, 5958 (1989).
69. C. Bellavia-Lund, M. Keshavarz, K. T. Collins and F. Wudl, *J. Am. Chem. Soc.*, **119**, 8101 (1997).
70. E. Brunner, M. Haake, A. Pines, J. A. Reimer and R. Seydoux, *Chem. Phys. Lett.*, **290**, 112 (1998).
71. C. Piskoti, J. Yarger and A. Zettl, *Nature*, **393**, 771 (1998).

The Chemistry of Dienes and Polyenes. Volume 2
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CHAPTER **3**

Photopericyclic reactions of conjugated dienes and trienes

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I. INTRODUCTION

The photochemistry of conjugated polyenes has played a central role in the development of modern molecular photochemistry, due in no small part to its ultimate relevance to the electronic excited state properties of vitamins A and D and the visual pigments, as well as to pericyclic reaction theory. The field is enormous, tremendously diverse, and still very active from both experimental and theoretical perspectives. It is also remarkably complex, primarily because the absorption spectra and excited state behavior of polyene systems are strongly dependent on conformation about the formal single bonds in the polyene chain, which has the main effect of turning on or off various pericyclic reactions whose efficiencies are most strongly affected by conformational factors.

The present review focuses on the excited singlet state photochemistry of non-phenylated conjugated dienes and trienes, emphasizing pericyclic reactions. Conjugated tetraenes and arylated polyenes will receive only brief, occasional mention, in spite of their obvious relevance and the huge amount of work that has been done on their photochemistry and photophysics. Triplet state photochemistry has also been omitted. This approach has been taken in order to provide a practical limit to the already overwhelming amount of literature which needs to be covered, and for 'chemical' reasons as well. Arylated polyenes tend to exhibit the same high reactivity toward photoinduced *E*,*Z*-isomerization as their non-arylated counterparts, but behave differently in most other respects: they fluoresce efficiently in fluid solution at room temperature and, in general, do not display the same rich reactivity toward pericyclic photoprocesses as non-arylated systems. The reader is directed to several excellent reviews[1−5] and particularly recent articles[6−10] on aryl-polyene photochemistry and polyene triplet state photochemistry for further information on these topics. The photochemistry of octatetraene has also been reviewed in detail recently[11].

Theoretical treatments of organic photochemical reactions have evolved enormously over the past ten years. Polyene photochemistry has been at the very center of this revolution, which would appear to be taking us away from the classic model of van der Lugt–Oosterhoff, who first detailed the critical role of the doubly-excited 2^1A_g state in directing the ring closure of 1,3-butadiene to cyclobutene along the favored disrotatory reaction pathway which is predicted by the Woodward–Hoffmann rules[12]. These and later calculations throughout the 1970s and 1980s treated the electrocyclization to cyclobutene [13−16], *E*,*Z*-isomerization[16−18] and *cis*,*trans*-conformer interconversion[16] of acyclic dienes (for example) in more-or-less separate fashion; that is to say, in terms of a model in which each of these reactions follow their own distinct reaction pathways on the excited state surface(s), to a series of minima which correspond to avoided crossings with the ground state surface at the same molecular geometries. Internal conversion to the ground state at the pericyclic minimum then results in branching between starting material and a single product. This model (as do the conceptually even simpler Woodward–Hoffmann rules) assumes a given, usually symmetrical excited state reaction coordinate which mirrors that for the identical process on the ground state surface. On a qualitative level, they generally conform to the essential features of most photochemical pericyclic reactions of conjugated polyenes, the most general exception being the photochemical ring opening of cyclobutene[19,20]. They clearly remain quite powerful from a predictive point of view.

However, more recent, much higher level calculations on a wide variety of systems suggest that the reaction funnel[21] where decay to the ground state surface occurs is more frequently a conical intersection (at which the ground and excited surfaces touch) than an avoided crossing (where they do not)[22–26], a concept which was first recognized by photochemists over thirty years ago[27,28] and then largely ignored. Perhaps the most important ramifications of this model result from the fact that decay to the ground state at a conical intersection must occur with unit efficiency; product selection occurs partly as a result of the structure of the excited molecule at the conical intersection and partly because it connects the excited reactant to two or more ground state products. The unit efficiency of internal conversion to the ground state at a conical intersection dictates that this process must occur on the vibrational timescale, which means that if there exists an essentially barrierless path linking the Franck–Condon region to the conical intersection, then product formation can be essentially complete within a hundred femtoseconds or so. Recent ultrafast time-resolved experiments indicate that, in fact, the photochemistry of a number of simple polyenes follows exactly these characteristics. More concise descriptions of these concepts and their relationship to earlier theoretical models are given in several recent reviews[21–25,29].

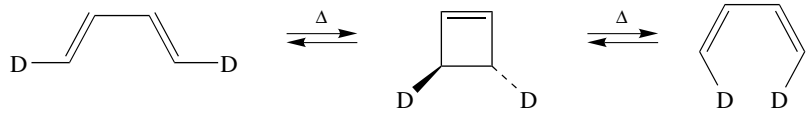
II. GROUND STATE CONFORMATIONAL EQUILIBRIA AND *E,Z*-ISOMERIZATION

Throughout this chapter, the *E*/*Z* nomenclature will be employed to denote geometric isomerism about the double bonds of the polyene chain, while the *cis*/*trans* (‘*c*/*t*’) nomenclature will be used only to denote conformational isomerism about the formal single bonds.

In the absence of substituents, the most stable conformer of linear polyenes is the all-*trans* conformer, with the energies of mono-*cis* conformers being higher by 0.8–2.7 kcal mol^{-1} and the barriers to single-bond rotation being on the order of 3–5 kcal mol^{-1} [30–32]. This means that at room temperature, the various single-bond conformers undergo essentially unrestricted interconversion, with the all-*trans* conformer comprising >95% of the mixture. Of course, the equilibrium composition can be displaced in favor of the less stable conformers at higher temperatures, a fact which frequently results in temperature-dependent photochemistry because polyene photochemistry tends to be highly dependent on ground state conformational factors (*vide infra*). As well, it has often been exploited for the preparation of samples enriched in the less stable conformers for study by matrix isolation techniques at very low temperatures, where conformational interconversion (‘conformerization’) is slow.

The barriers to rotation about the formal double bonds in aliphatic dienes and trienes are in the range 40–55 kcal mol^{-1}, depending on the degree of conjugation, substitution, and ring strain if the polyene moiety is incorporated in a ring. For example, aliphatic dienes such as *Z*-1,3-pentadiene (*Z*-**1**) and *E*,*Z*-1,4-dideuterio-1,3-butadiene undergo thermal *E*,*Z*- isomerization with E_a *ca* 53 kcal mol^{-1} and $\log A$ *ca* 14 in the gas phase[33]. This should be compared to the corresponding values for thermal isomerization of *Z*-2-butene, $E_a = 66.2$ kcal mol^{-1} and $\log A = 14.6$[34,35]. Thermal isomerization of *E*-1,3,5-hexatriene (*E*-HT), on the other hand, proceeds with $E_a = 44.3$ kcal mol^{-1} and $\log A = 12.9$[36]. Similar values have been determined for the Arrhenius parameters for thermal isomerization about the central bonds of other aliphatic trienes[37]. The trend toward decreasing E_a with increasing conjugation is consistent with the long-accepted view that thermal *E*,*Z*-isomerization of non-polarized alkene systems proceeds via rotation about the double bond, through a *ca* 90° twisted transition state with 1,2-biradical character at the isomerizing bond[35,37].

Interpretation of the rate constants and Arrhenius parameters for thermal *E*,*Z*-isomerization is not always straightforward mechanistically, however, since sequential electrocyclic ring closure/ring opening reactions can often provide a lower energy route to the same products as formal rotation about a single C=C bond. This can be illustrated by Brauman and coworkers' classic study of the thermal isomerization of *E*,*E*-, *E*,*Z*- and *Z*,*Z*-1,4-dideuterio-1,3-butadiene (*E*,*E*-**BD**-d_2)[33]. At 637 °C, the *E*,*E*- and *Z*,*Z*-isomers interconvert, but neither yield the *E*,*Z*-isomer. The rate constant for this interconversion is about twenty times larger than that for isomerization of the *E*,*Z*-isomer to *E*,*E* and *E*,*Z*, which can only proceed by the 'conventional' double-bond isomerization pathway (equation 1). The results are consistent with the $E, E \rightleftharpoons Z, Z$ isomerization proceeding via the intermediacy of *trans*-3,4-dideuteriocyclobutene (*trans*-**CB**-d_2), whose formation is expected to proceed with E_a *ca* 45 kcal mol^{-1}.



(1)

E,*E*-**BD**-d_2 *trans*-**CB**-d_2 *Z*,*Z*-**BD**-d_2

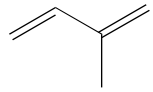
III. THE EXCITED SINGLET STATES OF CONJUGATED POLYENES: UV ABSORPTION AND EMISSION SPECTRA

The electronic spectroscopy of polyene systems has been so extensively investigated and is so thoroughly covered in numerous books and reviews[1,3,11,21,38] that only a brief general summary need be presented here.

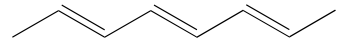
Two excited singlet states are relevant to the direct photochemistry of conjugated polyenes: the one-photon-allowed 1^1B state (S_2) and the two-photon-allowed 2^1A state (S_1). Excitation to the 1^1B state involves promotion of one electron from the highest occupied π-MO in the ground (1^1A) state to the lowest unoccupied π^*-MO, and is responsible for the prominent, often-structured band in the UV absorption spectra of conjugated polyenes. The 1^1B state of polyenes is well-accepted to be ionic in character, with the formal C−C single bonds enjoying increased double bond character and hence restricted rotation compared to the ground state[1,16,39]. The opposite is true of the formal C=C bonds. At the Franck−Condon geometry, the 2^1A state is the lower energy state in all conjugated polyenes from 1,3,5,7-octatetraene up[3,11,40]. Its placement in relation to the 1^1B state in 1,3-butadiene and 1,3,5-hexatriene has been the subject of some debate (see References 38, 41 and 42 and references cited there), but it is clear that the two states are at least very close in energy and in any event fairly minor geometric distortions cause them to cross; internal conversion from the spectroscopic (1^1B_u) state to the 2^1A state is almost always very efficient. The 2^1A state is thus the true 'photoactive state' in polyene photochemistry. This excited state is covalent in character with little π-bonding; thus, the electronic structures of the 2^1A states of shorter-chain polyenes are best described as polyradicaloid and, as a result, the barriers to twisting about any of the C−C bonds in the 2^1A state are very low[11].

Recent theoretical and spectroscopic studies indicate that in aliphatic dienes and trienes, excitation to the spectroscopic 1^1B state usually results in facile twisting about the termini in the stereochemical sense dictated by orbital symmetry selection rules for the appropriate electrocyclic ring closure, motions which are often accompanied by some degree of planarization of the carbon framework. In general, relatively minor distortions

along this reaction coordinate take the excited molecule via a barrierless route (and hence commonly within femtoseconds after excitation) to a geometry where the 1^1B and 2^1A states cross, and internal conversion to the latter state takes place. Further twisting, now involving several or all of the C−C bonds in the polyene framework, leads the molecule in the 2^1A state to a conical intersection with the ground state surface, from which partitioning between starting materials and one or more photoproducts occurs. As a result of the essentially barrierless decay to the ground state which such results imply, quantum yields for fluorescence of non-phenylated conjugated dienes and trienes are usually extremely low in the gas phase and in solution. For example, extremely weak fluorescence has been observed for isoprene **(2)** in cyclohexane solution at ambient temperatures ($\Phi_F < 10^{-6}$)[43], and for 1,3,5-hexatriene and 2,4,6-octatriene **(3)** as mixtures of isomers in the gas phase under isolated molecule conditions[44]. Experimental indications of the various distortions which take place in the first few hundred femtoseconds after excitation to the 1^1B state have been obtained using resonance Raman, fluorescence and other spectroscopic techniques[1,11,40,41,43,45−48]. Time-resolved resonance Raman and other spectroscopic techniques have been used to show that excited state deactivation (including product formation) in dienes and trienes is usually complete within a few picoseconds or less after excitation[49−52].

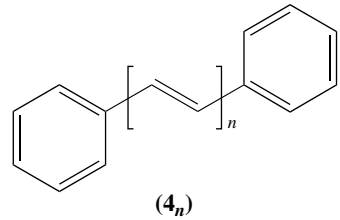


(2)



(3)

1,3,5,7-Octatetraene and higher unsubstituted polyenes, on the other hand, are well-known to exhibit (2^1A-1^1A) fluorescence at low temperatures, implying the presence of ever-deepening minima on the 2^1A surface as the degree of conjugation increases[1,11]. A recent theoretical paper describes the common structural features of the $2^1A/1^1A$ conical intersections of the series of all-*trans* linear polyenes and radicals [$H_2C(CH)_nCH_2$] from $n = 1-6$[53]. Fluorescence is readily observable at room temperature from the all-*E*-α,ω-diphenylpolyenes **(4_n)** irrespective of chain length, a property which has made possible very detailed measurements of the excited state dynamics of these systems[1−3]. The photochemistry of these more extensively conjugated systems tends to be dominated by *E*,*Z*-isomerization to a much greater extent than is the case with aliphatic dienes and trienes, and pericyclic reactivity is relatively rare[11,3]. This is almost certainly the direct result of the differences in the morphology of the 2^1A potential energy surfaces which are invoked by increasing conjugation.



(4_n)

Conformation about the formal single bond(s) has well-known effects on the position of the lowest energy ($1^1A \rightarrow 1^1B$) absorption band in dienes and the higher polyenes, which is primarily due to π-overlap effects on the energy of the highest occupied π molecular orbital[54–57]. It is also the single most important factor in determining the type of product(s) formed upon direct irradiation. Much of the complexity associated with the photochemistry of acyclic (or, more specifically, conformationally-mobile) polyenes is due to the fact that more than one conformer is present under the conditions of irradiation, and their photochemistries differ. Thus in general, the overall product distribution will depend on the equilibrium distribution of conformers present under the particular reaction conditions, their relative extinction coefficients at the excitation wavelength and the specific product distribution that each conformer yields upon excitation. This usually results in wavelength-dependent photochemistry.

IV. SINGLET STATE PHOTOCHEMISTRY OF CONJUGATED DIENES AND TRIENES

The direct irradiation of conjugated polyenes results in a rich and varied photochemistry, the course of which depends mainly on the degree of conjugation and the ground state conformational properties of the polyene system. In the absence of heavy atoms or substituents which specifically promote spin–orbit coupling, intersystem crossing is slow compared to reactive excited singlet state decay processes[58–60]. With systems in which more than one double bond geometric isomer exists, *E*,*Z*-isomerization almost invariably dominates the excited singlet state photochemistry, even when it results in the formation of a relatively unstable, transient ground state species. This is even more true of the excited triplet states of conjugated polyenes. The process is not subject to the same sort of conformational constraints as other polyene photoprocesses are, so in view of this and its overall importance to the photochemistry of all polyene systems, it will be treated separately.

Acyclic systems (particularly conjugated dienes) also undergo efficient conformational isomerization about one of the formal C–C single bonds upon direct excitation, although this can only be detected under conditions where the individual conformers do not interconvert in the ground state (such as in rigid matrices at very low temperatures). However, a large body of evidence indicates that individual conformers generally do not interconvert within the lifetime of the excited state, which forms the basis of the well-known 'NEER (Non-Equilibration of Excited-state Rotamers) Principle'[61].

Pericyclic isomerization reactions (electrocyclic reactions, sigmatropic rearrangements and formal intramolecular cycloadditions) constitute the most interesting aspect of polyene photochemistry (from our perspective), since the efficiencies of these reactions are critically dependent on the ground state conformational properties of the system, and the extent to which excited state decay by double- or single-bond twisting is impeded due to structural constraints. Although the quantum yields may be low, the chemical yields of these products can often be quite high, particularly when excited state decay by torsion about the formal double bonds is non-productive. When geometric isomerism about one or more of the double bonds is possible, then the observed product distributions from irradiation of individual geometric isomers are usually conversion-dependent, because *E*,*Z*-isomerization is generally much more efficient than other processes. The observed product distribution reflects that of the starting isomer only at very low conversions, and changes continuously as the system converges to a pseudo-photostationary state of geometric isomers, which generally have very similar absorption spectra and hence cannot be selectively excited.

Direct *E*,*Z*-photoisomerization is sufficiently ubiquitous in the photochemistry of all polyene systems that it will be considered first in its own separate section, although the

coverage will be brief. Next will be considered photochemical *cis–trans* conformational interconversion, a non-productive process which often dominates in the assortment of excited state decay pathways available to the excited singlet states of conjugated polyenes. The bulk of the review of polyene excited singlet state photochemistry is directed at rearrangement reactions, which include pericyclic and biradical-derived processes and is divided into specific reaction types.

A. Direct *E*,*Z*-Isomerization

Torsion about one of the formal double bonds is invariably the most efficient excited singlet state decay process of acyclic polyenes, and also often occurs efficiently in cyclic systems of moderate-to-large ring size[2,3,11,60,62]. *E*,*Z*-isomerization in the excited singlet state manifold takes place about only one of the double bonds per photon, as was initially demonstrated for 2,4-hexadiene **(5)** by Saltiel and coworkers[59] and has since been shown to be quite general. Table 1 contains a summary of quantum yields for the direct *E*,*Z*-photoisomerization, in solution, of acyclic and cyclic polyenes **1**, $\mathbf{4}_2$, $\mathbf{4}_3$, **5–18** bearing various substituents. For the most part, quantum yields for direct *E*,*Z*-photoisomerization of aliphatic dienes are not highly dependent on the structure of the system (i.e. acyclic, cyclic or exocyclic).

Because *E*,*Z*-isomerization is reversible and proceeds with quantum yields which are generally much higher than those for other productive decay processes, direct irradiation of polyenes in solution leads to the formation of a pseudo-equilibrium mixture of geometric isomers, whose composition is dependent on the quantum yields for isomer-interconversion, the extinction coefficients at the excitation wavelength (λ_{ex}) of the interconverting isomers and the quantum yields for formation of other products which do not revert to any of the geometric isomers of the original polyene[60,62].

The *E*,*Z*-photoisomerization of alkenes is accurately viewed in terms of the Mulliken model for ethene[74], in which the excited alkene relaxes to a discrete twisted excited state intermediate ($^1p^*$), from which internal conversion to the ground state occurs (for reviews see References 2, 3, 60, 62, 75 and 76). The geometry of $^1p^*$ is common to both alkene geometric isomers and corresponds roughly to that of the transition state for ground state *E*,*Z*-isomerization. The intermediate is then considered to partition itself between the *E*- and *Z*-isomers in a ratio $\alpha/(1-\alpha)$, which is often assumed (but not required) to be about 0.5[65]. This model and its extension to the direct *E*,*Z*-photoisomerization of conjugated dienes is shown in Scheme 1, where the twisted intermediates are represented as 1,2-biradicals[18,59,63,77,78]. Thus, the quantum yields for direct *E*,*Z*-photoisomerization of alkenes and conjugated dienes are given by equations 2, 3a and 3b, respectively, where the ϕ_{p^*} terms are the state efficiencies for formation of the twisted intermediates from the spectroscopic excited states of the starting compounds. We (gently) suggest that this model is inappropriate for aliphatic dienes and trienes, given the ultrafast timescale on which the ground state is populated in these systems, but it certainly remains valid (or at least very useful) for higher polyenes and arylated systems, whose photochemistry tends to be confined to *E*,*Z*-isomerization[3].

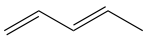
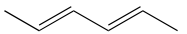
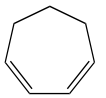
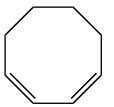
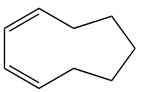
$$\Phi_{E\rightarrow Z} = (1-\alpha)\phi_{E\rightarrow p^*}; \qquad \Phi_{Z\rightarrow E} = \alpha\phi_{Z\rightarrow p^*} \tag{2}$$

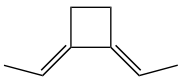
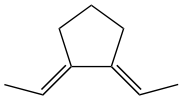
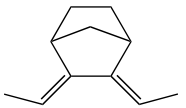
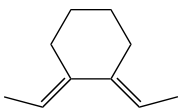
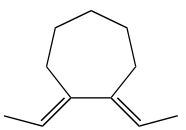
$$\Phi_{EE\rightarrow EZ} = (1-\alpha_{Ep^*})\phi_{EE\rightarrow Ep^*}; \quad \Phi_{EZ\rightarrow EE} = \alpha_{Ep^*}\phi_{EZ\rightarrow Ep^*} \tag{3a}$$

$$\Phi_{EZ\rightarrow ZZ} = (1-\alpha_{Zp^*})\phi_{EZ\rightarrow Zp^*}; \quad \Phi_{ZZ\rightarrow EZ} = \alpha_{Zp^*}\phi_{ZZ\rightarrow Zp^*} \tag{3b}$$

There has been considerable debate over whether the *E*,*Z*-photoisomerization (as well as other photoprocesses) of conjugated polyenes proceeds via neutral (2^1A) or zwitterionic

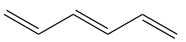
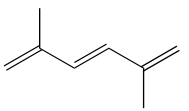
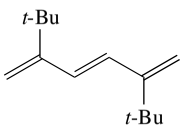
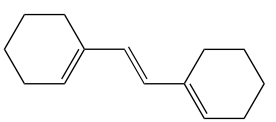
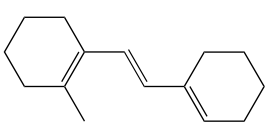
TABLE 1. Quantum yields for direct *E*,*Z*-photoisomerization of conjugated polyenes

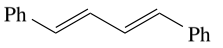
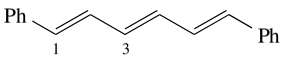
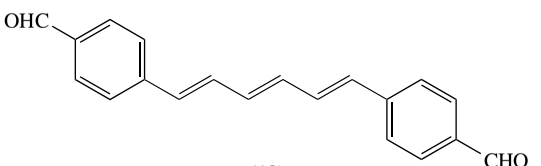
Compound	Solvent	λ_{ex} (nm)	$E \rightarrow Z$	$Z \rightarrow E$	Reference
 **(1)**	*c*-C_6H_{12}	254 228	0.08 0.022	0.10 0.025	63 64
 **(5)**	C_5H_{12}	254	0.37 (*EE*) 0.29 (*EZ*)	0.17 (*EZ*) 0.41 (*ZZ*)	59
 **(6)**	CH_3OH	254		~0.26	66
 **(7)**	C_6H_{14}	248		0.28	67
 **(8)**	C_5H_{12}	254		0.26	68

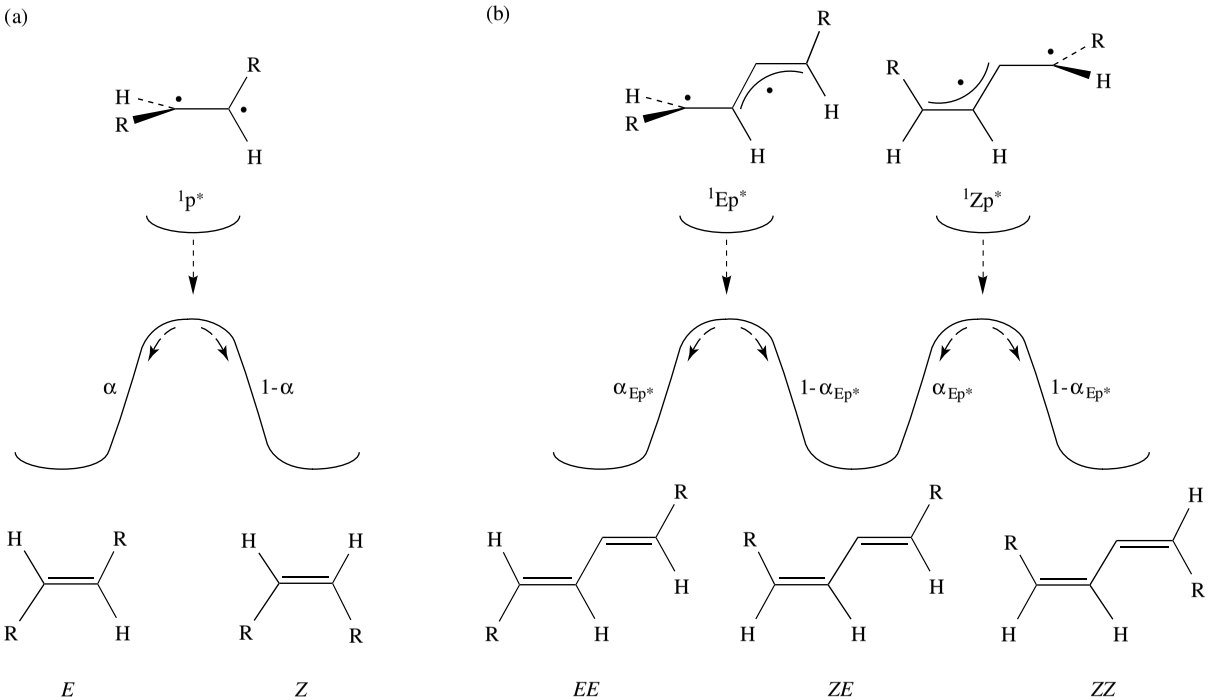
 **(9)**	C_5H_{12}	254	0.12 (*EE*) 0.011 (*EZ*)	0.11 (*EZ*)	69
 **(10)**	C_5H_{12}	254	0.24 (*EE*) 0.09 (*EZ*)	0.39 (*EZ*)	69
 **(11)**	C_5H_{12}	254	0.30 (*EE*) 0.06 (*EZ*)	0.28 (*EZ*)	69
 **(12)**	C_5H_{12}	254	0.20 (*EE*)	0.27 (*EZ*)	70
 **(13)**	C_5H_{12}	254	0.21 (*EE*)	0.14 (*EZ*)	70

(*continued overleaf*)

TABLE 1. (*continued*)

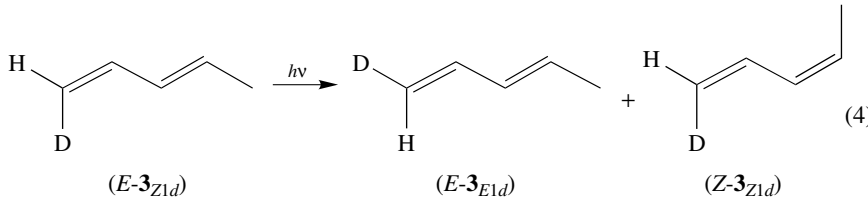
Compound	Solvent	λ_{ex} (nm)	$E \rightarrow Z$	$Z \rightarrow E$	Reference
 **(HT)**	C_5H_{12}	265	0.016	0.034	71
 **(14)**	C_5H_{12}	254	0.004	0.37	72
 **(15)**	C_5H_{12}	254	0.046	0.052	72
 **(16)**	Et_2O	296–312	~0.46	n.d.	73
 **(17)**	Et_2O	296–312	~0.40	n.d.	73

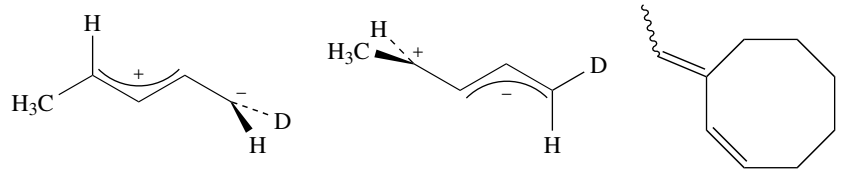
 (**4**$_2$)	c-C_6H_{12}	325	0.11 (*EE*)	0.04 (*EZ*) 0.20 (*ZZ*)	65
 (**4**$_3$)	c-C_7H_{14} MeCN	366	0.011 (*EEE*-1) 0.048 (*EEE*-3) 0.075 (*EEE*-1) 0.049 (*EEE*-3)	0.139 (*ZEE*-1) 0.221 (*EZE*-3) 0.171 (*ZEE*-1) 0.138 (*EZE*-3)	4
 (**18**)	Toluene $CHCl_3$ MeCN	*ca* 365	<0.003 (*EEE*-1) 0.13 (*EEE*-1) 0.33 (*EEE*-1)	0.68 (*ZEE*-1) 0.39 (*ZEE*-1) 0.29 (*ZEE*-1)	6



SCHEME 1. The biradical model for the direct *E*,*Z*-photoisomerization of (a) alkenes and (b) conjugated dienes

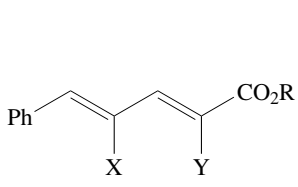
(1^1B) twisted excited state intermediates. The latter was first proposed by Dauben and Ritscher[79] and subsequently received considerable theoretical support[17,39,80–82] (however, see Reference 83). Experimental support for zwitterionic twisted intermediates in diene[79,84–86] and triene[4,86] photoisomerizations has come from studies of unsymmetrically substituted systems, albeit mostly aryl-substituted ones. For example, Squillacote and Semple showed that the direct irradiation of *E*-1,3-pentadiene-*Z1d* (*E*-$\mathbf{1}_{Z1d}$) with 229 nm light results in the formation of *E*-1,3-pentadiene-*E1d* (*E*-$\mathbf{3}_{E1d}$) and *Z*-1,3-pentadiene-*Z1d* (*Z*-$\mathbf{1}_{Z1d}$) in a ratio of about 25 : 1 (equation 4)[85]. They explained the result in terms of the intermediacy of a polarized allyl (cation)–methylene (anion) intermediate **(19a)**, rather than the oppositely-polarized structure **(19b)** proposed by Dauben and Ritscher to explain the regio- and stereoselective photoisomerizations of *E*- and *Z*-ethylidenecyclooctene (**20**; *vide infra*)[79]. Soon after, Muthuramu and Liu reported that the *E*,*Z*-photoisomerization of the fluorinated 1-phenyl-4-carboalkoxybutadienes **21** proceeds regioselectively about the phenyl-substituted double bond, consistent with the Dauben intermediate[86]. Saltiel and coworkers have reported a particularly interesting example of solvent- and substituent-dependent regioselectivity in the *E*,*Z*-photoisomerization of *E*,*E*,*E*-1,6-diaryl-1,3,5-hexatrienes **(22)**; the quantum yields for isomerization about the central double bond in the parent molecule (**22**; X = H) are insensitive to solvent polarity, while those for isomerization about a terminal bond are enhanced seven-fold in acetonitrile compared with hydrocarbon solvents[4]. Isomerization of the substituted derivatives proceeds regioselectively to yield the 1-*Z* and 3-*Z* isomers, and in both cases the quantum yield for terminal bond isomerization is enhanced dramatically in polar solvents. The results were explained in terms of competing torsional relaxation about the central and terminal bonds via biradicaloid and zwitterionic twisted intermediates, respectively. For the parent and cyano derivatives, the latter is polarized in the same sense proposed by Dauben and Ritscher. Interestingly, the polarization appears to be reversed in the case of the methoxy derivative.



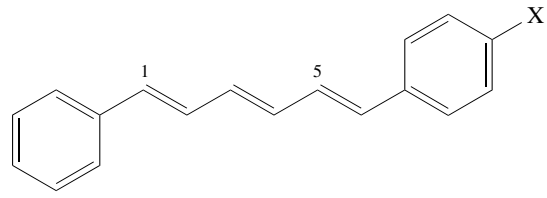


(19a) **(19b)** **(20)**

More recent high level *ab initio* calculations on 1,3-butadiene confirm that zwitterionic allylmethylene twisted species correspond to energy minima on the 1^1B potential

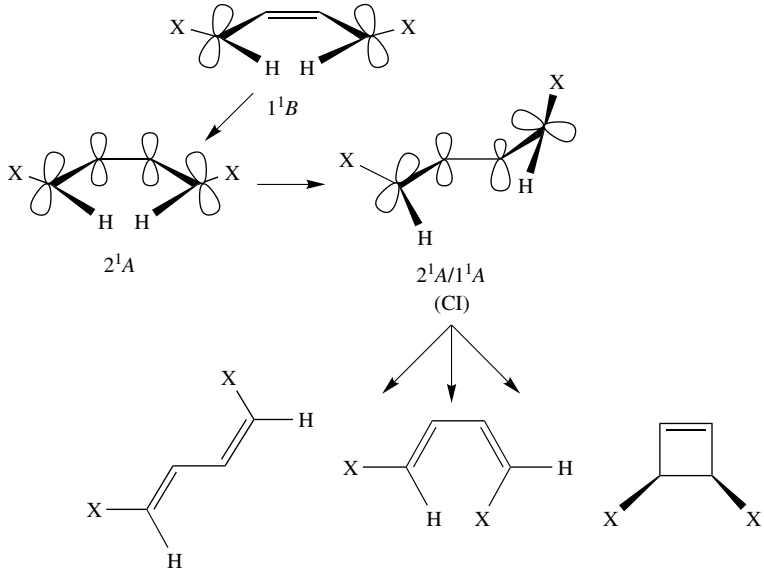


(21) X, Y = H and/or F



(22) X = H, CN, OMe

energy surfaces of both the s-*cis* and s-*trans* conformers, but suggest them to lie some 30 kcal mol^{-1} above the ground state surface at the same geometry[16,87]. The more recent calculations indicate the presence of a barrierless pathway linking the spectroscopic (1^1B_u) state to a $2^1A_g/1^1A$ conical intersection, which provides a far more efficient pathway to one-bond *E*,*Z*-isomerization and the formation of other products[88,89]. These calculations suggest that the funnels to the ground state surfaces for both s-*cis* and s-*trans* 1,3-butadiene are tetraradicaloid structures in which there is substantial twisting about all three C−C bonds. The favored pathways to the ground state surface proceed through conical intersections at which there is significant disrotatory twisting of the termini, hence providing a pathway for both cyclobutene formation (*vide infra*), *E*,*Z*-isomerization and s-*cis*/s-*trans* conformer interconversion via the same funnel geometry (Scheme 2). Calculations by the same group on a few substituted butadiene systems indicate that while their photochemistries should be dictated by similar pathways for excited state decay, both the structure at the conical intersection and the torsional dynamics of the molecule in the excited state are affected significantly by steric and polar factors associated with the substituents[87,90]. Calculations on the *E*,*Z*-photoisomerization of *Z*- and



SCHEME 2. Excited state reaction path for butadiene

E-1,3,5-hexatriene[91,92], *E*,*E*-1,3,5,7-octatriene[93] and longer polyenes related to the visual pigments[94–97] have been reported as well.

Clearly, substituents can be expected to have significant effects on the energy of the zwitterionic 1^1B minimum in butadiene, perhaps even to the point where it assumes the role of the funnel to the ground state surface. At the very least, they can be expected to affect the morphology of the 1^1B surface in the Franck–Condon region. Thus, even in cases where theory predicts that torsional decay to the ground state occurs at a (covalent, tetraradicaloid) $2^1A/1^1A$ conical intersection, polar factors could very well dictate the regiochemistry of *E*,*Z*-isomerization through their effects on the dynamics of the 1^1B-2^1A-1^1A internal conversion sequence.

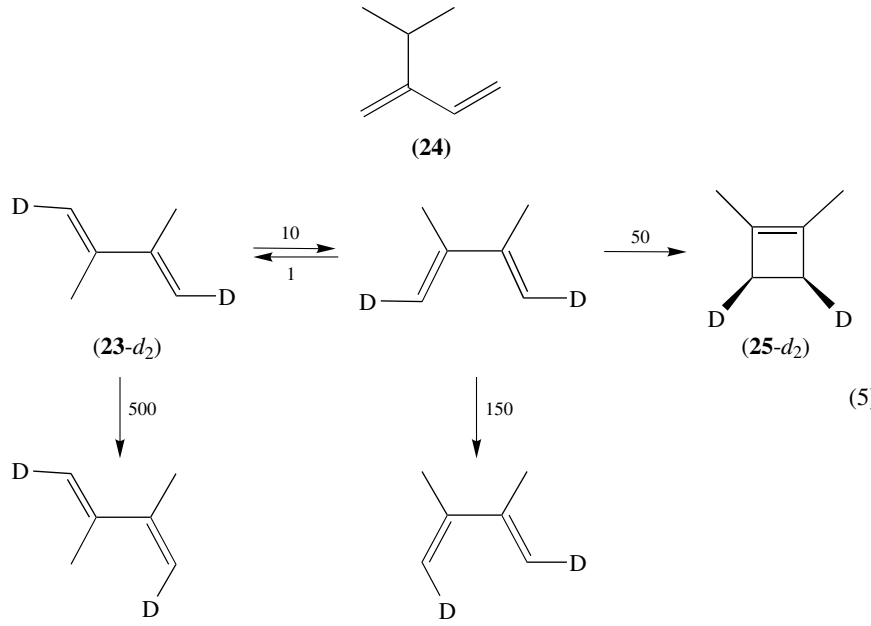
So far, experimental tests of the $2^1A/1^1A$ conical intersection mechanism for acyclic diene and triene excited singlet state decay have largely been confined to ultrafast time-resolved spectroscopic studies, which have recently been reviewed[98,99]. Leigh and Postigo addressed the ramifications of the model on the quantum yields for *E*,*Z*-photoisomerization of aliphatic s-*cis*-dienes, specifically to probe the possible effects of constraining the torsional mobility about the 'central' formal single bond (C2–C3 in 1,3-butadiene)[69]. Indeed $\Phi_{EE\rightarrow EZ}$ decreases regularly with decreasing central bond torsional mobility throughout the series of compounds **9–11** (Table 1), a trend which seems difficult (but not impossible) to explain in terms of the allylmethylene mechanism for diene *E*,*Z*-isomerization. Olivucci and coworkers have explained the trend as due to structurally-induced constraints on bending of the C1–C2–C3 bond angle, which approaches 90° at the $2^1A/1^1A$ conical intersection of s-*cis*-butadiene, rather than on torsional freedom about the central C–C bond[87]. The quantum yields for electrocyclic ring-closure to the isomeric cyclobutene derivatives (both in these and the 1,2-bismethylene analogs of **9–11**[100]) vary in the same way as those for *E*,*Z*-photoisomerization, which is consistent with the idea that the two processes proceed via decay through the same conical intersection.

Intriguingly, the conical intersection model also suggests that *E*,*Z*-isomerization of acyclic dienes might be accompanied by conformational interconversion about the central bond, reminiscent of the so-called 'Hula-Twist' mechanism for the efficient *E*,*Z*-photoisomerization of the visual pigment rhodopsin in its rigid, natural protein environment[101]. A study of the photochemistry of deuterium-labelled 2,3-dimethyl-1,3-butadiene (**23**-d_2) in low temperature matrices (*vide infra*) found no evidence for such a mechanism in aliphatic diene *E*,*Z*-photoisomerizations[102]. On the other hand, Fuss and coworkers have recently reported results consistent with the operation of this mechanism in the *E*,*Z*-photoisomerization of previtamin D_3 (*vide infra*)[103].

B. *cis*,*trans*-Conformational Interconversion

As mentioned earlier, conformational isomerization about the formal single bonds of polyene systems is facile in the ground state, where it occurs with activation barriers on the order of 2–4 kcal mol^{-1} in acyclic systems[104]. The process also occurs in acyclic dienes upon direct excitation, as was shown by Squillacote and coworkers using low temperature matrix isolation techniques, at temperatures where thermal conformational re-equilibration is suppressed (10–20 K)[105]. Thus, direct irradiation of *trans*-1,3-butadiene in an argon matrix at 15 K results in the efficient formation of the *cis*-conformer, distinguishable from the *trans*-conformer by its distinct UV absorption and infrared spectra[105,106]. The process is quite general, at least for aliphatic dienes such as isoprene **(2)**, 2-isopropyl-1,3-butadiene **(24)**, 2,4-hexadiene **(5)** and 2,3-dimethylbutadiene **(23)**[102,107]. Its efficiency is unusually low in the latter case, as has been established

by irradiation of the 1,4-d_2 isotopomer (**23**-d_2) in matrices at 15 K. These experiments allowed the relative efficiencies of *cis*,*trans*-conformer interconversion, *E*,*Z*-isomerization and electrocyclic ring-closure to **25**-d_2 to be determined quantitatively as shown on the arrows in equation 5[102].



(5)

Photochemical *cis*,*trans*-conformational interconversion is also known to occur in larger polyenes. Brouwer and Jacobs have reported the results of irradiation of *E*- and *Z*-2,5-dimethyl-1,3,5-hexatriene **(14)** in argon matrices at 10 K[108]. Irradiation of the *E*-isomer gives rise to various rotamers, while irradiation of the *Z*-isomer results only in *E*,*Z*-isomerization. Photochemical *trans*/*cis* conformer interconversion has also been observed for *E*,*E*-1,3,5,7-octatriene in matrices at temperatures below 10 K[32].

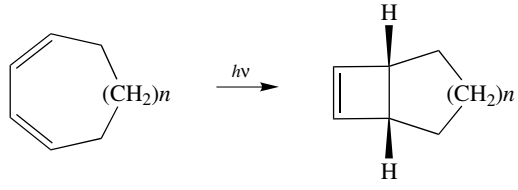
C. Photopericyclic Reactions of Conjugated Dienes

1. Cyclic and acyclic conjugated dienes

Aliphatic dienes undergo three main photochemical pericyclic processes, whose individual efficiencies depend largely on the torsional angle about the central bond in the specific diene conformer which is excited. These are (a) cyclobutene formation, (b) bicyclo[1.1.0] butane formation and (c) [1,5]-hydrogen migration. A fourth process, methylcyclopropene formation, has also been observed in minor amounts in several cases.

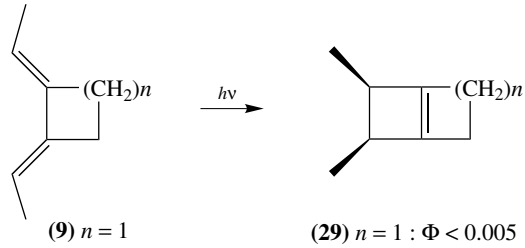
a. Cyclobutene formation. Electrocyclic ring closure to yield cyclobutenes is the best known photopericyclic reaction of 1,3-dienes, and occurs as well in higher polyenes which contain an s-*cis* butadienyl moiety. The process is highly stereospecific, proceeding with the disrotatory stereochemistry predicted by orbital symmetry selection rules[109], and occurs with quantum yields approaching *ca* 0.1 in conformationally-constrained s-*cis* dienes, so long as the C1−C2−C3−C4 dihedral angle is on the order of *ca* 40°

or less. This conclusion is derived from consideration of the quantum yields for cyclobutene (**26**–**32**) formation in the various cyclic and exocyclic 1,3-diene systems shown in equations 6 and 7. Thus, the quantum yields for cyclobutene formation decrease systematically throughout the series of cyclic and exocyclic dienes **6**–**8**[66–68] and **9**–**13**, respectively (the norbornyl analogue (**11**) closes with $\Phi = 0.03$)[69]. A similar trend was reported for the *E*,*Z*-isomers of **9**–**13**,[69] and for the bis-methylene homologues of these compounds[100].



(6)

(6) $n = 1$ **(26)** $n = 1 : \Phi = 0.09$
(7) $n = 2$ **(27)** $n = 2 : \Phi = 0.01$
(8) $n = 3$ **(28)** $n = 3 : \Phi = 0.002$

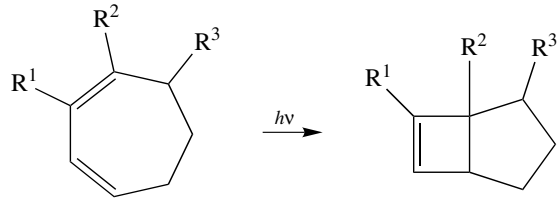


(7)

(9) $n = 1$ **(29)** $n = 1 : \Phi < 0.005$
(10) $n = 2$ **(30)** $n = 2 : \Phi = 0.10$
(12) $n = 3$ **(31)** $n = 3 : \Phi = 0.05$
(13) $n = 4$ **(32)** $n = 4 : \Phi = 0.15$

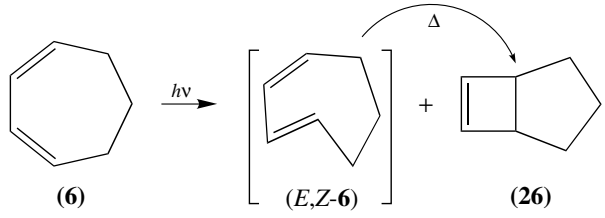
The direct irradiation of 1,3-cycloheptadiene **(6)**[110–113] and various substituted derivatives **(33)**[110,113–115] in hydrocarbon solvents provides a very clean, high yield route to the corresponding bicyclo[3.2.0]hept-6-ene derivatives (**34**; equation 8)[116]. The reaction also proceeds cleanly with a variety of heterocyclic analogues[117–121]. It should be noted that the value of Φ listed in equation 6 for the parent compound is that estimated for the direct, excited state ring closure pathway. In fact, **26** is formed with a quantum yield of 0.35 when the diene is irradiated in solution at room temperature[66,110,122]. The difference has been shown to be due to a second route for formation of this product which competes with the direct pathway: *E*,*Z*-photoisomerization to yield the highly strained (transient) *E*,*Z*-1,3-cycloheptadiene (*EZ*-**6**; Φ *ca* 0.26), which undergoes rapid ground state (conrotatory) ring closure at ambient temperatures (equation 9). This was demonstrated by acid-catalyzed trapping of *E*,*Z*-**6** as the methanol addition product, from which it was concluded that *ca* 75% of **26** is formed by the two-step pathway.[66,122] The analogous process does not occur upon direct irradiation of 1,3-cyclooctadiene **(7)** in solution at room temperature[123] since the *E*,*Z*-diene isomer (the major product) is thermally stable under these conditions; the ring closure product **(27)** is formed as a true primary photochemical product, with a quantum yield on the order of *ca* 0.01[67]. The lower quantum yield for ring closure of **7** compared to that of 1,3-cycloheptadiene is a reflection of the

larger central bond angle in the 8-membered ring diene; even lower quantum yields for ring closure are observed in *Z*,*Z*- and *E*,*Z*-1,3-cyclononadiene **(8)**[124].



(33) **(34)** (8)

R^1–R^3 = Me, Et, *i*-Pr, *t*-Bu, $CH_2CH_2OCH_3$
CH_2COCH_3, CO_2Me

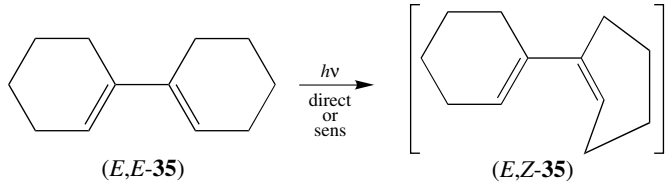


(6) (*E*,*Z*-**6**) **(26)** (9)

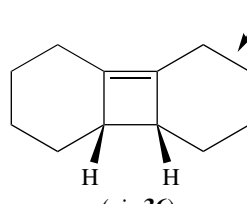
Φ_{EZ} *ca* 0.26 Φ_{CB} *ca* 0.09

A related example is that of 1,1′-bicyclohexenyl **(35)**, which photocyclizes to yield *cis*-tricyclo[6.4.0.0^{2,7}]dodec-1-ene (*cis*-**36**) upon either direct[112] or triplet-sensitized[58] excitation. The triplet-sensitized reaction proceeds via initial *E*,*Z*-isomerization to yield the strained *E*,*Z*-1,1′-bicyclohexenyl (*E*,*Z*-**35**), which undergoes rapid (conrotatory) thermal ring closure to the tricyclic cyclobutene derivative (equation 10). This mechanism was first suggested by Liu[123], and subsequently verified by Saltiel and coworkers on the basis of laser flash photolysis experiments, which allowed the direct detection of the strained diene[125]. In the direct irradiation, methanol trapping experiments demonstrated that *cis*-**36** is formed by two competing pathways: direct disrotatory ring closure and a two-step pathway involving thermal ring closure of *E*,*Z*-**35**[125]. Interestingly, direct irradiation of 1,1′-bicyclopentenyl **(37)** does not lead to ring closure[112,126], but instead results in the formation of a non-conjugated diene isomer in low efficiency[127].

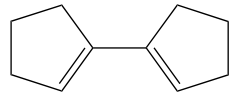
Photoelectrocyclic ring closure also occurs in some 1,3-cyclohexadiene systems, although, in general, the efficiency of the process is quite low unless the diene moiety is held in a planar conformation[128] or photoelectrocyclic (conrotatory) ring opening to the corresponding 1,3,5-hexatriene isomer (which is intrinsically more efficient than ring closure; *vide infra*) is structurally blocked[129]. The latter is aptly illustrated by the photochemistry of the pro-vitamin D isomers pyrocalciferol **(38)**, which leads to **39** (equation 11), and isopyrocalciferol **(40)**, which gives **41** (equation 12). In fact, this represents the first examples of this reaction to be reported[61,130,131]. Additional examples which illustrate the conformational requirements of the two possible electrocyclic pathways available to 1,3-cyclohexadienes will be discussed in a later section of this review.



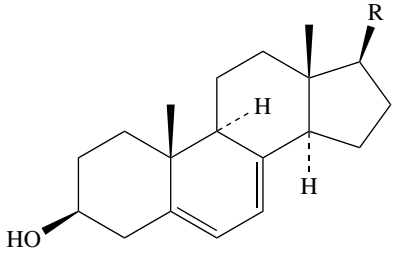
(*E*,*E*-**35**) (*E*,*Z*-**35**)

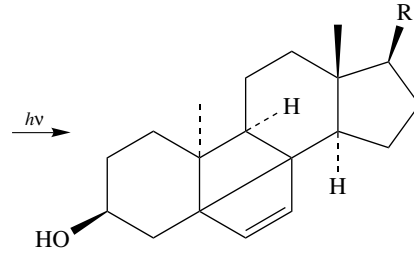


(*cis*-**36**) (10)



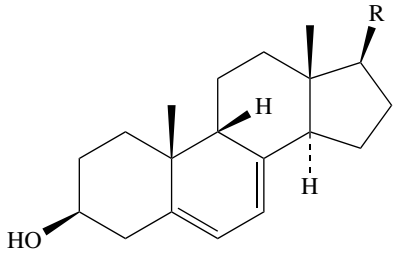
(37)

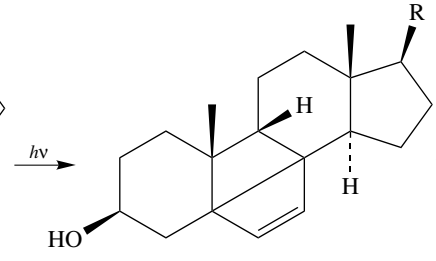




(38) **(39)** (11)

$\Phi = 0.011$



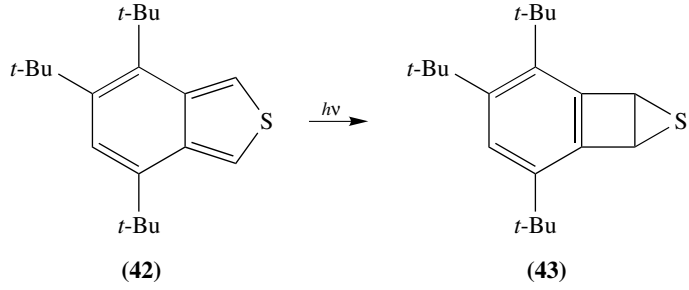


(40) **(41)** (12)

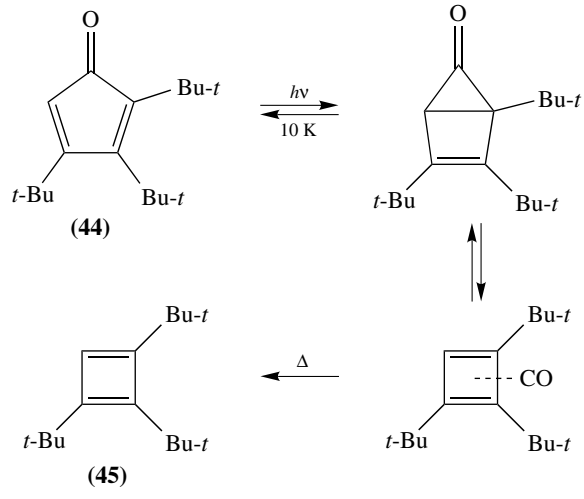
$\Phi = 0.068$

Because of the substantial strain involved in the formation of fused 3- and 4-membered rings, cyclopentadiene itself does not undergo ring closure upon irradiation[132]. The reaction is common, however, in heterocyclic cyclopentadiene analogues[133,134], a recent

example of which is shown in the formation of **43** from **42** (equation 13)[135]. It also occurs in certain substituted cyclopentadienones (e.g. **44**), as exemplified by Maier and coworkers' classic low-temperature synthesis of tri(*tert*-butyl)cyclobutadiene (**45**; equation 14)[136].



(42) **(43)** (13)

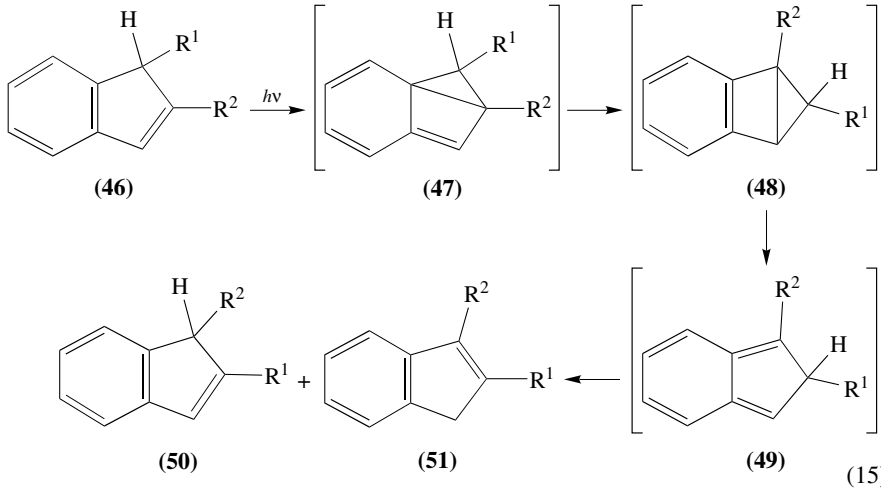


(44) **(45)** (14)

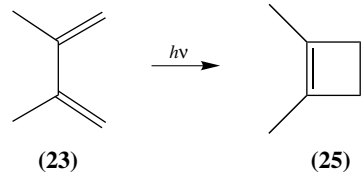
Indene derivatives **(46)** undergo phototransposition reactions which have been attributed to a multistep mechanism involving initial ring closure to the isomeric bicyclo[2.1.0]pent-2-ene **(47)**, followed by [1,3]-migration of the cyclopropyl ring to give **48**, ring opening to the isoindene structure **(49)**, and finally [1,5]-H migration to re-aromatize the system and yield **50/51** (equation 15)[137–139].

With acyclic dienes, the quantum yield for cyclobutene formation (Φ_{CB}) rarely exceeds *ca* 0.1, the expected result of the fact that the planar s-*trans* conformer normally comprises the bulk (96–99%) of the conformer distribution at room temperature. However, Φ_{CB} is often significantly larger than the mole fraction of s-*cis* form estimated to be present in solution. For example, 1,3-butadiene, whose near-planar (dihedral angle 10–15°[105,106]) s-*cis* conformer comprises *ca* 1% of the mixture at 25 °C, yields cyclobutene with $\Phi_{CB} = 0.04$[140], along with very small amounts of bicyclo[1.1.0]butane[141]. A second well-known example is that of 2,3-dimethyl-1,3-butadiene (**23**; *ca* 4% *gauche* s-*cis* at 25 °C[107]), which yields 1,2-dimethylcyclobutene **(25)** with $\Phi_{CB} = 0.12$ (equation 16)[111]. Most likely, these apparent anomalies can be explained as due to selective excitation of the s-*cis* conformers under the experimental conditions employed, since it is well established that s-*trans*

dienes do not lead to cyclobutene directly[102]. A clearer example of this is provided by the reported wavelength dependence of the photochemistry of *E*- and *Z*-1,3-pentadiene (**1**; equation 17)[64]. Irradiation of the two diene isomers at 229 nm, near the absorption maximum of the s-*trans* conformers, results only in *E*,*Z*-isomerization. Longer wavelength irradiation (254 nm) of the *E*-isomer leads to *E*,*Z*-isomerization (with different quantum yields than at shorter wavelengths), and formation of 3-methylcyclobutene **(52)** and 1,3-dimethylcyclopropene **(53)**. Cyclopropene formation is a relatively minor reaction of s-*cis* diene conformers and has been reported in relatively few instances[64,77,142].



(15)



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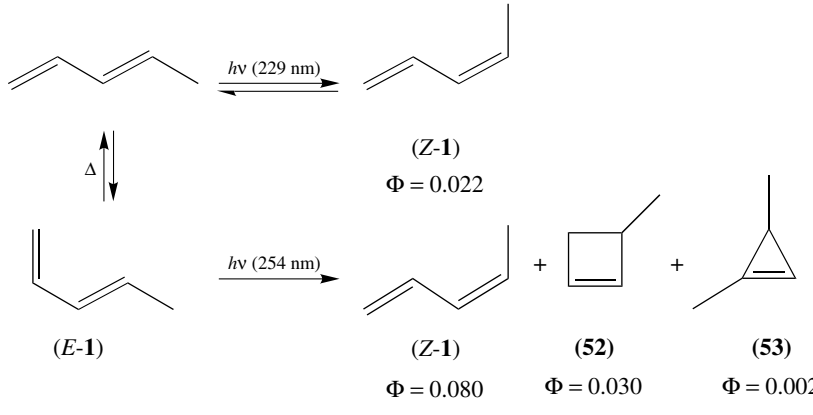
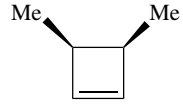


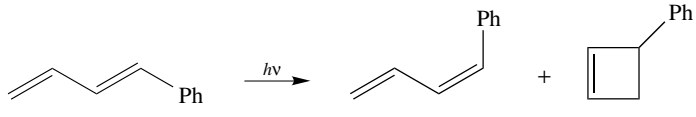
(17)

Other aliphatic acyclic dienes such as isoprene **(2)**[102,111], 2-isopropyl-1,3-butadiene **(24)**[102], and *E*,*E*-2,4-hexadiene **(5)**[78] also yield the corresponding cyclobutene, all via excitation of the s-*cis* conformer. The latter yields the disrotatory ring closure product, *cis*-3,4-dimethylcyclobutene **(54)**, stereospecifically[78].

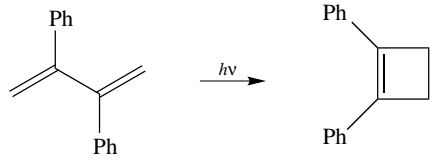


(54)

Phenylated systems generally close to cyclobutenes with extremely low efficiency or not at all. For example, *E*-1-phenylbutadiene **(55)** undergoes efficient *E*,*Z*-isomerization to *Z*-**55** upon direct irradiation[143] and affords 3-phenylcyclobutene **(56)** only after extended periods of time (equation 18)[144]. Various aryl-substituted derivatives of **55** undergo ring closure as well[145]. The quantum yield for cyclobutene formation is also extremely small for 2,3-diphenyl-1,3-butadiene (**57**, equation 19)[146], but because *E*,*Z*-isomerization is degenerate, the direct irradiation of this compound affords 1,2-diphenylcyclobutene **(58)** in useful chemical yields. 1,4-Diphenyl-1,3-butadiene (**4**$_2$) evidently does not undergo photochemical ring closure[147].



(*E*-**55**) (*Z*-**55**) **(56)** (18)



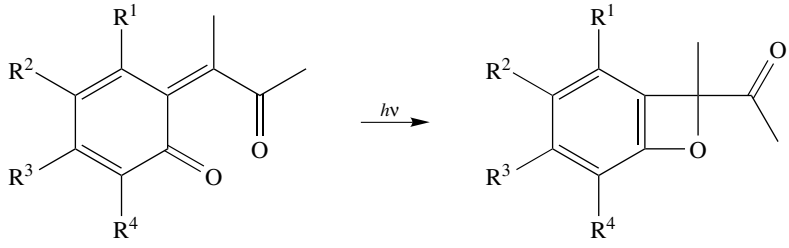
(57) **(58)** (19)

Systems in which one of the C-atoms in the diene unit is replaced by a heteroatom also undergo photoelectrocyclic ring closure in selected cases. For example, Adam and coworkers have recently reported the synthesis of an extended series of benzoxete derivatives **(60)** via photocyclization of the cyclohexadienones **59** (equation 20)[148].

A final example that is so remarkable to deserve mention is the photoisomerization of alkenyne **61** to its isomer **63** (equation 21)[149]. In a recent reinvestigation of the reaction, Johnson and coworkers have provided computational evidence for the intermediacy of the 1,2-cyclobutadiene isomer **62** in the phototransposition reaction[150].

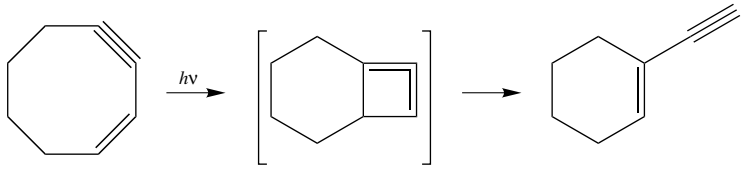
As mentioned in the Introduction, the ring closure of s-*cis* butadiene to cyclobutene has been at the very center of the evolution of theoretical understanding of polyene photochemistry to its current state[25,87–89,151]. Early *ab initio* calculations recognized the crucial role of the 2^1A_g state in the isomerization, and successfully accounted for the disrotatory stereospecificity of the reaction in terms of a 'two-dimensional' model in which the planarity of the carbon framework is more or less maintained throughout[12,13,15].

Within the confines of these geometric restrictions, internal conversion to the ground state surface is considered to occur at minima on the 2^1A_g surface, whose structures correspond roughly to those of the transition states for the ground state con- and disrotatory interconversion of 1,3-butadiene and cyclobutene. Disrotatory ring closure is preferred because internal conversion at the disrotatory 2^1A minimum is faster than that on the conrotatory side, basically because the energy gap to the ground state is smaller owing to the higher activation energy for thermally-forbidden disrotatory interconversion.



(20)

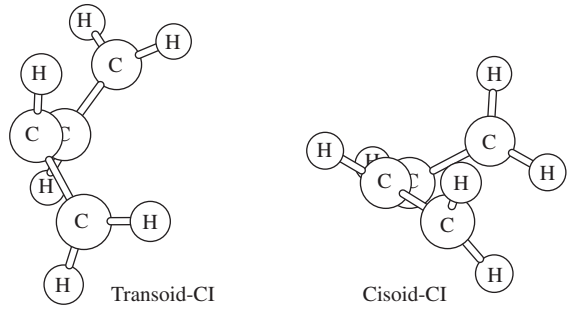
(59) **(60)**



(21)

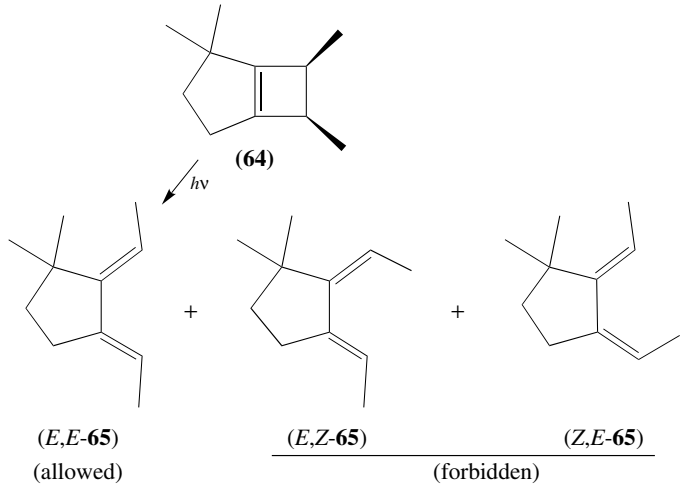
(61) **(62)** **(63)**

The more recent calculations of Bernardi, Robb and Olivucci and their groups suggest that the reaction involves much more profound skeletal distortions than are allowed for in the older models[151]. According to these calculations, the ground state surface is accessed at a conical intersection (CI) with the 2^1A surface, the most readily apparent structural feature of which is twisting about all three C−C bonds. $2^1A/1^1A$ conical intersections have been located at various angles of twist about the central bond, and with various angles of both conrotatory and disrotatory twisting about the termini[88]. The two conical intersection geometries which are thought to be most important in the photochemistry of s-*trans* and s-*cis* 1,3-butadiene are depicted in Scheme 3. In addition to being substantially twisted about the central bond, the termini in both structures are twisted in disrotatory fashion. Evolution along the disrotatory 2^1A pathway from an s-*cis* starting geometry to the disrotatory s-cisoid CI (Scheme 3) was found to encounter a lower barrier than that to the conrotatory s-cisoid CI, explaining the preferred stereochemistry which has been found experimentally. Later calculations at a higher level provided details on the ionic 1^1B surface of s-*cis* butadiene, and conclude that the complete evolution of the excited molecule from the Franck–Condon region to the ground state surface via disrotatory twisting should occur in less than *ca* 1 ps[89]. The calculations are consistent with the *ca* 10 fs lifetime estimated by Trulson and Mathies for the spectroscopic 1^1B state of isoprene[43]. Similar calculations have been carried out for 2,3-dimethylbutadiene **(23)** and 2-cyanobutadiene (*vide infra*)[87] and for dienes with bulky substituents at C2/C3[90], and successfully explain many of the features of diene photochemistry which result from conformational factors and the steric and electronic effects of substituents.



SCHEME 3. Calculated transoid and cisoid CIs for butadiene

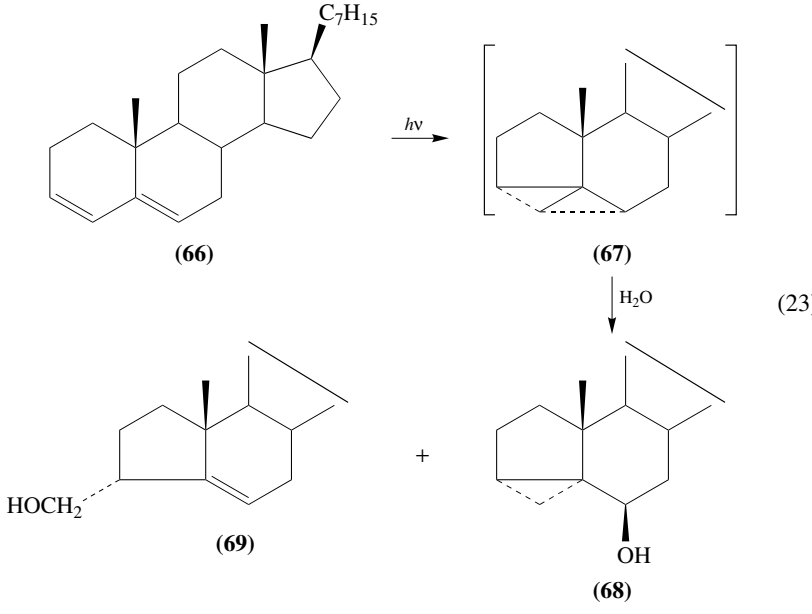
We note that the reverse reaction, the photochemical ring opening of cyclobutene, is one of the few photoelectrocyclic reactions which consistently does not proceed stereospecifically[19,20,152]. In fact, we believe that the reaction does proceed with the disrotatory stereospecificity predicted by the Woodward–Hoffmann rules[109], at least when the reaction is initiated by irradiation of the cyclobutene in its π,π^* (1^1B) absorption band. The loss of stereospecificity most likely occurs because ring opening proceeds entirely on the 1^1B surface, and the 2^1A state is not accessed until the diene is nearly fully formed. This would lead one to predict that the distribution of isomeric dienes obtained from the reaction should be that characteristic of the direct *E*,*Z*-photoisomerization of the allowed diene isomer[70]. Indeed, direct irradiation of the unsymmetrically substituted bicyclic cyclobutene derivative **64** yields the same mixture of forbidden diene isomers (*E*,*Z*- and *Z*,*E*-**65**) as are produced when the allowed isomer (*E*,*E*-**65**) is itself irradiated in solution (equation 22)[153]. The jury is still out, however, as more recent results indicate that the π,R(3s) excited state also contributes to the photochemical ring opening of alkylcyclobutenes, with the same stereochemistry as that associated with the thermal ring opening process[154]. Unlike the 1^1B-initiated process, the Rydberg-derived one appears to proceed with 100% (conrotatory) stereospecificity.



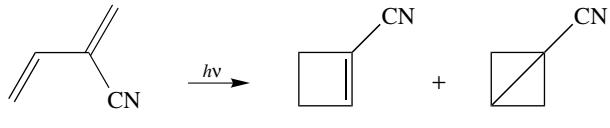
(22)

b. Bicyclo[1.1.0]butane formation. Bicyclobutane formation is usually a relatively minor process in diene photochemistry, but has been reasonably well studied nonetheless. Early reports of the reaction centered around steroidal, s-*trans* dienes such as $\Delta^{3,5}$-cholestadiene **(66)**, whose irradiation in the presence of water leads to the formation of alcohols (**68**, **69**) resulting from rapid hydrolysis of the isomeric bicyclo[1.1.0]butane derivative **67** (equation 23)[155]. As mentioned above, bicyclobutane formation occurs with very low efficiency from irradiation of 1,3-butadiene itself in solution (roughly one-sixth of the yield of cyclobutene or less, depending on the solvent)[141,156], in spite of the fact that the conformer distribution in the parent molecule is *ca* 99% s-*trans* under ambient conditions. While this might suggest that the reaction proceeds with highest efficiency from s-*trans* dienes only when there is built in some restriction to rotation about the central bond of the diene system, the fact that irradiation of 2-cyano-1,3-butadiene **(70)** in ether solution yields the corresponding cyclobutene **71** and bicyclobutane **72** in relative yields of 1 : 3.2 (equation 24)[157] indicates that electronic factors also play a role in discriminating between the two modes of reaction.

The reaction is highly stereospecific, as was shown by Dauben and Ritscher in their study of the photochemistry of the isomeric 3-ethylidenecyclooctenes **20** (equation 25 and 26)[79]. The fact that two isomeric bicyclobutanes (**73** and **74**) which are both epimeric at a single stereocenter are produced from *E*,*Z*-**20** is incompatible with an intramolecular $[\pi 2s + \pi 2s]$-cycloaddition mechanism for the process. This and other considerations led Dauben and Ritscher to propose that the reaction is initiated by twisting about one of the double bonds (the endocyclic one, in this case) to a relaxed allylmethylene geometry with zwitterionic (allyl anion/methylene cation) character, which proceeds to product by conrotatory 1,3-closure of the allyl moiety in concert with 2,4-bonding. In the present examples, the two conrotatory ring closure pathways available to the zwitterionic allylmethylene species lead to different products (**73** and **74**) in the case of *E*,*Z*-**20**, and to the same product **(75)** in the case of *Z*,*Z*-**20** (equation 27)[79].

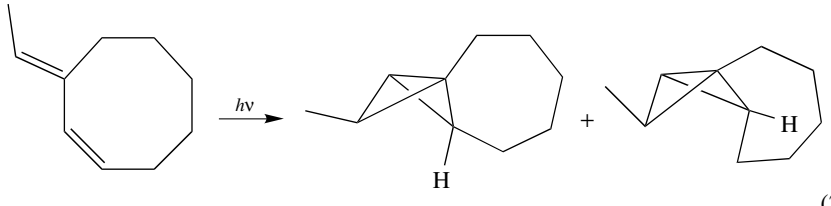


(23)



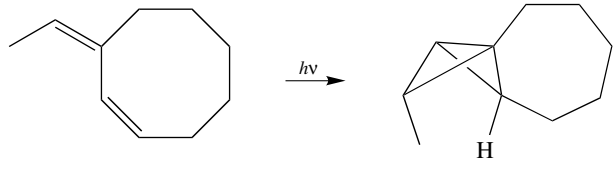
(70) (71) (72)

1 : 3.2 (24)

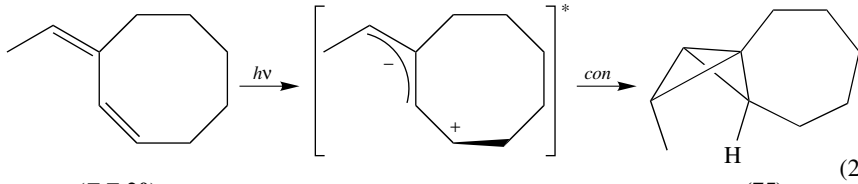


(*E*,*Z*-**20**) **(73)** **(74)**

75% 25% (25)



(*Z*,*Z*-**20**) **(75)** (26)

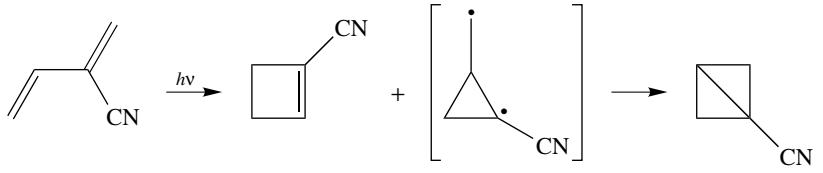


(*Z*,*Z*-**20**) **(75)** (27)

This suggests that the unusually high yields of bicyclo[1.1.0]butane **72** from irradiation of 2-cyano-1,3-butadiene (**70**; equation 24) might be due to a change in the preferred dynamics of the excited molecule, as a result of an effect on the 1^1B surface due to polar factors (*vide supra*); i.e., in Dauben's terminology, through stabilization of a zwitterionic (allyl anion/methylene cation) excited state intermediate by the 2-cyano substituent. CAS-SCF calculations on the covalent 2^1A surface of this molecule suggest that the cyano group has only slight effects on both the structures of the transoid and cisoid conical intersections of 1,3-butadiene and the favored pathways to them on the 2^1A surface; rather, the main factor is proposed to result from the radical-stabilizing effects of the cyano group, and the reaction is tentatively predicted to involve the formation of the ground state 1,3-biradical intermediate **76** (equation 28)[87].

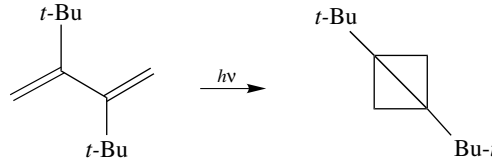
More recent results have provided additional detail on the conformational requirements for bicyclo[1.1.0]butane formation from conjugated dienes[158]. Hopf and coworkers have shown that high yields of the isomeric bicyclobutane **78** are obtained from irradiation of

2,3-di-*tert*-butyl-1,3-butadiene (**77**; equation 29)[158], whose X-ray crystal structure shows it to exist in a twisted s-*trans* conformation with a C1−C2−C3−C4 dihedral angle of 84°[159]. Irradiation of the permethylated derivative of this compound **(79)** also leads primarily to bicyclobutane **(80)** formation, along with minor amounts of cyclobutene **(81)** and [1,5]-H migration **(82)** products (equation 30)[158]. A recent computational study indicates that the bulky substituents at C2/C3 in **77** change the preferred excited state decay route from the disrotatory, cyclobutene-producing pathway favored by the parent s-*cis* 1,3-butadiene to a pathway involving concerted conrotatory rotation of the terminal methylenes which favors bicyclo[1.1.0]butane formation[90], in essential agreement with Dauben's simple model for the process.



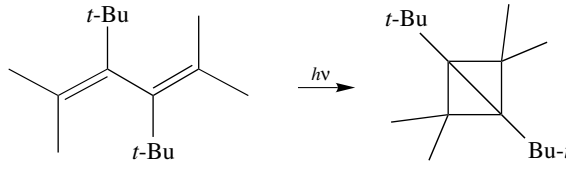
(28)

(70) **(71)** **(76)** **(72)**



(29)

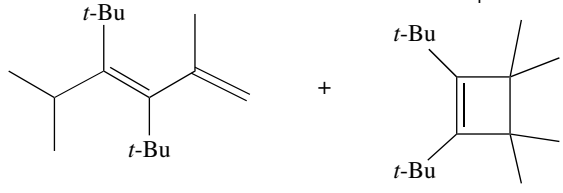
(77) **(78)**



(79) **(80)**

65%

+



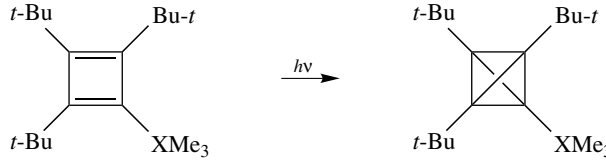
(30)

(82) **(81)**

10% 25%

A final, related example is the formation of tetrahedranes **(84)**, from irradiation of *tert*-butyl substituted cyclobutadienes such as **83** (equation 31), a reaction which has been

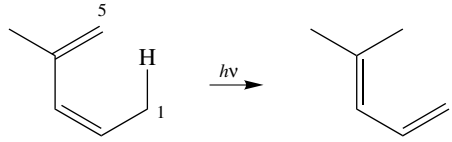
extensively exploited by Maier and coworkers[160–163].



(31)

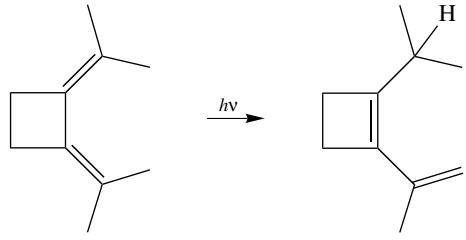
(83) X = C, Si, or Ge **(84)**

c. [1,5]-Hydrogen migration. Photochemical [1,5]-hydrogen migration competes with other reactive processes in s-cisoid dienes which bear a **Z**-alkyl group (most commonly, methyl) at either C1 or C4 of the butadienyl system. Orbital symmetry considerations predict that the reaction should proceed in supra-antarafacial fashion[109], although as far as we know this has never been explicitly proven. As with the other pericyclic photoreactions of conjugated dienes, [1,5]-hydrogen migration occurs in significant yields only when other reactive decay pathways lead to degenerate rearrangement or are structurally blocked[112,164,165]. A few examples of systems which undergo this reaction in reasonably high chemical yields involve the formation of **86** from **Z**–**85** (equation 32), and of **88** and **90** from **87** and **89**, respectively (equations 33 and 34)[112,165,166]. Many other examples are known as well[158,167,168].



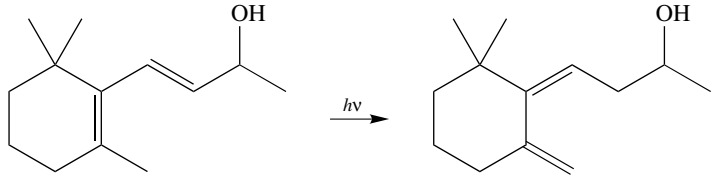
(*Z*-**85**) **(86)**

(32)



(87) **(88)**

(33)

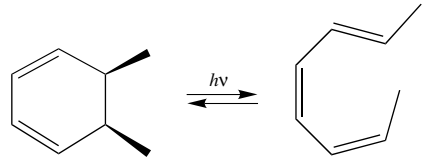


(89) **(90)**

(34)

2. Electrocyclic ring opening of 1,3-cyclohexadienes

a. Experimental studies. By far the most common photochemical reaction of 1,3-cyclohexadienes is electrocyclic ring opening to the corresponding *Z*-1,3,5-hexatriene derivative, as illustrated by the formation of **92** from *cis*-5,6-dimethyl-1,3-cyclohexadiene **(91)** (equation 35)[169]. The reaction is well-known to proceed with nearly 100% conrotatory stereospecificity[129], as predicted by orbital symmetry selection rules[109]. This is also true of the reverse reaction, the photochemical electrocyclic ring closure of *Z*-1,3,5-hexatrienes[170]. This reversibility, as well as the fact that 1,3,5-hexatrienes undergo a number of other conformation-dependent photoprocesses in addition to ring closure (*vide infra*), makes both systems exceedingly challenging to study experimentally.



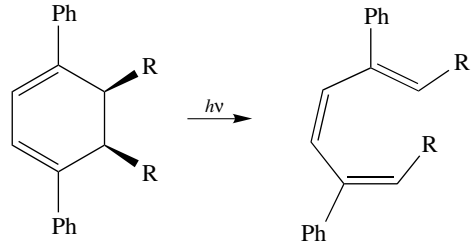
(35)

(91) **(92)**

Nevertheless, a great deal is known about the process, largely through the early pioneering work of the groups of Havinga and Jacobs[129,171] and of Dauben[172] on the photochemistry of Vitamin D, its various isomers and related systems. A large number of reviews have been published over the years on the photochemistry of 1,3-cyclohexadiene/1,3,5-hexatriene systems[116,128,129,170,173–175] and the reader is directed to these for more comprehensive treatments of the subject than can be provided here.

1,3-Cyclohexadiene itself undergoes smooth photochemical ring opening to *Z*-1,3,5-hexatriene in both the gas phase ($\Phi = 0.13$)[176] and in solution ($\Phi = 0.41$)[71,177]. As is almost always the case, extended irradiation in solution leads to the formation of a variety of isomeric products due to secondary irradiation of the *Z*-triene and its *E*-isomer (*vide infra*)[71].

Unlike other diene photopericyclic reactions, cyclohexadiene ring opening proceeds with reasonable efficiency in phenyl-substituted derivatives, although the quantum yields are generally significantly lower than those of non-arylated systems. Two examples of the conversion of **93** to **94** are shown in equation 36[178,179]



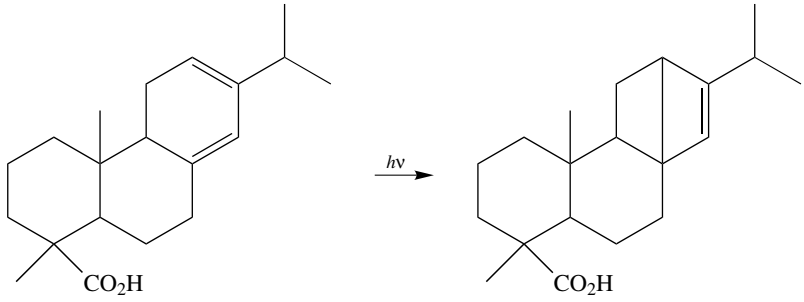
(36)

(93) **(94)**

(a) R = Me R = CO_2Me: $\Phi = 0.08$

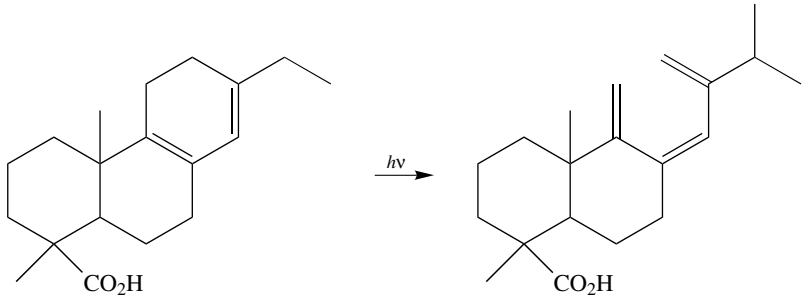
(b) R = CO_2Me

Through study of the photochemistry of a large number of polycyclic cyclohexadienyl systems coupled with conformational analyses, Dauben and his group established that the electrocyclic ring opening of 1,3-cyclohexadienes proceeds most efficiently from a half-chair conformation, in which the diene moiety is twisted about the C2−C3 bond at an angle of *ca* 20°, while (disrotatory) ring closure to the isomeric bicyclo[2.2.0]hex-2-ene is favored by planar or near-planar conformations. For example, laevopimaric acid **(95)**, which possesses a central bond dihedral angle on the order of *ca* 10°[180], undergoes predominant electrocyclic ring closure to yield **96** (equation 37)[181], while irradiation of its more highly twisted isomer, palustric acid **(97)**, leads only to ring opening giving **98** (equation 38)[182]. The competition between the two modes of reaction is also affected by steric effects of remote substituents on the cyclohexadienyl or an ancillary ring, most likely through their effects on the central bond dihedral angle[128]. Illustrative examples of fluorinated 1,3-cyclohexadienes which undergo highly selective ring closure are shown by the formation of **100** and **101** from **99** (equation 39)[183,184] and of **103** from **102** (equation 40)[185]; many more are cited in the review by Laarhoven[116].



(37)

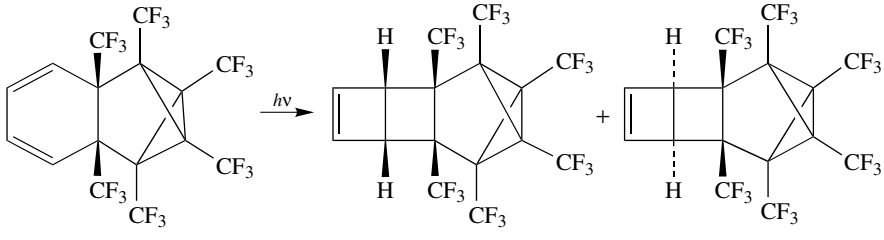
(95) **(96)**



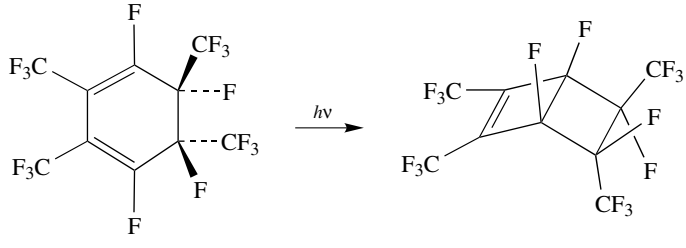
(38)

(97) **(98)**

The photochemistry of cyclohexadienyl systems is quite commonly wavelength-dependent, an effect which can be caused either by differences in the absorption spectra of various conformers of the substrate or by photostationary state effects which arise because the ring opening to the isomeric *Z*-triene is photochemically reversible. For example, *syn*-bicyclo[4.3.0]nona-1,4-diene **(104)** undergoes predominant ring opening to **107** upon irradiation in its main absorption band (254 nm), but yields the ring closure products **105** and **106** upon irradiation at 300 nm, at the extreme red edge of its absorption spectrum

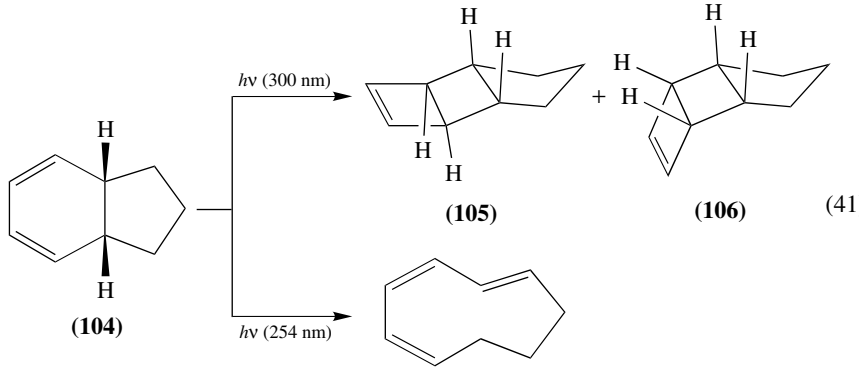


(99) **(100)** **(101)** (39)



(102) **(103)** (40)

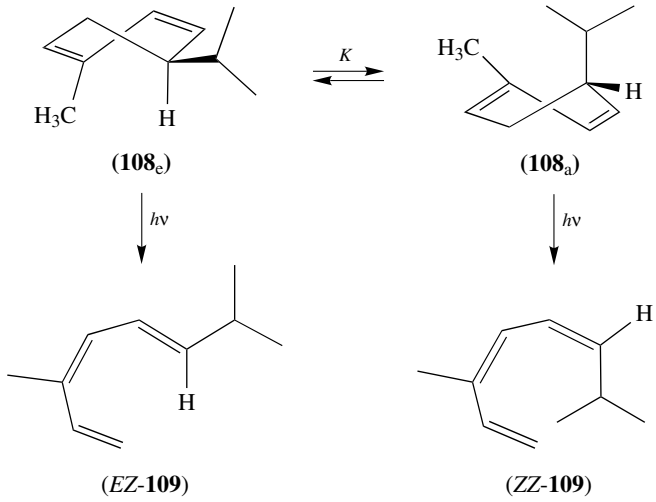
(equation 41). This could be due to specific excitation of a planar diene conformer, which is present in exceedingly low concentrations and absorbs at longer wavelengths relative to the most stable, twisted s-*cis* conformer of the diene. An alternative explanation for the long-wavelength result is that the **104** : **107** photostationary state at 300 nm lies so strongly in favor of the cyclohexadiene isomer (because of the much stronger absorption spectrum of the triene at this wavelength) that the triene is never present in detectable amounts in spite of the fact that the quantum yield for its formation may be high; the ring closure product builds up, even though it may be formed with a substantially lower quantum yield than the triene, simply because it is not photochemically active at this wavelength[128].



(104) **(105)** **(106)** **(107)** (41)

When substituents are present at C5 and/or C6 of the cyclohexadienyl system, two possible stereoisomers can be formed via conrotatory ring opening. In general, however, the

reaction exhibits a high degree of torquoselectivity — another manifestation of the ground state conformational control of photoreactivity which is a common feature of polyene photochemistry. This was first demonstrated by Baldwin and Krueger with an investigation of the photochemistry of α-phellandrene **(108)**[186]. The photochemistry of this molecule had been delineated earlier by Havinga and coworkers[187], who reported it to yield a 3 : 1 mixture of two geometric isomers of 3,7-dimethyl-1,3,5-octatriene **(109)** which reacted further on prolonged irradiation. Through comparison of the temperature dependences of the primary photoproduct ratios and the ORD and CD spectra of the starting material, Baldwin and Krueger provided strong evidence that the two primary products *EZ*- and ***ZZ*-109** are each formed selectively from different ground state conformers of the diene, as shown in equation 42. The major product of the photolysis is *E*,*Z*-**109**, the diene isomer derived from ring opening of the pseudoequatorial conformer ($\mathbf{108}_e$), which was calculated to be 0.46 kcal mol^{-1} more stable than the pseudoaxial conformer ($\mathbf{108}_a$)[186].



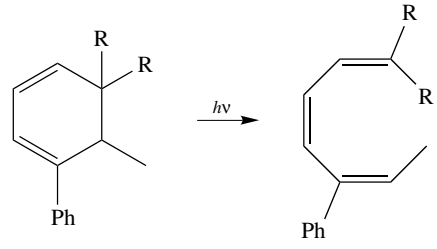
(42)

This feature of 1,3-cyclohexadiene ring opening is quite general, and is explained in terms of the Principle of Least Motion: the most favored conrotatory ring opening mode is generally that in which a pseudoaxial substituent at C5 or C6 is rotated inward (i.e., yielding *Z*-stereochemistry in the product) while a pseudoequatorial substituent is rotated outward, since these rotations require the least motion for the developing sp^2 centers to overlap with the existing π-system[188]. The distributions of *E*- and *Z*-triene isomers obtained from irradiation of a series of 5-alkyl-1,3-cyclohexadienes[189] and from several 6-methyl-1-phenylcyclohexadienes **(110)** also illustrate the principle. In the latter cases, direct irradiation produces only a single diene isomer **111** (equation 43)[179,188,190–192]. This has been termed 'accordant' ring opening, because it is in accord with the chirality of the diene[186].

The ring opening of 1,3-cyclohexadienes is normally well-behaved from a stereochemical point of view: the reaction proceeds to yield only the 3-*Z* triene isomer(s) corresponding to conrotatory ring opening. This indicates that the ring opening process is accompanied by diabatic funnelling to the ground state surface in the normal manner. Scattered reports exist, however, of examples in which the 3-*E* triene isomer has been observed in the very early stages of the reaction and concluded to be a primary ring

opening product[193–195]. If this is correct, then it suggests that ring opening of cyclohexadienes can in certain cases occur adiabatically to generate the 3-*Z* triene in an excited state[194], as is known to be the general case for the photochemical ring opening of alkylcyclobutenes (*vide supra*)[70]. In our experience, however, such observations are fraught with pitfalls due to secondary photolysis effects[154] and must be interpreted with a great deal of caution. The possibility deserves closer scrutiny, however.

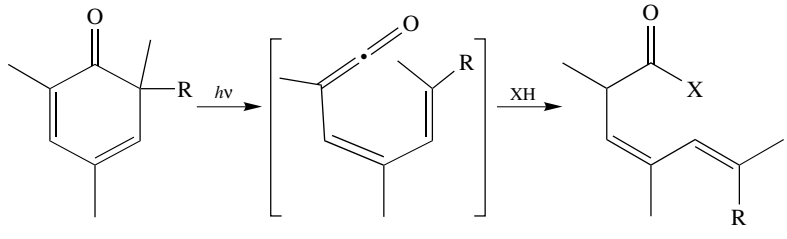
6,6-Disubstituted 2,4-cyclohexadienones **(112)** undergo photoinduced electrocyclic ring opening to the transient ketene derivatives **113**, which can be trapped by nucleophiles to prepare the corresponding carboxylic acid derivatives (**114**; equation 44)[196,197]. The reaction has been employed successfully for the synthesis of various carboxylic acids, esters and amides.



(43)

(110) **(111)**

R = H, Me, or Ph

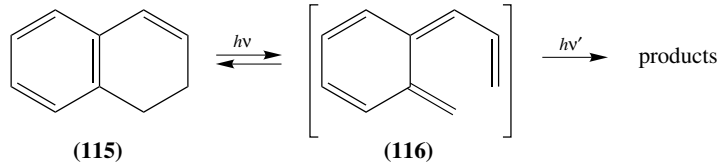


(44)

(112) **(113)** **(114)**

X = OH, OR′, NHR″, NR_2'''

1,2-Dihydronaphthalenes — benzannelated cyclohexadiene derivatives — e.g. **115**, undergo a rich photochemistry which is initiated by electrocyclic ring opening to yield the corresponding ω-vinyl-*ortho*-quinodimethane (equation 45)[170]. Depending on substitution, the *ortho*-quinodimethanes **116** can undergo a variety of fairly rapid thermal isomerizations (including ring closure to regenerate the dihydronaphthalene), but evidently build up in sufficiently high concentrations that secondary photochemical reactions typical of 1,3,5-hexatrienes can result (*vide infra*). A more complete account of 1,2-dihydronaphthalene photochemistry appears later in this review.

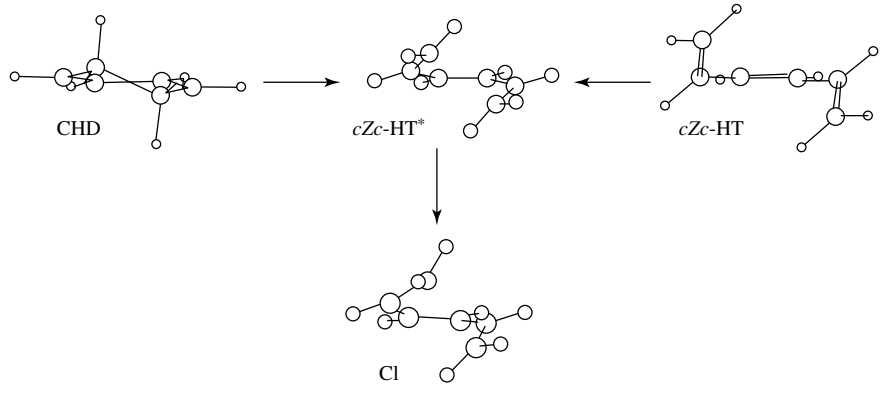


(45)

(115) **(116)**

b. Theoretical and time-resolved spectroscopic studies. The ring opening of 1,3-cyclohexadiene (CHD) has recently been studied by ultrafast time-resolved spectroscopic techniques, which afford information on the evolution of the excited molecule during the first few hundred femtoseconds after excitation. Using resonance Raman spectroscopic techniques, Mathies and coworkers concluded that relaxation of the spectroscopic 1^1B state occurs with a lifetime of *ca* 10 fs in cyclohexane solution and is accompanied by conrotatory motions of the sp^3 hydrogens; ground state *Z*-1,3,5-hexatriene (*Z*-HT) is formed with a time constant of *ca* 6 ps, probably via the intermediacy of the 2^1A state[51,198]. Similarly, an appearance time of τ *ca* 11 ps was determined for the formation of ground state **108** from photolysis of α-phellandrene **(108)**[51]. Transient absorption measurements, on the other hand, suggest a sub-picosecond time constant for product formation from CHD[199]. Using time-delayed photoionization or intense field ionization in conjunction with time-of-flight mass spectrometry[200], Fuss and coworkers have assigned gas-phase lifetimes of 43 and *ca* 80 fs for the 1^1B and 2^1A states, respectively, and have presented results consistent with the formation of *cZc*-HT within 200 fs of the initial excitation event[201,202]. The sub-picosecond appearance time of the ground state product provides strong evidence that the reaction proceeds via an essentially barrierless pathway from the spectroscopic 1^1B state to the ground state through a $2^1A/1^1A$ conical intersection.

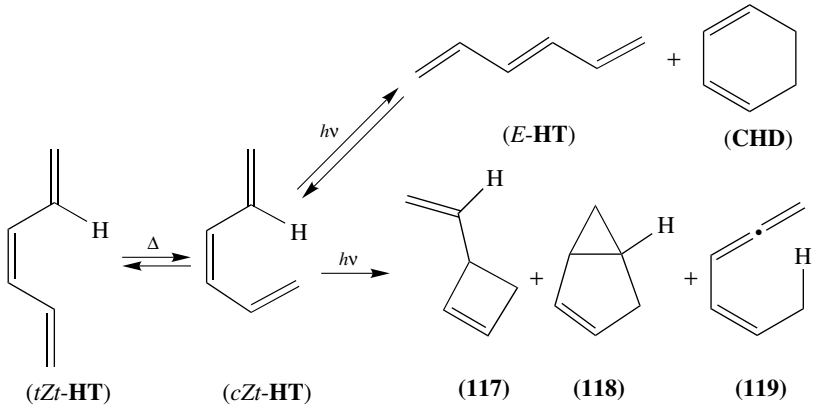
The photochemical interconversion of 1,3-cyclohexadiene (CHD) and *cZc*-1,3,5-hexatriene (*cZc*-HT) (*vide infra*) is a more demanding computational problem than butadiene ring closure, and, as a result, relatively few theoretical studies have been reported[203–206]. Again, however, the results which have been reported are consistent with the results of product and fast time-resolved spectroscopic studies of the process. For example, computation of the minimum energy pathway on the 1^1B state of cyclohexadiene starting from the Franck–Condon geometry indicates that conrotatory twisting and accompanying stretching of the 5,6 bond take the molecule by a barrierless pathway to a $1^1B/2^1A$ state crossing; thus, the stereochemistry of the process is defined and the 5,6 bond essentially broken by the time (*ca* 30 fs) the molecule enters the 2^1A state surface[205]. The molecule relaxes from there to a shallow biradicaloid minimum on the 2^1A surface (*cZc*-HT*; Scheme 4) which is common to both the ring opening and ring-closure processes. This intermediate then decays to the ground state surface via a $2^1A/1^1A$ conical intersection (CI) located *ca* 1 kcal mol^{-1} higher in energy[204,205]



SCHEME 4. Calculated excited state intermediates in the interconversions of CHD and *cZc*-HT[204,205]

D. Photopericyclic Reactions of Conjugated Trienes

The photochemistry of conjugated trienes has received a great deal more attention over the past 40 years than is the case with dienes, and has been reviewed in detail by many of the experts in the field[116,129,170–172,175,207]. As with dienes, *E*,*Z*-photoisomerization usually dominates the photochemistry, and most of the accompanying photorearrangement processes are strongly conformation-dependent. However, as the degree of conjugation increases, so too does the number of possible pericyclic and other photorearrangement processes. Most of these require the central C=C bond to have the *Z*-stereochemistry, and that at least one of the two single bonds be in an s-*cis* conformation. In addition to *E*,*Z*-isomerization and *cis*,*trans* interconversion of conformers, the processes characteristic of the *Z*-1,3,5-hexatrienyl moiety are (conrotatory) electrocyclic ring closure to the corresponding 1,3-cyclohexadiene, (disrotatory) electrocyclic ring closure to the corresponding 3-vinylcyclobutene, bicyclo[3.1.0]hex-2-ene formation, and antara-supra [1,5]-H migration to yield an isomeric vinylallene derivative (equation 46). In general, trienes with the *E*-stereochemistry at the central C=C bond tend to be relatively unreactive except toward isomerization to the *Z*-isomer, because the ground state conformational distribution normally favors the fully extended *tEt* form. As might be expected, however, 3-vinylcyclobutene formation has been found to occur in systems bearing substituents (such as 2-alkyl groups) which stabilize *cEt* relative to *tEt*-conformers[208]. Alkyl substitution also introduces several other common processes in 3-*E*- and 3-*Z*-hexatrienes as well, though they are usually minor and will not be discussed explicitly here. Examples include the formation of methylenecyclopropane and/or allylcyclopropene derivatives in systems bearing alkyl substituents at C2(5) (see References 72 and 209 for discussions of the mechanisms of these processes), and antarafacial [1,5]-hydrogen migrations in those containing alkyl substituents at C3(4) of the trienyl moiety[210]. As in the photochemistry of conjugated dienes, the observed product distributions are usually wavelength-dependent, which largely reflects the different absorption properties of the various triene conformers present at equilibrium.



(46)

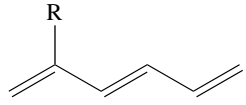
1. The photochemistry of Z-1,3,5-hexatriene

The simplest member of the family, *Z*-1,3,5-hexatriene (*Z*-HT), has been studied in detail in both the gas phase[176,211–213] and in solution[177,188,214] and illustrates all five of the productive photoreactions which are characteristic of the *Z*-1,3,5-hexatrienyl moiety.

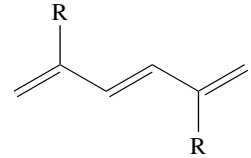
In solution, an initial photoequilibrium is established between the *Z*- and *E*-isomers, while the rearrangement products **117** and **118** are formed along with traces of cyclohexadiene (CHD) over much longer irradiation times (equation 46). In solution, the major products are 3-vinylcyclobutene **(117)** and bicyclo[3.1.0]hex-2-ene **(118)**; *Z*-1,2,4-hexatriene **(119)**, which is a major product in the gas phase[176,211], is formed in relatively low yields. The quantum yields for *E*,*Z*-photoisomerization of *Z*- and *E*-1,3,5-hexatriene in pentane solution (265 nm excitation) are $\Phi_{Z\rightarrow E} = 0.034$ and $\Phi_{E\rightarrow Z} = 0.016$, respectively[188].

2. The NEER Principle

One reason for the rather low quantum yields for product formation from *Z*-1,3,5-hexatriene is thought to be that the ground state conformer distribution is heavily weighted in favor of the relatively unreactive *tZt*-conformer[129]. Substituents and structural constraints have quite substantial effects on the conformer distribution, and hence on the quantum yields and distribution of products observed. These effects are well understood, having been worked out independently by Havinga and coworkers, who examined the photochemistry of various 2-alkyl- and 2,5-dialkyl-1,3,5-hexatrienes (**120** and **121**, respectively)[129,207,215,216], and by Dauben and coworkers with their studies of the photochemistry of substituted 6,6,9,9-tetramethyl-$\Delta^{3,5(10)}$-hexalins **(122)**[217]. Both bodies of work were predicated on the effects of substituents at the 2- and/or 5-positions of the 1,3,5-hexatrienyl moiety on the ground state conformational distribution, and provided the first systematic verification of the 'NEER' Principle, which was first proposed to explain some of the early results in the vitamin D field[61]. The NEER Principle states that each conformer of a given polyene affords its own specific assortment of photoproducts, and the individual excited conformers do not interconvert within their lifetimes. Such behavior is now known to govern both the singlet and triplet state photochemistry of almost all polyene systems.

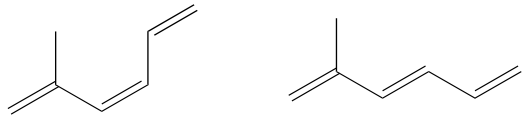


(120)

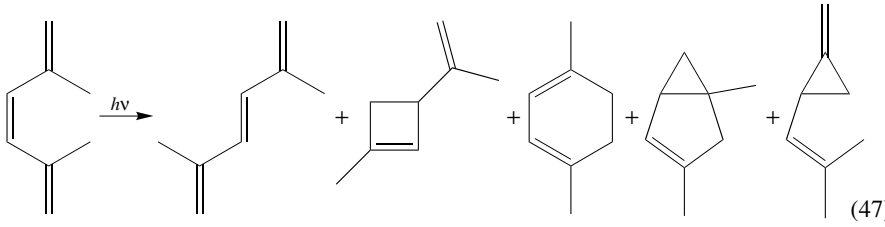


(121)

The validity of the principle can be demonstrated by comparing the product distributions obtained from irradiation of *Z*-1,3,5-hexatriene (*Z*-**HT**) with those of *Z*-2-methyl- and *Z*-2,5-dimethyl-1,3,5-hexatriene at 254 nm (*Z*-**123** and *Z*-**14**, respectively)[215]. The ^{1}H NMR and UV absorption spectra of these three compounds suggest that their ground state conformational equilibria differ significantly. The parent compound ($\lambda_{max} = 254$ nm; ε 41,000) exists predominantly as the *tZt* conformer and yields only small amounts of cyclization products (*vide supra* and equation 46); *Z*-**123** ($\lambda_{max} = 259$ nm; ε 22,400) exists predominantly in the *cZt* form and affords significantly higher yields of its bicyclo[3.1.0]hex-2-ene, 3-vinylcyclobutene and vinylallene isomers (along with *E*-**123**); *Z*-**14** ($\lambda_{max} = 237$ nm; ε 12,300) is rich in the *cZc* form and affords mainly the cyclohexadiene **125**, and the vinylcyclobutene **124**, in addition to *E*-**14** and small amounts of **126** and **127**. Much higher yields of cyclohexadiene **125** are obtained with longer-wavelength irradiation, where the *cZc* conformer absorbs more strongly than the other conformers (equation 47)[216]. Other *Z*-2,5-dialkyl-1,3,5-hexatrienes exhibit similar behavior[72,218].



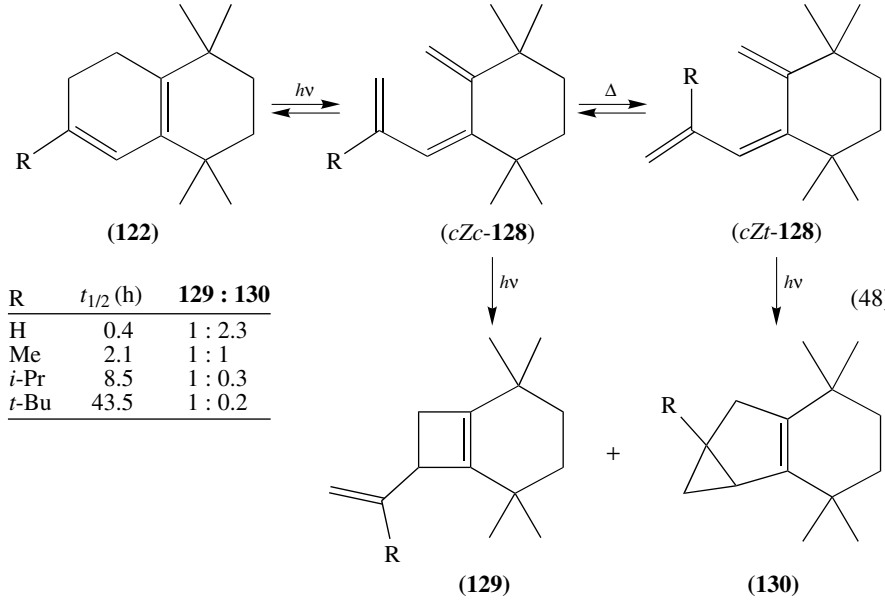
(*Z*-**123**) (*E*-**123**)



(47)

(*Z*-**14**)	(*E*-**14**)	**(124)**	**(125)**	**(126)**	**(127)**
254 nm :	8.05	0.93	0.75	0.05	0.27
313 nm :	1.13	0.01	8.85	0.05	0.01

Dauben and coworkers reached similar conclusions on the basis of their extensive investigations of the photochemistry of 3-alkyl-6,6,9,9-tetramethyl-$\Delta^{3,5(10)}$-hexalins **(122)**[217]. Direct irradiation of these compounds leads to the formation of **129** and **130** due to secondary irradiation of the initially formed triene **128**, which exists as an equilibrium mixture of conformers *cZc*-**128** and *cZt*-**128** (equation 48). Their results showed that as the steric bulk of the 3-substituent increases, the rate of disappearance of starting material decreases and the cyclobutene **(129)**: bicyclo[3.1.0]hex-2-ene **(130)** product ratio



(122) (*cZc*-**128**) (*cZt*-**128**)

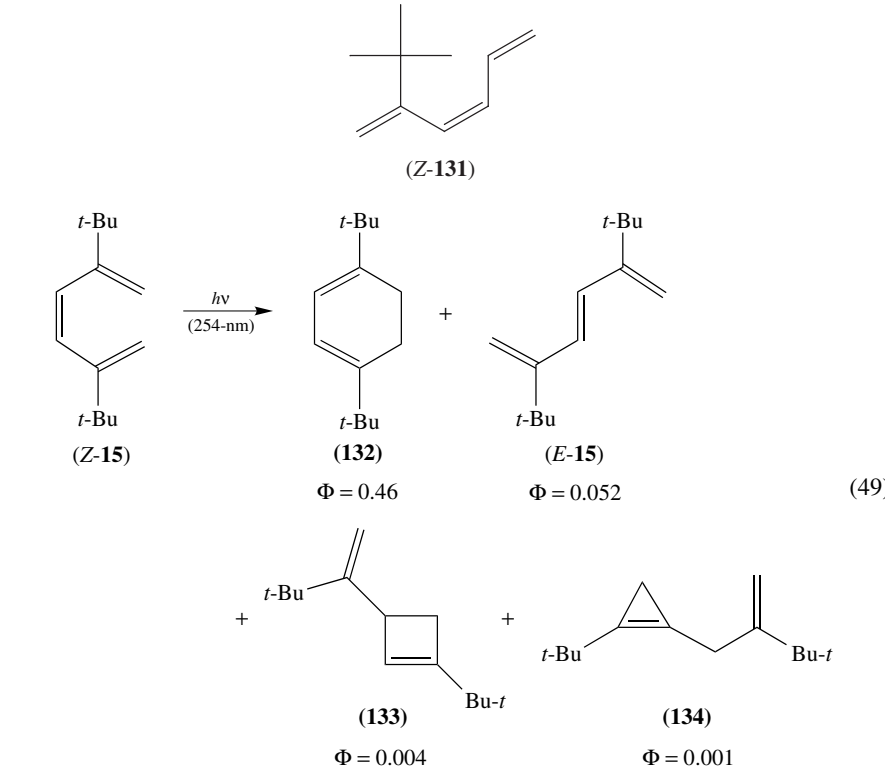
R	$t_{1/2}$ (h)	**129 : 130**
H	0.4	1 : 2.3
Me	2.1	1 : 1
i-Pr	8.5	1 : 0.3
t-Bu	43.5	1 : 0.2

(48)

(129) **(130)**

increases. This behavior is consistent with a steady increase in the proportion of *cZc*-**128** present at equilibrium, with increasing steric bulk of the 3-substituent. It also suggests that the cyclobutene product arises predominantly from excitation of the *cZc* conformer, while the bicyclo[3.1.0]hexene derivative is formed from the *cZt* form (*cZt*-**128**).

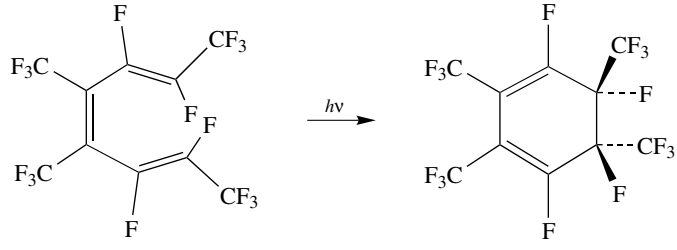
The proposal that the wavelength dependence of the product yields from irradiation of *Z*-**14** is due largely to selective excitation of specific conformers is supported by the observation that the UV spectrum of the compound can be simulated accurately by a 9 : 1 combination of the spectra of *Z*-2-*tert*-butyl- (*Z*-**131**) and *Z*-2,5-di-*tert*-butyl-1,3,5-hexatriene (*Z*-**15**), which serve as model compounds for the *cZt* and *cZc* conformers of *Z*-**14**, respectively[219]. Both *Z*-**15** and the perfluorinated *E*,*Z*,*E*-4,5-dimethyl-2,4,6-octatriene derivative **(135)** are thought to adopt preferred helical *cZc* conformations, and undergo highly selective electrocyclic ring closure to the corresponding cyclohexadienes **132** and **136**, respectively upon irradiation (equations 49[72] and 50[185]). In the reaction of *Z*-**15** the cyclobutene **133** and the cyclopropene **134** are also formed, but in low quantum yields (equation 49).



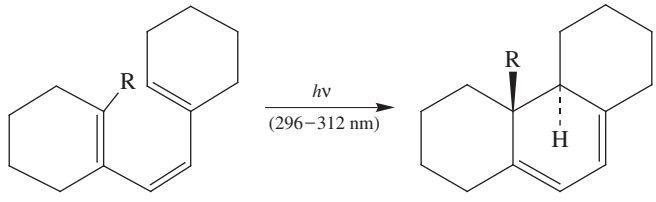
(49)

Very dramatic wavelength effects on the quantum yields for *E*,*Z*-isomerization to *E*-**16/17** and (especially) electrocyclic ring closure to **137** of the previtamin D_3 analogues *Z*-**16/17** (equation 51) have recently been reported[73], following an earlier report of similar behavior for previtamin D_3 itself (*vide infra*)[220]. The analogues exhibit an almost twofold increase in the quantum yields for ring closure over only a 3 nm range in excitation wavelength (306–309 nm). For example, the quantum yield for ring closure of

Z-**17** (R = Me) to **137** increases from 0.23 at 306 nm to 0.42 at 309 nm. It is suggested that at wavelengths below 306 nm, excitation populates the 1^1B state which can isomerize or decay to the 2^1A state, from which cyclization ensues. Excitation wavelengths above 306 nm result in direct promotion to the 2^1A state, accounting for the increased quantum yields for cyclization. To what extent this mechanism might contribute to the wavelength dependence observed with other triene systems is not yet clear.



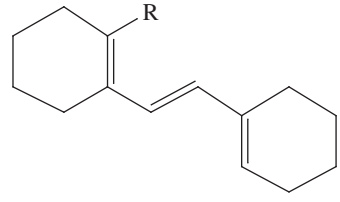
(135) **(136)** (50)



(R = H or Me) Φ = 0.10−0.44 (R = Me)

(*Z*-**16/17**) **(137)**

\+ (51)



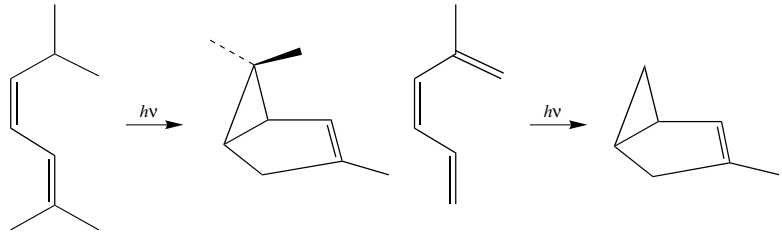
Φ = 0.35−0.46 (R = Me)

(*E*-**16/17**)

3. Formation of bicyclo[3.1.0]hex-2-enes: The 'photochemical Diels–Alder reaction'

The formation of bicyclo[3.1.0]hex-2-enes is a common reaction of cyclic and acyclic *cZt*-1,3,5-trienes. While it has been frequently depicted as a $[\pi 4 + \pi 2]$-cycloaddition and it often exhibits the stereochemistry expected of a concerted $[\pi 4s + \pi 2a]$ process[109], it is well known that it just as often does not. The stereochemistry, conformational requirements and scope of the reaction have been thoroughly studied by a number of workers, and have been extensively reviewed[116,128,170−172].

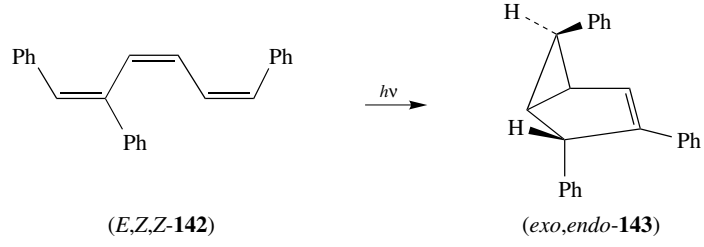
In general, the regiochemistry of the reaction is such that the more highly substituted terminal carbon of the 1,3,5-hexatrienyl moiety (e.g. of **138**) ends up as C6 of the bicyclo[3.1.0]hex-2-ene structure **(139)** while with 2-substituted trienes having identically substituted terminal carbons, such as **140**, the cyclopropyl group is formed at the opposite end of the system (cf **141**, equation 52)[188,210]. This is mainly due to steric factors which stabilize one *cZt* conformer relative to the other.



(52)

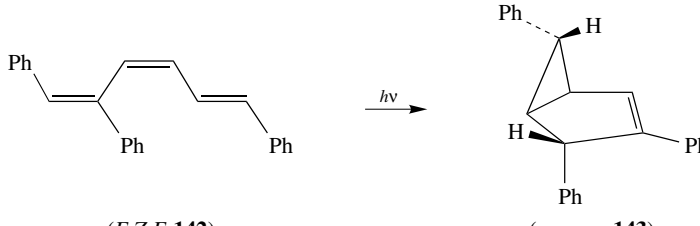
(138) **(139)** **(140)** **(141)**

The stereochemistry of the reaction varies. For example, irradiation of *E*,*Z*,*Z*- and *E*,*Z*,*E*-1,2,6-triphenylhexatriene (*E*,*Z*,*Z*- and *E*,*Z*,*E*-**142**, respectively) proceeds with formal [π4s + π2a] stereochemistry to yield the *exo*,*endo*- and *exo*,*exo*-bicyclo[3.2.0]hex-2-ene derivatives (**143**; equation 53), in chemical yields in excess of 75%[221]. Irradiation of the *Z*,*Z*,*E*- and *Z*,*Z*,*Z*-isomers leads to the same two products in nearly the same yields, via 2-photon processes of which the first is selective *E*,*Z*-isomerization to the *E*,*Z*,*E*- and *E*,*Z*,*Z*-isomers, respectively. In contrast, irradiation of *E*,*Z*,*Z*- and *E*,*Z*,*E*-**144** affords the *endo*,*endo*- and *endo*,*exo*-isomer **145**, the products corresponding to formal [π4a + π2a] cycloaddition (equation 54)[191,192].



(*E*,*Z*,*Z*-**142**) (*exo*,*endo*-**143**)

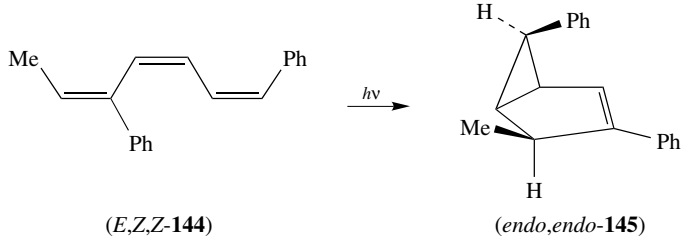
(53)



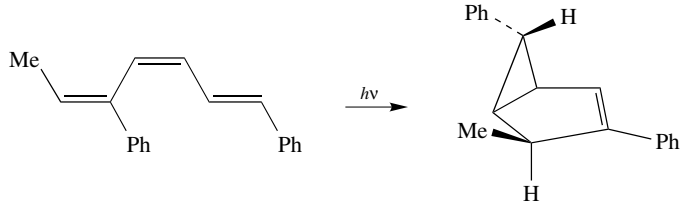
(*E*,*Z*,*E*-**142**) (*exo*,*exo*-**143**)

Dauben and coworkers produced a number of lovely examples of the reaction in the course of their studies of the photochemistry of large-ring (C_8–C_{11}) cyclic trienes, many of which were produced by photochemical electrocycloreversion of the isomeric annulated cyclohexadiene derivatives (cf Reference 172 and references cited therein). Two examples

of the photochemistry of the *Z*,*Z*,*E*-cyclic trienes **147** and **152**, formed by accordant ring opening of the corresponding *cis*-fused annulated cyclohexadienes **146** and **151**, respectively, are shown in equations 55 and 56[222]. The products are **148**–**150** in equation 55 and **153** and **154** in equation 56.

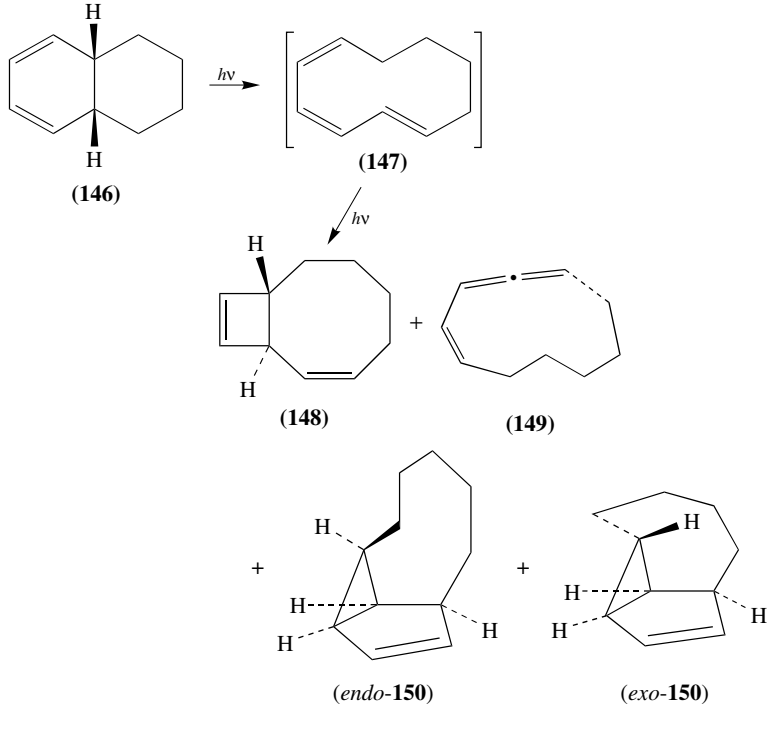


(*E*,*Z*,*Z*-**144**) (*endo*,*endo*-**145**)



(*E*,*Z*,*E*-**144**) (*endo*,*exo*-**145**)

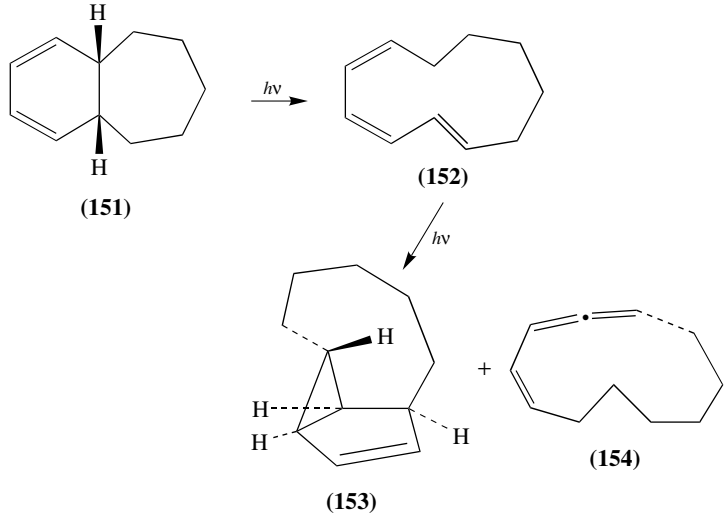
(54)



(146) **(148)** **(149)**

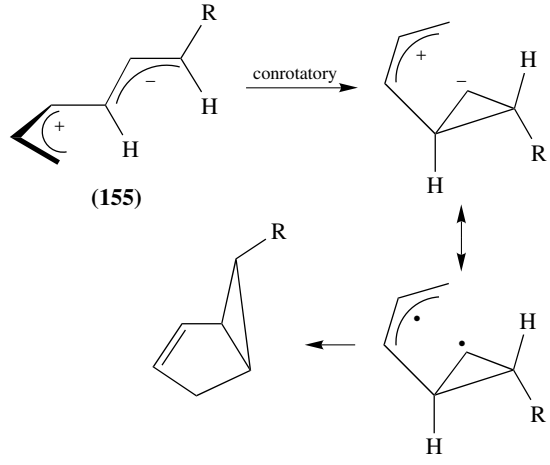
(55)

(*endo*-**150**) (*exo*-**150**)



(56)

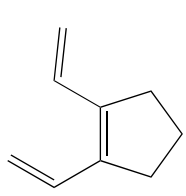
Dauben and coworkers proposed a stepwise mechanism for the reaction involving initial twisting about the central C=C bond, conrotatory ring closure of the s-*trans* half of the molecule, and then non-stereospecific ring closure to form the cyclopentene ring (equation 57)[172,170]. Both experimental evidence[128] and theoretical calculations[39,80,83] support a zwitterionic structure for the twisted intermediate **(155)**. This mechanism is analogous to that proposed by Dauben and Ritscher for the formation of bicyclobutanes from irradiation of s-*trans* dienes[79]. Tanaka and Fukui have discussed an alternative mechanistic treatment based on FMO theory[223]. Garavelli and coworkers have recently suggested that the formation of bicyclo[3.1.0]hexenes from *cZc*-1,3,5-hexatriene proceeds via the intermediacy of a ground state methylenecyclopentenyl biradical[206].



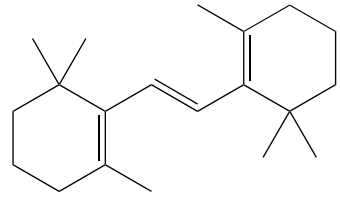
(57)

Jacobs and coworkers have recently reported an investigation of the photochemistry of the structurally locked *Z*-triene 1,2-divinylcyclopentene **(156)**, which suggests that

constraining the torsional mobility about the central C=C bond of the *Z*-hexatrienyl moiety has important ramifications on the excited state decay pathways leading to product formation[224]. The compound was found to be astonishingly stable to irradiation. Even more remarkable is the fact that it fluoresces at room temperature in methanol solution ($\Phi = 0.01$; $\tau = 8.5$ ns), providing the first reported example of fluorescence from a simple aliphatic triene in fluid solution. The emission was attributed to the 2^1A state, stabilized by the torsional rigidity about the central C=C bond of the 5-membered ring. Fluorescence can also be observed from trienes bearing large alkyl groups at the terminal carbons, such as previtamin D_3 (*vide infra*)[220] and the carotene analogue **157**[225], though only at low temperatures in viscous or rigid media. The quantum yield of fluorescence from the latter compound is $\Phi_F = 0.61$ in 3-methylpentane at 77 K, and it decreases to a value of 0.04 as the temperature is increased to 110 K. The viscosity of 3-methylpentane decreases by roughly 13 orders of magnitude over this temperature range[225].



(156)



(157)

4. The photochemistry of vitamin D and its isomers

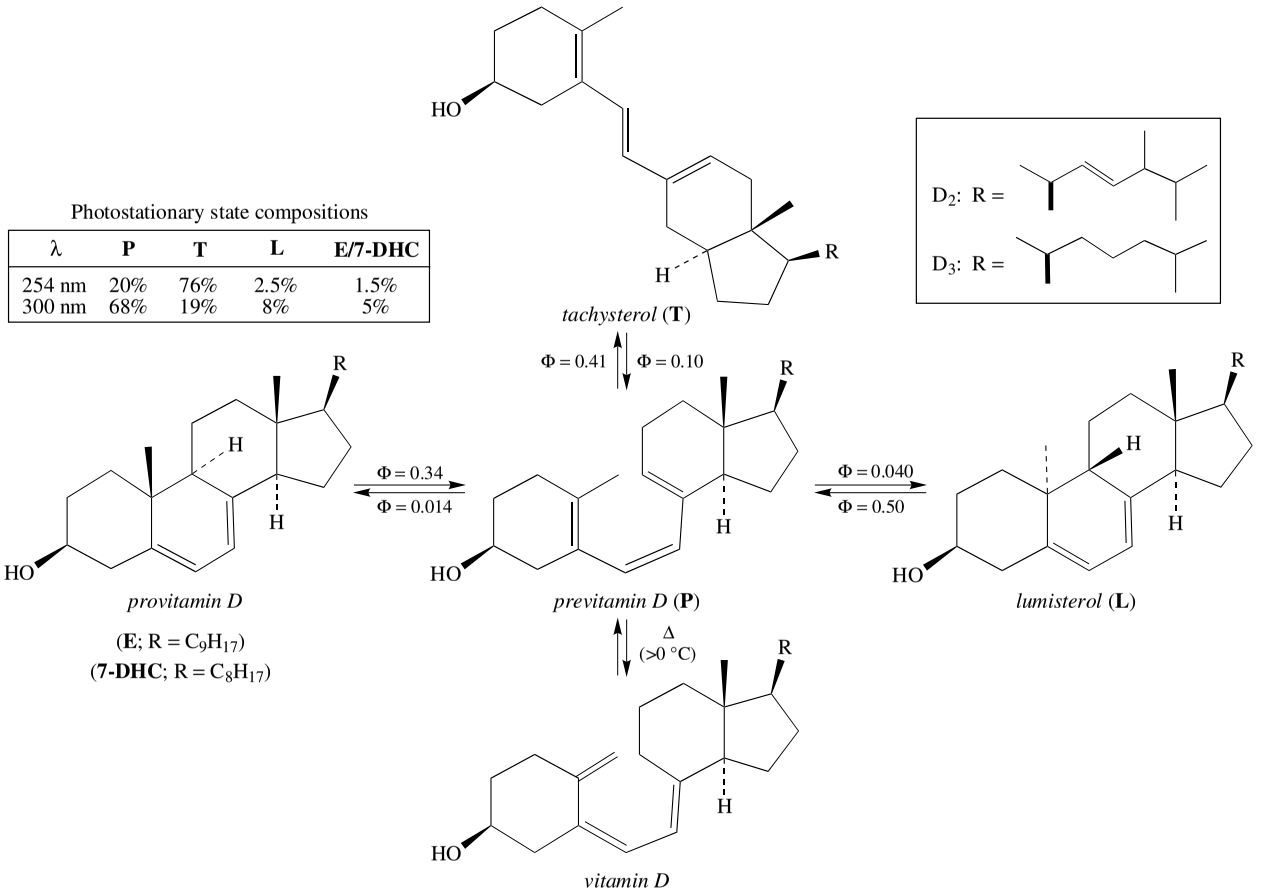
The photochemistry of vitamin D and its various isomers has been reviewed comprehensively many times[129,171,172,207,226], but as it lies at the very heart of hexatriene/cyclohexadiene photochemistry, it seems fitting to provide a very brief overview of the salient features here.

Vitamin D **(D)** is the generic name of two triene natural products which differ only in the structure of the side chain on the steroidal backbone. It is synthesized photochemically from the steroid natural product provitamin D: ergosterol (**E**; R = C_9H_{17}) in the D_2 series and 7-dehydrocholesterol (7-DHC); R = C_8H_{17} in the D_3 series. UV irradiation of provitamin D results in efficient conrotatory ring opening to yield previtamin D, which then yields vitamin D via a reversible antarafacial [1,7]-H shift which is rapid at room temperature and above. The irradiation actually leads to the rapid establishment of a pseudophotostationary state of four isomers which are linked via reversible photoreactions of previtamin D **(P)**: the double bond isomer tachysterol **(T)** and the steroids provitamin D and lumisterol **(L)**, which are interconverted with P via conrotatory electrocyclization and electrocycloreversion. Scheme 5 illustrates this photoequilibrium along with the quantum yields of the various interconversions[227] and the photostationary state compositions obtained with 254 nm irradiation[207]. The photostationary state compositions with 300 nm[228] irradiation are also included.

Prolonged irradiation of the mixture leads to the formation of a huge variety of secondary products due to competing photoreactions of the triene members of the series **P**, **T** and **D**. Many of these are formed as a result of the more common triene photoprocesses which have already been discussed. Many more are formed via less generic processes which involve the cyclic moieties at the two ends of the triene or intervention of the solvent in either catalytic or direct fashion. The so-called 'toxisterols' arise from irradiation

Photostationary state compositions

λ	P	T	L	E/7-DHC
254 nm	20%	76%	2.5%	1.5%
300 nm	68%	19%	8%	5%



SCHEME 5. Photochemical interconversions of vitamin D isomers

of **P** and **T** under various conditions, while 'suprasterols' are the products of irradiation of **D**: cyclobutene, bicyclo[3.1.0]hexene, vinylallene and 1,5-H shift isomers. The exact structures and mechanisms of formation of these compounds are covered comprehensively in the aforementioned reviews[129,171,172,207,226] and hence will not be discussed here.

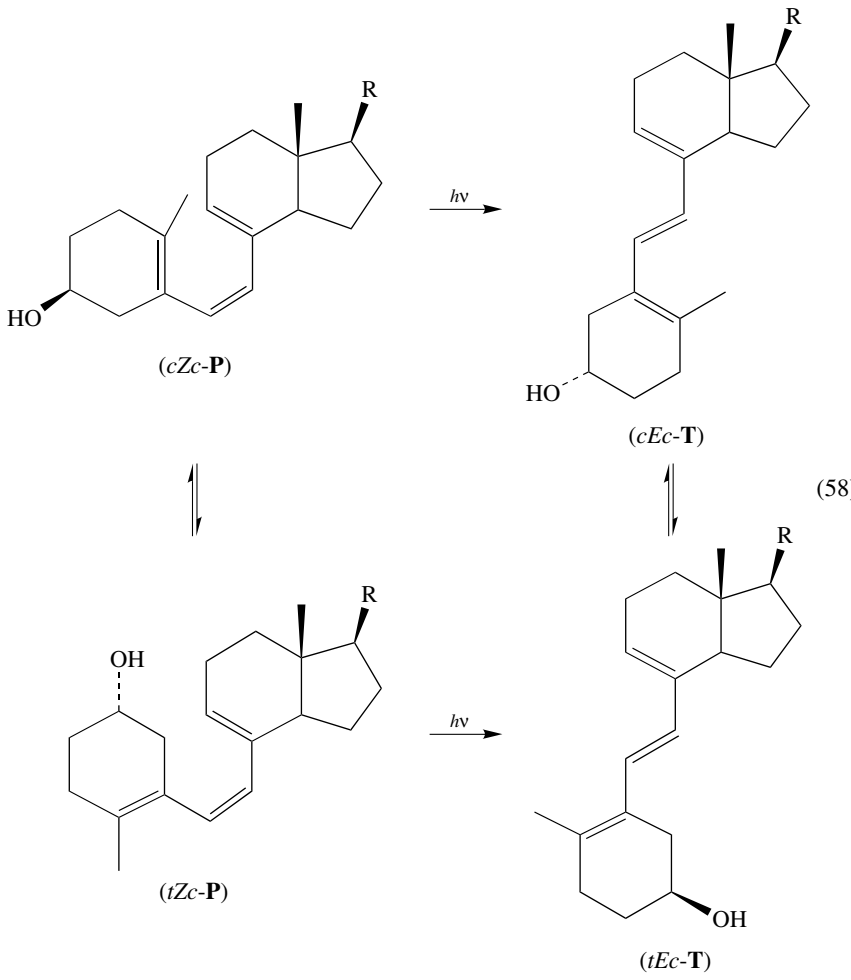
The wavelength dependence of the photochemistry of the system has been extensively investigated[129,220,227–229]. The quantum yields for the ring-opening reactions of **E**/7-DHC and **L** are wavelength dependent, but those of ring closure and *E*,*Z*-isomerization of **P** change markedly with excitation wavelength. This is now thought to be due to some combination of both ground state conformational effects (the 'NEER' principle)[227,230] and excited state effects associated with the excited state properties of previtamin D[220,228]. Dauben and Phillips found that the major change in quantum yields occurs over a very narrow wavelength range (302.5–305 nm), which is too abrupt to be accounted for by the relative extinction coefficients of the various single-bond conformers[228]. A thorough investigation of the fluorescence of previtamin D (lifetime, wavelength dependence of the quantum yield and temperature dependence) led Dauben, Kohler and their coworkers to the conclusion that excitation wavelengths above 305 nm results in selective excitation of the 2^1A state, which leads to preferential ring closure[220]. This pattern was shown to apply as well to the related trienes **137**, in a more recent paper from Dauben's group (*vide supra*)[73]. Recently, Fuss and Lochbrunner have suggested an alternative mechanism based on a direct competition on the excited state surface between ring closure and isomerization[231]. They suggested that the partitioning between the two reaction modes is dependent on sufficient photon energy to overcome an excited state barrier to *E*/*Z*-isomerization.

The *E*,*Z*-photoisomerization of previtamin D to tachysterol has also received recent attention. Jacobs and coworkers examined the process in various solvents at 92 K and found evidence for the formation of a triene intermediate which converts thermally (E_a *ca* 6.5 kcal mol^{-1}) to the more stable *tEc* rotamer of tachysterol (*tEc*-**T**; equation 58)[230]. The rate of this conversion is viscosity dependent. They identified this intermediate as the *cEc* rotamer, produced by selective excitation of the *cZc* rotamer of previtamin D. In a re-examination of the low temperature *E*,*Z*-photoisomerization of previtamin D as a function of excitation wavelength, Fuss and coworkers have suggested an alternative mechanism, in which *tEc*-**T** is produced directly from *cZc*-**P** and *cEc*-**T** directly from *tZc*-**P** (equation 59)[103]. This mechanism involves isomerization about both the central double bond and one of its associated single bonds — the 'hula-twist' mechanism of Liu and Browne[101] — and involves a smaller volume change than the conventional mechanism for *E*,*Z*-isomerization. The vitamin D system has also been the subject of recent theoretical study by Bernardi, Robb and Olivucci and their coworkers[232].

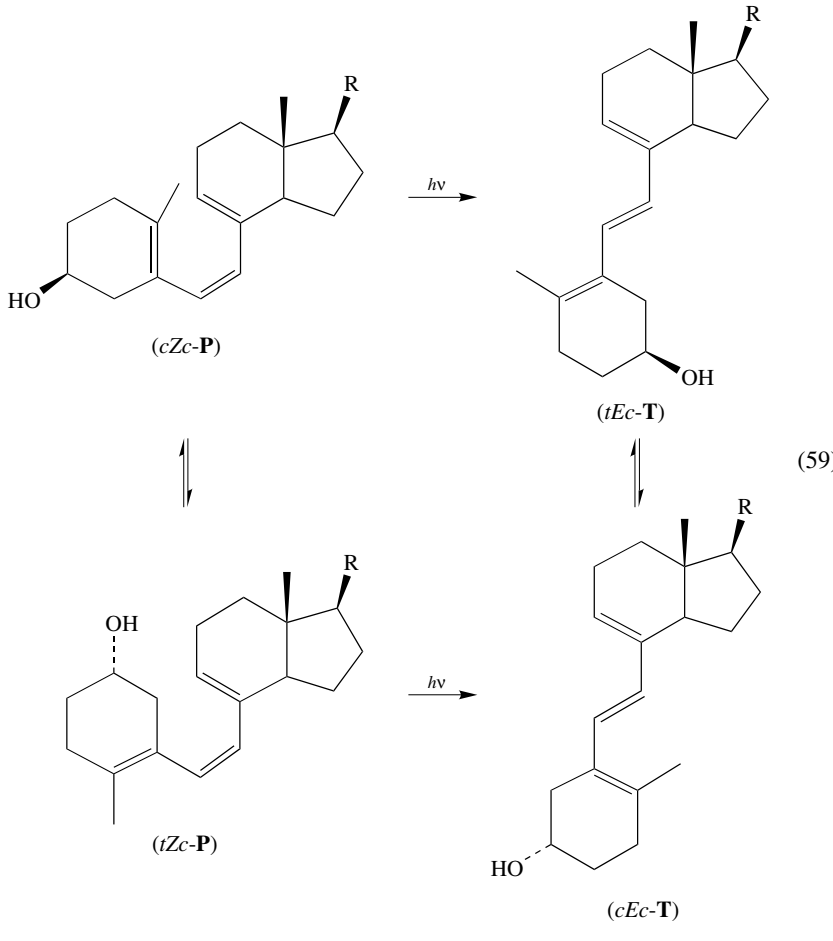
Other recent studies have examined the effects of substituents on the photochemistry of vitamin D analogues[233,234].

5. Theoretical and time-resolved spectroscopic studies of triene photochemistry

The dynamics of relaxation of the excited singlet states of *E*- and *Z*-1,3,5-hexatriene (HT) have recently been studied in the gas phase and in solution. In the gas phase, population of the 2^1A state of the *Z*-isomer by internal conversion from the spectroscopic 1^1B state has been estimated to occur with a lifetime τ_{1B} of about 20 fs, while the lifetime of the 2^1A state has been determined to be $\tau_{2A} = 730$ fs[47]. The lifetime of the latter in ethanol solution has been determined by Fuss and coworkers to be $\tau_{2A} = 470$ fs[52]. A similar 2^1A lifetime has been reported for *E*-1,3,5-hexatriene in cyclohexane and acetonitrile solution by Ohta and coworkers[48].



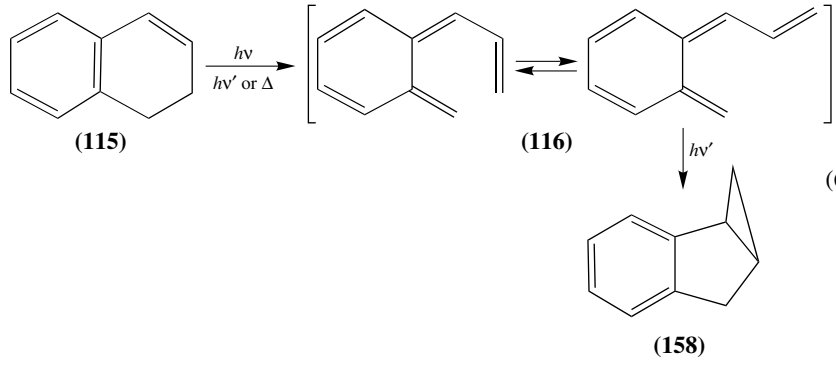
As mentioned earlier, computational studies of the photochemical ring closure of *cZc*-1,3,5-hexatriene (*cZc*-**HT**) have been reported only relatively recently. Pichko and coworkers studied the reaction using semi-empirical methods, along with those of a few heteroatomic analogs[235], while *ab initio* CAS-SCF calculations have been reported by Robb and Olivucci and their coworkers[205,206]. The latter find evidence for evolution of the initially excited (1^1B) molecule on the femtosecond timescale to an acyclic biradicaloid intermediate on the 2^1A surface, in which there is little bonding character between C5 and C6 (Scheme 4). Bond formation and partitioning between overall *E*,*Z*-isomerization, *cis*/*trans* conformer interconversion, electrocyclic ring closure and bicyclo[3.1.0]hexene formation is proposed to occur mainly on the ground state surface, after it is entered at a $2^1A/1^1A$ conical intersection about 1 kcal mol^{-1} higher in energy[204,206]. In the case of *tZt*-**HT**, which was discussed in Section IV.D.1, this partitioning is thought to occur on both the 2^1A and ground state potential energy surfaces[91].



6. Benzannelated dienes and trienes[116,170,175]

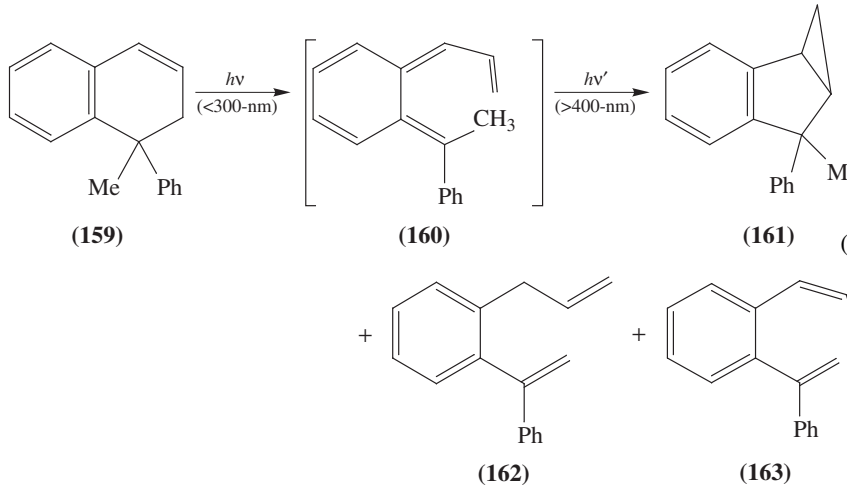
As mentioned earlier, direct irradiation of 1,2-dihydronaphthalenes leads to a variety of photoisomerization reactions which can be attributed to the initial formation of the *ω*-vinyl-*ortho*-quinodimethane isomer by electrocyclic ring opening. For example, irradiation of the parent compound **115** with an intense, broad-band light source yields the isomeric benzobicyclo[3.1.0]hexene derivative **(158)** as the main photoproduct, via secondary photolysis of the initially-produced *ω*-vinyl-*ortho*-quinodimethane isomer **116** (equation 60)[236,237]. Such compounds are short-lived due to rapid thermal ring closure to regenerate the starting material, but have been detected by low temperature spectroscopic techniques ($\lambda_{max} > 400$ nm) in derivatives bearing 1- or 4-phenyl substituents[238−240].

The photochemistry of *ω*-vinyl-*ortho*-quinodimethanes is typical of trienes in which at least one of the two C−C bonds is frozen in the s-*cis* conformation: competing electrocyclic ring closure to regenerate the precursor, formation of benzobicyclo[3.1.0]hex-2-enes and [1,5]-H shifts to arylallenes. The only triene photoproduct which is not generally



(115) **(116)** **(158)** (60)

formed is the isomeric 3-vinylbenzocyclobutene. The presence of alkyl substituents at C1 and/or C2 leads to the formation of other, additional products due to rapid thermal and/or photochemical hydrogen migrations in the *ortho*-quinodimethane intermediate, as exemplified by the photochemistry of 1-methyl-1-phenyl-1,2-dihydronaphthalene **(159)** which gives products **161**–**163** via the ω-vinyl-*ortho*-quinodimethane **160** (equation 61)[238].



(159) **(160)** **(161)** (61)

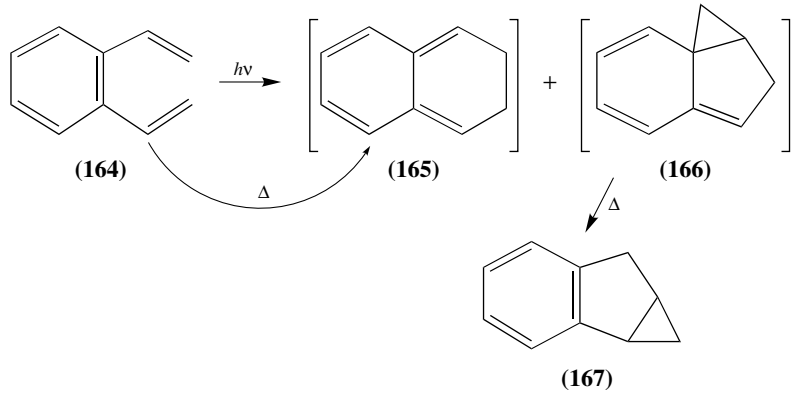
(162) **(163)**

Direct irradiation of *ortho*-divinylbenzene **(164)** leads to the formation of the benzobicyclo[3.1.0]hex-2-ene isomer **167** as the major product. Deuterium labelling and methanol trapping experiments suggested the intermediacy of both **165** and **166**, the expected products of irradiation of a benzannelated 1,3,5-hexatriene (equation 62)[144].

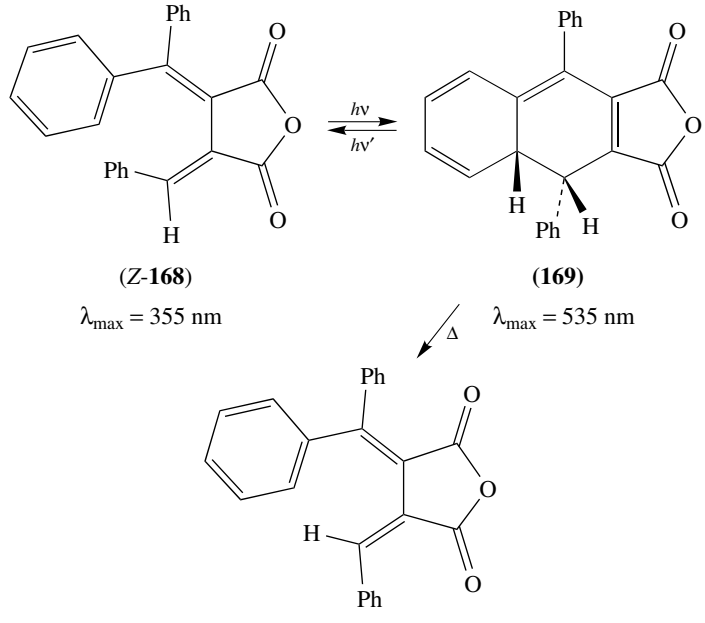
7. Photochromic materials based on cyclohexadiene/hexatriene interconversions

Aryl-substituted fulgides are the products of condensation of aromatic ketones with succinic anhydride, and form one of the oldest and most important groups of organic photochromic materials[241]. First discovered in the early part of the last century by Stobbe[242], they are now well known to owe their photochromic behavior to reversible (conrotatory)

electrocyclic interconversion with the dihydronaphthalene isomer. For example, *Z*-**168** interconverts photochemically with **169** via conrotatory electrocyclization/electrocycloreversion (equation 63)[243]. As is often typical with fulgide-derived dihydronaphthalenes, **169** is thermally labile with respect to disrotatory electrocyclic ring opening to yield *E*-**168**.



(164) **(165)** **(166)** **(167)** (62)



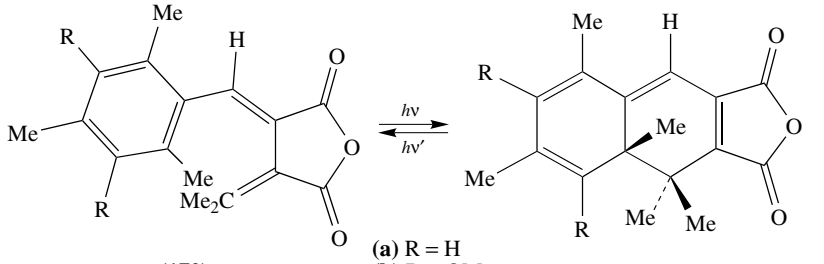
(*Z*-**168**) **(169**) (63)

λ_{max} = 355 nm λ_{max} = 535 nm

(*E*-**168**)

E,*Z*-isomerization is the main competing singlet state photoreaction of aryl fulgides. The effects of substituents on the UV absorption spectra of both the open and closed forms, and on the quantum yields for *E*,*Z*-isomerization and electrocyclic ring closure, are quite dramatic, and an impressively large number of compounds in this class have been studied in detail, mostly by Heller and his group. The most useful class of materials are those containing only one aryl ring, substituted in the 2- and 2′-positions so as to

block the occurrence of irreversible thermal, photochemical or oxidative reactions of the colored (closed) form, which lead to 'fatigue'. For example, the pale yellow materials **170** undergo photochemical ring closure to the highly colored 1,8-dihydronaphthalenes **171**, which are thermally stable up to 160°C, but undergo efficient electrocycloreversion on exposure to white light (equation 64)[244].

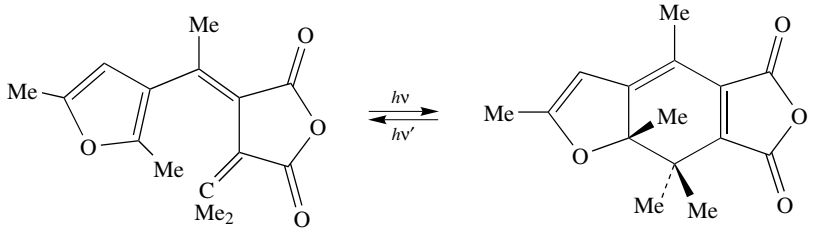


(64)

(a) R = H
(b) R = OMe

(170) **(171)**

The furyl fulgide **172** has found use as a stable, recyclable actinometer for conventional photochemical experiments in the 313–366 nm wavelength range, where $\Phi_{173} = 0.20$ and is independent of temperature and concentration[245]. It has also been developed as an actinometer in one- and two-laser flash photolysis experiments[246]. The colored form **173** can be converted back to **172** by simple exposure to visible light (equation 65).

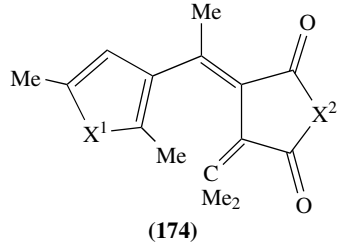


(65)

(172) **(173)**

λ_{max} = 346 nm (log ε 3.81) λ_{max} = 494 nm (log ε 3.89)

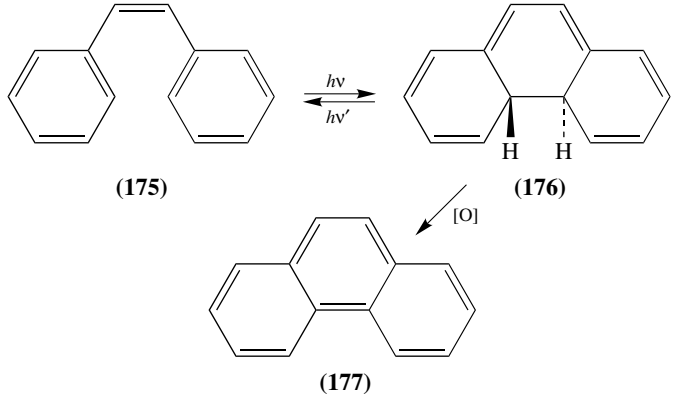
A number of related systems (e.g. **174**) have also been examined for their potential as photochromic materials, and the field continues to be an active one[247–250].



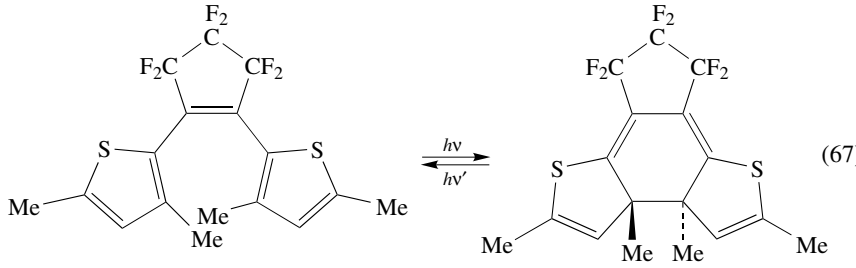
(174)

X^1 = O, S, NR
X^2 = O, NR

Another important class of photochromic materials based on reversible triene photocyclization are 1,2-diarylalkenes, of which the *Z*-stilbene **(175)**/9,10-dihydrophenanthrene **(176)** system is the prototype (equation 66)[251,252]. As with the fulgide systems, it is necessary to replace the *ortho*-hydrogens on the aryl rings with alkyl groups, in order to prevent irreversible thermal and photochemical oxidative processes (e.g. to **177**) involving the ring-closed forms. Accordingly, materials such as **178/179** (equation 67)[253,254] show excellent absorption properties and fatigue resistance, and continue to be of great interest[255–258]. Irie and Uchida have recently reviewed this field in detail[259].



(175) **(176)** **(177)** (66)

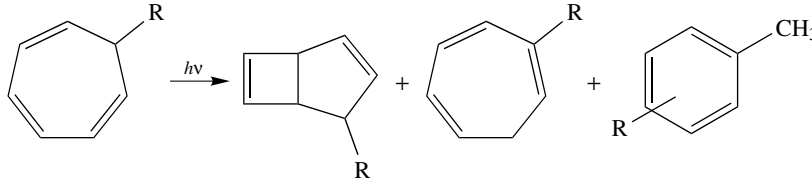


(178) **(179)** (67)

8. Cyclic trienes

Substituted 1,3,5-cycloheptatrienes **(180)** exhibit three photochemical reactions: 4π-electrocyclic ring closure to yield the isomeric bicyclo[3.2.0]hepta-2,6-dienes **181**, suprafacial [1,7]-hydrogen migration to give **182**, and rearrangement to toluenes **183** (equation 68)[110,116,122,260–266]. The major photoproduct in solution is frequently that of electrocyclic ring closure, which occurs via a true excited state process with no detectable competition from the *E*,*Z*-photoisomerization/thermal ring closure pathway that is known for 1,3-cycloheptadiene[122]. In most cases, however, [1,7]-hydrogen migration is known to be significantly more efficient than ring closure[267,268]; for example, the process occurs *ca* 500 times more rapidly than ring closure in the parent molecule[262,263]. In substituted systems, the high efficiency of [1,7]-H shifts compared to ring closure frequently leads to the formation of a variety of isomeric photocyclization products.

The quantum yield for toluene formation is very low in solution but approaches unity in the gas phase at low pressures[269]. The toluene was suggested to be formed from vibrationally excited ground state molecules, following rapid internal conversion from the excited singlet state manifold, perhaps involving the intermediacy of norcaradiene (bicyclo[4.1.0]hepta-2,4-diene)[269,270]. The hot ground state mechanism for toluene formation has received considerable support from time-resolved and steady-state experiments on cycloheptatriene and several of its derivatives[180,271–274].

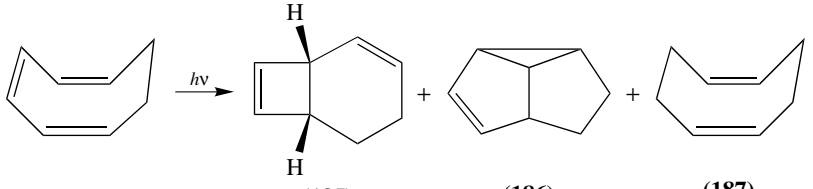


(68)

(180) **(181)** **(182)** **(183)**

The photochemistry of the parent molecule (R = H) has recently been studied using ultrafast time-resolved spectroscopic techniques[49,98,99,198,275–277]. Within *ca* 20 fs of excitation to the spectroscopic $1^1A''$ state (the 1^1B_u state of 1,3,5-hexatriene) the molecule flattens, a process which has been associated with internal conversion to the lower lying $2^1A'$ state (the 2^1A_g state of 1,3,5-hexatriene)[50,277]. Deactivation of the $2^1A'$ state then takes place within the next 60–80 fs, followed by competing [1,7]-H migration, ring closure and internal conversion on the ground state surface[98,99,275]. The fact that these processes occur so quickly suggests that at least part of the photoreaction is coupled with internal conversion, which is a characteristic of a reaction which proceeds through a conical intersection between the ground and excited states[23,278].

The direct irradiation of 1,3,5-cyclooctatriene **(184)** in ether or hydrocarbon solvents leads to the slow formation of two stable isomers corresponding to disrotatory 4π-electrocyclization **(185)** and bicyclo[3.1.0]pentene **(186)** formation along with small amounts of the reduced product **187** (equation 69)[279–281]. Conventional flash photolysis experiments later showed that, in fact, the main primary photochemical process is the formation of a short-lived stereoisomer (τ = 91 ms)[282], most likely identifiable as *E*,*Z*,*Z*-**184**. The transient decays to yield a second transient species (τ = 23 s) identified as *Z*,*Z*-1,3,5,7-octatetraene **(188)**, which in turn decays by electrocyclic ring closure to regenerate **184**[282] (equation 70). The photochemistry of **184** has been studied on the picosecond timescale using time-resolved resonance Raman spectroscopy[49].

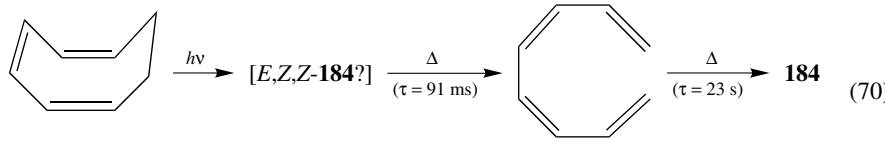


(69)

(184) **(185)** **(186)** **(187)**

Several examples of the photochemistry of larger-ring (C_9–C_{12}) cyclic trienes have already been cited (*vide supra*), and a great many more have been studied, particularly by Dauben and coworkers. These have been reviewed thoroughly elsewhere; in general,

they tend to be well-defined conformationally and exhibit much of the photochemistry discussed earlier for acyclic systems[116,172,175].



(70)

(184) **(188)**

V. CONCLUSION

The field of polyene photochemistry certainly cannot be given proper justice in a single chapter and so we have limited our coverage rather severely, focussing on pericyclic reactions originating from the excited singlet state manifolds of conjugated dienes and trienes. Even this rather small part of the field is incredibly large, and we have been admittedly terse in our coverage of it. Our main goal was to summarize the salient features of this aspect of polyene photochemistry, emphasizing the interplay between classical product studies, time-resolved spectroscopy and theoretical chemistry. We hope that we have been successful in conveying a reasonably accurate picture of the impressive breadth of the work that has been done in this area and that more will be stimulated as a result.

VI. REFERENCES

1. B. S. Hudson, B. E. Kohler and K. Schulten in *Excited States* (Ed. E. Lim), Academic Press, New York, 1982, pp. 1–95.
2. M. T. Allen and D. G. Whitten, *Chem. Rev.*, **89**, 1691 (1989).
3. J. Saltiel and Y.-P. Sun, in *Photochromism: Molecules and Systems* (Eds. H. Durr and H. Bouas–Laurent), Elsevier, New York, 1990, pp. 64–162.
4. P. J. Wagner and G. S. Hammond, *Adv. Photochem.*, **5**, 21 (1968).
5. T. Arai and K. Tokumaru, *Adv. Photochem.*, **20**, 1 (1995).
6. J. Saltiel, D.-H. Ko and S. A. Fleming, *J. Am. Chem. Soc.*, **116**, 4099 (1994).
7. (a) Y. Sonoda and Y. Suzuki, *J. Chem. Soc., Perkin Trans. 2*, 401, (1996).
   (b) Y. Sonoda and Y. Suzuki, *Chem. Lett.*, 659 (1996).
   (c) Y. Sonoda, H. Morii, M. Sakuragi and Y. Suzuki, *Chem. Lett.*, 349 (1998).
8. J. Saltiel, D. F. Sears, Y.-P. Sun and J.-O. Choi, *J. Am. Chem. Soc.*, **114**, 3607 (1992).
9. E. F. Hilinski, W. M. McGowan, D. F. Sears and J. Saltiel, *J. Phys. Chem.*, **100**, 3308 (1996).
10. J. Saltiel and S. Wang, *J. Am. Chem. Soc.*, **117**, 10761 (1995).
11. B. E. Kohler, *Chem. Rev.*, **93**, 41 (1993).
12. W. Th. A. M. van der Lugt and L. J. Oosterhoff, *J. Am. Chem. Soc.*, **91**, 6042 (1969).
13. D. Grimbert, G. Segal and A. Devaquet, *J. Am. Chem. Soc.*, **97**, 6629 (1975).
14. K. Morihashi, O. Kikuchi and K. Suzuki, *Chem. Phys. Lett.*, **90**, 346 (1982).
15. K. Morihashi and O. Kikuchi, *Theor. Chim. Acta.*, **67**, 293 (1985).
16. M. Aoyagi and Y. Osamura, *J. Am. Chem. Soc.*, **111**, 470 (1989).
17. P. Bruckmann and L. Salem, *J. Am. Chem. Soc.*, **98**, 5037 (1976).
18. I. Baraldi, M. C. Bruni, F. Momicchioli, J. Langlet and J. P. Malrieu, *Chem. Phys. Lett.*, **51**, 493 (1977).
19. W. J. Leigh, *Can. J. Chem.*, **71**, 147 (1993).
20. W. J. Leigh, in *CRC Handbook of Organic Photochemistry and Biology* (Ed. W. Horspool), CRC Press, Boca Raton, 1996, pp. 123–142.
21. J. Michl and V. Bonaic–Koutecky, *Electronic Aspects of Organic Photochemistry*, Wiley, New York, 1990.
22. F. Bernardi, M. Olivucci and M. A. Robb, *Isr. J. Chem.*, **33**, 265 (1993).
23. M. A. Robb, F. Bernardi and M. Olivucci, *Pure Appl. Chem.*, **67**, 783 (1995).

24. F. Bernardi, M. Olivucci and M. A. Robb, *Chem. Soc. Rev.*, 321 (1996).
25. F. Bernardi, M. Olivucci and M. A. Robb, *J. Photochem. Photobiol. A, Chem.*, **105**, 365 (1997).
26. S. Zilberg and Y. Haas, *J. Phys. Chem. A*, **103**, 2364 (1999).
27. H. E. Zimmerman, *J. Am. Chem. Soc.*, **88**, 1566 (1966).
28. J. Michl, *Mol. Photochem.*, **4**, 243 (1972).
29. M. Klessinger, *Angew. Chem., Int. Ed. Engl.*, **34**, 549 (1995).
30. J. C. Tai and N. L. Allinger, *J. Am. Chem., Soc.*, **98**, 7928 (1976).
31. W. R. Roth, H. W. Lennartz, W. v. E. Doering, W. R. Dolbier Jr. and J. C. Schmidhauser, *J. Am. Chem., Soc.*, **110**, 1883 (1988).
32. J. R. Ackerman and B. E. Kohler, *J. Chem. Phys.*, **80**, 45 (1984).
33. L. M. Stephenson, R. U. Gemmer and J. I. Brauman, *J. Am. Chem. Soc.*, **94**, 8620 (1972).
34. W. Marley and P. M. Jeffers, *J. Phys. Chem.*, **79**, 2085 (1975).
35. P. M. Jeffers, *J. Phys. Chem.*, **78**, 1469 (1974).
36. S. W. Orchard and B. A. Thrush, *J. Chem. Soc., Chem. Commun.*, 14 (1973).
37. W. v. E. Doering and G. H. Beasley, *Tetrahedron*, **29**, 2231 (1973).
38. G. Orlandi, F. Zerbetto and M. Z. Zgierski, *Chem. Rev.*, **91**, 867 (1991).
39. L. Salem, *Acc. Chem. Res.*, **12**, 87 (1979).
40. B. E. Kohler, *J. Chem. Phys.*, **93**, 5838 (1990).
41. R. R. Chadwick, M. Z. Zgierski and B. S. Hudson, *J. Chem. Phys.*, **95**, 7204 (1991).
42. L. Serrano–Andres, M. Merchan and I. Nebot–Gil, *J. Chem. Phys.*, **98**, 3151 (1993).
43. M. O. Trulson and R. A. Mathies, *J. Phys. Chem.*, **94**, 5741 (1990).
44. H. Petek, A. J. Bell, R. L. Christensen and K. Yoshihara, *J. Chem. Phys.*, **96**, 2412 (1992).
45. X. Ci and A. B. Myers, *J. Chem. Phys.*, **96**, 6433 (1992).
46. D. L. Phillips, M. Z. Zgierski and A. B. Myers, *J. Phys. Chem.*, **97**, 1800 (1993).
47. D. R. Cyr and C. C. Hayden, *J. Chem. Phys.*, **104**, 771 (1996).
48. K. Ohta, Y. Naitoh, K. Saitow, K. Tominaga, N. Hirota and K. Yoshihara, *Chem. Phys. Lett.*, **256**, 629 (1996).
49. P. J. Reid, S. J. Doig and R. A. Mathies, *J. Phys. Chem.*, **94**, 8396 (1990).
50. P. J. Reid, S. D. Wickham and R. A. Mathies, *J. Phys. Chem.*, **96**, 5720 (1992).
51. P. J. Reid, S. J. Doig, S. D. Wickham and R. A. Mathies, *J. Am. Chem. Soc.*, **115**, 4754 (1993).
52. S. Lochbrunner, W. Fuss, K. L. Kompa and W. E. Schmid, *Chem. Phys. Lett.*, **274**, 491 (1997).
53. P. Celani, M. Garavelli, S. Ottani, F. Bernardi, M. A. Robb and M. Olivucci, *J. Am. Chem. Soc.*, **117**, 11584 (1995).
54. M. Beez, G. Bieri, H. Bock and E. Heilbronner, *Helv. Chim. Acta*, **56**, 1028 (1973).
55. G. Bieri, F. Burger, E. Heilbronner and J. P. Maier, *Helv. Chim. Acta*, **60**, 2213 (1977).
56. E. Honegger, Y. Zhong–zhi, E. Heilbronner, W. v. E. Doering and J. C. Schmidhauser, *Helv. Chim. Acta*, **67**, 640 (1984).
57. N. H. Werstiuk, K. B. Clark and W. J. Leigh, *Can. J. Chem.*, **68**, 2078 (1990).
58. W. G. Dauben, R. L. Cargill, R. M. Coates and J. Saltiel, *J. Am. Chem. Soc.*, **88**, 2742 (1966).
59. J. Saltiel, L. Metts and M. Wrighton, *J. Am. Chem. Soc.*, **92**, 3227 (1970).
60. J. Saltiel, J. D'Agostino, E. D. Megarity, L. Metts, K. R. Neuberger, M. Wrighton and O. C. Zafiriou, *Org. Photochem.*, **3**, 1 (1973).
61. E. Havinga and J. L. M. A. Schlatmann, *Tetrahedron*, **16**, 146 (1961).
62. J. Saltiel and J. L. Charlton, in *Rearrangements in Ground and Excited States* (Ed. P. De Mayo), Academic Press, New York, 1980, pp. 25–89.
63. M. Bigwood and S. Boue, *Tetrahedron Lett.*, 4311 (1973).
64. P. Vanderlinden and S. Boue, *J. Chem. Soc., Chem. Commun.*, 932 (1975).
65. W. A. Yee, S. J. Hug and D. S. Kliger, *J. Am. Chem. Soc.*, **110**, 2164 (1988).
66. Y. Inoue, S. Hagiwara, Y. Daino and T. Hakushi, *J. Chem. Soc., Chem. Commun.*, 1307 (1985).
67. W. J. Nebe and G. J. Fonken, *J. Am. Chem. Soc.*, **91**, 1249 (1969).
68. K. B. Clark, K. Zheng and W. J. Leigh, *J. Org. Chem.*, **56**, 1574 (1991).
69. W. J. Leigh and J. A. Postigo, *J. Chem. Soc., Chem. Commun.*, 1836 (1993).
70. W. J. Leigh, J. A. Postigo and K. Zheng, *Can. J. Chem.*, **74**, 951 (1996).
71. N. G. Minnaard and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **92**, 1315 (1973).

72. A. M. Brouwer, J. Cornelisse and H. J. C. Jacobs, *J. Photochem. Photobiol. A, Chem.*, **42**, 117 (1988).
73. W. G. Dauben, B. Zhou and J. Y. L. Lam, *J. Org. Chem.*, **62**, 9005 (1997).
74. A. J. Merer and R. S. Mulliken, *Chem. Rev.*, **69**, 639 (1969).
75. D. H. Walbeck, *Chem. Rev.*, **91**, 415 (1991).
76. D. G. Whitten, *Acc. Chem. Res.*, **26**, 502 (1993).
77. S. Boue and R. Srinivasan, *J. Am. Chem. Soc.*, **92**, 3226 (1970).
78. R. Srinivasan, *J. Am. Chem. Soc.*, **90**, 4498 (1968).
79. W. G. Dauben and J. S. Ritscher, *J. Am. Chem. Soc.*, **92**, 2925 (1970).
80. C. M. Meerman–van Benthem, H. J. C. Jacobs and J. J. C. Mulder, *Nouv. J. Chim.*, **2**, 123 (1978).
81. W. Rettig, *Angew. Chem., Int. Ed. Engl.*, **25**, 971 (1986).
82. V. Bonaic–Koutecky, J. Koutecky and J. Michl, *Angew. Chem., Int. Ed. Engl.*, **26**, 170 (1987).
83. J. P. Malrieu, I. Nebot–Gil and J. Sanchez–Marin, *Pure Appl. Chem.*, **56**, 1241 (1984).
84. B. H. Baretz, A. K. Singh and R. S. H. Liu, *Nouv. J. Chim.*, **5**, 297 (1981).
85. M. E. Squillacote and T. C. Semple, *J. Am. Chem. Soc.*, **109**, 892 (1987).
86. K. Muthuramu and R. S. H. Liu, *J. Am. Chem. Soc.*, **109**, 6510 (1987).
87. M. Olivucci, F. Bernardi, S. Ottani and M. A. Robb, *J. Am. Chem. Soc.*, **116**, 2034 (1994).
88. M. Olivucci, I. N. Ragazos, F. Bernardi and M. A. Robb, *J. Am. Chem. Soc.*, **115**, 3710 (1993).
89. P. Celani, F. Bernardi, M. Olivucci and M. A. Robb, *J. Chem. Phys.*, **102**, 5733 (1995).
90. M. Garavelli, B. Frabboni, M. Fato, P. Celani, F. Bernardi, M. A. Robb and M. Olivucci, *J. Am. Chem. Soc.*, **121**, 1537 (1999).
91. M. Olivucci, F. Bernardi, P. Celani, I. N. Ragazos and M. A. Robb, *J. Am. Chem. Soc.*, **116**, 1077 (1994).
92. M. Garavelli, P. Celani, F. Bernardi, M. A. Robb and M. Olivucci, *J. Am. Chem. Soc.*, **119**, 11487 (1997).
93. M. Garavelli, P. Celani, N. Yakamoto, F. Bernardi, M. A. Robb and M. Olivucci, *J. Am. Chem. Soc.*, **118**, 11656 (1996).
94. T. Vreven, F. Bernardi, M. Garavelli, M. Olivucci, M. A. Robb and H. B. Schlegel, *J. Am. Chem. Soc.*, **119**, 12687 (1997).
95. F. Bernardi, M. Garavelli, M. Olivucci and M. A. Robb, *Mol. Phys.*, **92**, 359 (1997).
96. M. Garavelli, F. Bernardi, S. Clifford, M. A. Robb and M. Olivucci, *J. Photochem. Photobiol. A, Chem.*, **114**, 109 (1998).
97. M. Garavelli, T. Vreven, P. Celani, F. Bernardi, M. A. Robb and M. Olivucci, *J. Am. Chem. Soc.*, **120**, 1285 (1998).
98. W. Fuss, P. Hering, K. L. Kompa, S. Lochbrunner, T. Schikarski, W. E. Schmid and S. A. Trushin, *Ber. Bunsenges. Phys. Chem.*, **101**, 500 (1997).
99. W. Fuss, S. Lochbrunner, A. M. Muller, T. Schikarski, W. E. Schmid and S. A. Trushin, *Chem. Phys.*, **232**, 161 (1998).
100. D. H. Aue and R. N. Reynolds, *J. Am. Chem. Soc.*, **95**, 2027 (1973).
101. R. S. H. Liu and D. T. Browne, *Acc. Chem. Res.*, **19**, 42 (1986).
102. M. E. Squillacote and T. C. Semple, *J. Am. Chem. Soc.*, **112**, 5546 (1990).
103. A. M. Muller, S. Lochbrunner, W. E. Schmid and W. Fuss, *Angew. Chem., Int. Ed. Engl.*, **37**, 505 (1998).
104. P. W. Mui and E. Grunwald, *J. Am. Chem. Soc.*, **104**, 6562 (1982).
105. M. E. Squillacote, R. S. Sheridan, O. L. Chapman and F. A. L. Anet, *J. Am. Chem. Soc.*, **101**, 3657 (1979).
106. B. R. Arnold, V. Balaji and J. Michl, *J. Am. Chem. Soc.*, **112**, 1808 (1990).
107. M. E. Squillacote, T. C. Semple and P. W. Mui, *J. Am. Chem. Soc.*, **107**, 6842 (1985).
108. A. M. Brouwer and H. J. C. Jacobs, *Recl. Trav. Chim. Pays-Bas*, **114**, 449 (1995).
109. R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie GmbH, Academic Press, Aschaffenburg, 1970.
110. O. L. Chapman, D. J. Pasto, G. W. Borden and A. A. Griswold, *J. Am. Chem. Soc.*, **84**, 1220 (1962).
111. R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 4141 (1962).
112. K. J. Crowley, *Tetrahedron*, **21**, 1001 (1965).

113. L. A. Paquette, S. E. Wilson, R. P. Henzel and G. R. Allen Jr., *J. Am. Chem. Soc.*, **94**, 7761 (1972).
114. (a) G. Zon and L. A. Paquette, *J. Am. Chem. Soc.*, **96**, 215 (1974).
(b) L. A. Paquette and G. Zou, *J. Am. Chem. Soc.*, **96**, 224 (1974).
115. P. G. Gassman and T. J. Atkins, *J. Am. Chem. Soc.*, **94**, 7748 (1972).
116. W. H. Laarhoven, *Org. Photochem.*, **9**, 129 (1987).
117. K. Shudo and T. Okamoto, *Chem. Pharm. Bull.*, **22**, 1204 (1974).
118. J. F. W. Keana and R. H. Morse, *Tetrahedron Lett.*, 2113 (1976).
119. K. Sato, H. Hagiwara, H. Uda, M. Sato and N. Harada, *J. Am. Chem. Soc.*, **98**, 8281 (1976).
120. J. W. Pavlik and C. A. Seymour, *Tetrahedron Lett.*, 2555 (1977).
121. H. Hart, C.-T. Peng and E.-M. Shih, *J. Org. Chem.*, **42**, 3635 (1977).
122. Y. Daino, S. Hagiwara, T. Hakushi, Y. Inoue and A. Tai, *J. Chem. Soc., Perkin Trans. 2*, 275 (1989).
123. R. S. H. Liu, *J. Am. Chem. Soc.*, **89**, 112 (1967).
124. K. M. Shumate and G. J. Fonken, *J. Am. Chem. Soc.*, **88**, 1073 (1966).
125. J. Saltiel, G. R. Marchand and R. Bonneau, *J. Photochem.*, **28**, 367 (1985).
126. G. D. Andrews, M. Davalt and J. E. Baldwin, *J. Am. Chem. Soc.*, **95**, 5044 (1973).
127. B. H. O. Cook, A. A. Asim and W. J. Leigh, unpublished results (1999).
128. W. G. Dauben, M. S. Kellogg, J. I. Seeman, N. D. Vietmeyer and P. H. Wendschuh, *Pure Appl. Chem.*, **33**, 197 (1973).
129. H. J. C. Jacobs and E. Havinga, *Adv. Photochem.*, **11**, 305 (1979).
130. W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **81**, 4060 (1959).
131. A. M. Bloothoofd–Kruisbeek and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, **91**, 1364 (1972).
132. G. S. Hammond, P. A. Leermakers and N. J. Turro, *J. Am. Chem. Soc.*, **83**, 2396 (1961).
133. A. Padwa, in *Rearrangements in Ground and Excited States* (Ed. P. De Mayo), Academic Press, New York, 1980, pp. 501–547.
134. A. Lablache–Combier, in *Photochemistry of Heterocyclic Compounds* (Ed. O. Buchard), Wiley, New York, 1976, pp. 123.
135. R. M. El–Shishtawy, K. Fukunishi and S. Miki, *Tetrahedron Lett.*, **36**, 3177 (1995).
136. G. Maier, U. Schafer, W. Sauer and H. Hartan, *Tetrahedron Lett.*, 1837 (1978).
137. D. Giacherio and H. Morrison, *J. Am. Chem. Soc.*, **100**, 7109 (1978).
138. H. Morrison, D. Giacherio and F. J. Palensky, *J. Org. Chem.*, **47**, 1051 (1982).
139. F. J. Palensky and H. Morrison, *J. Am. Chem. Soc.*, **99**, 3507 (1977).
140. S. Boue, D. Rondelez and P. Vanderlinden, in *Excited States in Organic Chemistry and Biochemistry* (Eds. B. Pullman and N. Goldblum), D. Reidel, Dordrecht, 1977, 199.
141. R. Srinivasan, *Adv. Photochem.*, **4**, 113 (1966).
142. S. Boue and R. Srinivasan, *Mol. Photochem.*, **4**, 93 (1972).
143. O. Grummitt and F. J. Christoph, *J. Am. Chem. Soc.*, **73**, 3479 (1951).
144. M. Pomerantz and G. W. Gruber, *J. Am. Chem. Soc.*, **93**, 6615 (1971).
145. P. J. Baldry, *J. Chem. Soc., Perkin Trans. 2*, 805 (1980).
146. E. H. White and J. P. Anhalt, *Tetrahedron Lett.*, 3937 (1965).
147. G. J. Fonken, *Chem. Ind.*, 1327 (1962).
148. W. Adam, M. Sauter and C. Zunkler, *Chem. Ber.*, **127**, 1115 (1994).
149. H. Meier and P. Konig, *Nouv. J. Chim.*, **10**, 437 (1986).
150. M. Zheng, K. J. DiRico, M. M. Kirchhoff, K. M. Phillips, L. M. Cuff and R. P. Johnson, *J. Am. Chem. Soc.*, **115**, 12167 (1993).
151. F. Bernardi, S. De, M. Olivucci and M. A. Robb, *J. Am. Chem. Soc.*, **112**, 1737 (1990).
152. W. J. Leigh and K. B. Clark, *J. Am. Chem. Soc.*, **109**, 6086 (1987).
153. P. C. Venneri, J. A. Postigo and W. J. Leigh, *J. Am. Chem. Soc.*, **117**, 7826 (1995).
154. W. J. Leigh and B. H. O. Cook, *J. Org. Chem.*, **64**, 5256 (1999).
155. W. G. Dauben and F. G. Willey, *Tetrahedron Lett.*, 893 (1962).
156. R. Srinivasan, *J. Am. Chem. Soc.*, **85**, 4045 (1963).
157. D. M. Gale, *J. Org. Chem.*, **35**, 970 (1970).
158. H. Hopf, H. Lipka and M. Traetteberg, *Angew. Chem., Int. Ed. Engl.*, **33**, 204 (1994).
159. W. R. Roth, O. Adamczak, R. Breuckmann, H. W. Lennartz and R. Boese, *Chem. Ber.*, **124**, 2499 (1991).
160. G. Maier, *Angew. Chem., Int. Ed. Engl.*, **27**, 309 (1988).

161. G. Maier, D. Born, I. Bauer, R. Boese and D. Cremer, *Chem. Ber.*, **127**, 173 (1994).
162. G. Maier, R. Wolf, H. O. Kalinowski and R. Boese, *Chem. Ber.*, **127**, 191 (1994).
163. G. Maier, R. Wolf and H. O. Kalinowski, *Chem. Ber.*, **127**, 201 (1994).
164. M. Mousseron–Canet, M. Mousseron and P. Legendre, *Bull. Chem. Soc. Fr.*, 50 (1964).
165. E. F. Kiefer and C. H. Tanna, *J. Am. Chem. Soc.*, **91**, 4478 (1969).
166. M. Mousseron, *Adv. Photochem.*, **4**, 195 (1966).
167. V. Ramamurthy and R. S. H. Liu, *J. Org. Chem.*, **41**, 1862 (1975).
168. F. W. A. M. Miesen, H. C. N. Baeten, H. A. Langermans, L. H. Koole and H. A. Claessens, *Can. J. Chem.*, **69**, 1554 (1991).
169. G. J. Fonken, *Tetrahedron Lett.*, 549 (1962).
170. W. H. Laarhoven and H. J. C. Jacobs in *CRC Handbook of Organic Photochemistry and Biology* (Ed. W. Horspool), CRC Press, Boca Raton, 1996, pp. 143–154.
171. H. J. C. Jacobs and W. H. Laarhoven, in *CRC Handbook of Organic Photochemistry and Biology* (Ed. W. Horspool), CRC Press, Boca Raton, 1995, 155–164.
172. W. G. Dauben, E. L. McInnis and D. M. Michno in *Rearrangements in Ground and Excited States* (Ed. P. De Mayo), Academic Press, New York, 1980, pp. 91–129.
173. G. J. Fonken, *Org. Photochem.*, **1**, 197 (1963).
174. R. Srinivasan, *Adv. Photochem.*, **4**, 113 (1966).
175. W. H. Laarhoven, in *Photochromism: Molecules and Systems* (Eds. H. Durr and H. Bouas–Laurent), Elsevier, New York, 1990, pp. 270–313.
176. R. Srinivasan, *J. Chem. Phys.*, **38**, 1039 (1963).
177. Y. L. Bahurel, D. J. MacGregor, T. L. Penner and G. S. Hammond, *J. Am. Chem. Soc.*, **94**, 637 (1972).
178. P. Courtot and R. Rumin, *Bull. Chem. Soc. Fr.*, 3665 (1969).
179. P. Courtot and R. Rumin, *Bull. Soc. Chim. Fr.*, 4238 (1972).
180. U. Weiss, W. B. Whalley and I. L. Karle, *J. Chem. Soc., Chem. Commun.*, 16 (1972).
181. W. G. Dauben and R. M. Coates, *J. Am. Chem. Soc.*, **86**, 2490 (1964).
182. W. G. Dauben and R. M. Coates, *J. Org. Chem.*, **29**, 2761 (1964).
183. Y. Kobayashi, I. Kumadaki, A. Oshawa, Y. Hanzawa, M. Honda and W. Miyashita, *Tetrahedron Lett.*, 1795 (1977).
184. R. N. Warrener, E. E. Nunn and M. N. Paddon–Row, *Tetrahedron Lett.*, **30**, 2639 (1976).
185. W. R. Dolbier Jr. and K. W. Palmer, *Tetrahedron Lett.*, **34**, 6201 (1993).
186. J. E. Baldwin and S. M. Krueger, *J. Am. Chem. Soc.*, **91**, 6444 (1969).
187. R. J. De Kock, N. G. Minnaard and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **79**, 922 (1960).
188. P. Courtot, R. Rumin and J.-Y. Salaun, *Pure Appl. Chem.*, **49**, 317 (1977).
189. C. W. Spangler and R. P. Hennis, *J. Chem. Soc., Chem. Commun.*, 24 (1972).
190. P. Courtot and J.-Y. Salaun, *J. Chem. Soc., Chem. Commun.*, 124 (1976).
191. P. Courtot, R. Rumin and J.-Y. Salaun, *Recl. Trav. Chim. Pays-Bas*, **98**, 192 (1979).
192. P. Courtot and J.-Y. Salaun, *Tetrahedron Lett.*, **21**, 1851 (1979).
193. K. J. Crowley, *J. Org. Chem.*, **33**, 3679 (1968).
194. V. Ramamurthy and R. S. H. Liu, *Tetrahedron Lett.*, 1393 (1973).
195. W. G. Dauben and M. S. Kellogg, *J. Am. Chem. Soc.*, **102**, 4456 (1980).
196. D. H. R. Barton, S. K. Chung and T. W. Kwon, *Tetrahedron Lett.*, **37**, 3631 (1996).
197. D. H. R. Barton, S. K. Chung, Y. M. Kim and T. W. Kwon, *Biorg. Med. Chem. Lett.*, **7**, 733 (1997).
198. P. J. Reid, M. K. Lawless, S. D. Wickham and R. A. Mathies, *J. Phys. Chem.*, **98**, 5597 (1994).
199. S. Pullen, L. A. Walker II., B. Donovan and R. J. Sension, *Chem. Phys. Lett.*, **242**, 415 (1995).
200. W. Fuss, K. L. Kompa, T. Schikarski, W. E. Schmid and S. A. Trushin, *SPIE*, **3271**, 114 (1998).
201. S. A. Trushin, W. Fuss, T. Schikarski, W. E. Schmid and K. L. Kompa, *J. Chem. Phys.*, **106**, 9386 (1997).
202. W. Fuss, T. Schikarski, W. E. Schmid, S. A. Trushin and K. L. Kompa, *Chem. Phys. Lett.*, **262**, 675 (1996).
203. P. E. Share, K. L. Kompa, S. D. Peyerimhoff and M. C. van Hemert, *Chem. Phys.*, **120**, 411 (1988).
204. P. Celani, S. Ottani, M. Olivucci, F. Bernardi and M. A. Robb, *J. Am. Chem. Soc.*, **116**, 10141 (1994).

205. P. Celani, F. Bernardi, M. A. Robb and M. Olivucci, *J. Phys. Chem.*, **100**, 19364 (1996).
206. M. Garavelli, P. Celani, M. Fato, M. J. Bearpark, B. R. Smith, M. Olivucci and M. A. Robb, *J. Phys. Chem. A*, **101**, 2023 (1997).
207. E. Havinga, *Experientia*, **29**, 1181 (1973).
208. J. M. G. Bonfrer, H. J. C. Jacobs and E. Havinga, *Tetrahedron Lett.*, **43**, 3741 (1975).
209. P. Hinrich, J. A. van der Hart and H. J. C. Jacobs, *J. Photochem. Photobiol. A, Chem.*, **80**, 121 (1994).
210. P. Courtot and R. Rumin, *Tetrahedron*, **32**, 441 (1976).
211. R. Srinivasan, *J. Am. Chem. Soc.*, **83**, 2806 (1961).
212. S. W. Orchard and B. A. Thrush, *Proc. Chem. Soc. (London)*, **337**, 257 (1974).
213. S. W. Orchard and B. A. Thrush, *Proc. Chem. Soc. (London)*, **337**, 243 (1974).
214. J. Meinwald and P. H. Mazzocchi, *J. Am. Chem. Soc.*, **88**, 2850 (1966).
215. P. J. Vroegop, J. Lugtenburg and E. Havinga, *Tetrahedron*, **29**, 1393 (1973).
216. J. W. J. Gielen, H. J. C. Jacobs and E. Havinga, *Tetrahedron Lett.*, 3751 (1976).
217. W. G. Dauben, J. Rabinowitz, N. D. Vietmeyer and P. H. Wendschuh, *J. Am. Chem. Soc.*, **94**, 4285 (1972).
218. A. M. Brouwer, L. Bezemer, J. Cornelisse and H. J. C. Jacobs, *Recl. Trav. Chim. Pays-Bas*, **106**, 613 (1987).
219. A. M. Brouwer, J. Cornelisse and H. J. C. Jacobs, *Tetrahedron*, 435 (1987).
220. W. G. Dauben, B. Disanayaka, D. J. H. Funhoff, B. E. Kohler, D. F. Schilke and B. Zhou, *J. Am. Chem. Soc.*, **113**, 8367 (1991).
221. A. Padwa, L. Brodsky and S. Clough, *J. Am. Chem. Soc.*, **94**, 6767 (1972).
222. W. G. Dauben and M. S. Kellogg, *J. Am. Chem. Soc.*, **94**, 8951 (1972).
223. K. Tanaka and K. Fukui, *Bull. Chem. Soc. Jpn.*, **51**, 2209 (1978).
224. A. ten Wolde, H. P. J. M. Dekkers and H. J. C. Jacobs, *Tetrahedron*, **49**, 6045 (1993).
225. P. P. Andersson, T. Gillbro, A. Asato and R. S. H. Liu, *Chem. Phys. Lett.*, **235**, 76 (1995).
226. H. J. C. Jacobs, *Pure Appl. Chem.*, **67**, 63 (1995).
227. H. J. C. Jacobs, J. W. J. Gielen and E. Havinga, *Tetrahedron Lett.*, **22**, 4013 (1981).
228. W. G. Dauben and R. B. Phillips, *J. Am. Chem. Soc.*, **104**, 5780 (1982).
229. M. Braun, W. Fuss, K. L. Kompa and J. Wolfrum, *J. Photochem. Photobiol. A, Chem.*, **61**, 15 (1991).
230. P. A. Maessen, H. J. C. Jacobs, J. Cornelisse and E. Havinga, *Angew. Chem., Int. Ed. Engl.*, **22**, 718 (1983).
231. W. Fuss and S. Lochbrunner, *J. Photochem. Photobiol. A, Chem.*, **105**, 159 (1997).
232. F. Bernardi, M. Olivucci, I. N. Ragazos and M. A. Robb, *J. Am. Chem. Soc.*, **114**, 8211 (1992).
233. R. B. Koolstra, J. Cornelisse and H. J. C. Jacobs, *Recl. Trav. Chim. Pays-Bas*, **106**, 526 (1987).
234. S. Yamada, H. Ishizaka, H. Ishida and K. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 423 (1995).
235. V. A. Pichko, B. Ya. Simkin and V. I. Minkin, *J. Org. Chem.*, **57**, 7087 (1992).
236. R. C. Cookson, S. M. deB. Costa and J. Hudec, *J. Chem. Soc., Chem. Commun.*, 1272 (1969).
237. K. Salisbury, *Tetrahedron Lett.*, 737 (1971).
238. H. Kleinhuis, R. L. C. Witjing and E. Havinga, *Tetrahedron Lett.*, 255 (1971).
239. H. Heimgartner, L. Ulrich, H.-J. Hansen and H. Schmid, *Helv. Chim. Acta*, **54**, 2313 (1971).
240. U. Widmer, H. Heimgartner and H. Schmid, *Helv. Chim. Acta*, **58**, 2210 (1975).
241. J. Whittal, in *Photochromism: Molecules and Systems* (Eds. H. Durr and H. Bouas–Laurent), Elsevier, New York, 1990, pp. 467–492.
242. H. Stobbe, *Chem. Ber.*, **37**, 2236 (1904).
243. R. J. Hart and H. G. Heller, *J. Chem. Soc., Perkin Trans. 1*, 1321 (1972).
244. H. G. Heller, in *Fine Chemicals for the Electronics Industry* (Ed. P. Bamfield), CRC Press, Boca Raton, 1987, p. 120.
245. H. G. Heller and J. R. Langan, *J. Chem. Soc., Perkin Trans. 2*, 341 (1981).
246. V. Wintgens, L. J. Johnston and J. C. Scaiano, *J. Am. Chem. Soc.*, **110**, 511 (1988).
247. (a) H. G. Heller, C. C. Elliot, K. Koh, S. Al-Shihry and J. Whittal, in *Photochemistry and Polymeric Systems* (Eds. J. M. Kelly, C. B. McArdle and M. J. deF. Maunder), The Royal Society of Chemistry, Cambridge, 1993, pp. 156–168.

(b) H. G. Heller, in *CRC Handbook of Organic Photochemistry and Photobiology* (Ed. W. Horspool), CRC Press, Boca Raton, 1995, pp. 173.
248. S. Z. Janicki and G. B. Schuster, *J. Am. Chem. Soc.*, **117**, 8524 (1995).
249. Y. Yokoyama, K. Ogawa, T. Iwai, K. Shimazaki, Y. Kajihara, T. Goto, Y. Yokoyama and Y. Kurita, *Bull. Chem. Soc. Jpn.*, **69**, 1605 (1996).
250. H. G. Heller, K. S. V. Koh, M. Kose and N. Rowles, in *Colour Science '98. Proceedings of the CIBA Specialty Chemicals Symposium* (Ed. J. Griffiths), 1998, pp. 147–156.
251. F. B. Mallory and C. W. Mallory, *Org. React.*, **30**, 1 (1984).
252. H. Gorner and H. J. Kuhn, *Adv. Photochem.*, **19**, 1 (1995).
253. K. Uchida, S. Nakamura and M. Irie, *Res. Chem. Intermed.*, **21**, 861 (1995).
254. K. Uchida and M. Irie, *Chem. Lett.*, 969 (1995).
255. M. Irie, O. Miyatake, K. Uchida and T. Eriguchi, *J. Am. Chem. Soc.*, **116**, 9894 (1994).
256. M. Irie, K. Sakemura, M. Okinaka and K. Uchida, *J. Org. Chem.*, **60**, 8305 (1995).
257. N. Tamai, T. Saika, T. Shimidzu and M. Irie, *J. Phys. Chem.*, **100**, 4689 (1996).
258. M. Irie, T. Lifka, K. Uchida, S. Kobatake and Y. Shindo, *J. Chem. Soc., Chem. Commun.*, 747 (1999).
259. M. Irie and K. Uchida, *Bull. Chem. Soc. Jpn.*, **71**, 985 (1998).
260. W. G. Dauben and R. L. Cargill, *Tetrahedron*, **12**, 186 (1961).
261. B. A. Thrush and J. J. Zwolenik, *Bull. Soc. Chim. Belg.*, **71**, 642 (1962).
262. A. P. T. Borg and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **84**, 241 (1965).
263. A. P. T. Borg and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **88**, 266 (1969).
264. S. H. Luu and J. Troe, *Ber. Bunsenges. Phys. Chem.*, **77**, 325 (1973).
265. V. C. Freestone and A. A. Gorman, *Tetrahedron Lett.*, 3389 (1977).
266. W. Paulick, W. Abraham, C. Jung and D. Kreysig, *Mol. Photochem.*, **9**, 443 (1979).
267. O. L. Chapman and G. W. Borden, *Proc. Chem. Soc. (London)*, 221 (1963).
268. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **2**, 688, (1963).
269. R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 3432 (1962).
270. U. Samuni, S. Kahana and Y. Haas, *J. Phys. Chem.*, **102**, 4758 (1998).
271. H. Hippler, K. Luther, J. Troe and R. Walsh, *J. Chem. Phys.*, **68**, 323 (1978).
272. J. Benzier, S. Linkersdorfer and K. Luther, *J. Chem. Phys.*, **106**, 4992 (1997).
273. H. Hippler and J. Troe, in *Bimolecular Collisions* (Eds. M. N. R. Ashfold and J. E. Baggott), Royal Society of Chemistry, London, 1986, pp. 209–262.
274. G.-Y. Chung and R. W. Carr, *J. Phys. Chem.*, **91**, 2831 (1987).
275. P. M. Borell, H. G. Lohmannsroben and K. Luther, *Chem. Phys. Lett.*, **136**, 371 (1987).
276. R. J. Olsen, J. C. Minniear, W. M. Overton and J. M. Sherrick, *J. Org. Chem.*, **56**, 989 (1991).
277. P. J. Reid, A. P. Shreve and R. A. Mathies, *J. Phys. Chem.*, **97**, 12691 (1993).
278. F. Bernardi, M. Olivucci, J. Michl and M. A. Robb, *Spectrum*, **9**, 1 (1996).
279. J. Zirner and S. Winstein, *Proc. Chem. Soc. (London)*, 235 (1964).
280. W. R. Roth and B. Peltzer, *Angew. Chem., Int. Ed. Engl.*, **3**, 440 (1964).
281. O. L. Chapman, G. W. Borden, R. W. King and B. Winkler, *J. Am. Chem. Soc.*, **86**, 2660 (1964).
282. T. D. Goldfarb and L. Lindqvist, *J. Am. Chem. Soc.*, **89**, 4588 (1967).

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CHAPTER **4**

Photochemistry of non-conjugated dienes

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I. INTRODUCTION

Photochemistry in the area of non-conjugated dienes has burgeoned over the past decade or so and many topics of interest appear under this general heading. Obviously, such a chapter cannot be encyclopaedic and therefore some selection of areas to be covered has been made. In addition, a choice has been made in the time covered. The general area of diene photochemistry under review here has been of interest practically since the re-awakening of interest in organic photochemistry. Thus there is at least forty years of modern study. An excellent compendium was published more than thirty years ago by Schönberg[1]. This dealt with photochemical reactions in general but includes many examples related to the non-conjugated dienes. The subject matter is also covered to some extent in most of the standard texts dealing with organic photochemistry[2] and also in specialized texts[3]. In the last thirty years there have also been useful annual compendia of photochemical results and advances and these have provided an extensive source of references[4]. In addition, there are some general reviews from the earlier periods which are also of value[5,6].

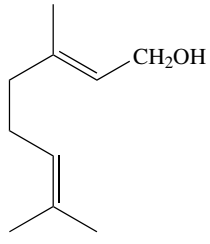
II. ELECTRON TRANSFER REACTIONS

A. Acyclic and Cyclic Dienes

There are a variety of photochemical reactions that non-conjugated dienes can undergo. One of these that is currently of considerable interest is the reactivity brought about by electron-accepting sensitizers such as the cyanoarenes. The photoreactivity of these systems involves the photochemical excitation of the sensitizer to an excited state[7]. Thereafter, the reactivity is dependent on the ease of oxidation of the alkene or diene. With the transfer of an electron from the diene to the photoexcited sensitizer a radical cation is formed. It is this intermediate that brings about the various processes which occur within the diene systems under investigation.

There are many examples of such reactivity and some of these have been reviewed by Roth and coworkers[8], a research group that is extremely active in this area. An example that is typical of the processes encountered involves the cyclization of the diene geraniol (**1**). In this case the sensitizer is 9,10-dicyanoanthracene (DCA) and the reactions are carried out in methylene chloride. The authors[9] state that a contact radical-ion pair is involved, i.e. the radical cation of the diene is in close proximity to the radical anion of the DCA. Reaction within this yields the cyclopentane derivatives **2** and **3** in the yields shown. The ring formation is the result of a five centre CC cyclization within the radical cation of **1**. When a more powerful oxidant such as *p*-dicyanobenzene is used as the sensitizer in acetonitrile as solvent, separated radical-ion pairs are involved. This leads to intramolecular trapping and the formation of the bicyclic ethers **4** and **5**[9]. The bicyclic ether incorporates an aryl group by reaction of the radical cation of the diene with the radical anion of the sensitizer (DCB). This type of reactivity is referred to later. Other naturally occurring compounds such as (*R*)-(+)-α-terpineol **(6)** and (*R*)-(+)-limonene **(7)**

can also be converted into the corresponding radical cations using *p*-dicyanobenzene (DCB) as the electron-accepting sensitizer[10]. Cyclizations can also be brought about with tetraenes such as **8** under SET conditions in aqueous acetonitrile solution. A variety of electron-accepting sensitizers was used but 1,4-dicyano-2,3,5,6-tetramethylbenzene was found to be especially effective. The radical cation formed from **8** undergoes a cascade cyclization to yield the product **9**[11].



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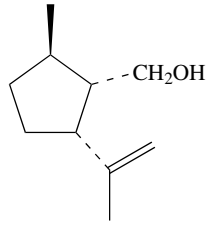

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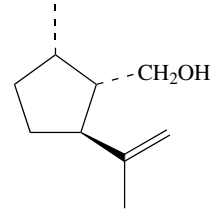

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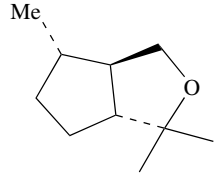

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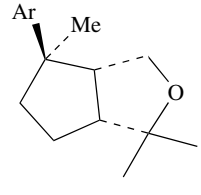
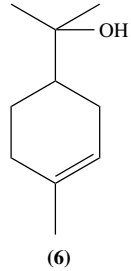


(5)

Ar = *p*-NCC_6H_4



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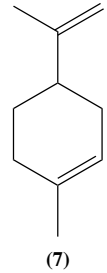

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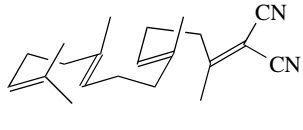

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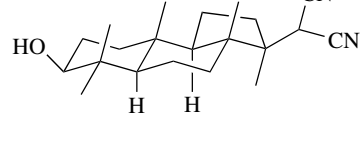
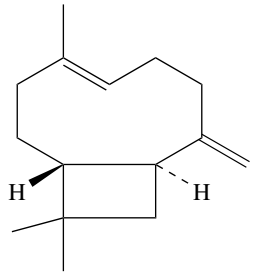
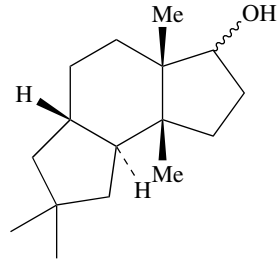


(9)

The radical cations of diene systems in cyclic molecules are also capable of reaction as demonstrated by Demuth, Roth and their coworkers[12]. They have studied the influence of phase on the photochemical reactivity of some naturally occurring dienes. Thus the irradiation of the diene **10** in homogeneous solution (acetonitrile/water) in the presence of an electron-accepting sensitizer such as cyanonaphthalene (CN) or DCB brings about *trans*,*cis*-isomerization only. However, when the electron transfer reaction is carried out in the presence of sodium dodecyl sulphate, transannular hydrogen abstraction reactions yield the two products **11** and **12**. Similar reactivity is observed with *trans*-geranyl acetate **13** and all-*trans*-farnesyl acetate **14**. The authors[12] report that these cyclizations are the first examples of biomimetic processes brought about under SET conditions.



(10)



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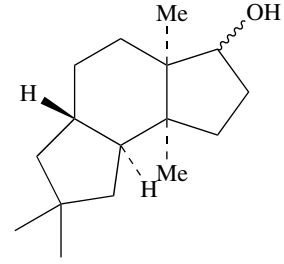
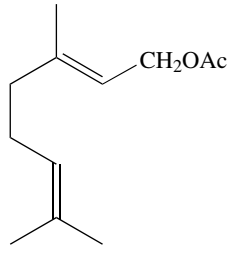
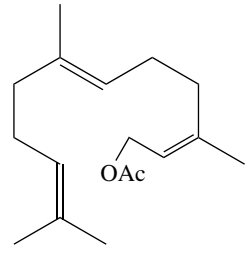


(12)

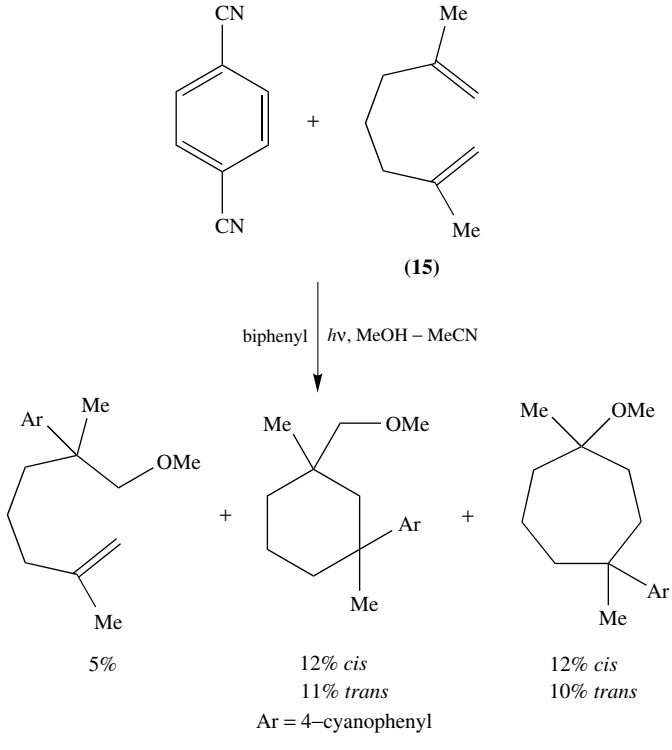


(13)



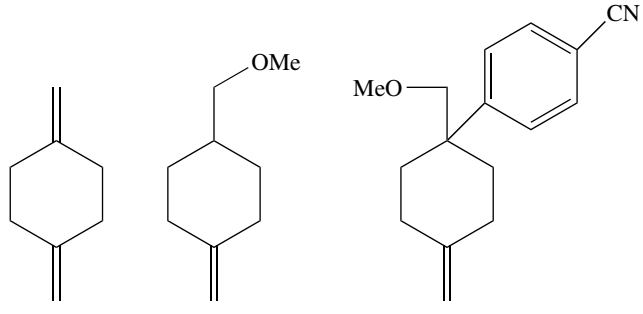
(14)

In some instances the intermediate radical cations formed from non-conjugated dienes undergo addition to the cyanoarene sensitizer. Such reactions involve the replacement of a cyano group on the arene by the diene moiety. These reactions have been termed photo-NOCAS (photochemical Nucleophile–olefin combination, Aromatic substitution) processes. Such behaviour is observed with the 2,6-dimethylhepta-1,6-diene **15**. When this is irradiated in methanol solution under electron-transfer conditions with DCB as the electron-accepting sensitizer and biphenyl as the co-sensitizer, the products (obtained in low yields) formed from this treatment are shown in Scheme 1. In this there are three distinct reaction types, each involving combination between the diene, MeOH and the sensitizer. These reaction types are addition of MeOH to the open chain system, cyclization to a cyclohexane product and cyclization to a cycloheptane[13]. Considerable effort has been expended on the study of the photo-NOCAS processes and Arnold and his coworkers have supplied details of the factors that control the regiochemistry[14]. As can be seen, reaction with an alkene moiety is quite common and is also illustrated for the diene **16**. In this molecule cyclization of the radical cation is unlikely and all the reactions

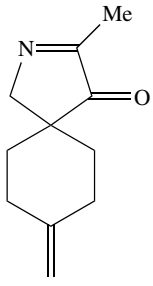


SCHEME 1

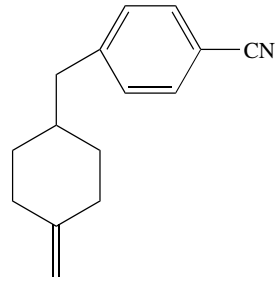
encountered involve addition to an alkene group. The reaction is again carried out in methanol with DCB as the sensitizer and biphenyl as the co-sensitizer. This treatment gives low yields of **17** and **18** by trapping of the radical cation of the diene **16** by methanol[15]. In acetonitrile as solvent, many products are formed such as **19** and **20** by reaction with the solvent acetonitrile or the sensitizer, respectively.



(16) **(17)** 3% **(18)** 20%

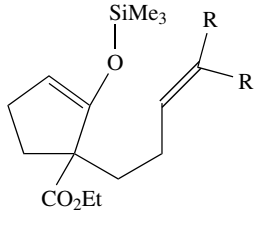


(**19**) 2%

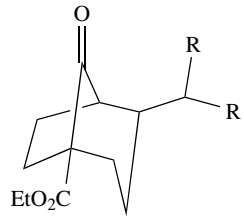


(**20**) 2%

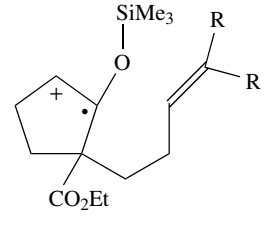
The synthetic application of SET processes is also of considerable interest since viable synthetic routes to a variety of molecules can be devised. For example, Heidbreder and Mattay[16] have shown that silyl derivatives of enols can undergo cyclization following radical cation formation. Irradiation at 450 nm of **21** in acetonitrile using DCA as the electron-accepting sensitizer ultimately brings about the formation of bicyclic compounds **22**. The process involves cyclization within the radical cation **23**. Several other examples of this type of cyclization have been reported, again using the same reaction conditions. This has helped to demonstrate the scope of the process. Thus the parent system **24**, R = H, affords the cyclic ketone **25** in 25% yield. The effect of chain length and substituents on the reaction has also been evaluated. Thus **24**, R = Me, is converted into the mixture of isomers **26** while **27** affords **28**. Tricyclic products such as **29** can also be obtained in moderate yields from the cyclization of **30**. The basic reaction of **24** is solvent-sensitive. This is demonstrated by the formation of three products when the reaction is carried out in acetonitrile/propan-2-ol. These were identified as the original product (**25**, 30%) and two minor products **31** formed in 11% and **32** formed in 9%[17].



(21) **(a)** R = H
(b) R = Me

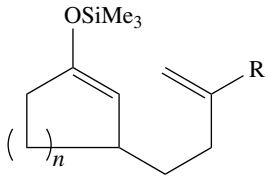


(22) **(a)** 24%
(b) 59%



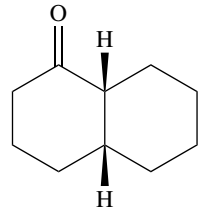
(23)

The presence of hetero-atoms within the system, remote from the alkene double bonds, does not have an adverse influence on the SET processes that occur. Thus irradiation of the diene **33** in benzene solution with 1,4-dicyanonaphthalene as the electron-transfer sensitizer affords the cyclobutane **34** in 78% yield. Various examples of the reaction were described giving cyclobutane derivatives in 54–69% yield. Benzene, or an arene solvent, is vital for the success of the reaction. When acetonitrile is used, allylation of the sensitizer (akin to the photo-NOCAS reaction) results in the formation of the three products **35**–**37**[18]. (2 + 2)-Cyclization of this type described for **33** is also seen with the dialkenyl ether **38**. When **38** is irradiated using $\lambda > 350$ nm or $\lambda > 450$ nm in acetonitrile

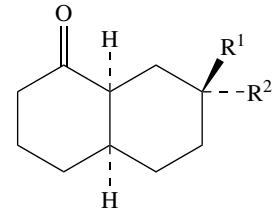


(24) $n = 2$

(27) $n = 1$, R = H

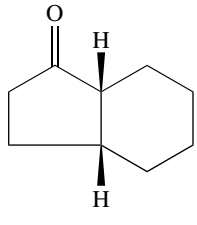


(25)

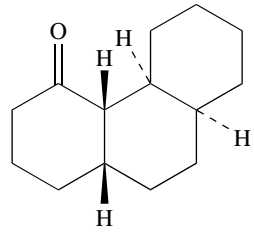


(26)

R^1	R^2	
Me	H	9%
H	Me	11%



(28)



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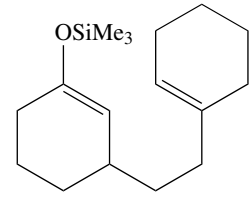

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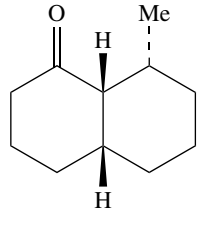

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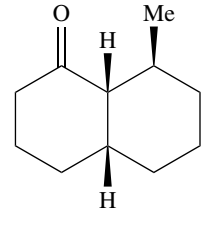
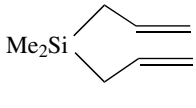
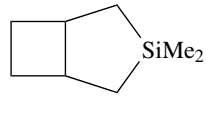


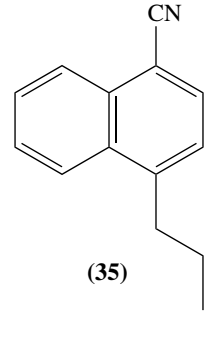
(32)



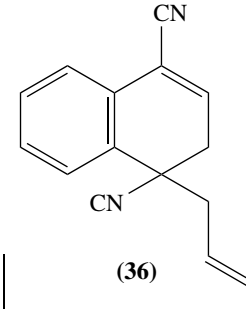
(33)



(34)

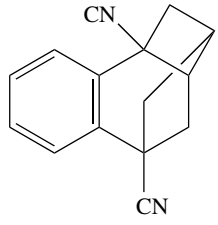


(35)

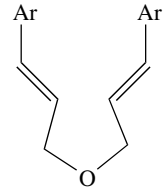


(36)

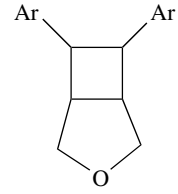
solution with tetracyanoethylene as the electron-accepting sensitizer, the product **39** is obtained. Again a radical cation cyclization is proposed to account for this[19].



(37)



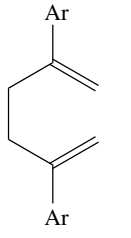
(38)



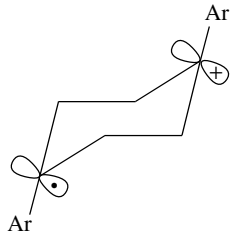
(39)

Ar = 4-$MeOC_6H_4$

A study of the photochemical Cope reaction of the hexadienes **40** has been carried out under photoinduced electron-transfer conditions. Evidence was gathered for the formation of a chair cyclohexane-1,4-radical cation **41**[20]. In such systems, where the radical cation is formed using DCA as the sensitizer, a degenerate Cope process is operative. Thus when the tetradeuterio derivative **42** is used, rearrangement affords a (52 : 48) mixture of the two dienes **42** and **43**[21]. Related to this general problem, DCA-sensitized reactions of the isomeric dienes **44** and *E*,*E*-**45** and the cyclization product, the bicyclohexane **46**, have been studied in considerable detail[22]. At low conversions, the irradiation of **46** affords a mixture of the dienes **44** and *E*,*E*-**45** in ratios that are independent of temperature. The influence of the position of the aryl groups on the diene skeleton has also been studied. This does not appear to affect the conversion to a cyclic radical cation. Thus the SET-induced reaction of the diene **47** has shown that the open chain radical cation of the diene **48** cyclizes preferentially to the radical cation **49**[23].

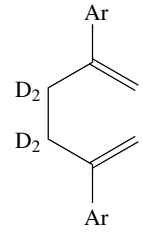


(**40**)

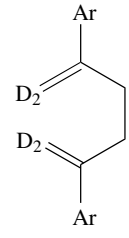


(**41**)

Ar = *p*-$MeOC_6H_4$

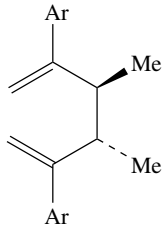


(**42**)

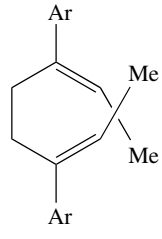


(**43**)

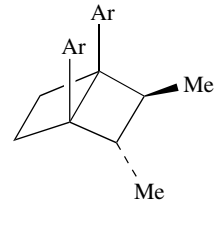
Ar = 4-XC_6H_4
X = OMe, Me, Cl



(**44**)

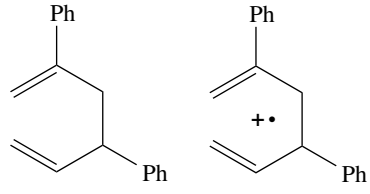


(**45**)



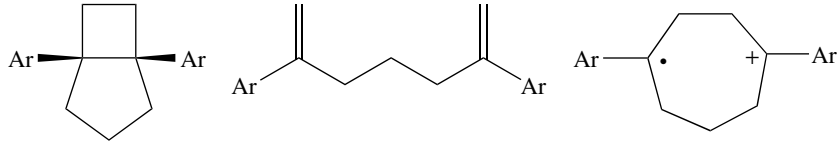
(**46**)

Ar = 4-$MeOC_6H_4$



(47) **(48)** **(49)** * = + or •

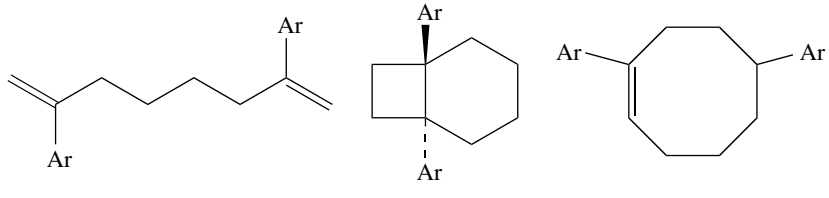
Cyclization of the type that leads to the formation of **46** from **44** and **45** is also observed with a longer insulator between the two alkene components of the non-conjugated diene. Thus the cyclobutane derivatives **50** can be formed from the dienes **51**. Again a radical cation **52** is formed from **51** using SET to DCA. This provides an efficient path to the bicyclic compounds **50**[24]. Griesbeck and coworkers[25] have also reported on the cyclization of **51**. In addition, they have examined the reactions encountered with the dienes **53** where cyclization to the bicyclo[4.2.0]octane system **54** takes place via the radical cation. The cyclization in these molecules is not quite as efficient as in the previous examples. The head:head product, i.e. the cyclooctenes **55**, are formed in competition with the other process. A further study of these cyclizations has examined the influence of solvent on the conversion of **56** into the two products **57** and **58**. The mechanism proposed again utilizes a cyclic radical cation as intermediate and this has been substantiated by trapping experiments with oxygen[26]. Further study has examined the influence of an alkyl substituent on one of the double bonds of the dienes **59** and **60**. Stereoselective intramolecular (2 + 2)-cycloadditions occurred on DCA sensitization, yielding the *endo* and *exo* bicycloheptanes **61** and **62**, respectively. Although the reactions with the *E*-isomer **59** appeared not to be stereoselective, this effect was found to be time-dependent and shorter irradiation times gave better selectivity[27].



(50) yield (%)
53
80
76

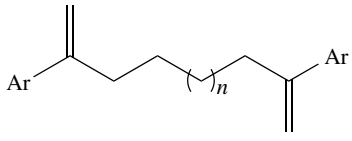
(51) Ar = 4-$MeOC_6H_4$
Ar = 4-MeC_6H_4
Ar = Ph

(52)



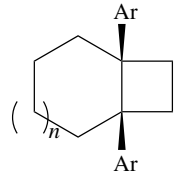
(53) **(54)** **(55)**

Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$

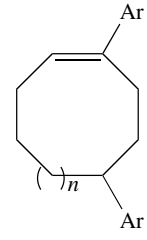


(56)

n = 1 or 2, Ar = 4-$MeOC_6H_4$ or Ph

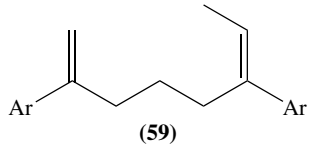


(57)



(58)

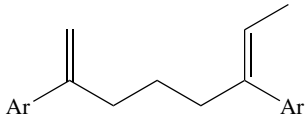
		yield (%)	Solvent
n = 1 a	0	86	MeCN
a	65	31	C_6H_6
b	58	24	MeCN
n = 2 a	0	9	MeCN
b	10	21	MeCN



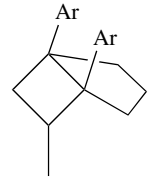
(59)

(a) R = 4-$MeOC_6H_4$

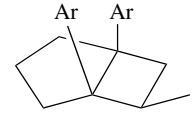
(b) Ar = Ph



(60)



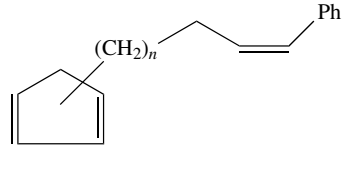
(61)



(62)

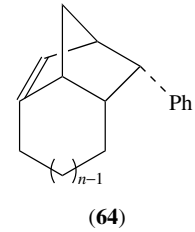
	61	**62**		
$E_{a'}$	65	0	ratio *endo*: *exo*	0
$E_{b'}$	70	0		0
$Z_{a'}$	27	45		1 : 1.7
$Z_{b'}$	32	34		1 : 1.7

Yoon and Chae[28] have described the DCA-induced photochemical conversion of the cyclopentadiene derivatives **63** into several products. However, only the *anti*-Bredt adduct **64** is different from those obtained by thermal activation. The experimental data collected have implicated a triplex intermediate **65** in the formation of **64**. This triplex is the result of interaction between the diene, the non-conjugated alkene component and the sensitizer. While a mixture of cyclopentadienes was used, it is likely that the products **64** are formed exclusively from the 2-isomer **66**.



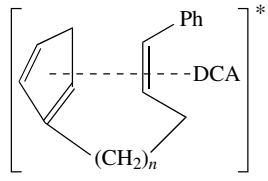
(63)

n = 2 or 3

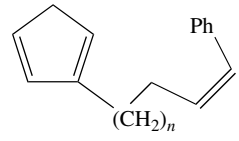


(64)

n = 2	12%
n = 3	13%

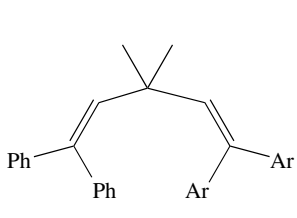


(**65**)



(**66**)

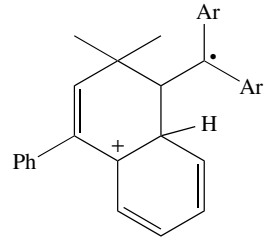
Zimmerman and Hofacker[29] have studied the photochemically induced SET reactivity (using DCA or DCN) of the heavily arylated 1,4-dienes **67**. The radical cations formed by this treatment undergo regioselective cyclization to the cyclic radical cation **68** that ultimately affords the final products **69**. Other dienes with 1,1-diphenyl substituents are also reactive. Thus 1,1-diphenylhepta-1,6-diene **(70)** can be converted into its radical cation **(71)**. This cyclizes under attack from the solvent acetonitrile (or propionitrile) via the six-membered transition state shown in **72**. This affords the adduct **73**. Cyclization of the radical cation is not exclusive and trapping by adventitious water, affording the alcohol **74**, takes pace in competition. The length of the chain linking the two alkene moieties is fairly critical for the success of the reaction. When this is shortened to two methylene groups, only the alcohol **75** is formed on irradiation of the diene **76**[30]. Multiple phenyl substituents on the diene as in **77** influence the eventual outcome of the reaction. Cyclization still involves a radical cation **(78)** that is formed on irradiation (through Pyrex at $\lambda > 280$ nm) in acetonitrile/benzene in the presence of DCB as the electron-accepting sensitizer. However, attack on a phenyl group is the principal reaction mode and this yields **79** in 87%[31].



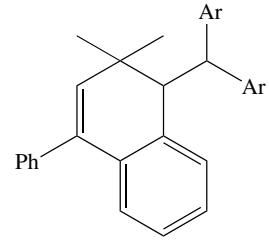
(**67**)

Ar = *p*–XC_6H_4

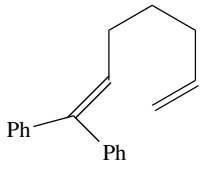
X = H, MeO, Me, Cl, CN



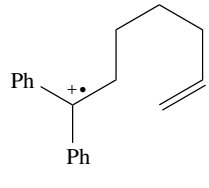
(**68**)



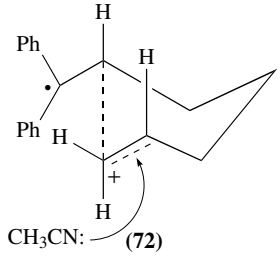
(**69**)



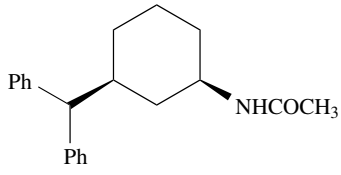
(**70**)



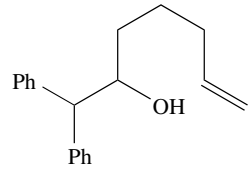
(**71**)



(**72**)



(73)



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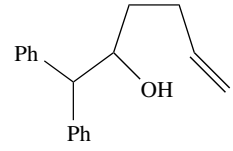
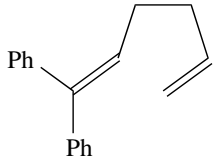
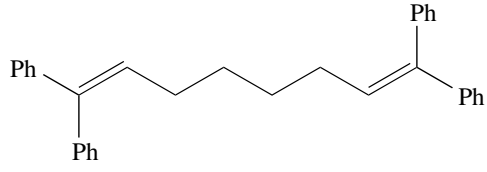


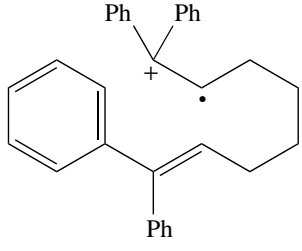
(75)



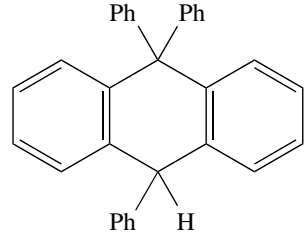
(76)



(77)



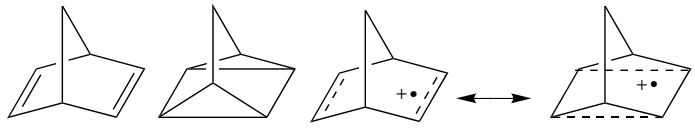
(78)



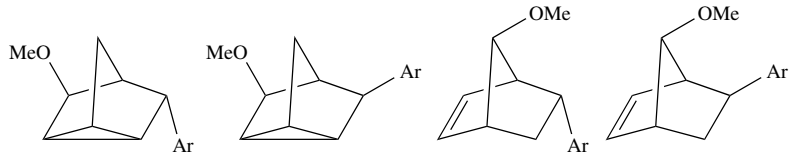
(79)

B. Norbornadienes and Related Systems

One of the interesting molecules that has been studied in considerable detail is norbornadiene **(80)**. Much of this interest has been associated with the interactions between the double bonds of the system. Thus irradiation affords quadricyclane **(81)**. This area of study will be discussed later in this chapter. The radical cation **82** can also be formed from both norbornadiene and quadricyclane by irradiation in acetonitrile/methanol solution with the DCB/phenanthrene sensitizer system. Several products (Scheme 2) are formed in low yield and it should be noted that there is little difference in the yields of products obtained from either starting material. However, it is evident that attack by methanol occurs from the *exo* face[32].



(80) **(81)** **(82)**

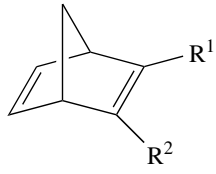


norbornadiene	6	5	6	3
quadricyclane	5	4	4	2

Ar = *p*-NCC_6H_4

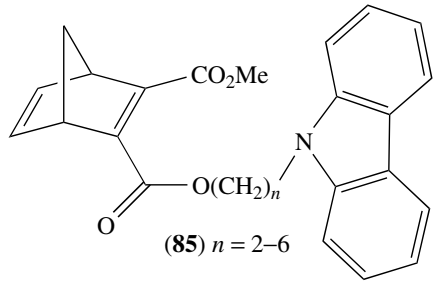
SCHEME 2

The cyclization of norbornadienes into quadricyclanes can also be achieved by electron-transfer sensitization by donation. Such a process obviously will form the radical anion of the norbornadiene. For the formation of the radical anion, suitable electron-accepting substituents must be attached to the norbornadiene skeleton as in the derivatives **83** and **84**. The results using these derivatives have shown that a variety of sensitizers such as phenanthrene, anthracene, pyrene and *N*-methylcarbazole are effective although the most efficient was phenanthrene[33]. Other sensitizers such as acridine yellow and acridine orange are also effective. The photo-isomerization is accompanied by quenching of the fluorescence of the dye[34]. The mechanism by which the cyclization takes place using electron-donating sensitizers is thought to involve an exciplex of the radical-ion pair. The excited triplet state of the diene is produced by back electron transfer in the radical-ion pair within a solvent cage[35]. Intramolecular SET within a norbornadiene system is also a possibility and has been investigated using the norbornadienes **85**. Here the influence of both chain length and conformation was assessed[36,37].



(**83**) $R^1 = R^2 = CN$

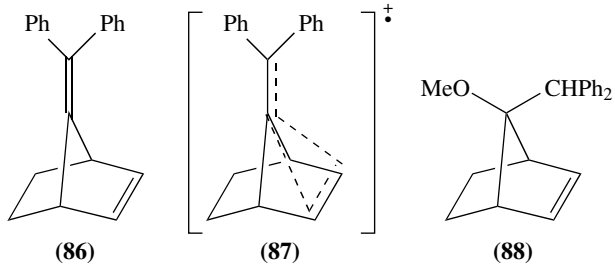
(**84**) $R^1 = R^2 = COOH$ or CO_2Me



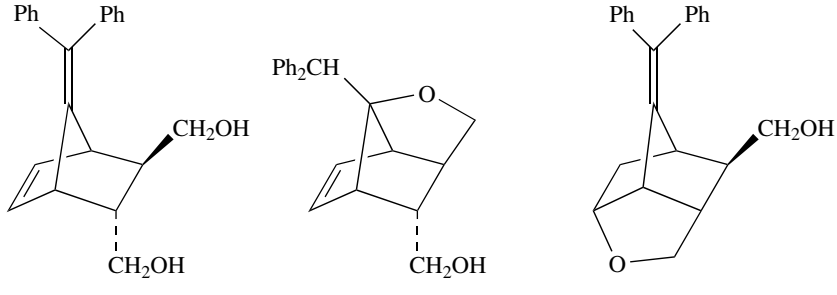
(**85**) $n = 2–6$

Dienes closely related to the norbornadiene system have also proved of interest in SET-induced reactions. Thus, the diene **86** can be transformed into the corresponding radical

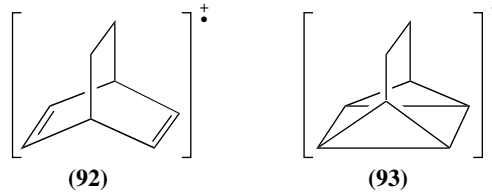
cation **87** on irradiation in the presence of an electron-accepting sensitizer. This radical cation reacts with methanol to yield the ether **88**. Such reactivity is reminiscent of the behaviour of the radical cation of norbornadiene under similar conditions. Intramolecular trapping of these non-classical radical cations has also been studied using the diene **89**. The resultant radical cation formed by irradiation in the presence of a suitable electron-accepting sensitizer gives the two products **90** and **91**[38]. Irradiation of the radical cation **92** with visible light brings about cyclization to the radical cation **93**[39].



(86) **(87)** **(88)**



(89) **(90)** **(91)**

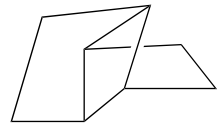


(92) **(93)**

III. CYCLOBUTANE FORMATION

A. Copper(I) Triflate Controlled Reactions

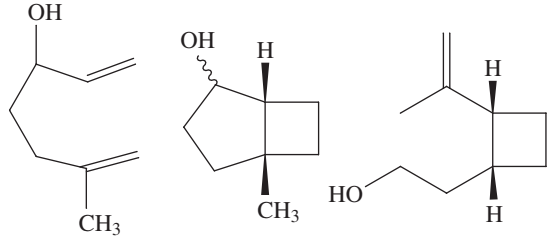
One of the exciting areas that has gained importance over the recent decade is the photochemical cyclization of non-conjugated dienes in the presence of species that can act as templates. One such species that has been used is copper(I) salts. The earliest example of the use of copper salts in the intramolecular photocycloaddition of non-conjugated dienes is that described for cycloocta-1,5-diene. When this is irradiated in the presence



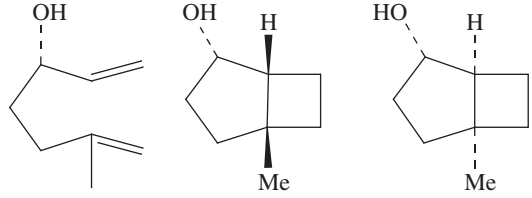
(94)

of copper(I) chloride, the tricyclic compound **94** is formed in 30% yield. The authors[40] suggested that the cyclization to this product involved free radicals.

More modern studies have made use of copper(I) triflate (CuOTf) as the reagent. This compound is well known to form complexes with dienes and it provides a template on which cycloadditions can be effected[41]. Several examples of this type of cyclization have been reported and cycloadditions based on this approach provide a useful route to cyclobutane derivatives. Thus, a new stereochemical synthesis of grandisol has been developed using the copper(I)-catalysed cycloaddition of the dienol **95** to afford the isomeric bicycloheptenols **96**[42]. The *exo*/*endo* ratio in this cyclization is solvent-dependent. The racemic grandisol **(97)** can be synthesized starting from the heptenol **(96)** in eight steps. A more detailed study by Langer and Mattay[43] has reported on the use of the copper triflate controlled (2 + 2)-cycloaddition of 1,6-dienes such as the (*S*)-diene **98**. This affords the two enantiomerically pure cyclobutane derivatives **99** and **100**. These can be converted into enantiomerically pure (+)-grandisol **(97)** and the corresponding (−)-grandisol. The use of chiral copper catalysts was also examined. This only gave products with low enantiomeric excesses (ee) <5%. The authors[43] reason that low ee values are due to the low reactivity of the chiral copper complexes.



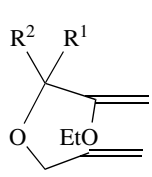
(95) **(96)** **(97)**



(98) **(99)** **(100)**

The presence of an oxygen atom in the chain linking the two alkene moieties does not appear to affect the efficiency of the cyclizations encountered. Thus, the (2 + 2)-intramolecular cycloaddition of the divinyl ether **101a** in ether solution with CuOTf

affords a reasonable yield of 67% of the tetrahydrofuran derivative **102a**. The influence of substituents was studied using **101b,c** and stereoselectivity in the cycloaddition was observed[44]. Copper triflate controlled cyclizations of this type can be used to construct suitable key molecules for the synthesis of naturally occurring compounds. To this end the dienes **103** and **104** have been cyclized intramolecularly to yield the cyclobutanes **105** and **106**, respectively, in moderate to good yields. The products from these reactions are key intermediates in the synthesis of natural products such as cedrene **(107)**[45]. Other examples of this type of cyclization have been used as a route to cyclopentanone derivatives. This involves the copper triflate influenced (2 + 2)-photocycloaddition of the dienes **108** to afford the cyclobutane derivatives **109**. The stereochemistry of the cycloaddition was studied and it can be seen that the dienes **108a**, **108c** and **108d** afford mixtures of *exo* and *endo* isomers while diene **108b** yields only a single isomer. The conversion to the cyclopentanones that were the main target of the work is carried out by rearrangement of the products **109**[46,47]. These adducts are key components in an approach to the synthesis of $\Delta^{9(12)}$-capnellene. Approaches to other systems involve the cyclization of the dienes **110** under the copper(I) controlled conditions. This affords the adducts **111** that can be transformed by thermal reactions into variously substituted derivatives of cyclopentane[48].



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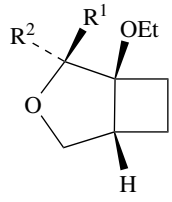
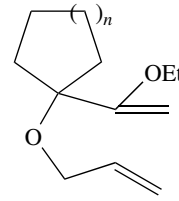
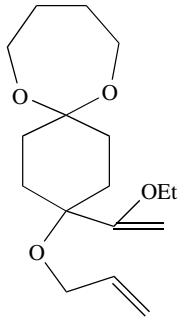


(102)



(103)

(a) $R^1 = R^2 = Et$
(b) $R^1 = CH_2CH_2Ph$, $R^2 = Me$
(c) $R^1 = Et$, $R^2 = Me$



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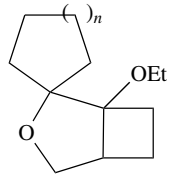
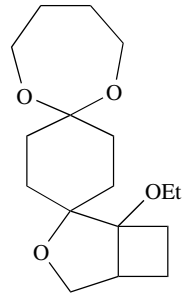
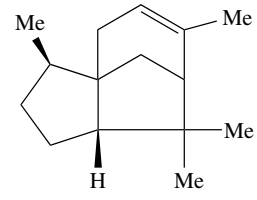


(105)

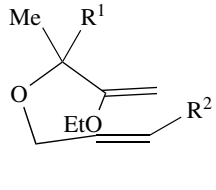


(106)

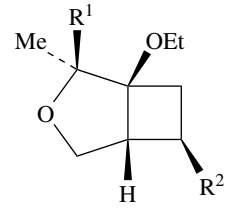


(107)

n = 2,3 or 1

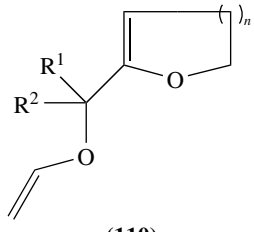


(108)

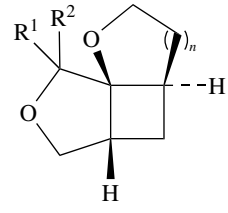


(109)

R^1	R^2	yield (%)	*exo* : *endo*
(a) Me	Me	41	2.5:1
(b) Me	Ph	53	0:100
(c) Me		52	2.2:1
(d) $PhCH_2$		52	3:1



(110)



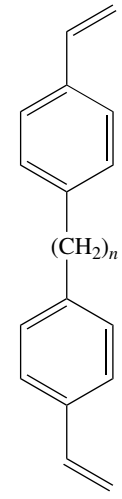
(111)

R^1	R^2	yield (%)	
		$n = 1$	$n = 2$
(a) Me	Me	50	46
(b) Me	CH_2CH_2Ph	59	45
(c) Me	CH_2Ph	70	40
(d)	$-(CH_2)_4-$	45	58
(e)	$-(CH_2)_5-$	60	57

B. Cyclophane Syntheses

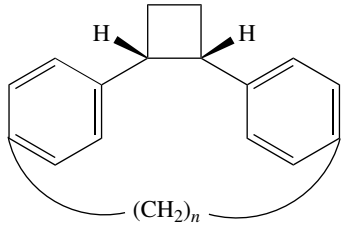
An interesting reaction that has been developed over the past decade is the application of (2 + 2)-cycloaddition reactions to the synthesis of cyclophanes[49]. One of the earliest examples of this is the selective conversion of the bis(arylalkenes) **112** into the adducts **113**. The yield of product is dependent to some extent on the chain length separating the aryl groups and the best yield of 41% is obtained when the separation includes four methylene units ($n = 4$). Lower yields are recorded with the other derivatives. Mixtures of products are formed when the *m*-isomers **114** are used. This affords **115** and **116**. The yields of these are better than those obtained from the *p*-isomers **112**[50,51]. Nishimura and coworkers[52] have examined the ease with which such cyclobutanes, e.g. **115**, $n = 2$,

undergo thermal reversal to starting material **114**. Other more constrained systems have been synthesized by chemical modification of **115**, $n = 3$. This yielded the derivative **117** as a mixture of *exo*- and *endo*-isomers[53]. Naphthalenophane analogues can also be obtained in moderate yield by the photochemical cyclization of the corresponding alkenes **118**, **119**[54] and **120**[55]. Phenanthrene-based cyclophanes can also be prepared in moderate yields by the intramolecular photocycloaddition of the vinylphenanthrene derivatives **121**. The *syn*-cyclophanes **122** are formed exclusively[56].

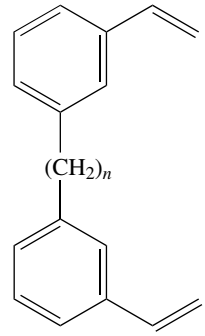


(**112**)

$n = 3$, 4, 5 or 6

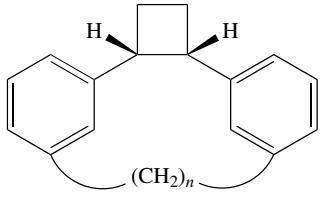


(113)

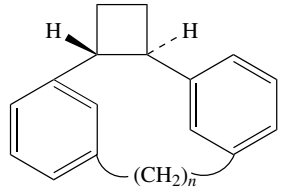


(114)

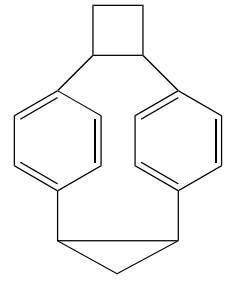
$n = 2$, 3, 4, 5 or 6



(115)

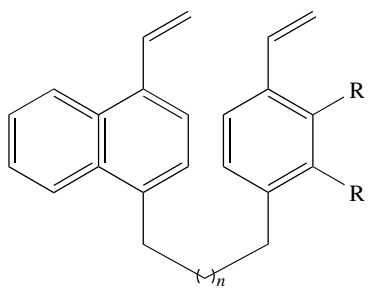


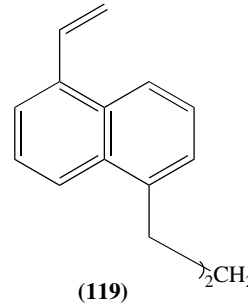
(116)



(**117**)

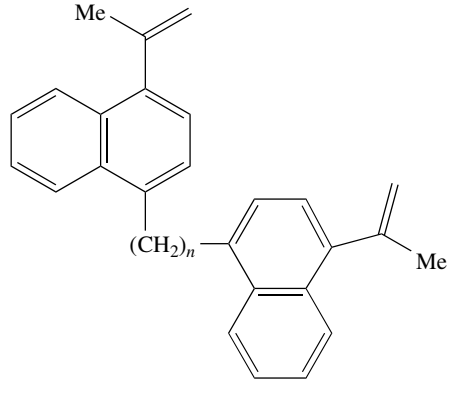
Similar intramolecular cycloadditions are encountered where an ether linkage has been incorporated into the *meta* or *para* linking groups **123**. In these cyclizations the better yields were obtained from the *para*-attached systems. The yields obtained are again dependent on the chain length of the separator and are indicated below the appropriate structures **(124)**[57]. Other hetero-atom-substituted cyclophanes **(125)** can be obtained by irradiation of the divinyl compounds **(126)**[58,59]. The use of tin and germanium derivatives



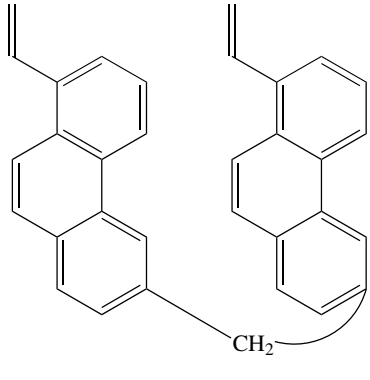


(119)

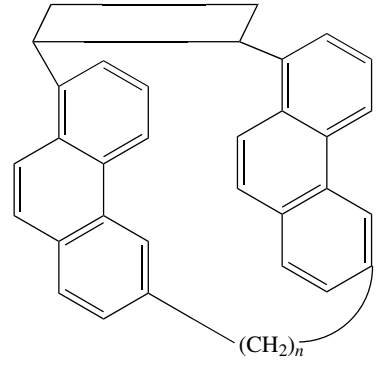
(118) (a) $n = 1$, R = H
(b) $n = 1$, 2, or 3
RR = $(CH{=}CH)_2$



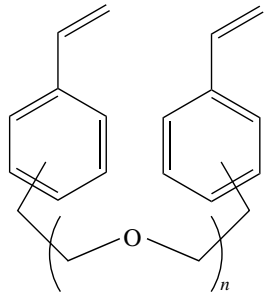
(120) $n = 3$ or 4



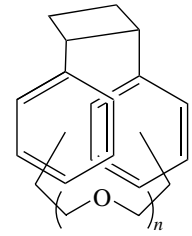
(121)



(122) $n = 3$ 49%
$n = 4$ 38%

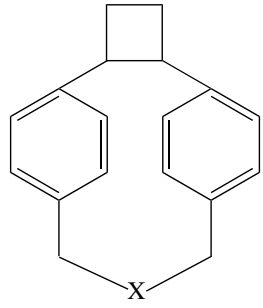


(123)

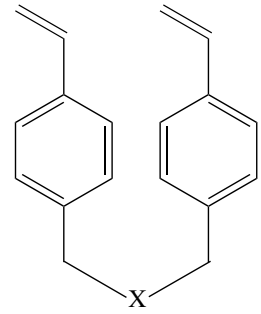


(124)

$n = 1$ *para* - attachment	85%
$n = 1$ *meta* - attachment	40%
$n = 2$ *para* - attachment	63%
$n = 2$ *meta* - attachment	mixture of *cis* 26% and *trans* 6%

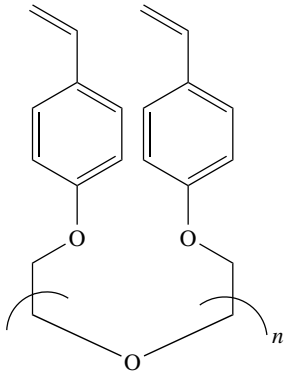


(**125**) X = S or Se, $SiMe_2$

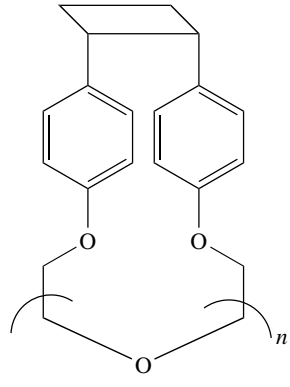


(**126**)

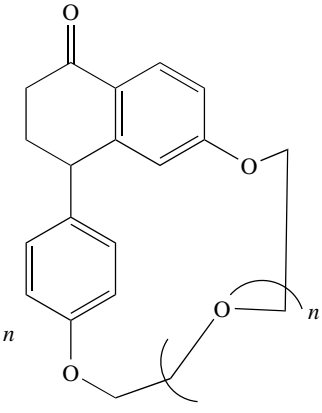
has also been examined[59]. A natural extension of the study has been the development of synthetic approaches to crown-ether based systems. These **(128)** can be formed in high yield (up to 90%) by the irradiation $\lambda > 280$ nm of the derivatives **(127)**. Some evidence for the involvement of biradicals within the cycloaddition process was found from the fact that a low yield of **129** was obtained. This is presumed to be the result of trapping of the biradical by oxygen[60,61]. The high yield of adducts obtained from these irradiations is thought to be due to the flexibility of the ether linkages that permits facile face-to-face approach of the two alkenyl groups. The use of the $(2 + 2)$-photocycloaddition reactions in the synthesis of so-called paddlanes **(130)** has been studied. Irradiations of the starting materials **(131)** are carried out through Pyrex and yields are best when cyclohexane is used as the solvent. The yields of the adducts formed by the double $(2 + 2)$-cycloaddition which forms two cyclobutane moieties is excellent. These products are accompanied by small amounts of the cycloaddition product **132** formed by a single $(2 + 2)$-cycloaddition process[62]. Other cyclophanes with two cyclobutane moieties have also been isolated following the irradiation of the derivative **133**. In this instance, however, the yields are not good and the three isomers **134**, **135** and **136** are obtained in a total yield of 20%[63]. Further examples of compounds of this type have been synthesized by cyclization of **137**[64].



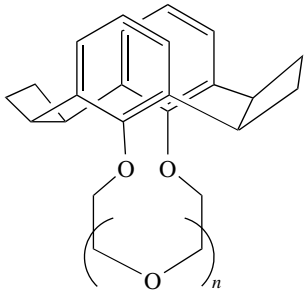
(127)



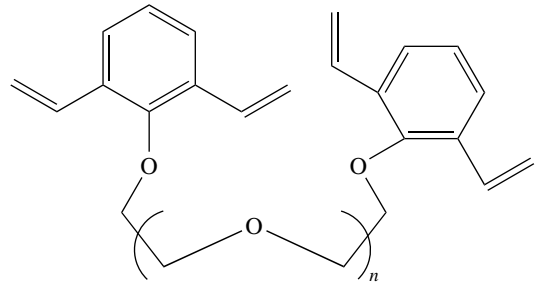
(128) $n = 3$ or 4



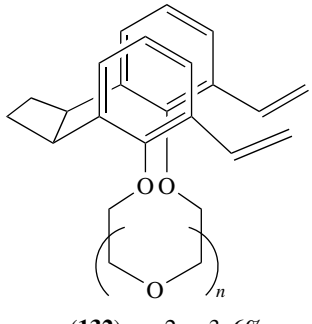
(129)



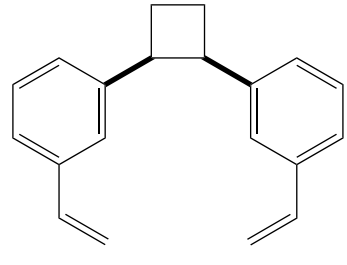
(130) $n = 2$ 84%
$n = 3$ 92%



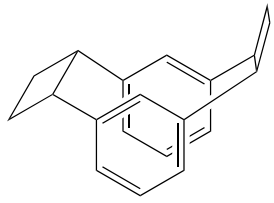
(131) $n = 2$
$n = 3$



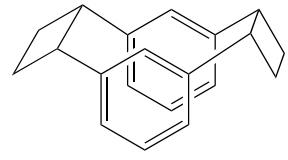
(**132**) $n = 2$ or 3 6%



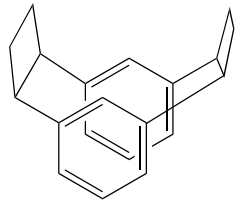
(133)



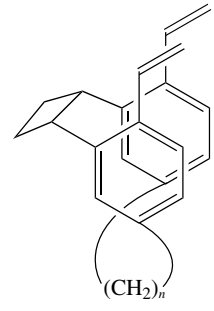
(134)



(135)

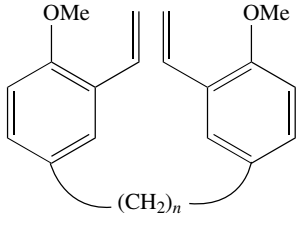


(136)

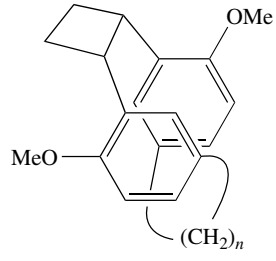


(137)

The aryl groups of the styryl systems need not be unsubstituted, as has been illustrated before for the cyclizations encountered in the synthesis of naphthalenophanes from **120**. Indeed cyclization to afford a cyclobutane derivative where methoxy groups are on the adjacent ring position to the vinyl moieties has also been studied. The irradiation of **138** affords the *m*-cyclophanes **139** and **140**[65]. Further study has sought to evaluate the steric effect of *o*-methoxy groups in such molecules[66].

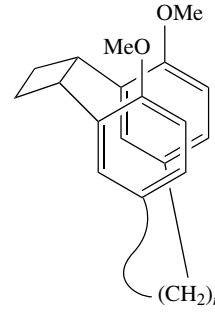


(138)



(139)

$n = 2–6$



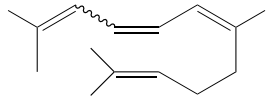
(140)

C. Other Cycloadditions

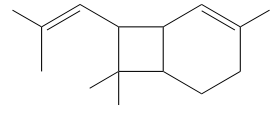
1. Open-chain Systems

Before illustrating the scope of this method for the synthesis of complex structures, there are examples in the literature where non-conjugated dienes are in open-chain systems but

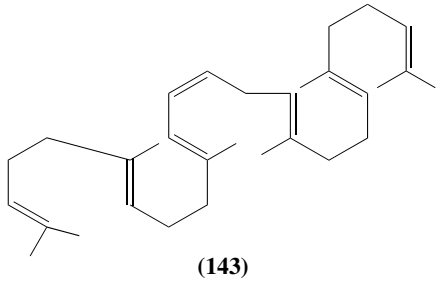
also undergo such (2 + 2)-cycloaddition reactions. Typical of this is the irradiation of the tetraene **141** that yields the bicyclooctene **142**[67]. This cycloaddition probably involves excitation of the diene component and it is the excited state of this that adds to the terminal alkene. In the more complex system **143** the conjugated triene component is the most likely chromophore of the heptaene that will be excited. Addition within this molecule also occurs to an isolated double bond to yield the product **144**. Cycloaddition to form a cyclobutane derivative is also observed as a result of mercury-sensitized vapour-phase photolysis at 254 nm of the fluorinated diene **145**. This yields the two cyclobutane derivatives **146** and **147** as well as the cross-addition product **148** in ratios of 5.7 : 1.0 : 2.8. When the reaction system was diluted with nitrogen the formation of the (2 + 2)-cycloadducts became dominant. Similar additions were observed for the diene **149**. The straight (2 + 2)-adduct **150** and the cross-addition product **151** are formed in a ratio of 1 : 4[68]. One of the double bonds can be contained within a ring as in the cycloaddition encountered in the study of cyclopropene **(152)**. Sensitized irradiation affords the tricyclic compounds **153** by a head-to-head (2 + 2)-cycloaddition[69].



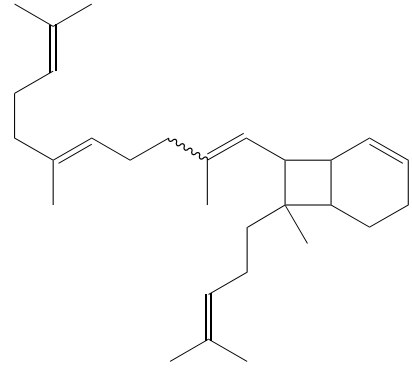
(141)



(142)



(143)



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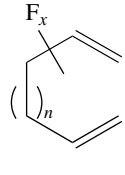
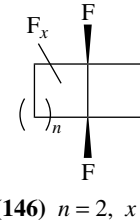


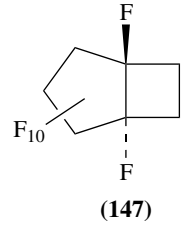
(145) $n = 2,\ x = 12$

(149) $n = 1,\ x = 10$



(146) $n = 2,\ x = 10$

(150) $n = 1,\ x = 8$



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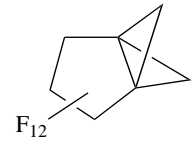
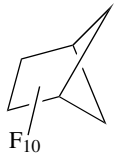


(148)



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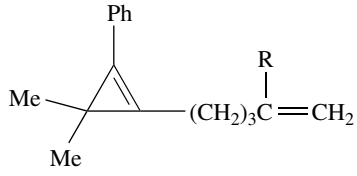
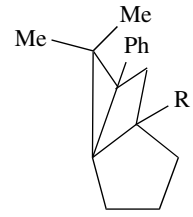
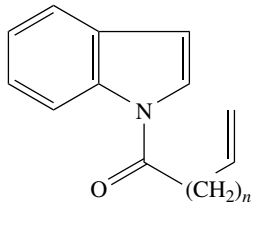


(152) **(a)** R = H
(b) R = Me

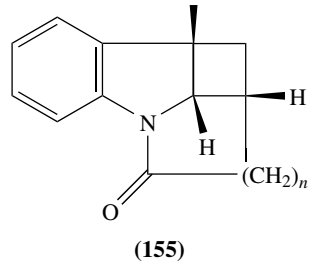


(153)

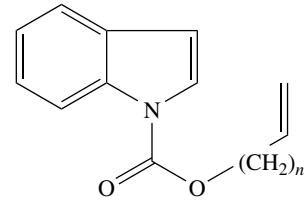
(2 + 2)-Cycloadditions have also been reported for the indole derivatives **154** as an effective method for the synthesis of the polycyclic adducts **155**. The yields, as can be seen from those quoted, range from moderate to good. The quantum efficiencies for the cyclizations are also reasonable. Interestingly, the ester derivatives **156** are photo-unreactive[70,71]. Head-to-head (2 + 2)-cycloaddition is also observed on irradiation of the diallylic amines **157**. This yields the cyclobutanes **158**. The reaction is diastereoselective and detailed semi-empirical calculations supported the proposed mechanism for the formation of these products[72,73]. The silyl ethers **159**–**161** are reactive by a (2 + 2)-cycloaddition in the singlet state while sensitization only brings about *trans*–*cis* isomerization. Irradiation of **159** brings about cyclization to cyclobutane derivatives. Thereafter the silyl ethers groups can be cleaved to afford cyclobutane diastereoisomers such as **162**. It is interesting to note that in the cycloaddition of **159**, R = cyclopropyl leading to **162**, R = cyclopropyl, the cyclopropane ring remains intact. This presumably gives information about the intermediates involved in the cycloaddition and any cyclopropyl methyl radical species that could be formed is not sufficiently long-lived to undergo ring-opening. Cycloaddition can also occur to the furan double bond of **160** and to the alkyne moiety in **161** to yield, in this instance, cyclobutene derivatives[74,75]. In other dienes where the alkene moieties are held more rigidly within the tethered system, as with **163**, irradiation readily affords the cyclobutane derivative **164**[76].



(154)



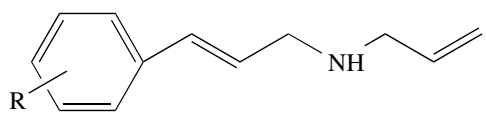
(155)



(156)

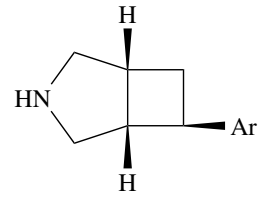
$n = 1$ 29% $\phi = 0.0078$
$n = 2$ 92% $\phi = 0.017$
$n = 3$ 25% $\phi = 0.0032$

Intramolecular (2 + 2)-photocycloaddition has proved to be an excellent route to the synthesis of the so-called cage compounds. Ideally, this route utilizes substrates where the two alkene moieties are held face-to-face within a pre-formed structure. The irradiation brings about excitation and coupling of the two groups to afford a cyclobutane ring.



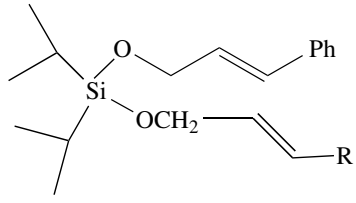
(157)

R = H, 4-F, 4-Cl, 4-NO_2, 3-Cl, 2-F

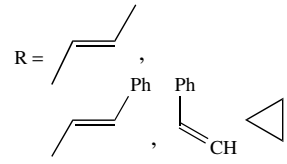


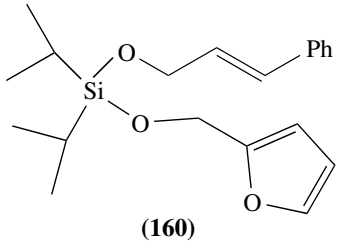
(158)

Ar = RC_6H_4

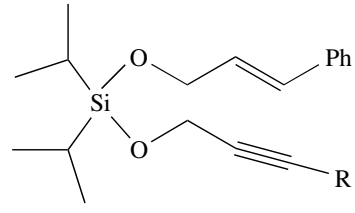


(159)



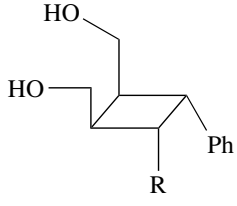


(160)

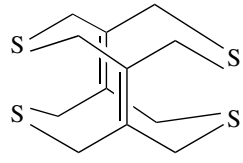


(161)

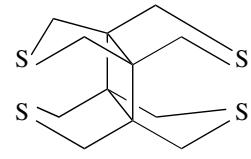
R = Ph, CO_2Me



(162)



(163)

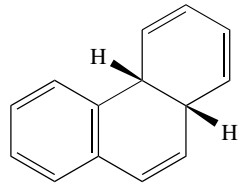


(164)

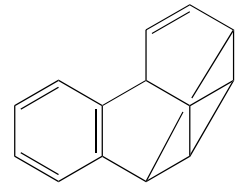
Such compounds are of use in the study of ring strain and also in synthetic approaches to starting materials for more complex systems. Several review articles have highlighted this[77]. The ring systems formed by these reactions are generally quite complex. In order to classify the reactions, a simple approach has been adopted. Not all the complexity is described in this nomenclature and only the atoms involved in the ring system formed are included.

2. Bicyclo[2.1.0]pentane systems

An example of this type of ring system is given by the photochemical cyclization observed within the hydrocarbon **165**. Irradiation converts it into the tetracyclic isomer **166**[78].



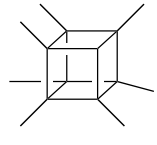
(165)



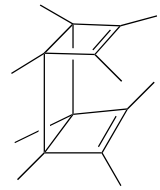
(166)

3. Cubanes and related compounds

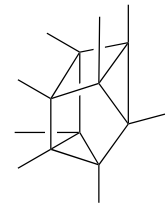
Only a trace of the corresponding cubane **167** is formed on irradiation of the tricyclooctadiene **168** in pentane at ambient temperatures using a 125-watt mercury arc lamp. The principal product **169** is the result of rearrangement within a biradical intermediate[79]. A review of the synthetic approaches to cubane and to its reactions has been published[77]. The diene **170** photochemically converts on irradiation in pentane solution at 254 nm to yield a photostationary mixture of the cubane **171**, the starting material **170** and the isomeric diene **172**[80]. Other additions of this type have been used for synthesis of the propellaprismane **173**, essentially a heavily substituted cubane, by the intramolecular (2 + 2)-photocycloaddition of the diene **174**[81].



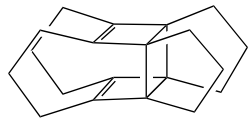
(167)



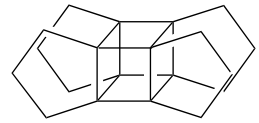
(168)



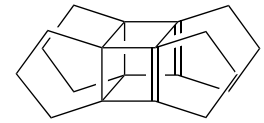
(169)



(170)

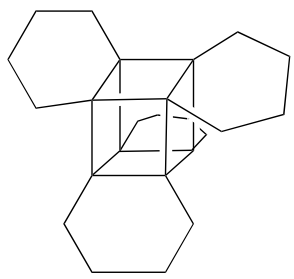


(171)



(172)

Less complex non-conjugated diene systems also lead to cubane-like derivatives as in the diene **175**. Here the outcome of the reaction is dependent upon the excited state. Thus, direct irradiation brings about fragmentation with the formation of 1,4-difluorobenzene and excited-state naphthalene while triplet-sensitized irradiation follows a different path with the formation of the cage compound **176**[82].



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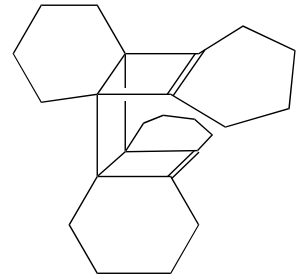
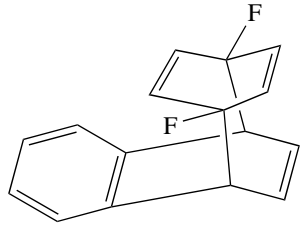


(174)



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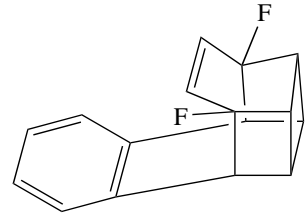
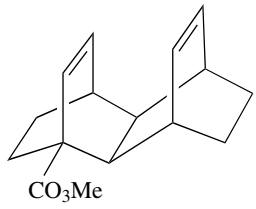


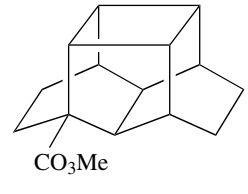
(176)

4. Hexacyclotetradecane systems

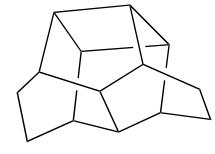
Normal (2 + 2)-photocycloaddition takes place on the acetone-sensitized irradiation of the per-ester **177** to yield the cage compound **178** in 76%. This product can be transformed chemically into the hexacyclotetradecane **179**[83]. Analogously, the tetraene **180** undergoes photochemical cage formation yielding **181**[84]. These cyclizations are typical of the type where the π-moieties are held rigidly face-to-face within the framework. There are many examples of cycloaddition within such systems. A further example is the irradiation of the triene **182** through quartz in a mixture of acetone and benzene. The reaction is chemically efficient and the cycloaddition product **183** is formed in 80% yield[85]. Other cyclizations such as the formation of the cage compound **184** in 90% from direct irradiation of a benzene solution of the diene **185** and **186** from **187** have been reported[86]. The presence of hetero-atoms does not seem to effect the cyclization adversely and the irradiation of **188** results in a quantitative (2 + 2)-cycloaddition yielding **189**[87]. The irradiation of **190** in acetone is also efficient. This irradiation presumably involves the triplet state and gives an almost quantitative yield of the cycloadduct **191**[88].



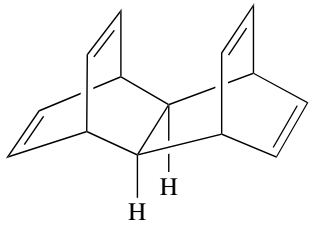
(177)



(178)



(179)



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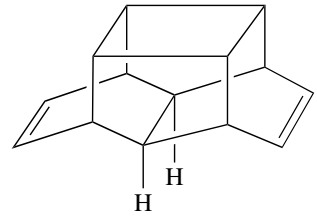
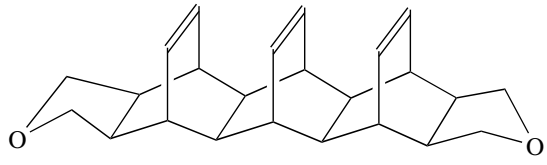


(181)



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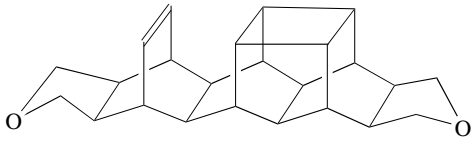

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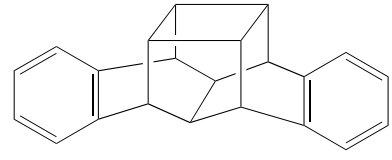

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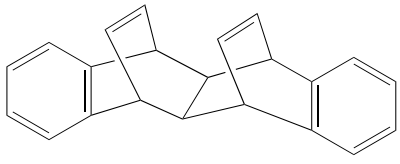

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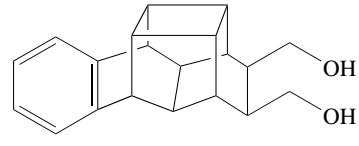

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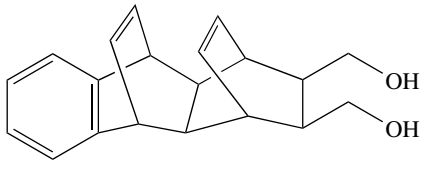

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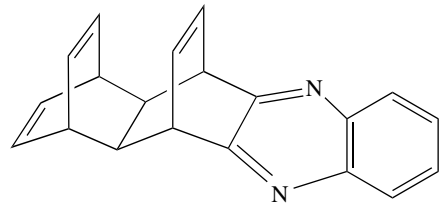

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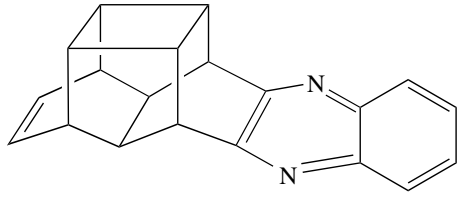

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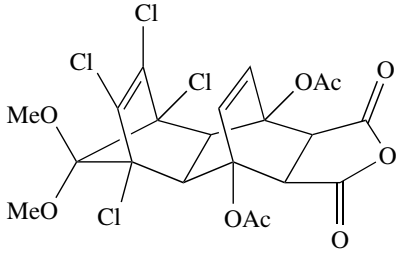

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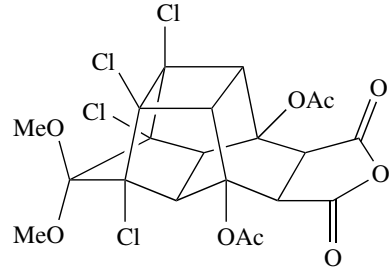
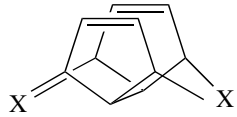


(191)

5. Pagodanes and related molecules

It seems from the examples cited above that, provided the alkene moieties are held in a rigid framework, addition is often highly efficient. This is again demonstrated by the conversion of **192** into **193** or **194** into the pagodanes **195** by either direct irradiation in ether with a quartz filter or by acetone-sensitization through Pyrex[89]. Prinzbach and Weber[77d] have reviewed the synthesis of such compounds. A benzene ring can also be one of the components of the reaction system as demonstrated by the photo-ring closure of **196a** into **197a**. In the case of the resultant diene **197a**, the remaining double bonds of the aromatic ring were trapped by Diels–Alder addition[90]. The bis arene **196b** is also reactive and gives the cycloaddition product **197b**[91]. Melder and coworkers[92] have made use of such cycloadditions, using the slightly more substituted derivative **198**, as a path to [1.1.1.1]pagodanes. Irradiation at 254 nm of **198** affords the (2 + 2)-cycloaddition product **199**.



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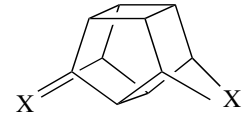

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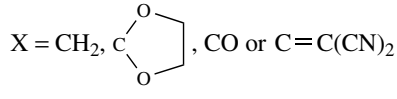

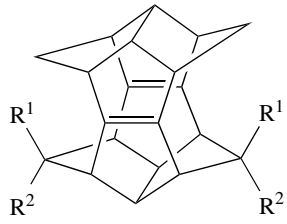

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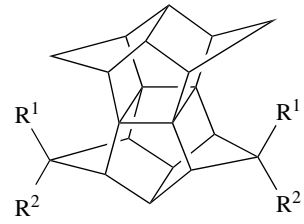
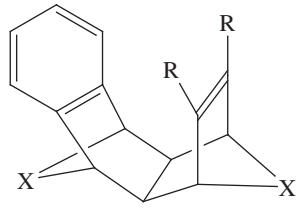
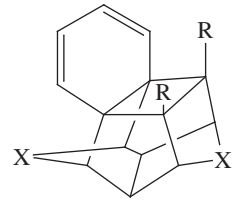
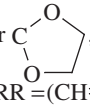


(195)

$R^1 = R^2 = H$
$R^1 = CO_2Me$, $R^2 = H$
$R^1R^2 = O$

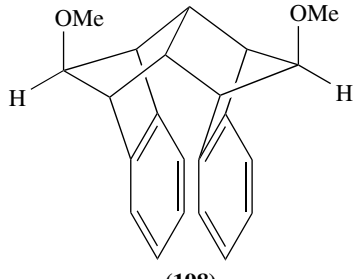




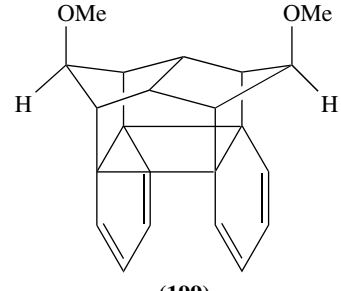
(196) (a) X = CH_2 or  , R = H

(197a)
(197b)

(196) (b) X = CH_2, RR =$(CH{=}CH)_2$



(198)

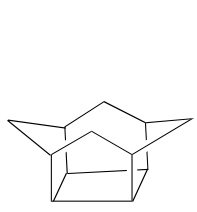


(199)

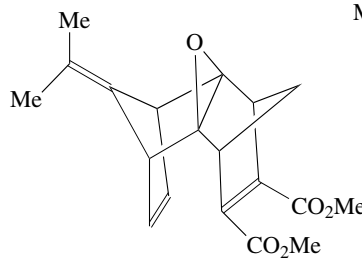
6. Peristylane and related molecules

Syntheses of the complicated structures such as the peristylane system **200**, a 4[peristylane], can also be approached by (2 + 2)-photocycloadditions. Thus, irradiation of the

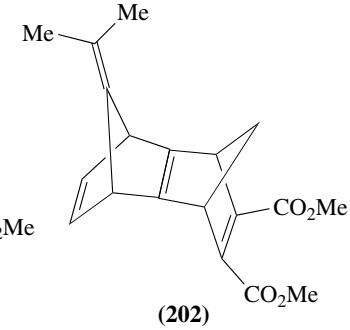
adduct **201**, formed by epoxidation of the air-sensitive adduct **202**, affords the cage compound **203** when acetone-sensitization is employed[93]. Triplet-sensitized irradiation (350 nm) in acetone of the triene **204a** and the tetraene **204b** affords the cage compounds **205** in 32% yield[94,95].



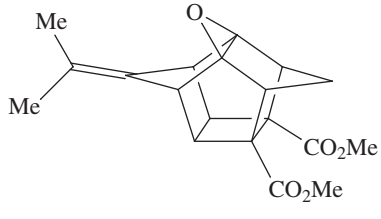
(200)



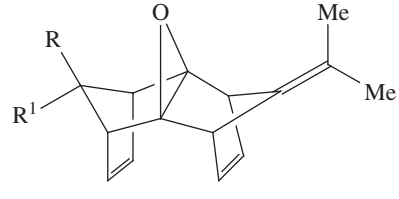
(201)



(202)

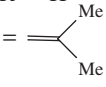


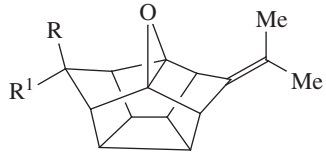
(203)



(204) (a) $R = R^1 = H$

(204) (b) R R =

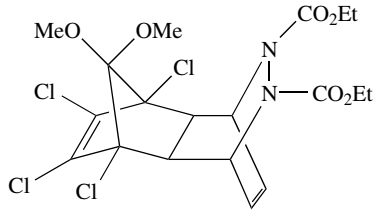




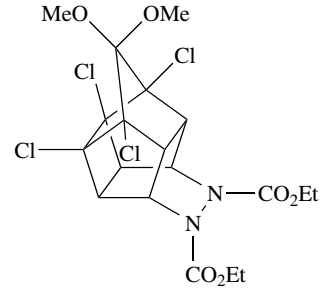
(205) (a) $R = R^1 = H$

(205) (b) RR =

Cycloaddition is also observed on irradiation of the diene **206** to yield the adduct **207**. This product can be hydrolysed and decarboxylated to afford the corresponding azo compound[96]. The adduct **208** is photochemically converted into the cage compound **209** in 38% yield on irradiation at 254 nm[97].



(206)



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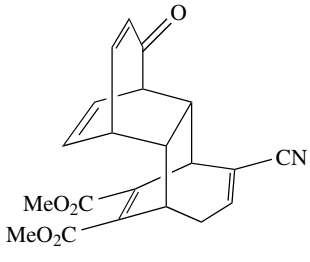
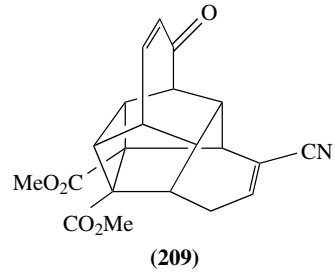


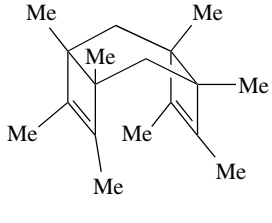
(208)



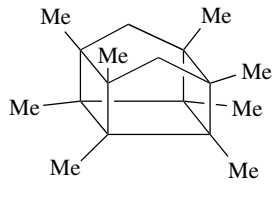
(209)

7. Miscellaneous cycloadditions

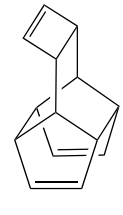
Irradiation of the bis-alkene **210** brings about the formation of the bishomocubane **211** in good yield[98]. The triene **212** is of interest and has been shown to be photochemically reactive, yielding the adduct **213** on irradiation. Several approaches to **212** have been reported over the years. One such approach follows the path of photocyclization of **214** to yield **215** that can be converted to the desired product **212**[99]. A variety of sensitizers can be used for the excitation of alkenes to bring about the $(2 + 2)$-cycloaddition. Commonly, acetone has been used but, in at least one case, the formation of the cage compound **216** from the diene **217**, tetraphenylporphine has been found to be of use[100].



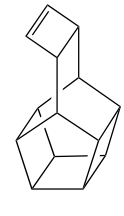
(210)



(211)



(212)



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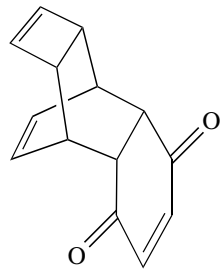
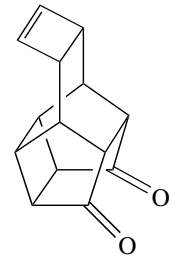


(214)



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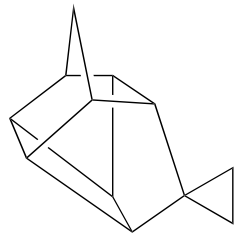

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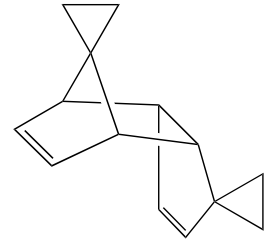
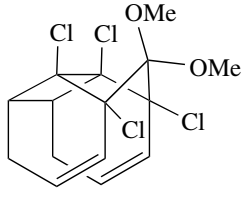


(217)

The approach to highly complex cage systems is not always straightforward. Thus while (2 + 2)-cycloaddition within **218** readily affords **219**, the more highly strained diene **220** fails to cyclize upon irradiation[101]. Previously, it has been mentioned that Prinzbach and his coworkers[77] have synthesized a variety of complex structures using a photochemical (2 + 2)-cycloaddition as a key step in the approach. Another complex structure, the isopagodane, has also been synthesized. One of the approaches leading to these compounds involves a double (2 + 2)-photocycloaddition. Thus irradiation in benzene solution brings about the formation of **221** from **222**. Cycloaddition is also possible in **221** and this yields **223**[102]. Cycloaddition by acetone-sensitized irradiation also brings about the ring closure of the diene **224**. This yields the heptacyclic product **225** that is a key intermediate in the synthesis of bishomohexaprismane molecule **226**[103,104].



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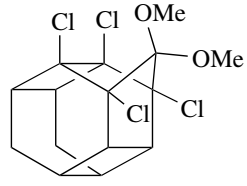
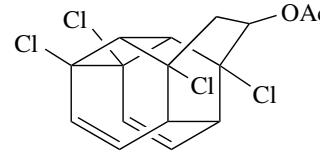


(219)



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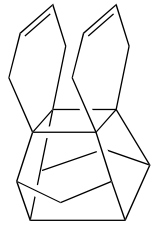
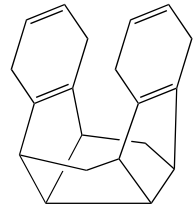


(221)



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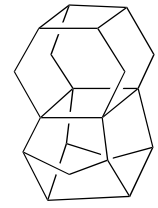

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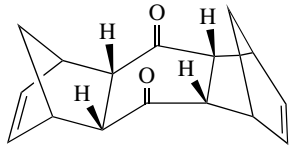

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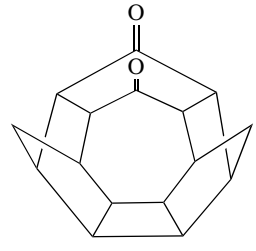

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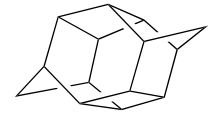


(226)

IV. CYCLIZATION OF NORBORNADIENES AND RELATED COMPOUNDS

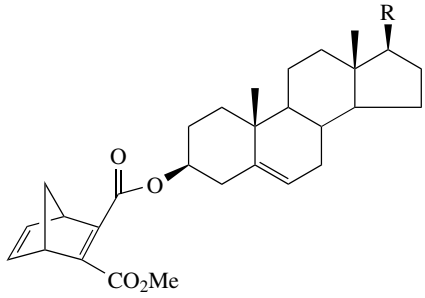
A. All Carbon Systems

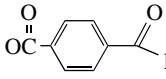
One of the areas that has been studied in considerable detail is that of the cyclization reaction of norbornadiene to quadricyclane that can be brought about either by direct or by sensitized irradiation. This was first reported by Cristol and Snell[105] and soon became an area of interest to others[106,107]. Since these early investigations where much of the work focused on the homoconjugation of the system, a great deal of research has been carried out and a good understanding of the processes involved has now been acquired. Much of this earlier work has appeared in most textbooks devoted to photochemistry and, in addition, most of the standard textbooks and monographs on the subject now have details of these reactions. Since this is the case the present section will highlight what has been achieved in the last decade or so.

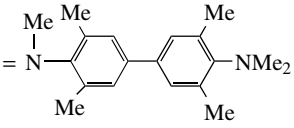
As mentioned above, the ring closure of norbornadiene to quadricyclane can be brought about by sensitization. Interest in this area has shown that tetraphenylporphine can be a useful sensitizer for the conversion of norbornadiene into quadricyclane[108]. Part of this research is associated with energy storage systems and several copper(I)-based photosensitizers have been synthesized in an attempt to improve the norbornadiene/quadricyclane solar energy storage system [109]. In this respect, also, Yang and coworkers[110] have reported that the conversion of quadricyclane back into norbornadiene can be sensitized by dibenzoylmethanatoboron difluoride.

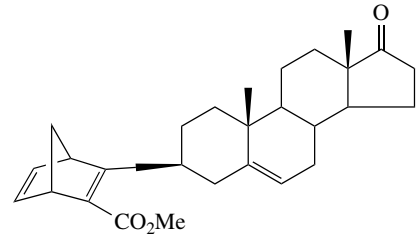
Interest in intramolecular energy transfer has also been reported and bichromophoric norbornadiene derivatives have been synthesized for this study[111]. Cao and coworkers[112]

report that intramolecular triplet energy transfer from the benzophenone moiety to the norbornadiene unit in **227** takes place with a rate constant of $6.1 \times 10^4\ s^{-1}$. The bichromophoric system **228** undergoes intramolecular electron transfer by a through-bond mechanism on irradiation. The transfer is from the benzidine moiety to the norbornadiene moiety and occurs with 12% efficiency. The ultimate intermediate is the triplet radical ion pair[113]. Irradiation ($\lambda > 300$ nm) of the norbornadiene derivative **229** results in excitation of the androstene carbonyl group. Apparently, this affords the triplet excited state that transfers triplet energy by a through-bond mechanism to the norbornadiene. This undergoes cyclization to the corresponding quadricyclane. The energy transfer occurs with 18.6% efficiency[114]. Calculations have dealt with the energetics of the photoisomerization within the norbornadiene/quadricyclane system[115]. Constrained environments have also been of interest in a number of areas and norbornadiene cyclization has not been excluded. Thus, a study of the photoisomerization of some norbornadienes has been carried out within the constrained environment of β-cyclodextrin[116].



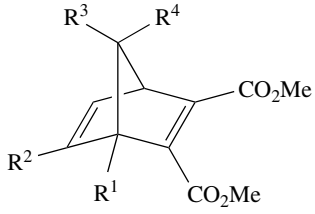
(**227**) R = 

(**228**) R = 

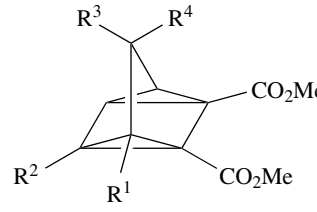


(**229**)

The simple systems such as **230** are also of interest. These readily undergo cyclization to the quadricyclanes **231** in good yield. The principal reason for the study of these systems was an attempt to obtain energy storage molecules. Thus the reverse reaction is important and the quadricyclanes **231** can undergo ring-opening when treated with silver ion[117]. If the use of the norbornadiene/quadricyclane as energy storage systems is to be exploited, systems have to be devised that can be cyclized using sunlight. This is the case with the water-soluble norbornadiene **232** which is efficiently converted into the corresponding quadricyclane on irradiation with sunlight[118]. Other norbornadienes with carboxylic acid functional groups, e.g. **233**, also undergo efficient cyclization to **234**[119] as does **235** into **236** in a yield of 75%[120]. The photochemical formation of the quadricyclanes **237** by acetophenone-sensitized irradiation of **238** has been reported. The quadricyclanes were used as substrates in an approach to the synthesis of 1,5-dehydroquadricyclane[121].

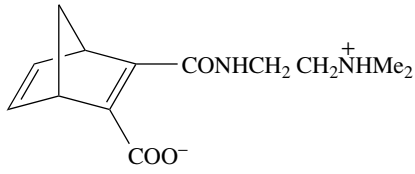


(230)



(231)

$R^1 = R^2 = R^3 = R^4 = H$
$R^1 = Me,\ R^2 = R^3 = R^4 = H$
$R^2 = Me,\ R^1 = R^3 = R^4 = H$
$R^3 = Me,\ R^1 = R^2 = R^4 = H$
$R^4 = Me,\ R^1 = R^2 = R^3 = H$
$R^1 = R^2 = H,\ R^3 = R^4 = Me.$



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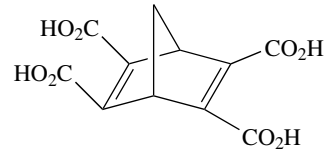

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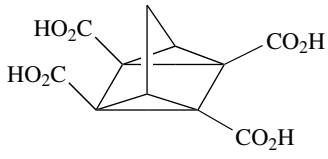

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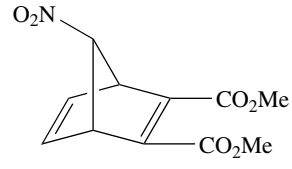

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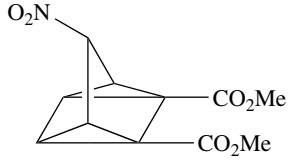

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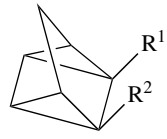

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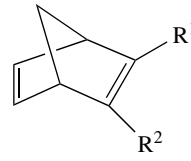
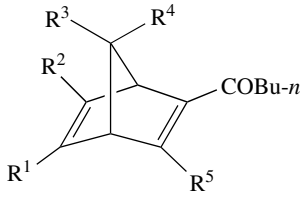


(238)

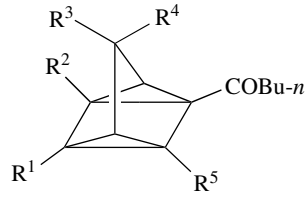
$R^1 = Br,\ R^2 = Br$ or Cl

The variety of derivatives that undergoes cyclization is almost limitless, as shown by the conversion of **239** into **240**. Here, one of the functional groups on the norbornadiene is ketonic[122]. The isomerization of other keto or aldehydo derivatives of norbornadiene into

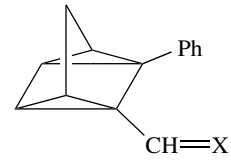


(239)

R^1—R^4 = H or Me
R^5 = CHFEt, CF_2Et or CF_3

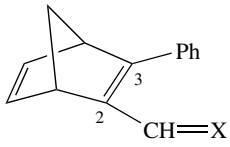


(240)

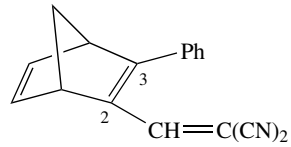


(241)

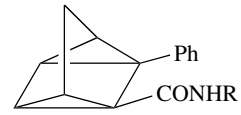
(a) X = O
(b) X = NPh
(c) X = NC_6H_4OMe-*p*



(242) **(a)** X = O
(b) X = NPh
(c) X = NC_6H_4OMe-*p*



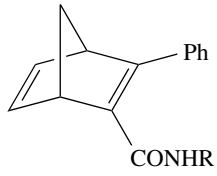
(243)



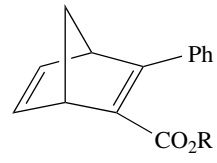
(244)

R = Ph, 1-Naphthyl, 2-Naphthyl

the corresponding quadricyclanes has also been reported[123]. Thus, the formation of the quadricyclane **241a** occurs on irradiation of the phenyl-substituted norbornadiene **242a**. The imines **241b** and **241c** are photoreactive under the same conditions. Again interest in these was centred on quadricyclanes as energy storage systems and copper(II) porphyrins rapidly brought about reformation of the photoreactive norbornadiene[124]. The imines **242b** and **242c** are also photoreactive[124] as is **243**[125], and the corresponding quadricyclanes are formed on irradiation. The conversion of the norbornadienes **243** and **242b**, has sought to examine structural effects. These derivatives showed a substantial lengthening of the C2−C3 double bond in comparison with unsubstituted derivatives. The authors[125] observe that the quantum yield for the conversion of norbornadienes to quadricyclanes increases with shortening of the C2−C3 double bond. Efficiency of cyclization is also affected by changes in substitution as in the formation of the quadricyclanes **244** that can be obtained by irradiation of the norbornadienes **245** at 313 nm. The quantum yield for the cyclization, which can be as high as 0.71, can be enhanced by the change in substitution on the amide group[126,127]. Other studies have focused on the kinetics of the photochemical isomerization of the norbornadienes **246** into the corresponding quadricyclanes. The quantum yields for the processes were found to be in the range of 0.18 to 0.36. In these examples the authors[128] suggest that the results are in agreement with the involvement of a radical cation mechanism (see earlier for examples of electron transfer processes applied to the norbornadiene system) in the cyclization. Others have studied the changes in efficiency of cyclization brought about by substituents on the aryl group in the conversion of the norbornadienes **247** into the quadricyclanes **248**[129]. The yields shown under the products illustrate the qualitative effect on the overall yields of product. This is also the case in measurements of the quantum yields of the processes.

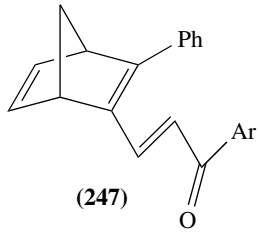


(245)

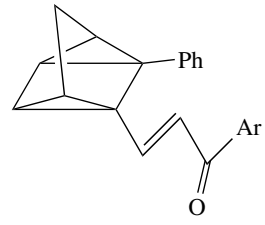


(246)

R = H, $PhCH_2$, *p*-$MeOC_6H_4(CH_2)_n$ (*n* = 1, 6)



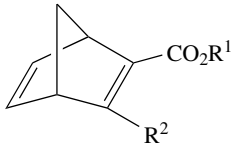
(247)



(248)

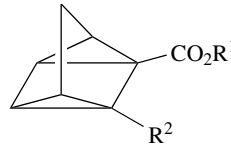
Ar =	yield (%)
p-MeC_6H_4	40
p-ClC_6H_4	96–100
p-BrC_6H_4	96–100
m-$O_2NC_6H_4$	96–100

Investigations have also examined the photochemical outcome of the inclusion of other aromatic substituents onto the norbornadienes. Examples of this are the direct and sensitized irradiation of the naphthyl-substituted derivatives **249** that brings about cyclization to **250**. Sensitization of the cyclization with ketones such as benzophenone leads to a much cleaner reaction. Biacetyl has also been used as the sensitizer[130,131]. Cyclization also occurs with the norbornadiene **251**[132].



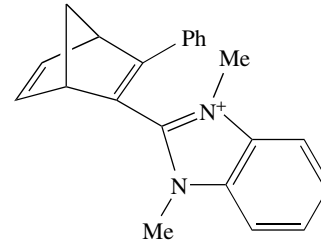
(249)

R^1 = 1- or 2-naphthyl
R^2 = H or CO_2R^1



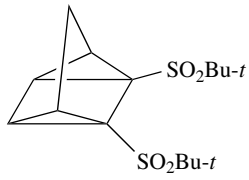
(250)

R^1 = 1- or 2-naphthyl
R^2 = H or CO_2R^1

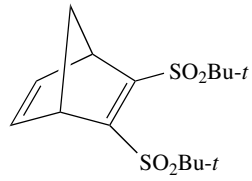


(251)

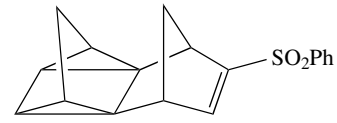
The incorporation of sulphonyl groups does not inhibit the cyclization process as demonstrated by Gleiter and Ohlbach[133], who have reported the efficient synthesis of the quadricyclane **252** by irradiation of the norbornadiene derivatives **253**. A study has also been made of the sulphonyl-substituted norbornadiene derivatives **254**[134,135].



(252)

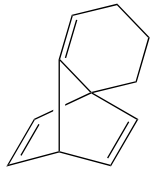


(253)

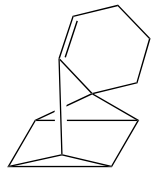


(254)

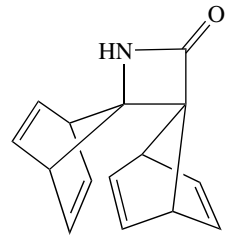
Cyclizations have also been reported within strained systems such as the conversion of **255** to **256**[136] or the formation of **258** from **257**[137].



(255)



(256)



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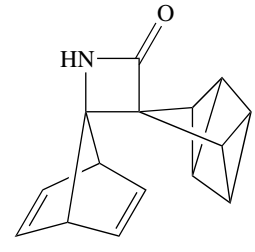
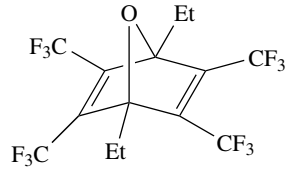


(258)

B. Hetero Norbornadiene Systems

Like the cyclization of the parent system, the photocyclization of hetero analogues of norbornadiene was reported many years ago. Recent interest in this area will serve to illustrate the potential of the conversions. Thus the irradiation of the oxanorbornadiene system **259** brings about conversion to the oxepine **260**[138]. The formation of **260** presumably arises by quadricyclane **261** formation, followed by secondary photolytic ring-opening. Other research has shown that irradiation of the oxanorbornadiene **262** follows the same reaction mode and it undergoes (2 + 2)-cycloaddition to the quadricyclane derivative **263**. Apparently, in this instance, cycloreversion affords the ylide **264** that can be trapped by suitable addends, giving the adducts illustrated in Scheme 3[139].



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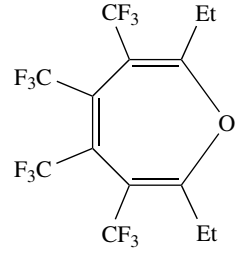

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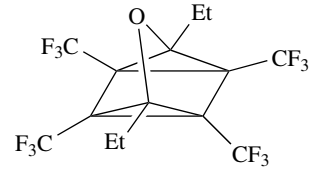
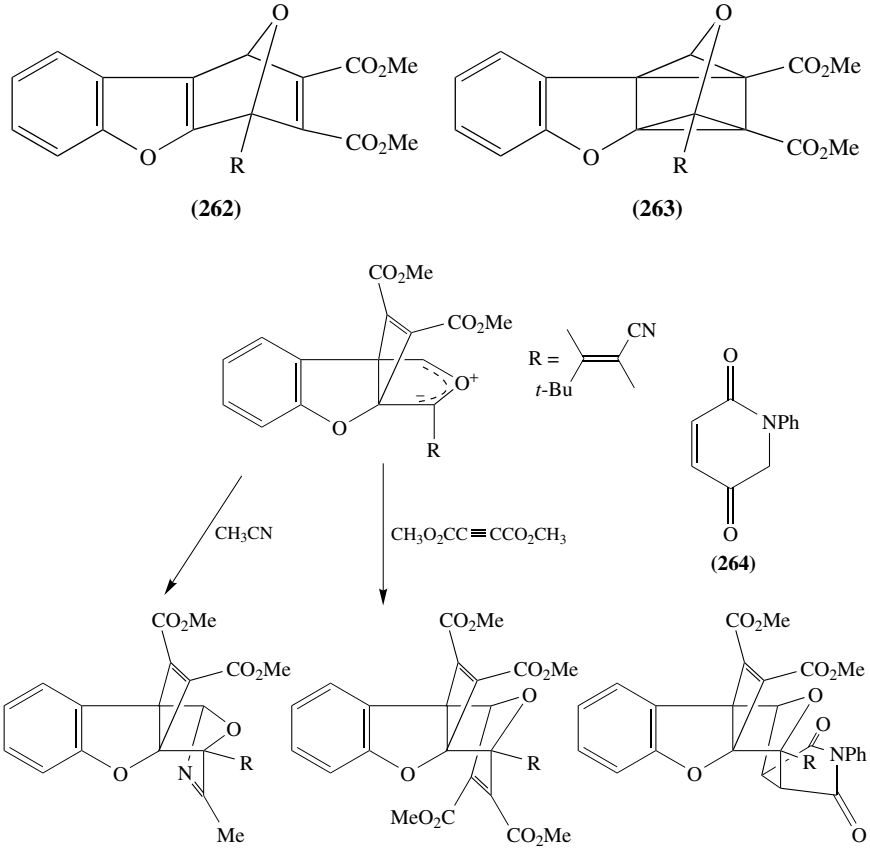


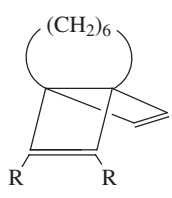
(261)



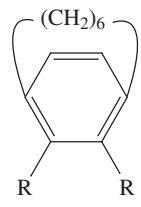
SCHEME 3

C. Prismanes

Benzenoid compounds on irradiation can be converted into the corresponding 'Dewar' benzene amongst other derivatives[140]. These Dewar derivatives, exemplified by **265**, are also photochemically reactive and can undergo conversion into the corresponding prismane structure. This is probably the path followed on irradiation of the *para*-cyclophanes **266** at wavelengths greater than 270 nm. This yields the prismanes **267**[141]. Gleiter and coworkers[142,143] have also reported the photochemical behaviour of a number of benzene derivatives such as **268**. Irradiation of this compound leads to the formation of the Dewar benzene **269** and the prismane **270**. Isomers of **270** can also be formed by cyclization of the Dewar benzene derivatives **271a**. Other examples, such as **271b**, also cyclize efficiently, giving high yields of product. The irradiation of these derivatives uses a variety of wavelengths to achieve the cyclization. Structural proof for the prismanes formed by cyclization of **271c**[144] has been obtained by X-ray crystallography[145]. With the bis-system **272**, the photo (2 + 2)-cycloaddition also occurs on irradiation at $\lambda > 320$ nm in ether. However, the initial prismane product undergoes a 1,5-hydrogen migration to yield **273** in 90% yield[146].



(265)



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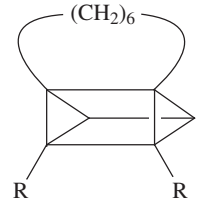
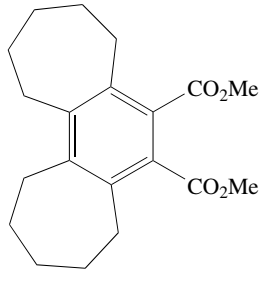
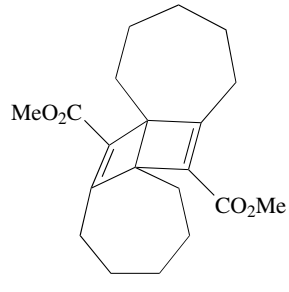


(267)

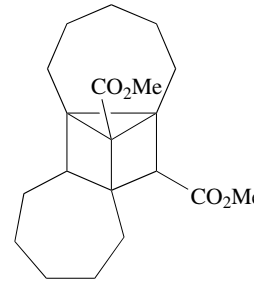
R = CH_2OH, $CH_2OCONHC_6H_{11}$, $CH_2OCONHC_6H_5$, CO_2Et or CH_2OAc



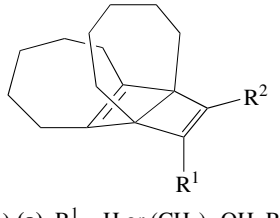
(268)

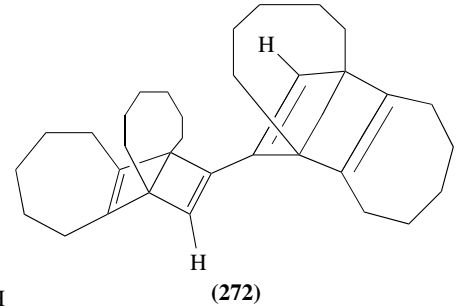


(269)



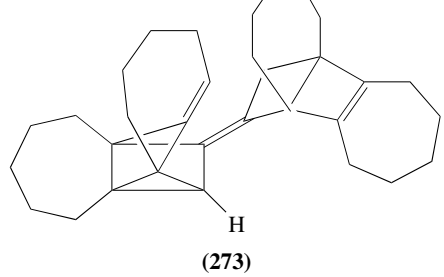
(270)





(271) **(a)** R^1 = H or $(CH_2)_2$ OH, R^2 = H
(b) $R^1 = SO_2Bu$-*t*, R^2 = H, Me, Ph
(c) $R^1 = R^2 = CO_2Me$

(272)



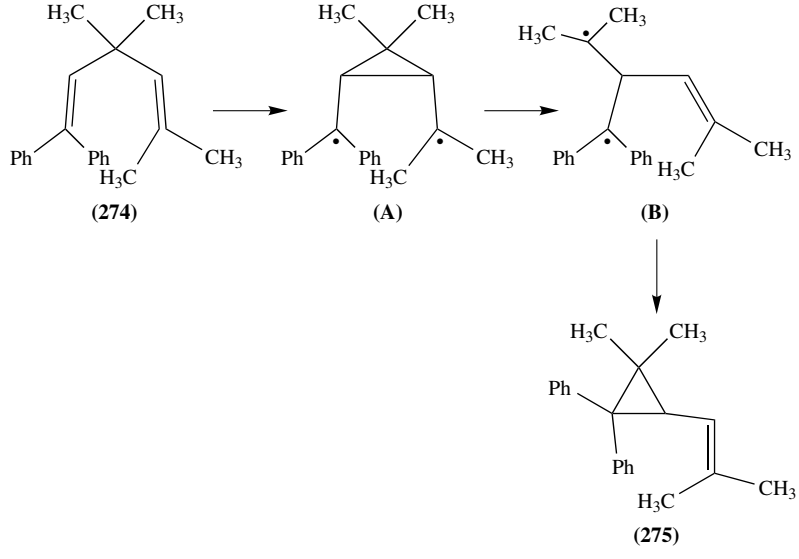
(273)

V. DI-π-METHANE PROCESSES

A. Open-chain Systems

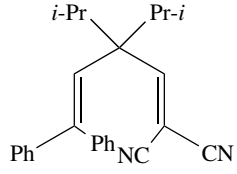
Perhaps one of the most ubiquitous photochemical reactions undergone by non-conjugated dienes is that encountered in the 1,4-diene system. This is referred to as the all-carbon di-π-methane reaction. This system is one in which a central tetrahedral carbon atom is flanked by two vinyl groups. The fundamental reaction was discovered and reported in 1967 by Zimmerman and his coworkers[147]. A detailed account of this reaction and the closely related oxa-di-π- and the aza-di-π-methane rearrangements has been published recently[148]. This review gives the history of how and when the reaction was discovered and its developments in all its guises up to the present time. Others have reviewed other aspects of the reaction[149]. This section of this review will be devoted to the last decade of results.

The basic skeletal transformation exhibited by this system is shown in Scheme 4. Regardless of whether or not the reaction involves a singlet or a triplet, this scheme is a reasonable interpretation of the rearrangement. This shows the fundamentals of the reaction with the two alkene moieties separated from each other by the saturated carbon atom. The usual outcome of the irradiation is conversion to a vinyl cyclopropane, a 1,2-migration. Thus the two steps shown in Scheme 4, the formation of the 1,4-biradical **A** and then its transformation into the 1,3-biradical **B**, fundamentally brings about a 1,2-migration of a vinyl group. Calculations dealing with the outcome of the di-π-methane rearrangement of 1,4-dienes have been reported[150].

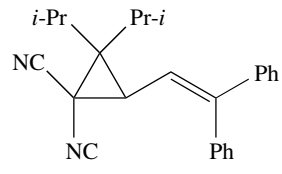


SCHEME 4

The reaction in its basic form is illustrated by the conversion of **274** into **275**. This transformation shows the control exercised within the two biradicals **A** and **B** on the final outcome of the reaction[151]. Another typical di-π-methane process, this time with electron-withdrawing substituents on one of the vinyl moieties, arises on acetophenone-sensitized irradiation of the diene **276**. This yields the cyclopropane **277** in 35% yield. The

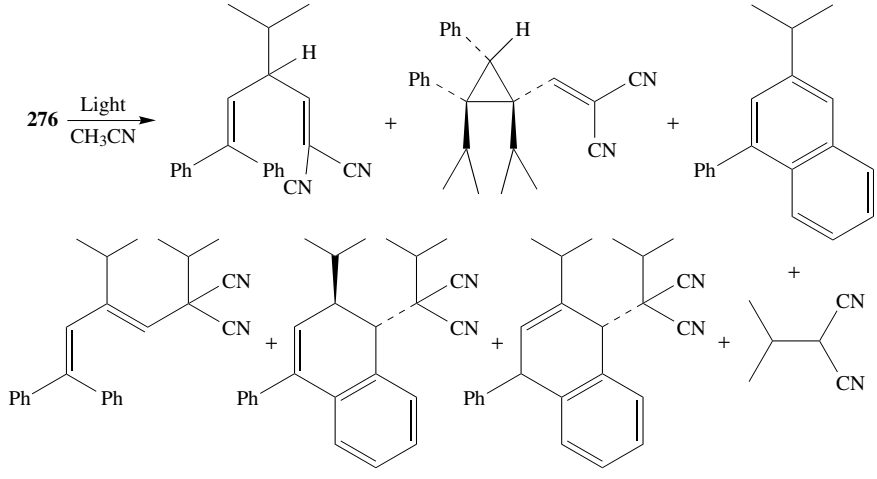


(276)

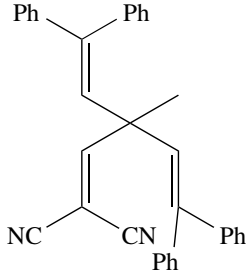


(277)

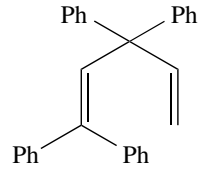
reaction is reasonably efficient with a quantum yield of 0.041[152]. The outcome of direct irradiation in acetonitrile shows how a change in the excited state provides other reaction paths. Certainly in this instance with **276** the reaction is much more complex and, even though the di-π-methane rearrangement is still operative, six other products are formed as a result of rearrangement, cyclization or fragmentation. These products are shown in Scheme 5. Environment has also been shown to change the outcome of reactions and this is demonstrated by the photochemistry of the dienes **278** and **279** in the crystalline phase. The dicyanodiene **278** yields only the cyclopentene **280**. This is formed via the 1,4-biradical intermediate **281**. Normally one would expect this to transform by the di-π-methane path, but in the crystalline phase the cyclopentene is the principal product. The tetraphenyl diene **279** also shows different behaviour under the same reaction conditions as above and reacts only by vinyl–vinyl bridging to afford the 1,4-biradical **282** and ultimately product **283**. The authors[153,154] suggest that 'confinement control' is responsible for the selectivity observed. The quantum yield for product formation in the crystalline phase is much lower than the quantum efficiency in solution phase. Other studies[155] have shown the influence on the outcome of irradiation when the diene **284** is entrapped in poly(methyl methacrylate). The products from the reactions are shown in Scheme 6 and illustrate that the least motion path is involved in the photochemical reactions. Note that the di-π-methane product is analogous to that formed from the irradiation of **276** with the cyano groups on the cyclopropane ring. The solution phase reactivity of **284** has been studied previously[156].



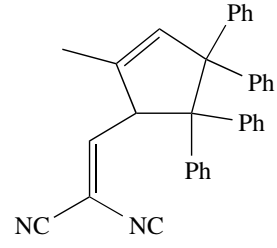
SCHEME 5



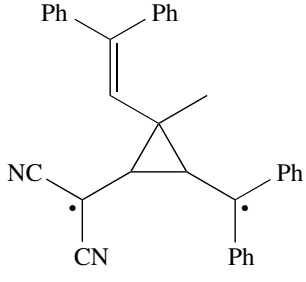
(278)



(279)



(280)



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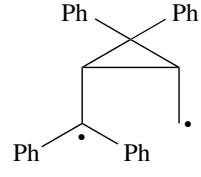
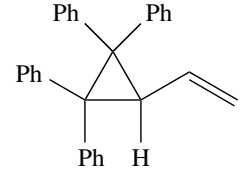
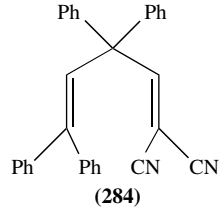


(282)

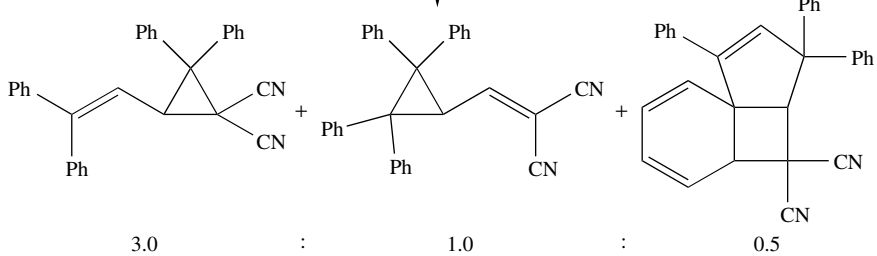


(283)



(284)

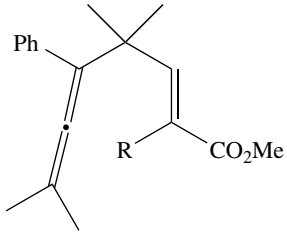
40% conversion



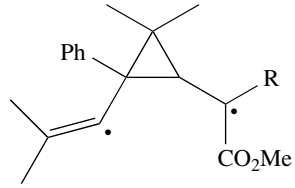
3.0 : 1.0 : 0.5

SCHEME 6

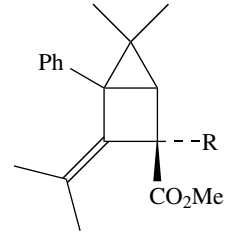
Not every 1,4-diene undergoes the di-π-methane rearrangement. In the case of the allenyl alkenes **285** direct irradiation at 254 nm in hexane excites the molecule to its triplet state. Bridging within this affords the intermediate 1,4-biradical **286**. Bond formation then yields the major products **287**, a housane and **288**. The latter compound is formed by trapping within the biradical, using an ester function. Minor products are also formed. Irradiation at $\lambda > 280$ nm fails to yield products. However, acetophenone sensitization is effective[157]. A housane derivative **289** is also formed in 53% yield on irradiation of **290** using acetone sensitization. Interestingly, in this example there is competition from a di-π-methane process that gives a low yield of the cyclopropane **291**[158]. The ring-opening of the bridging 1,4-biradical in this example follows the normal path to yield the more heavily substituted 1,3-biradical prior to the formation of **291**.



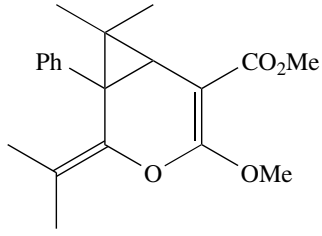
(285) **(a)** R = CO_2Me
(b) R = H



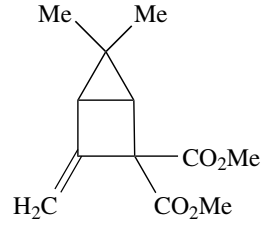
(286)



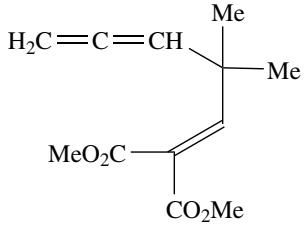
(287) **(a)** 15%
(b) 25%



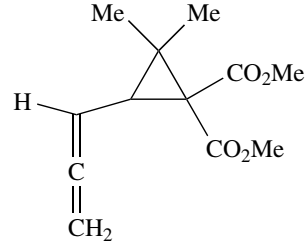
(288) **(a)** 18%
(b) 15%



(289)



(290)

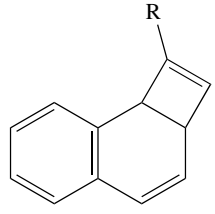


(291)

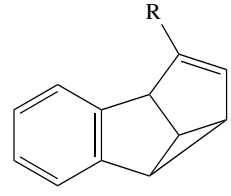
B. Cyclic Systems

1. Benzotrienes

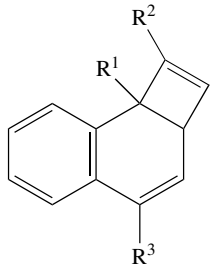
The benzotrienes **292** and **293**, which have the di-π-methane 1,4-diene system, are both photochemically and thermally reactive. Irradiation of **292** under either direct or sensitized conditions results in the formation of the semibullvalene **294** in 46% and 45% yield, respectively. This product arises by a di-π-methane process in either the singlet or triplet excited states. The involvement of such a reaction has been proven by the use of suitable labelled compounds. Other products, isomeric benzocyclooctatetraenes and naphthalene, are also formed[159]. Like the methyl analogue the parent **293** is also photochemically reactive on both direct (wavelengths >280 nm) or sensitized (*p*-dimethylaminobenzophenone using wavelengths >345 nm) irradiation. The quantum yields for the formation of the semibullvalene **295** are 0.069 on direct irradiation and 0.082 for the sensitized approach. In this instance the authors[160] have shown that the semibullvalene formed on direct irradiation is obtained by two reaction paths, a 1,2-shift process in competition with a di-π-methane rearrangement, in a ratio of 17 : 83. The triplet process leading to **295** occurs exclusively by the di-π-methane reaction path. Semibullvalene products are also formed on irradiation of the cyano-substituted dienes **296**. Direct irradiation of **296a** gives the semibullvalene **297** in 55%. Sensitized irradiation is also effective and yields a mixture of the same semibullvalene **297** in 78% and the isomer **298** in 7%[161]. Direct or sensitized



(292) R = Me
(293) R = H

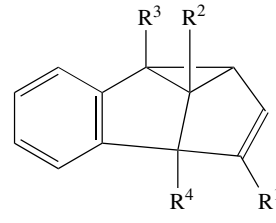


(294) R = Me
(295) R = H



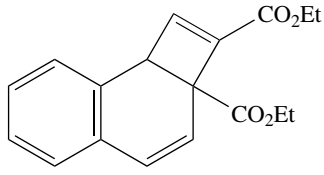
(296)

	R^1	R^2	R^3
(a)	H	CN	CN
(b)	CH	H	CN
(c)	CN	H	H

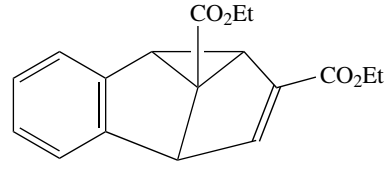


	R^1	R^2	R^3	R^4
(297)	CN	H	H	H
(298)	H	CN	H	H
(299)	H	H	CN	H
(300)	H	H	H	CN

irradiation of **296b** affords the semibullvalene **299** as the main product (63% direct, 30% sensitized). Again, in this example the route to the semibullvalene is different, depending on which irradiation mode is employed. Labelling studies have provided evidence for this divergence of reaction path. Direct irradiation involves a 1,2-shift path while sensitization utilizes only the di-π-methane path[162]. The corresponding semibullvalene **300** is obtained from irradiation of **296c** but only in 5% yield. Again the dual paths to this have been demonstrated to be operative[163]. The ester-substituted derivatives, e.g. **301**, are also photochemically reactive and follow the di-π-methane rearrangement path to afford the semibullvalene **302**[164].



(301)



(302)

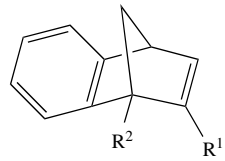
2. Benzonorbornadienes

The di-π-methane rearrangement is also operative within the benzonorbornadiene system. In these cases the interaction within the excited state will involve the vinyl group and the benzo moiety. Considerable detail has been recorded for the rearrangement of such systems such as the triplet state reactivity of the derivatives **303**. This work focused upon the influence of the bridgehead substituents on the outcome of the reactions and the control that these substituents have on the stability of the radicals formed on excitation. The result indicate that there is either bridgehead (intermediates $\mathbf{A}_1$ and $\mathbf{B}_1$) or vinylic control (intermediates $\mathbf{A}_2$ and $\mathbf{B}_2$) and the results are shown in Scheme 7[165]. Both acetone and acetophenone sensitization as well as direct irradiation bring about the cyclizations of **304**. The triplet state processes are more efficient. The reactions encountered show some regiospecificity, as illustrated by the transformation of **304a–c** quantitatively into **305**. Only with **304d** is a mixture of products **305d** and **306d** obtained. The influence of substituents within this system is also evidenced by the fact that some derivatives are unreactive or poorly reactive, as in **307**[166]. Other studies have also examined the influence on the outcome of the reaction of the inclusion of substituents within the arene ring, in this instance a pyridine group. Again, the ratio of products obtained appears to be dependent upon the nature of the substituents and perhaps also on the stability that these exercise on the biradical intermediates (Schemes 8 and 9)[167].

In more recent times interest has been shown in the effects of constrained environment on the outcome of such reactions. Some enantioselectivity in the product **308** has been reported following the irradiation of benzonorbornadiene **309** in a TlY zeolite. (−)-Ephedrine was used as the chiral inductor and sensitization brought about the reaction in 30 min. An ee of about 14% was obtained[168].

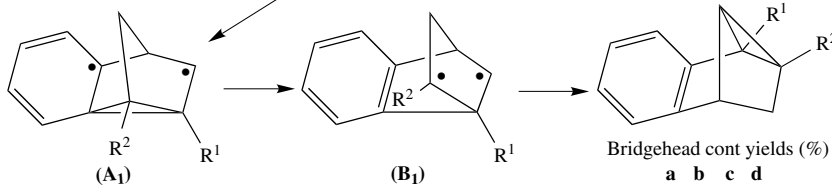
3. Bicyclo[2.2.2]octadienes

The increase in ring size from the norbornadiene-type to bicyclo[2.2.2]octadiene systems appears not to affect the overall reaction outcome. Again the interaction involves



(303)

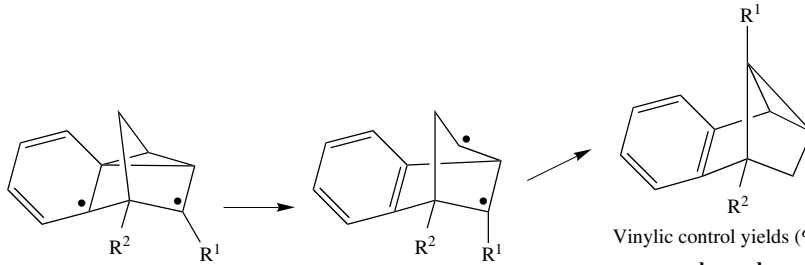
(a) $R^1 = R^2 =$ Me
(b) $R^1 = R^2 = SiMe_3$
(c) $R^1 =$ Me, $R^2 =$ Br
(d) $R^1 =$ Me, $R^2 =$ CN



(A_1) **(B_1)**

Bridgehead cont yields (%)

a	**b**	**c**	**d**
42	45	10	10

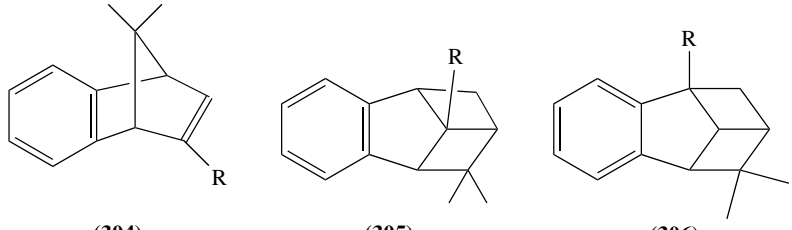


(A_2) **(B_2)**

Vinylic control yields (%)

a	**b**	**c**	**d**
58	55	90	–

SCHEME 7



(304)

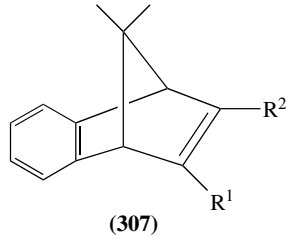
(a) R = CN
(b) R = MeO
(c) R = CO_2Me
(d) R = Me

(305)

(a) 100 %
(b) 100 %
(c) 100 %
(d) 70 %

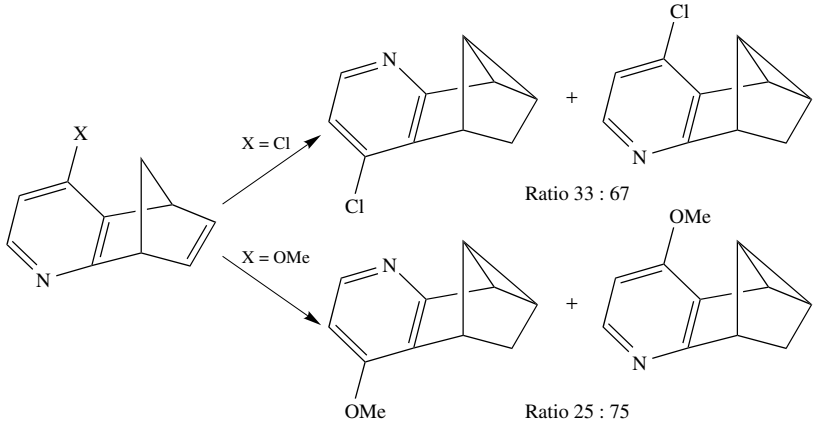
(306)

(a) —
(b) —
(c) —
(d) 30%

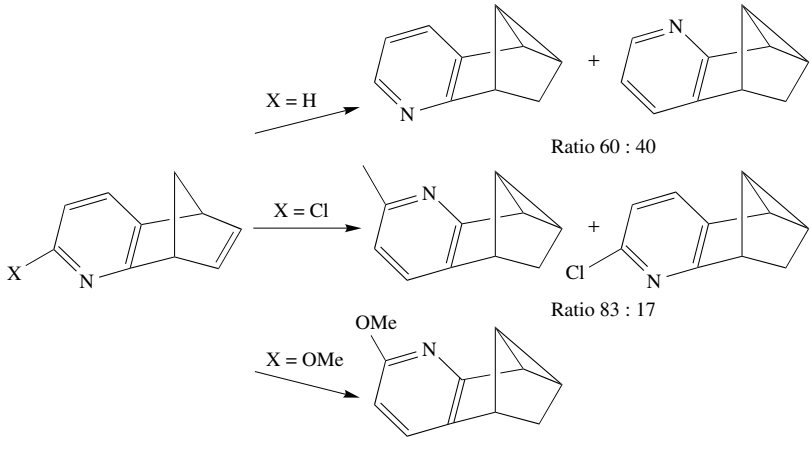


(307)

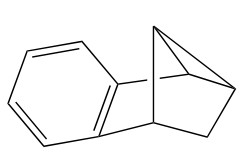
R^1	R^2
Cl	H
CN	CN
CO_2Me	CO_2Me



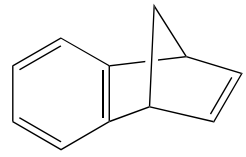
SCHEME 8



SCHEME 9

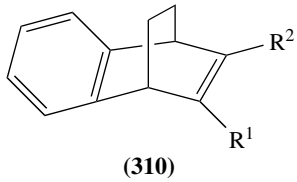


(308)

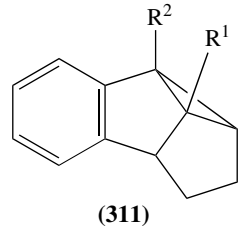


(309)

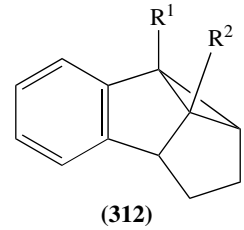
benzo/vinyl bridging. For example, the derivatives **310** can be effectively cyclized, with some evidence for regiospecificity, into the products **311** and **312**. There is obviously some control upon the reaction from substituents since the derivatives **310** (R^1 = OMe, Cl, CN or CO_2Me, R^2 = H, CN or CO_2Me) fail to cyclize[166].



(310)



(311)

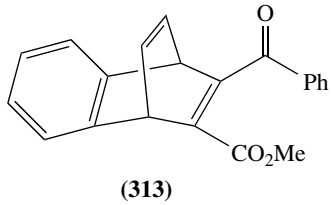


(312)

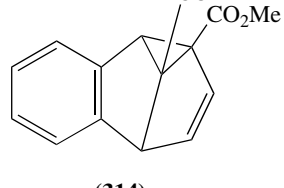
	R^1	R^2	**(311)**	**(312)**
(a)	CN	H	**(a)** 100%	**(a)** 0%
(b)	Me	H	**(b)** 73%	**(b)** 27%
(c)	CF_3	H	**(c)** 86%	**(c)** 14%
(d)	Me	Me	**(d)** 50%	**(d)** 50%
(e)	CN	Me	**(e)** 100%	**(e)** 0%

4. Benzobarrelenes

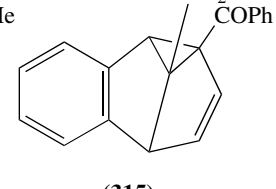
Benzobarrelenes are an important class of molecule where the di-π-methane rearrangement is operative. Clearly, within this class there is a possibility that benzo–vinyl interactions can be in competition with vinyl–vinyl processes. The direct irradiation ($\lambda > 330$ nm) of the benzobarrelene **313** in a variety of solvents (benzene, acetonitrile, methanol or hexane) affords two principal products **314** and **315** in a ratio of 1 : 1. The products are formed via a di-π-methane process involving vinyl–vinyl bridging which



(313)

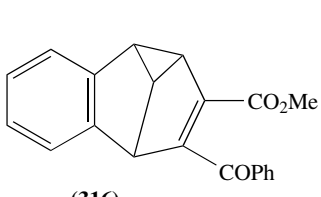


(314)

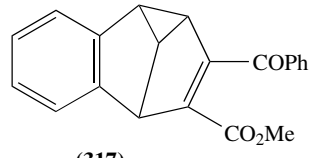


(315)

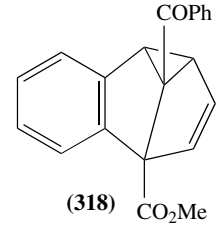
yields the more stable biradicals. Interestingly, the process is dependent on environment and, in the crystalline phase, different reactions are encountered. Thus, irradiation in the solid state using $\lambda > 290$ nm yields the three products **316**, **317** and **318**, which are produced in ratios of 5 : 3 : 2. The major product again arises by the di-π-methane path but involves less stable biradicals. The involvement of the less stable radicals is thought to be due to topochemical restrictions of molecular movement in the crystalline phase[169]. Not all such systems undergo the di-π-methane rearrangement and this is illustrated in the direct irradiation of **319** in benzene or acetonitrile which affords only a cyclooctatetraene derivative[170,171]. Benzophenone sensitization is required to activate this compound and irradiation under these conditions gives the semibullvalene **320**[172]. Vinyl benzo-bridging is the path followed on direct irradiation of **321** in benzene or acetonitrile. This again yields a 1 : 1 mixture of a cyclooctatetraene and the semibullvalene **322**. The authors[173] suggest that steric influences play a major part in determining the outcome of the reaction. In these examples an unusual example of Me–Me strain relief is operative. Other substituted barrelenes **(323)** are also reported to rearrange readily to the corresponding semibullvalenes[174].



(316)



(317)



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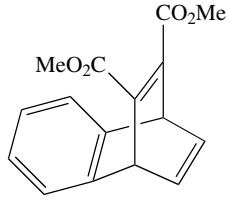

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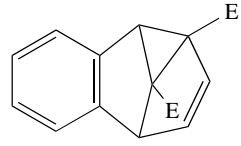
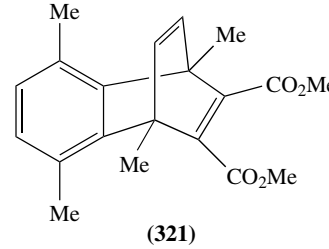


E = CO_2Me

(320)



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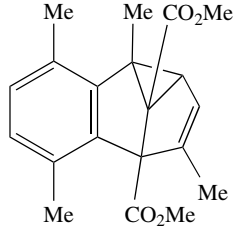

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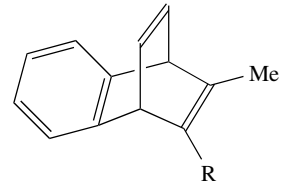
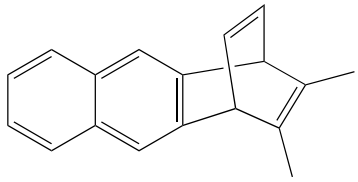


(323)

R = CN, CO_2H or CO_2Me

Vinyl–vinyl bridging reactions are also operative in the barrelene derivatives **324**. The reaction arises from the triplet and is brought about by xanthene sensitizaion[175]. The semibullvalenes **325** and **326** are formed in a ratio of 8.3 : 1 in this rearrangement. Even when hetero-atoms are present, there are some instances when vinyl–vinyl bridging is operative. This is demonstrated by the conversion of **327**, R = H, into **328**. This reaction mode is in competition with the pyrazino–vinyl bridging path that yields **329**, R = H, and **330**, R = H[176]. Others have also examined the reactivity of such pyrazine derivatives[177]. The pyrazino–vinyl system is an example of the aza-di-π-methane system originally discovered by Armesto and his coworkers and reviewed recently by Zimmerman and Armesto[148].



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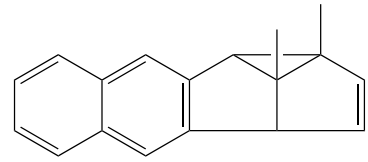

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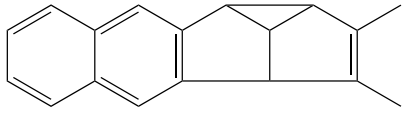

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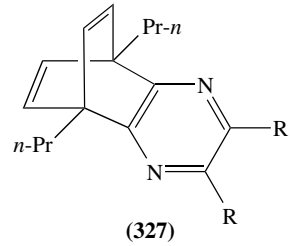

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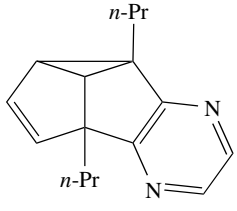

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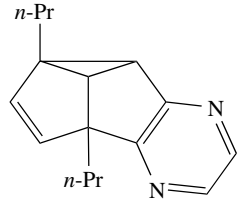

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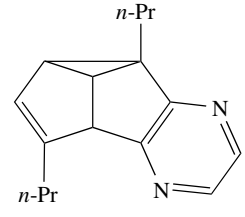
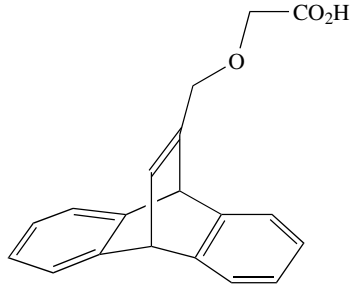


(330)

5. Dibenzobarrelenes

The influence of radical stabilization on the outcome of the rearrangement reactions of a variety of dibenzobarrelenes has been evaluated[178]. A detailed analysis of the acetophenone-sensitized conversion of the cyano-substituted barrelenes into the corresponding semibullvalenes has been presented[179]. The outcome of the irradiation of the dibenzobarrelene **331** is dependent upon the excited state involved. Thus direct irradiation affords a cyclooctatetraene and sensitized irradiation converts it into the two

semibullvalene derivatives **332** and **333** in a ratio of 3 : 1[180]. The diol **334** can be photochemically converted (by irradiation at 254 nm) into the semibullvalene **335** in ethanol solution. Acetone sensitization is also effective, affording the same product[181].



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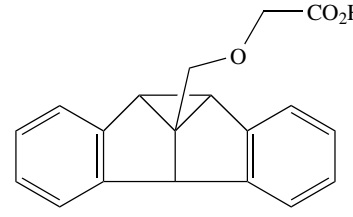

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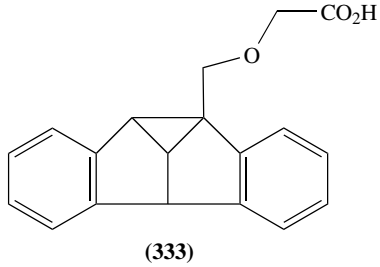
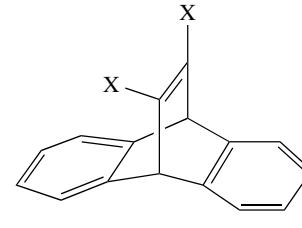


(333)



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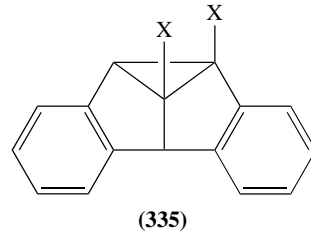
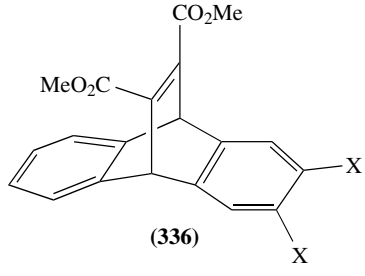


X = C(OH)Ph$_2$

(335)

The di-π-methane rearrangement of **336** arises from both the singlet and the triplet excited states and affords the regioisomeric products **337** and **338**[182]. The influence of substituents on the di-π-methane rearrangement of the dibenzobarrelene **339** has been studied. All the compounds undergo photoconversion into the corresponding dibenzosemibullvalenes. Where the substituents on the ester groups were different, two regioisomeric paths were observed[183]. Previous studies on the photochemical rearrangement of the dibenzobarrelene **340** had shown that acetone-sensitization affords the two products **341** and **342** by way of the two possible biradicals formed by benzo–vinyl bridging[184]. Other more heavily substituted derivatives **343** have also been studied and both direct irradiation and acetone sensitization affords the di-π-methane product **344**[185]. Variations in the substituents do not appear to affect adversely the outcome of the reaction. Thus the irradiation of **345**, as a solution in deuteriochloroform, brings about efficient di-π-methane rearrangement, $\phi = 0.28$, affording the corresponding semibullvalene[186]. Demuth and his

coworkers[187] have described the design of a 'solar' reactor for carrying out photochemical reactions. The reaction demonstrated is the *p*-hydroxyacetophenone sensitized conversion of the barrelene derivative **346** into **347**. IR studies of **348**, show that hydrogen-bonded structures, both monomeric and dimeric, are present. In non-polar solvents irradiation of **348** afforded two products, **349** and **350**, in a ratio of 4 : 1 formed by a di-π-methane rearrangement. The ratio of the products from the irradiation are in accord with the ratio of the hydrogen-bonded species detected in the IR work[188]. Scheffer and coworkers[189] have also studied the di-π-methane reactivity of a series of dibenzobarrelenes in an attempt at establishing the features which controlled the regiospecificity of the conversion into semibullvalene derivatives. Associated with this they[190] have demonstrated with some molecules, e.g. **351**, that only one product **(352)** is obtained. When substituents are introduced into the lactone ring, as in **353**, only two photo-products **354** and **355** are obtained. From these results the authors[189,190] reason that the relief of steric crowding is the principal factor governing regioselectivity in such transformations.



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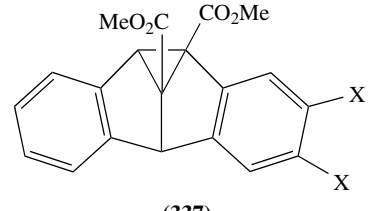
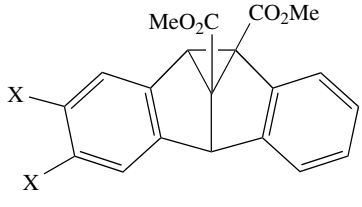


(337)

X = alkyl



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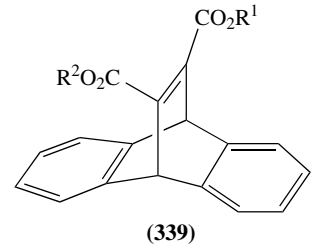

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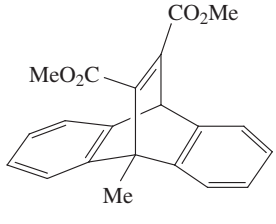

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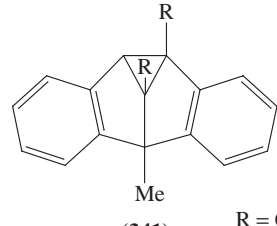
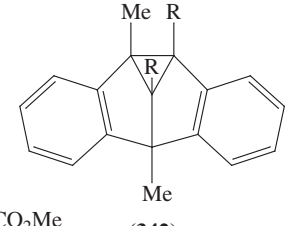


(341)

R = CO_2Me



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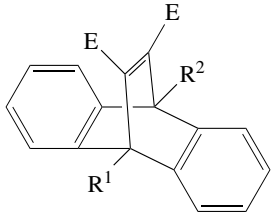

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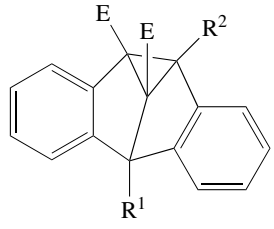

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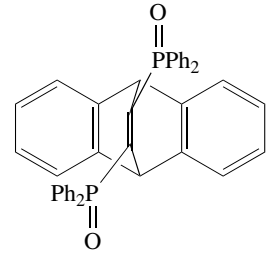
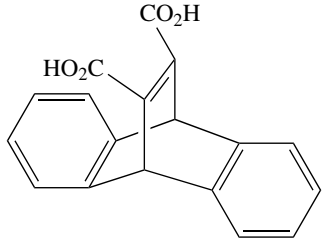


(345)

(a) E = CO_2Me, $R^1 = R^2 = Me$
(b) E = CO_2Me, $R^1 = Me$, $R^2 = Ph$
(c) E = CO_2Me, $R^1 = Ph$, $R^2 = H$



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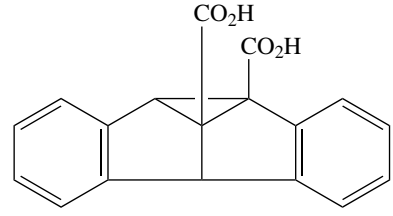

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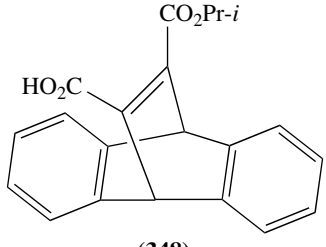

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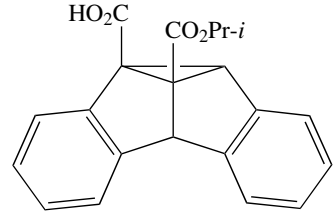

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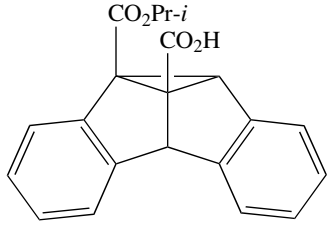

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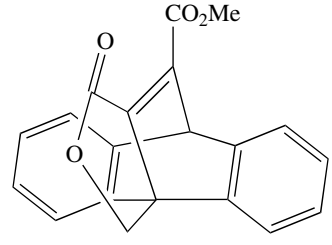

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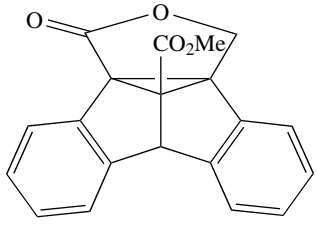

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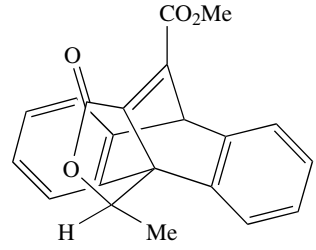

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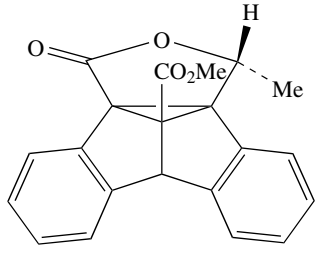

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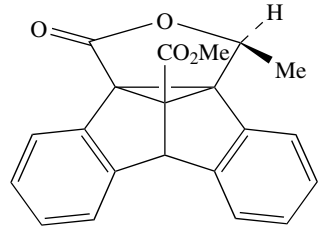
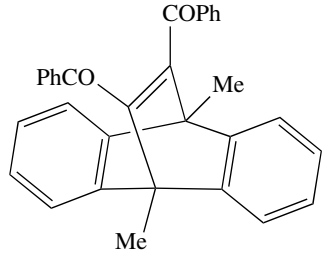


(355)

In some instances the semibullvalene product is not isolated and alternative routes are operative. Related to this is the work of George and his coworkers[191] who reported the results of the irradiation of the dibenzobarrelene **356**. The original structural assignments were shown to be incorrect by Scheffer and his coworkers[192]. A reinvestigation has shown that the products from the reaction are a cyclooctatetraene, and the products **357** and **358**[193]. The compound **358** is formed by a secondary photo reaction: **356** is converted into the usual semibullvalene product. Thus, under the conditions of the reaction it undergoes bond fission. Trapping of the resultant biradicals by oxygen eventually results in the production of the isolated product **358**. The transformation arises by way of a semibullvalene derivative involving the di-π-methane transformation of the starting material. A further example of such a process is shown in the steady state and laser-flash photolysis of the barrelene derivative **359**. Irradiation of this in a variety of solvents (benzene, acetone or methanol) results in its efficient conversion (70%) into the dibenzopentalene ketone **360**[194].



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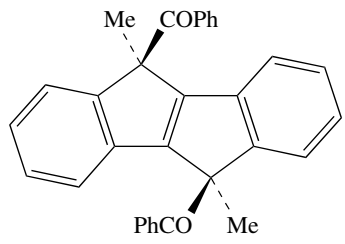

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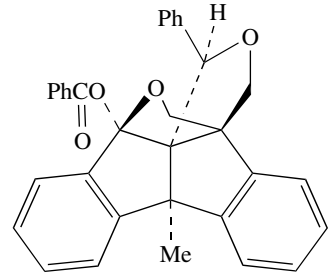
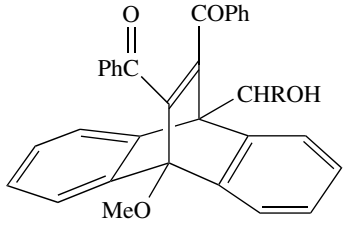


(358)



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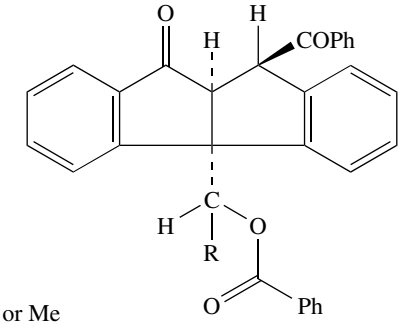
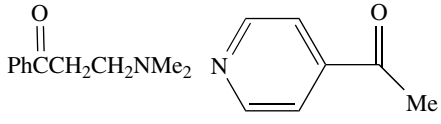


R = H or Me

(360)

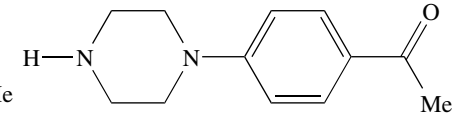
a. Phase effects. Considerable interest has been shown in the influence of phase on the outcome of the irradiation of dibenzobarrelene derivatives. For example, the ammonium salts of the acid function of **331**, using the amines **361**, **362** and **363**, have been used to study triplet energy transfer in the solid state. Under these conditions the amine groups were irradiated specifically (at $\lambda > 330$ nm) and gave only the two semibullvalenes **332** and **333** with no evidence for the formation of the cyclooctatetraene that is formed from the singlet state. The semibullvalenes were obtained in ratios of 6 : 1, 5 : 1 and 15 : 4, respectively. This is indicative of triplet energy transfer within the solid state[180]. In another example crystals of **334** were shown to have close interactions of the hydroxy groups. Irradiation in the solid resulted in the suppression of the di-π-methane process and intramolecular proton transfer results in the formation of the ether **364**[181]. Other detailed studies have shown that a variety of paths can be operative in the crystalline phase. In this regard an analysis has indicated that the photochemical cyclization of the dibenzobarrelene **365** to the semibullvalene **366** can occur by four possible paths only involving vinyl/benzo bridging. These paths are bridging between carbons 9a and 11 and between 4a and 12 on one side of the molecule, and between 8a and 11 and 10a and 12. It is possible to differentiate between paths by determining the absolute configuration in the reactant crystal. The crystal of the barrelene **365** is homochiral and irradiation in the solid gives laevorotatory **366**. This means that there is a preference for the path using 9a/11or 10a/12 interaction. It is argued that within this pair of routes the interaction between 10a/12 is favoured[195]. Dibenzobarrelene **343a** also shows different reactivity in the crystalline phase. Irradiation does afford the same semibullvalene **344** as is obtained from the solution-phase reaction, but a new product **367** is also obtained. This

is reminiscent of the reactivity of **356** previously mentioned. A re-investigation of this has suggested that the biradical **368** is involved in the formation of this new product. The formation of the biradical such as **368** must involve a possible tri-π-methane intermediate **369**[185].

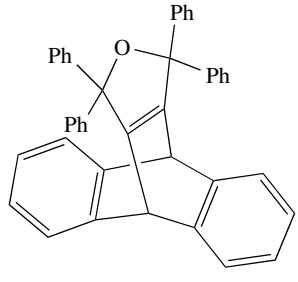


(361)

(362)



(363)



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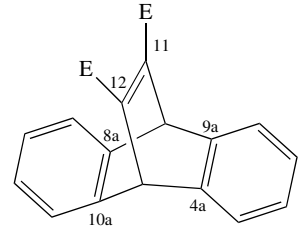
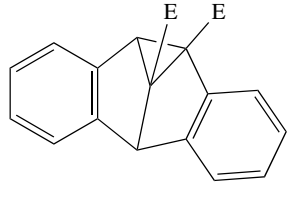


(365) E = CO_2Pr-*i*



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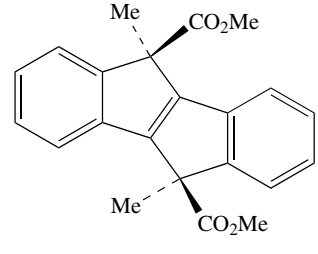
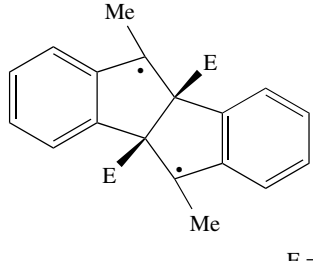
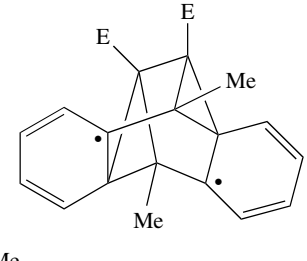


(367)



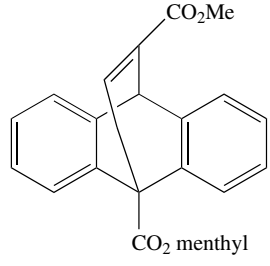
(368)

E = CO_2Me

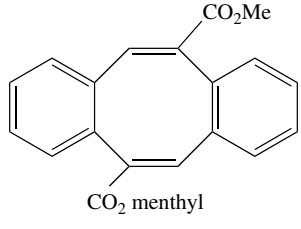


(369)

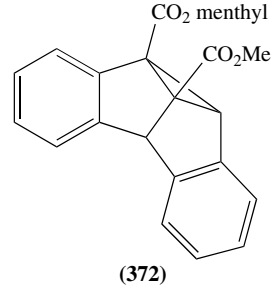
Asymmetric induction in the di-π-methane rearrangement is also of interest and studies on this have examined the influence of chiral esters. Thus the irradiation of **370** yields a cyclooctatetraene **371** and a diastereoisomeric mixture of the semibullvalenes **372** and **373** in a ratio of 60 : 40 in solution and 20 : 80 in the solid phase. The position of attachment is vital and the diastereoselectivity shown by the barrelene **374** is very poor and yields a 1 : 1 mixture of products[196]. Further examples of the control exercised when dibenzobarrelenes are irradiated in the crystalline phase have used the derivatives **375** and **376** as the acid salts formed with chiral amines. Irradiation affords the products **377** and **378** respectively, obtained after esterification with MeOH, with an ee of >95%[197]. The influence of a chiral crystal lattice on the outcome of the di-π-methane reaction of achiral **379** has been studied. The irradiation in the crystalline phase gives two chiral di-π-methane products **380** and **381**. The former of these is racemic but the latter is obtained in high enantiomeric excess which, under the best conditions, i.e. at $-20\,^{\circ}C$, approaches 100%[198]. The irradiation of crystals of **345**, as an ethanol complex, affords **382** with an ee of 94%. Carrying out the irradiation at temperatures lower than ambient enhances the specificity of the reaction[186].



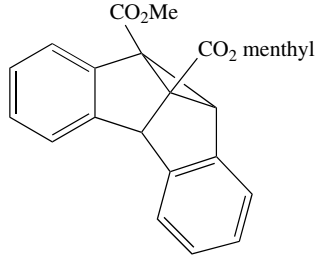
(370)



(371)



(372)



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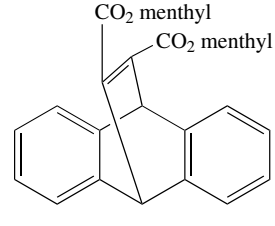
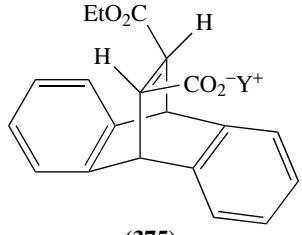


(374)



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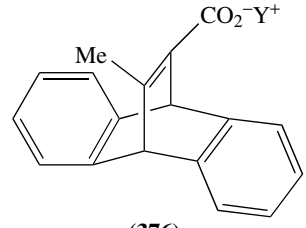
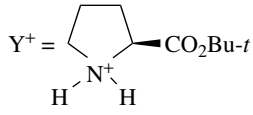
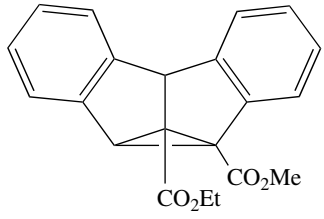
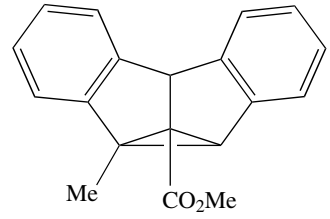


(376)

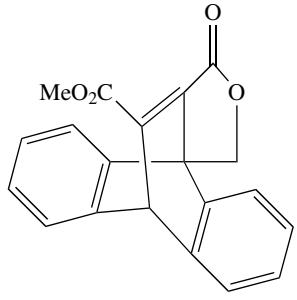




(377)



(378)



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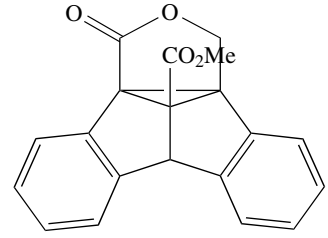
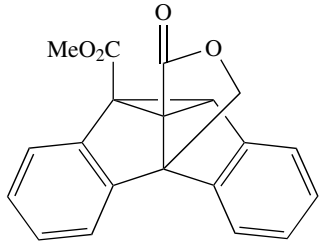
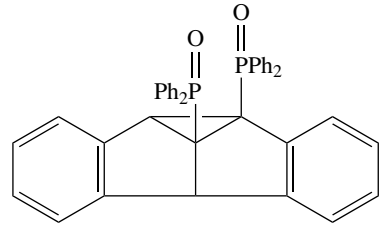


(380)



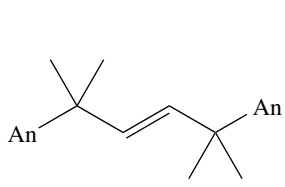
(381)



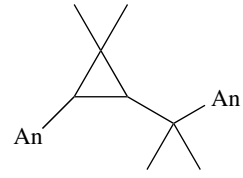
(382)

6. Other systems undergoing the di-π-methane rearrangement

a. All-carbon systems. The triplet state of **383** is also reactive by the di-π-methane rearrangement yielding **384**. This involves an aryl/vinyl bridging reaction. Direct irradiation has a completely different outcome and yields four products that are probably formed by secondary reaction of the cyclopropane **384**[199]. A vinyl–aryl interaction is also found in the irradiation of the alkenes **385** under nitrogen in benzene and results in the formation of the cyclopropanes **386**[200]. Both direct and sensitized irradiation of the biphenylylbutene **387** brings about the formation of the cyclopropane **388** with a quantum yield of 7.6×10^{-3}. The authors[201] suggest that the low reactivity of this substrate in the di-π-methane rearrangement is a result of localization of the excitation energy within the biphenyl moiety. The irradiation of the alkene **389** affords the cyclopropanol **390** by a di-π-methane rearrangement. The dienol **391** is also reactive in this mode and affords the isomeric cyclopropanes **392**[202].

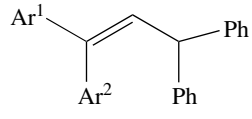


(383)



(384)

An = *p*-$MeOC_6H_4$



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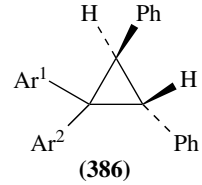


(386)

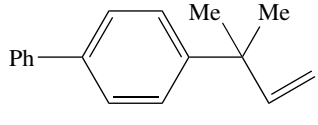
$Ar^1 = Ar^2 = Ph$

Ar^1 = *p*-tolyl, $Ar^2 = Ph$

$Ar^1 = Ar^2$ = *p*-tolyl

Ar^1 = *p*-$MeOC_6H_4$, $Ar^2 = Ph$

$Ar^1 = Ar^2$ = *p*-$MeOC_6H_4$



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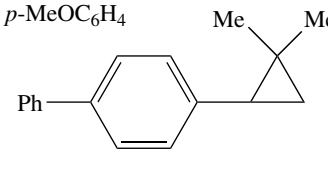
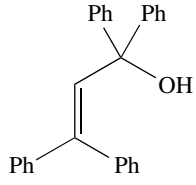
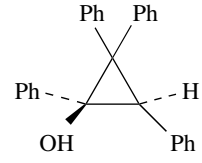


(388)

As pointed out earlier, there is a growing interest in the control that can be exercised on the reactions of molecules constrained within the solid state. The previous focus on this dealt with rearrangements of dibenzobarrelenes, but control has also been demonstrated for open-chain systems. This has been shown by Demuth and his coworkers[203] in a study



(389)



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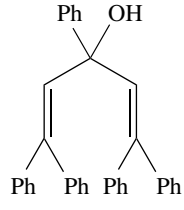
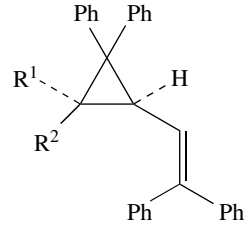


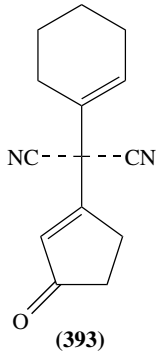
(391)



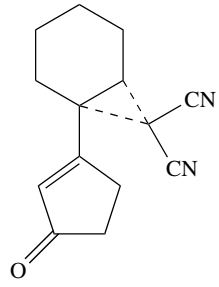
(392)

R^1 = Ph, R^2 = OH
or *vice versa*

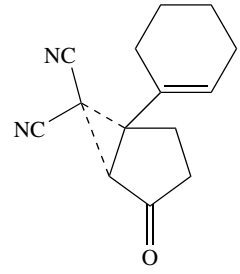
of the homochiral crystals of the enone **393**. This is converted into the two products, **394** with 44% ee and **395** with 96% ee. Here again the outcome of the reaction is dependent on the amount of available space within the crystal. X-ray analysis has shown that there is more movement for the cyclohexene moiety in the crystal than there is for the cyclopentenone and it is this which controls the stereochemical outcome of the reaction. In solution phase, other enone systems such as **396** are also reactive. This undergoes di-π-methane rearrangement into the two products **397** and **398**[204]. The related furanone **399** is also reactive and is converted into the cyclopropane derivative **400**. The route to this product involves the biradical **401**; bond-breaking brings about re-aromatization and the formation of a primary radical[205]. The cyclic-1,4-dienes **402** all undergo the di-π-methane rearrangement affording bicyclic products, as illustrated for **402a** in Scheme 10[206].



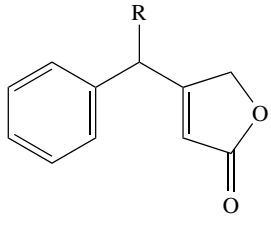
(393)



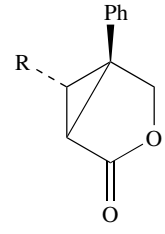
(394)



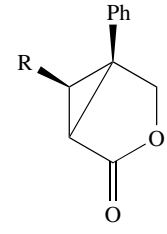
(395)



(**396**)

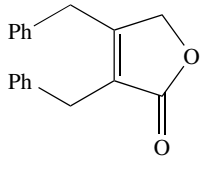


(**397**)

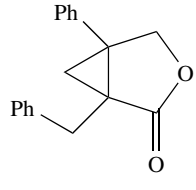


(**398**)

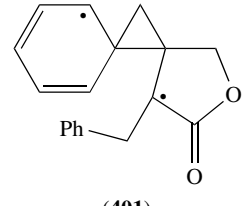
R = Me, Ph or cyclohexyl



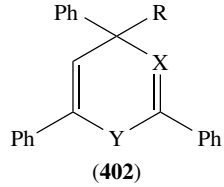
(**399**)



(**400**)



(**401**)

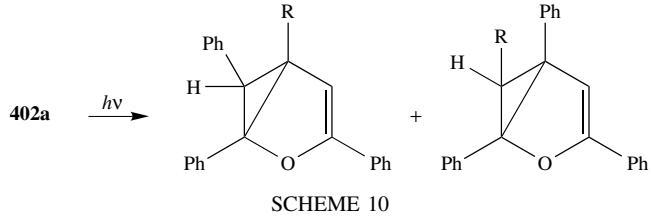


(**402**)

(**a**) X = CH, Y = O, R = Ph, 4-BrC_6H_4 or 4-MeC_6H_4

(**b**) X = CH, Y = S, R = Ph, 4-BrC_6H_4 or Me

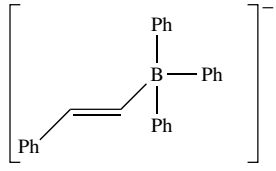
(**c**) X = N, Y = O, R = Ph



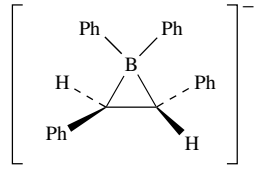
SCHEME 10

b. Hetero-di-π-methane systems. The di-π-borate process has also been investigated. This concerns the conversion of **403** into **404** by direct irradiation at 254 nm. The reaction is efficient and involves a vinyl–phenyl interaction, similar to that encountered in the all-carbon system. The product **404** is formed in a reasonable yield of 60%[207]. An alkynyl–phenyl interaction is also observed in the photochemical conversion of the ethynyltriphenyl borate salts **405** which undergo the rearrangement to yield unstable cyclopropene derivatives **406**[208–210]. Earlier studies had suggested that the irradiation of such compounds gave only *cis*-stilbene and biphenyl[211]. Phenyl–phenyl bridging is

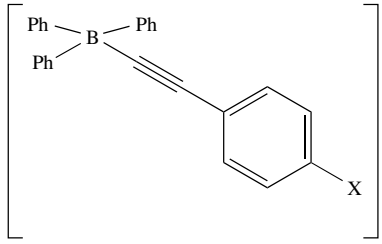
also possible as in the conversion of **407** into **408**[212]. A review has highlighted aspects of the photochemical behaviour of unsaturated borane chemistry[213].



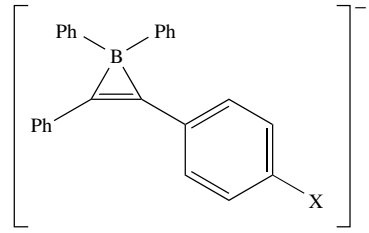
(**403**)



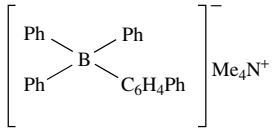
(**404**)



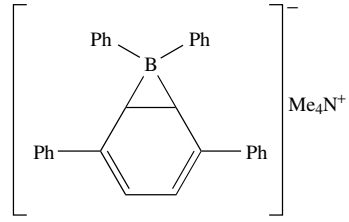
(**405**) X = H, F or MeO



(**406**)



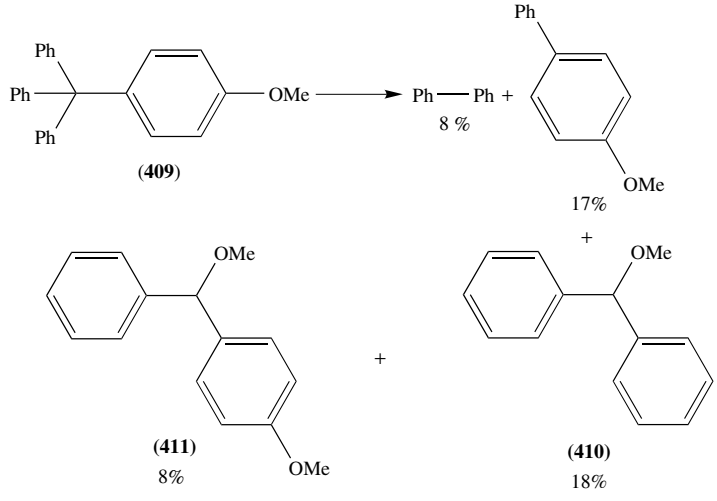
(**407**)



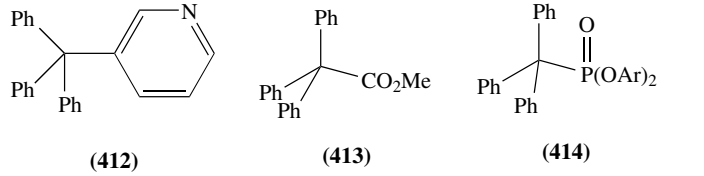
(**408**)

c. Triphenylmethyl derivatives. Phenyl–phenyl interactions are also the key processes in the photochemical rearrangements encountered with the tetraarylmethane derivatives such as **409**. As can be seen from Scheme 11, a variety of products are obtained on irradiation, usually in methanol as solvent and through a quartz filter. Here two types of bridging take place, one between two phenyl groups and one between a phenyl and the *p*-methoxyphenyl group, the di-π-methane type of interaction. Extrusion of the biphenyl moiety affords carbenes that are trapped as the ethers **410** and **411** when the reaction is carried out in methanol[214]. Analogous reactivity has been recorded for the pyridyl derivatives **412**[214], the esters **413**[215] and the phosphonate **414**[216]. The rearrangements within these compounds all involve the di-π-methane rearrangement accounting for the formation of the appropriate biphenyls and derivatives of the carbenes formed on extrusion of the biphenyl moiety. Thus methyl 2-methoxyphenylacetate is the carbene product from reaction of the ester **413**. Similar behaviour is seen on irradiation of the two derivatives **415** and **416** as shown in Schemes 12 and 13[217,218].

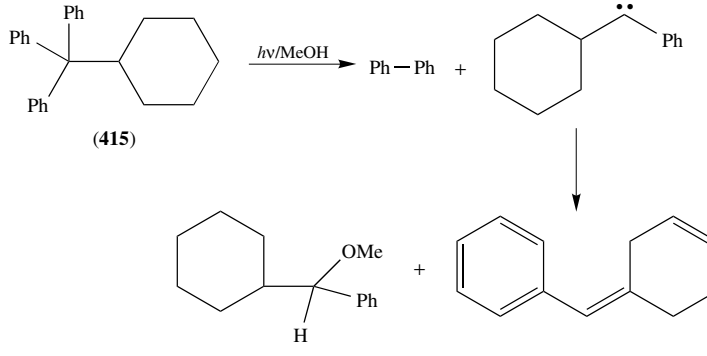
When one of the components of the molecule undergoing reaction is a double bond, an alternative reaction mode is operative. Thus it can be seen that **417** follows the usual path involving aryl–aryl bridging affording biphenyl and a carbene that is trapped by solvent. However, in addition a vinyl–aryl di-π-methane process is also operative and affords the



SCHEME 11

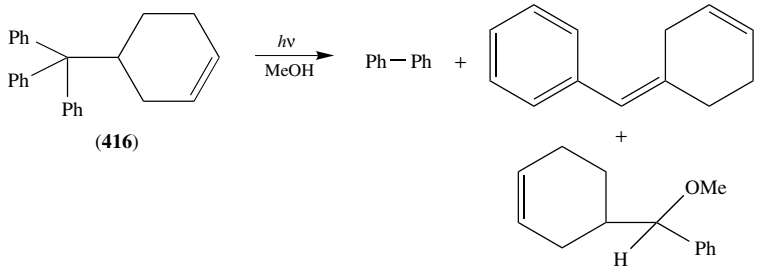


Ar = p-XC_6H_4, X = Me, MeO, Cl



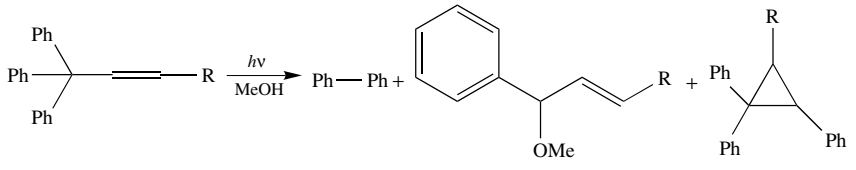
SCHEME 12

cyclopropanes **418** (Scheme 14)[219,220]. Shi and coworkers[221] have also reported the photochemical conversion of the alkyne **419a** into biphenyl and its derivatives (Scheme 15). The reaction is brought about by irradiation under argon in methanol solution. Again the reaction is a typical aryl–aryl di-π-methane interaction. It has been suggested that the proposed bridged intermediate is zwitterionic as shown in **420**. Such a postulate has been substantiated by substituent effects.



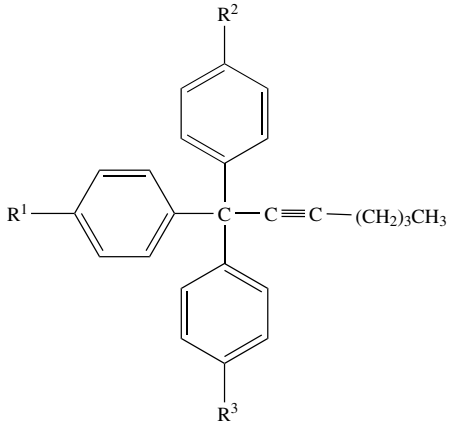
(**416**)

SCHEME 13

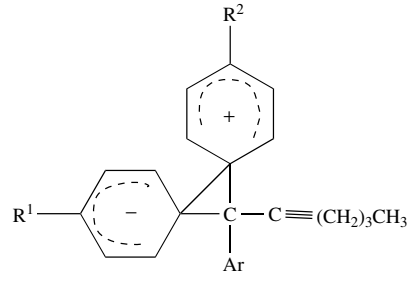


(**417**)			(**418**)
R = H	8%	5%	14%
R = Me	16%	15%	8%
R = Et	24%	16%	9%

SCHEME 14

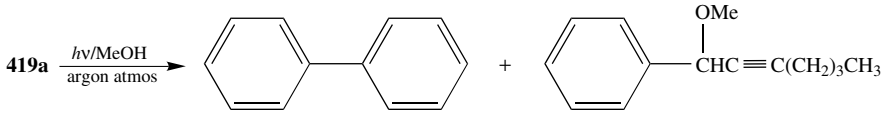


(**419**)



(**420**)

(a) $R^1 = R^2 = R^3 = H$
(b) $R^1 = R^2 = H$, $R^3 = Me$
(c) $R^1 = R^2 = R^3 = Me$
(d) $R^1 = R^2 = H$, $R^3 = MeO$
(e) $R^1 = R^2 = R^3 = MeO$



SCHEME 15

VI. REFERENCES

1. A. Schönberg, *Preparative Organic Photochemistry*, Springer-Verlag, Berlin, 1968.
2. W. M. Horspool and D. Armesto, *Organic Photochemistry*, Ellis Horwood-PTR Prentice Hall, New York and London, 1992.
3. W. M. Horspool and P. S. Song (Eds.), *Handbook of Organic Photochemistry and Photobiology*, CRC Press, Boca Raton 1995.
4. *Photochemistry Volumes 1–30*, Royal Society of Chemistry, London, 1970.
5. W. L. Dilling, *Chem. Rev.*, **66**, 373 (1966).
6. H. Prinzbach, *Pure Appl. Chem.*, **16**, 17 (1968).
7. P. S. Mariano and J. L. Stavinoha, in *Synthetic Organic Photochemistry*, (Ed. W. M. Horspool), Plenum Press, New York and London, 1984, p. 145.
8. H. D. Roth, H. Weng, D. Zhou and T. Herbertz, *Pure Appl. Chem.*, **69**, 809 (1997).
9. H. Weng, C. Scarlata and H. D. Roth, *J. Am. Chem. Soc.*, **118**, 10947 (1996).
10. D. R. Arnold, M. S. W. Chan and K. A. McManus, *Can. J. Chem.*, **74**, 2143 (1996).
11. H. Goerner, K.-D. Warzecha and M. Demuth, *J. Phys. Chem. A*, **101**, 9964 (1997).
12. U. Hoffmann, Y. Gao, B. Pandey, S. Klinge, K. D. Warzecha, H. D. Roth and M. Demuth, *J. Am. Chem. Soc.*, **115**, 10358 (1993).
13. D. A. Connor, D. R. Arnold, P. K. Bakshi and T. S. Cameron, *Can. J. Chem.*, **73**, 762 (1995).
14. D. R. Arnold, M. S. W. Chan and K. A. McManus, *Can. J. Chem.*, **74**, 2143 (1996).
15. H. J. P. De Lijser and D. R. Arnold, *J. Chem. Soc., Perkin Trans. 2*, 1369 (1997).
16. A. Heidbreder and J. Mattay, *Tetrahedron Lett.*, **33**, 1973 (1992).
17. S. Hintz, J. Mattay, R. van Eldik and W. F. Fu, *Eur. J. Org. Chem.*, 1583 (1998).
18. K. Nakanishi, K. Mizuno and Y. Otsuji, *J. Chem. Soc., Chem. Commun.*, 90 (1991).
19. T. S. Kim, H. Sarker and N. L. Bauld, *J. Chem. Soc., Perkin Trans. 2*, 577 (1995).
20. T. Miyashi, A. Konno and Y. Takahashi, *J. Am. Chem. Soc.*, **120**, 3676 (1998).
21. H. Ikeda, T. Minegishi, H. Abe, A. Konno, J. L. Goodman and T. Miyashi, *J. Am. Chem. Soc.*, **120**, 87 (1998).
22. H. Ikeda, A. Ishida, T. Takasaki, S. Tojo, S. Takamuku and T. Miyashi, *J. Chem. Soc., Perkin Trans. 2*, 849 (1997).
23. H. Ikeda, T. Oikama and T. Miyashi, *Tetrahedron Lett.*, **34**, 2323 (1993).
24. Y. Takahashi, O. Okitsu, M. Ando and T. Miyashi, *Tetrahedron Lett.*, **35**, 3953 (1994).
25. A. G. Griesbeck, O. Sadlek and K. Polborn, *Justus Liebigs Ann. Chem.*, 545 (1996).
26. Y. Takahashi, M. Ando and T. Miyashi, *Tetrahedron Lett.*, **36**, 1889 (1995).
27. Y. Takahashi, M. Ando and T. Miyashi, *J. Chem. Soc., Chem. Commun.*, 521 (1995).
28. H. Yoon and W. Chae, *Tetrahedron Lett.*, **38**, 5169 (1997).
29. H. E. Zimmerman and K. D. Hofacker, *J. Org. Chem.*, **61**, 6526 (1996).
30. H. Ishii, T. Hirano, S. Maki, H. Niwa and M. Ohashi, *Tetrahedron Lett.*, **39**, 2791 (1998).
31. D. Mangion, R. M. Borg and W. Errington, *J. Chem. Soc., Chem. Commun.*, 1963 (1995).
32. H. Weng and H. D. Roth, *J. Org. Chem.*, **60**, 4136 (1995).
33. Q. H. Wu, B. W. Zhang, Y. F. Ming and Y. Cao, *J. Photochem. Photobiol. A: Chem.*, **61**, 53 (1991).
34. Y. Ming, Q. Wu and Y. Cao, *Huaxue Xuebao*, **47**, 618 (1989); *Chem. Abstr.*, **111**, 231687 (1989).
35. H. Yang, X. Qi and M. Fan, *Ganguang Kexue Yu Kuang Huaxue*, 7 (1988); *Chem. Abstr.*, **111**, 56767 (1989).
36. Q. Wu, B. Zhang and Y. Cao, *Youji Huaxue*, **11**, 590 (1991); *Chem. Abstr.*, **116**, 106021 (1992).
37. Y. Ming, Q. Wu and Y. Cao, *Chin. Chem. Lett.*, **1**, 161 (1990); *Chem. Abstr.*, **115**, 207286 (1991).

38. T. Hirano, S. Shima and M. Ohashi, *J. Chem. Soc., Chem. Commun.*, 1544 (1992).
39. G. F. Chen, R. S. Pappas and F. Williams, *J. Am. Chem. Soc.*, **114**, 8314 (1992).
40. J. E. Baldwin and R. H. Greeley, *J. Am. Chem. Soc.*, **87**, 4514 (1965).
41. Copper(I) has been known to complex alkenes.
42. K. Langer J. Mattay, A. Heidbreder and M. Moeller, *Justus Liebigs Ann. Chem.*, 257 (1992); *Chem. Abstr.*, **116**, 174449 (1992).
43. K. Langer and J. Mattay, *J. Org. Chem.*, **60**, 7256 (1995).
44. S. Ghosh and D. Patra, *Tetrahedron Lett.*, **34**, 4565 (1993).
45. D. Patra and S. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, 2635 (1995).
46. S. Ghosh, D. Patra and S. Samajdar, *Tetrahedron Lett.*, **37**, 2073 (1996).
47. S. Samajdar, D. Patra and S. Ghosh, *Tetrahedron*, **54**, 1789 (1998).
48. A. Haque, A. Ghatak, S. Ghosh and N. Ghoshal, *J. Org. Chem.*, **62**, 5211 (1997).
49. J. Nishimura, Y. Okada, S. Inokuma, Y. Nakamura and S. R. Gao, *Synlett*, 884 (1994).
50. J. Nishimura, A. Ohbayashi, H. Doi and K. Nishimura, *Chem. Ber.*, **121**, 2019 (1988).
51. J. Nishimura, A. Ohbayashi, Y. Wada and A. Oku, *Tetrahedron Lett.*, **29**, 5375 (1988).
52. J. Nishimura, Y. Wada and Y. Sano, *Bull. Chem. Soc. Jpn.*, **65**, 618 (1992).
53. J. Nishimura and Y. Horikoshi, *Bull. Chem. Soc. Jpn.*, **65**, 941 (1992).
54. J. Nishimura, M. Takeuchi, H. Takahashi, Y. Ueda, Y. Matsuda and A. Oku, *Bull. Chem. Soc. Jpn.*, **62**, 3161 (1989).
55. J. Nishimura, M. Takeuchi, H. Takahashi and M. Sato, *Tetrahedron Lett.*, **31**, 2911 (1990).
56. M. Takeuchi and J. Nishimura, *Tetrahedron Lett.*, **33**, 5563 (1992).
57. J. Nishimura, Y. Horikoshi, Y. Wada, H. Takahashi, S. Machino and A. Oku, *Tetrahedron Lett.*, **30**, 5439 (1989).
58. K. Mizuno, K. Nakanishi and Y. Otsuji, *Phosphorus, Sulfur Silicon Relat. Elem.*, **67**, 257 (1992); *Chem. Abstr.*, **117**, 48739 (1992).
59. K. Nakanishi, K. Mizuno and Y. Otsuji, *J. Chem. Soc., Perkin Trans. 1*, 3362 (1990).
60. S. Inokuma, T. Yamamoto and J. Nishimura, *Tetrahedron Lett.*, **31**, 97 (1990).
61. Y. Nakamura, T. Fuji, S. Inokuma and J. Nishimura, *J. Phys. Org. Chem.*, **11**, 79 (1998).
62. S. Inokuma, M. Takezawa, H. Satoh, Y. Nakamura, T. Sasaki and J. Nishimura, *J. Org. Chem.*, **63**, 5791 (1998).
63. J. Nishimura, Y. Horikoshi, Y. Wada, H. Takahashi and M. Sato, *J. Am. Chem. Soc.*, **113**, 3485 (1991).
64. F. Ishii, I. Akiyama and J. Nishimura, *Chem. Lett.*, 1579 (1992).
65. Y. Okada, S. Mabuchi, M. Kurahayashi and J. Nishimura, *Chem. Lett.*, 1345 (1991).
66. Y. Okada, F. Ishii, Y. Kasai and J. Nishimura, *Tetrahedron*, **50**, 12159 (1994).
67. W. W. McWhorter and B. Jaun, *Helv. Chim. Acta*, **70**, 1095 (1987).
68. N. Y. Jing and D. M. Lemal, *J. Org. Chem.*, **60**, 89 (1995).
69. A. Padwa, K. E. Krumpe, L. W. Terry and M. W. Wannamaker, *J. Org. Chem.*, **54**, 1635 (1989).
70. D. L. Oldroyd and A. C. Weedon, *J. Chem. Soc., Chem. Commun.*, 1491 (1992).
71. D. L. Oldroyd and A. C. Weedon, *J. Org. Chem.*, **59**, 1333 (1994).
72. G. Steiner, R. Munschauer, G. Klebe and L. Siggel, *Heterocycles*, **40**, 319 (1995).
73. G. Steiner, Ger. Offen. DE 4,219,975; *Chem. Abstr.*, **120**, 244657 (1994).
74. S. C. Ward and S. A. Fleming, *J. Org. Chem.*, **59**, 6476 (1994).
75. S. A. Fleming and S. C. Ward, *Tetrahedron Lett.*, **33**, 1013 (1992).
76. G. W. Shriver and T. A. Thomas, *J. Am. Chem. Soc.*, **109**, 4121 (1987).
77. (a) See References 5 and 6.
    (b) P. E. Eaton, *Angew. Chem., Int. Ed. Engl.*, **31**, 1421 (1992).
    (c) J. P. Melder, F. Wahl, H. Fritz and H. Prinzbach, *Chimia*, **41**, 426 (1987); *Chem. Abstr.*, **109**, 148909 (1988).
    (d) H. Prinzbach and K. Weber, *Angew. Chem., Int. Ed. Engl.*, **33**, 2239 (1994).
78. I. J. Anthony, L. T. Byrne, R. K. McCulloch and D. Wege, *J. Org. Chem.*, **53**, 4123 (1988).
79. R. Gleiter and S. Brand, *Tetrahedron Lett.*, **35**, 4969 (1994).
80. R. Gleiter and M. Korcher, *Angew. Chem., Int. Ed. Engl.*, **27**, 840 (1988).
81. S. Brand and R. Gleiter, *Tetrahedron Lett.*, **38**, 2939 (1997).
82. H. Okamoto, M. Kimura, K. Satake and S. Morosawa, *Bull. Chem. Soc. Jpn.*, **66**, 2436 (1993).
83. H. Takeshita, H. Kawakami, Y. Ikeda and A. Mori, *J. Org. Chem.*, **59**, 6490 (1994).

84. C.-T. Lin, B. P. Hwang and T.-C. Chou, *J. Chin. Chem. Soc. (Taipei)*, **40**, 159 (1993); *Chem. Abstr.*, **119**, 180430 (1993).
85. C.-T. Lin, N.-J. Wang, H.-Z. Tseng and T.-C. Chou, *J. Org. Chem.*, **62**, 4857 (1997).
86. C.-T. Lin, N.-J. Wang, Y.-L. Yeh and T.-C. Chou, *Tetrahedron*, **51**, 2907 (1995).
87. J. Behr, R. Braun, H.-D. Martin, M. B. Rubin and A. Steigel, *Chem. Ber.*, **124**, 815 (1991).
88. T.-C. Chou, Y.-L. Yeh and G.-H. Lin, *Tetrahedron Lett.*, **37**, 8779 (1996).
89. B. A. R. C. Murty, R. Pinkos, P. R. Spurr, W.-D. Fessner, G. Lutz, H. Fritz, D. Hunkler and H. Prinzbach, *Chem. Ber.*, **125**, 1719 (1992).
90. B. A. R. C. Murty, P. R. Spurr, R. Pinkos, C. Grund, W.-D. Fessner, D. Hunkler. H. Fritz, W. Roth and H. Prinzbach, *Chimia*, **41**, 32 ((1987); *Chem. Abstr.*, **107**, 217128 (1987).
91. W.-D. Fessner, G. Sedelmeier, P. R. Spurr, G. Rihs and H. Prinzbach, *J. Am. Chem. Soc.*, **109**, 4626 (1987).
92. J. P. Melder, H. Fritz and H. Prinzbach, *Angew. Chem., Int. Ed. Engl.*, **28**, 300 (1989).
93. L. A. Paquette, L. Waykola, C.-C. Shen, U. S. Racherla, R. Gleiter and E. Litterest, *Tetrahedron Lett.*, **29**, 4213 (1988).
94. L. A. Paquette and C.-C. Shen, *Tetrahedron Lett.*, **29**, 4069. (1988).
95. L. A. Paquette, C.-C. Shen and P. Engel, *J. Org. Chem.*, **54**, 3329 (1989).
96. T.-C. Chou and J. H. Chiou, *J. Chin. Chem. Soc. (Taipei)*, **33**, 227 (1986); *Chem. Abstr.*, **107**, 133945 (1987).
97. K. Ito, Y. Noro, K. Saito and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **63**, 2573 (1990).
98. S. A. Osadchii, Yu. V. Gatilov, Yu. I. Bagryanskii, T. V. Rybalov and V. G. Shubin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1440 (1991); *Chem. Abstr.*, **115**, 207280 (1991).
99. W.-D. Fessner and M. Rodriguez, *Angew. Chem., Int. Ed. Engl.*, **30**, 1020 (1991).
100. M. V. Aranson, V. R. Flid and A. N. Kozyrev, *Zh. Obshch. Khim.*, **62**, 2363 (1992); *Chem. Abstr.*, **119**, 72271 (1993).
101. G. Mehta and S. Padma, *Tetrahedron Lett.*, **28**, 1295 (1987).
102. M. Wollenweber, R. Pinkos, J. Leonhardt and H. Prinzbach, *Angew. Chem., Int. Ed. Engl.*, **33**, 117 (1994).
103. G. Mehta and S. Padma, *J. Am. Chem. Soc.*, **109**, 7230 (1987).
104. G. Mehta, S. Padma, E. D. Jemmis and G. Leela, *Tetrahedron Lett.*, **29**, 1613 (1988).
105. S. J. Cristol and R. L. Snell, *J. Am. Chem. Soc.*, **80**, 1950 (1958).
106. W. G. Dauben and R. L. Cargill, *Tetrahedron*, **18**, 197 (1962).
107. G. S. Hammond, N. J. Turro and A. Fischer, *J. Am. Chem. Soc.*, **83**, 4674 (1961).
108. M. V. Aranson, V. R. Flid and A. N. Kozyrev, *Zh. Obshch. Khim.*, **62**, 2363 (1992); *Chem. Abstr.*, **119**, 72271 (1993).
109. F. Franceschi, M. Guardigli, E. Solari, C. Floriani, A. Chiesi-Villa and C. Rizzoli, *Inorg. Chem.*, **36**, 4099 (1997).
110. L. Yang, M.-X. Zhang, Y.-C. Liu, Z.-L. Liu and Y. L. Chow, *J. Chem. Soc., Chem. Commun.*, 1055 (1995).
111. V. A. Bren, V. I. Minkin, A. D. Dubonosov, V. A. Chernoivanov, V. P. Rybalkin and G. S. Gennadii, *Mol. Cryst. Liq. Cryst. Sci. Technol., Sect. A*, **297**, 247 (1997); *Chem. Abstr.*, **127**, 212366 (1997).
112. H. Cao. Y. Akimoto, Y. Fujiwara, Y. Tanimoto, L.-P. Zhang and C.-H. Tung, *Bull. Chem. Soc. Jpn.*, **68**, 3411 (1995).
113. C.-H. Tung, L.-P. Zhang, Y. Li, H. Cao and Y. Tanimoto, *J. Am. Chem. Soc.*, **119**, 5348 (1997).
114. C. Tung, L. Zhang and Y. Li, *Chin. J. Chem.*, **14**, 377 (1996); *Chem. Abstr.*, **125**, 276282 (1996).
115. R. D. Bach, H. Schilke and H. B. Schlegel, *J. Org. Chem.*, **61**, 4845 (1996).
116. (a) M. Maafi, J.-J. Aaron and C. Lion, *J. Inclusion Phenom. Mol. Recognit. Chem.*, **30**, 227 (1998); *Chem. Abstr.*, 166730 (1998).
(b) S. Wu, *Huaxue Jinzhan*, **9**, 160 (1997); *Chem. Abstr.*, 501188 (1997).
117. K. Maruyama and H. Tamiaki, *Chem. Lett.*, 683 (1987).
118. H. Tamioka and K. Maruyama, *Chem. Lett.*, 1875 (1988).
119. R. Herges and W. Reif, *Justus Liebigs Ann. Chem.*, 761 (1996).
120. A. P. Marchand, S. P. Reddy and D. R. Dave, *Synthesis*, 565 (1991).
121. J. Kenndorf, K. Polborn and G. Szeimies, *J. Am. Chem. Soc.*, **112**, 6117 (1990).
122. K. Hirao, A. Yamashita and O. Yonemitsu, *J. Fluorine Chem.*, **36**, 293 (1987).

123. V. A. Chernoivanov, A. D. Dubonosov, V. A. Bren, V. I. Minkin, S. V. Galichev and A. N. Suslov, *Zh. Org. Khim.*, **28**, 1647 (1992); *Chem. Abstr.*, **118**, 233529 (1993).
124. V. A. Chernoivanov, A. D. Dubonosov, V. I. Minkin, V. A. Bren, and A. E. Lyubarskaya, *Zh. Org. Khim.*, **25**, 443 (1989); *Chem. Abstr.*, **111**, 194166 (1989).
125. S. M. Aldoshin, V. A. Bren, A. D. Dubonosov, O. A. Kozina, V. I. Minkin, V. A. Chernoivanov and I. I. Chuev, *Izv. Akad. Nauk, Ser. Khim.*, 504 (1995); *Chem. Abstr.*, **124**, 8063 (1995).
126. V. A. Chernoivanov, A. D. Dubonosov, L. L. Popova, S. V. Galichev, G. S. Borodkin, V. A. Bren and V. I. Minkin, *Zh. Org. Khim.*, **29**, 2148 (1993); *Chem. Abstr.*, **121**, 230119 (1994).
127. V. A. Chernoivanov, A. D. Dubonosov, V. A. Bren, V. I. Minkin, A. N. Suslov and G. S. Gennadii, *Mol. Cryst. Liq. Cryst. Sci. Technol., Sect. A*, **297**, 239 (1997); *Chem. Abstr.*, **127**, 212365 (1997).
128. M. Maafi, C. Lion and J.-J. Aaron, *New. J. Chem.*, **20**, 559 (1996).
129. A. D. Dubonosov, V. A. Chernoivanov, L. L. Popova, V. A. Bren and V. I. Minkin, *Zh. Org. Khim.*, **30**, 148 (1994); *Chem. Abstr.*, **121**, 280287(1994).
130. C. G. Aloisi, G. Favaro, A. Spalletti, G. Cavicchio and V. Marchetti, *Gazz. Chim. Ital.*, **116**, 281 (1986); *Chem. Abstr.*, **106**, 195680 (1987).
131. G. Favaro and G. G. Aloisi, *Z. Phys. Chem. (Munich)*, **159**, 11 (1988); *Chem. Abstr.*, **110**, 211844 (1989).
132. A. N. Suslov, V. A. Chernoivanov, A. D. Dubonosov, O. A. Kozina, V. A. Bren and V. I. Minkin, *Zh. Org. Khim.*, **31**, 1255 (1995); *Chem. Abstr.*, **124**, 317054 (1996).
133. R. Gleiter and F. Ohlbach, *J. Chin. Chem. Soc. (Taipei)*, **43**, 117 (1996); *Chem. Abstr.*, **124**, 287118 (1996).
134. L. A. Paquette, H. Kuenzer and M. A. Kesselmayer, *, J. Am. Chem. Soc.*, **120**, 6521 (1998).
135. L. A. Paquette and H. Kuenzer, *J. Am. Chem. Soc.*, **108**, 7431 (1986).
136. L. A. Paquette and U. S. Racherla, *J. Org. Chem.*, **52**, 3250 (1987).
137. S. Trah, K. Weidmann, H. Fritz and H. Prinzbach, *Tetrahedron Lett.*, **28**, 4399 (1987).
138. M. Nishida, Y. Hayakawa, M. Matsui, K. Shibita and H. Muramatsu, *J. Heterocycl. Chem.*, **29**, 113 (1992).
139. J. Bussenius, M. Keller, and W. Eberbach, *Justus Liebigs Ann. Chem.*, 1503 (1995).
140. D. Bryce-Smith, *Pure Appl. Chem.*, **16**, 47 (1968).
141. F. Bockisch, H. Dreeskamp, T. von Haugwitz and W. Tochtermann, *Chem. Ber.*, **124**, 1831 (1991).
142. R. Gleiter and B. Treptow, *J. Org. Chem.*, **58**, 7740 (1993); R. Gleiter and B. Treptow, *Angew. Chem., Int. Ed. Engl.*, **31**, 862 (1992).
143. R. Gleiter, F. Ohlbach, G. Haberhauer, H. Irngartinger and T. Oeser, *Justus Liebigs Ann. Chem.*, 1627 (1996).
144. R. Gleiter and F. Ohlbach, *J. Chem. Soc., Chem. Commun.*, 2049 (1994).
145. R. Gleiter and B. Treptow, *Angew. Chem., Int. Ed. Engl.*, **29**, 1427 (1990).
146. R. Gleiter, B. Treptow, H. Irngartinger and T. Oeser, *J. Org. Chem.*, **59**, 2787 (1994).
147. H. E. Zimmerman, R. W. Binkley, R. S. Givens and M. A. Sherwin, *J. Am. Chem. Soc.*, **89**, 3932 (1967).
148. (a) H. E. Zimmerman and D. Armesto, *Chem. Rev.*, **96**, 3065 (1996).
(b) H. E. Zimmerman, in *The Chemistry of the Cyclopropyl Group* (Ed. Z. Rappoport), Vol. 2, Wiley, Chichester, 1995, p. 319.
149. D. De Keukeleire and S. L. He, *Chem. Rev.*, **93**, 359 (1993).
150. M. Reguero, F. Bernardi, H. Jones, M. Olivucci, I. N. Ragazos and M. A. Robb, *J. Am. Chem. Soc.*, **115**, 2073 (1993).
151. H. E. Zimmerman and A. C. Pratt, *J. Am. Chem. Soc.*, **92**, 6259, 6267 (1970).
152. H. E. Zimmerman and J. M. Cassel, *J. Org. Chem.*, **54**, 3800 (1989).
153. H. E. Zimmerman and M. J. Zuraw, *J. Am. Chem. Soc.*, **111**, 2358 (1989).
154. H. E. Zimmerman and M. J. Zuraw, *J. Am. Chem. Soc.*, **111**, 7974 (1989).
155. H. E. Zimmerman and M. E. O'Brien, *J. Org. Chem.*, **59**, 1809 (1994).
156. H. E. Zimmerman, D. Armesto, M. G. Amezua, T. P. Gannett and R. P. Johnson, *J. Am. Chem. Soc.*, **101**, 6367 (1979).
157. T. Tsuno, H. Hoshino and K. Sugiyama, *Tetrahedron Lett.*, **38**, 1581 (1997).
158. K. Sugiyama and T. Tsuno, *Chem. Express*, **7**, 929 (1992); *Chem. Abstr.*, **118**, 147215 (1993).

159. C. O. Bender, D. L. Bengston, D. Dolman and R. T. McKay, *Can. J. Chem.*, **72**, 1556 (1994).
160. C. L. Asplund, C. O. Bender and D. Dolman, *Can. J. Chem.*, **72**, 1999 (1994)
161. C. O. Bender, D. Dolman and G. K. Murphy, *Can. J. Chem.*, **66**, 1656 (1988).
162. C. O. Bender, D. Dolman and N. Tu, *J. Org. Chem.*, **56**, 5015 (1991).
163. C. O. Bender, D. S. Clyne and D. Dolman, *Can. J. Chem.*, **69**, 70 (1991).
164. J. R. Scheffer and M. Yap, *J. Org. Chem.*, **54**, 2561 (1989).
165. L. A. Paquette and L. D. Burke, *J. Org. Chem.*, **52**, 2674 (1987).
166. H. Hemetsberger and M. Nobbe, *Tetrahedron*, **44**, 67 (1988).
167. L. A. Paquette, L. D. Burke, T. Irie and H. Tanida, *J. Org. Chem.*, **52**, 3246 (1987).
168. A. Joy, R. J. Robbins, K. Pitchumani and V. Ramamurthy, *Tetrahedron Lett.*, **38**, 8825 (1997).
169. R. P. Pokkuluri, J. R. Scheffer, J. Trotter and M. Yap, *J. Org. Chem.*, **57**, 1486 (1992).
170. E. Grovenstein, Jr., T. C. Campbell and T. Shibata, *J. Org. Chem.*, **34**, 2418 (1969).
171. C. O. Bender and D. W. Brooks, *Can. J. Chem.*, **53**, 1684 (1975).
172. J. R. Scheffer and M. Yap, *J. Org. Chem.*, **54**, 2561 (1989).
173. R. Jones, J. R. Scheffer, J. Trotter and M. Yap, *Tetrahedron Lett.*, **34**, 31 (1993).
174. R. Altundas and M. Balci, *Kim. Kim. Muhendisligi Semp., 8th*, **2**, 71 (1992); *Chem. Abstr.*, **120**, 244305 (1994).
175. H. E. Zimmerman, A. G. Kutateladze, Y. Maekawa and J. E. Mangette, *J. Am. Chem. Soc.*, **116**, 9795 (1994).
176. C.-C. Liao, H.-P. Hsieh and S.-Y. Lin, *J. Chem. Soc., Chem. Commun.*, 545 (1990).
177. L. Trifonov and A. Orakhovats, *Helv. Chim. Acta*, **72**, 648 (1989).
178. G. Rattray, J. Yang, A. D. Gudmundsdottir and J. R. Scheffer, *Tetrahedron Lett.*, **34**, 35 (1993).
179. H. E. Zimmerman, H. M. Sulzbach and M. B. Tollefson, *J. Am. Chem. Soc.,* **115**, 6548 (1993).
180. (a) J. N. Gamlin, G. Olovsson, K. Pitchumani, V. Ramamurthy, J. R. Scheffer and J. Trotter, *Tetrahedron Lett.*, **37**, 6037 (1996).
(b) J. Chen, J. R. Scheffer and J. Trotter, *Tetrahedron*, **48**, 3251 (1992).
181. T. Y. Fu, G. Olovsson, J. R. Scheffer and J. Trotter, *Tetrahedron Lett.*, **36**, 4353 (1995).
182. R. Sieckmann, *J. Chem. Res. (S)*, 370 (1994).
183. J. R. Scheffer, J. Trotter, M. Garcia-Garibay and F. Wireko, *Mol. Cryst. Liq. Cryst.*, **156** (Pt. A), 63 (1988); *Chem. Abstr.*, **110**, 74562 (1989).
184. P. R. Pokkuluri, J. R. Scheffer and J. Trotter, *Tetrahedron Lett.*, **30**, 1607 (1989).
185. P. R. Pokkuluri, J. R. Scheffer and J. Trotter, *J. Am. Chem. Soc.*, **112**, 3676 (1990).
186. T. Y. Fu, Z. Liu, J. R. Scheffer and J. Trotter, *J. Am. Chem. Soc.*, **115**, 12202 (1993).
187. A. Huelsduenker, A. Ritter and M. Demuth, *Sol. Therm. Energy Util.*, **6**, 443 (1992); *Chem. Abstr.*, **119**, 225394 (1993).
188. M. A. Garcia-Garibay and J. R. Scheffer, *J. Org. Chem.*, **57**, 241 (1992).
189. J. Chen, P. R. Pokkuluri, J. R. Scheffer and J. Trotter, *Tetrahedron Lett.*, **33**, 1535 (1992).
190. J. Chen, P. R. Pokkuluri, J. R. Scheffer and J. Trotter, *Tetrahedron Lett.*, **31**, 6803 (1990).
191. C. V. Kumar, B. A. R. C. Murty, S. Lahiri, E. Chackachery, J. C. Scaiano and M. V. George, *J. Org. Chem.*, **49**, 4923 (1984).
192. P. R. Pokkuluri, J. R. Scheffer and J. Trotter, *J. Am. Chem. Soc.*, **112**, 3673 (1990).
193. C. V. Asokan, S. A. Kumar, S. Das, N. P. Rath and M. V. George, *J. Org. Chem.*, **56**, 5890 (1991).
194. D. Ramaiah, S. A. Kumar, C. V. Asokan, T. Mathew, S. Das, N. P. Rath and M. V. George, *J. Org. Chem.*, **61**, 5468 (1996).
195. M. Garcia-Garibay, J. R. Scheffer, J. Trotter and F. Wireko, *J. Am. Chem. Soc.*, **111**, 4985 (1989).
196. J. Chen, M. Garcia-Garibay and J. R. Scheffer, *Tetrahedron Lett.*, **30**, 6125 (1989).
197. A. D. Gudmundsdottir, J. R. Scheffer and J. Trotter, *Tetrahedron Lett.*, **35**, 1397 (1994).
198. J. Chen, P. R. Pokkuluri, J. R. Scheffer and J. Trotter, *Tetrahedron Lett.*, **31**, 6803 (1990).
199. H. E. Zimmerman and A. P. Kamath, *J. Am. Chem. Soc.*, **110**, 900 (1988).
200. K. Gollnick and U. Paulmann, *J. Org. Chem.*, **55**, 5954 (1990).
201. G. Wu, J. Hu, J. Li and J. Xu, *Chin. J. Chem.*, **10**, 529 (1992); *Chem. Abstr.*, **119**, 48803 (1993).
202. H. E. Zimmerman, J. M. Nuss and A. W. Tantillo, *J. Org. Chem.*, **53**, 3792 (1988).
203. A. L. Roughton, M. Muneer, M. Demuth, I. Klopp and C. Kruger, *J. Am. Chem. Soc.,* **115**, 2085 (1993).

204. O. Muraoka, G. Tanabe and T. Momose, *Heterocycles*, **31**, 1589 (1990).
205. T. Momose, G. Tanabe, H. Tsujimori and O. Muraoka, *Chem. Pharm. Bull.*, **40**, 2525 (1992); *Chem. Abstr.*, **118**, 124321 (1993).
206. F. Muller and J. Mattay, *Angew. Chem., Int. Ed. Engl.*, **31**, 209 (1992).
207. M. A. Kropp, M. Baillargeon, K. M. Park, K. Bhamidapaty and G. B. Schuster, *J. Am. Chem. Soc.*, **113**, 2155 (1991).
208. K. M. Park and G. B. Schuster, *J. Org. Chem.*, **57**, 2502 (1992).
209. M. A. Kropp and G. B. Schuster, *J. Am. Chem. Soc.*, **111**, 2316 (1989).
210. J. J. Eisch, M. P. Boleslawski and K. Tamano, *J. Org. Chem.*, **54**, 1627 (1989).
211. J. J. Eisch, K. Tamano and R. J. Wilcsek, *J. Am. Chem. Soc.*, **97**, 895 (1975).
212. J. D. Wilkey and G. B. Schuster, *J. Am. Chem. Soc.*, **110**, 7569 (1988).
213. J. J. Eisch, B. Shafii and M. P. Boleslawski, *Pure Appl. Chem.*, **63**, 365 (1991).
214. M. Shi, Y. Okamoto and S. Takamuku, *Bull. Chem. Soc. Jpn.*, **63**, 2731 (1990).
215. M. Shi, Y. Okamoto and S. Takamuku, *Bull. Chem. Soc. Jpn.*, **63**, 3345 (1990).
216. M. Shi, Y. Okamoto and S. Takamuku, *Bull. Chem. Soc. Jpn.*, **63**, 1269 (1990).
217. M. Shi, Y. Okamoto and S. Takamuku, *Tetrahedron Lett.*, **30**, 6709 (1989).
218. M. Shi, Y. Okamoto and S. Takamuku, *J. Org. Chem.*, **55**, 3821 (1990).
219. M. Shi, K. Shouki, Y. Okamoto and S. Takamuku, *J. Chem. Soc., Perkin Trans. 1*, 2443 (1990).
220. M. Shi, Y. Okamoto and S. Takamuku, *Chem. Lett.*, 1079 (1990).
221. M. Shi, Y. Okamoto and S. Takamuku, *Chem. Lett.*, 1297 (1989).

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CHAPTER **5**

Intermolecular cyclization reactions to form carbocycles

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I. GENERAL INTRODUCTION

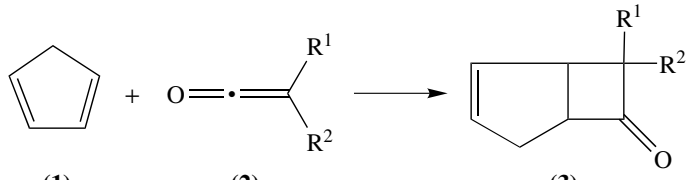
Dienes and polyenes can undergo a variety of intermolecular cyclization reactions, the exact nature of which is dependent on the number of double bonds, the relative positions of these bonds with respect to each other, the preferred conformation of the diene or polyene system and the reaction partner.

This chapter deals with [2 + 2], [4 + 2], [6 + 4], [8 + 2] and [2 + 2 + 2] cycloaddition reactions of dienes and polyenes. Most attention is devoted to the [4 + 2] cycloaddition reaction (Diels–Alder reaction) which is likely to be the most studied reaction in the chemical literature.

II. [2 + 2] CYCLOADDITION REACTIONS

A. Conjugated Dienes

Conjugated dienes may undergo [2 + 2] cycloadditions, if they have a fixed or strongly biased *transoid* conformation or if they are reacted with specific dienophiles. Classic examples of the latter are cycloadditions of dienes with ketenes leading to [2 + 2] cycloadducts, even when the dienes have a *cisoid* conformation. [2 + 2] Cycloadditions of cyclopentadiene **(1)** to ketenes **2** (equation 1) have been studied extensively[1], as the cycloadducts **3** are suitable precursors of prostaglandines. The corresponding Diels–Alder adducts can be prepared using ketene equivalents with masked carbonyl groups[2].

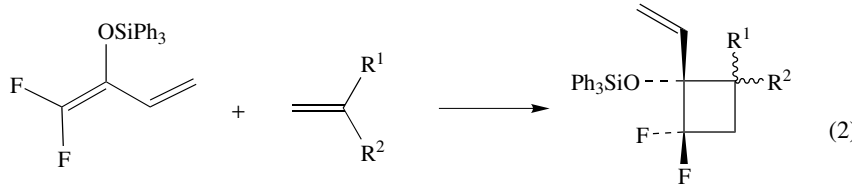


(1)

(1) **(2)** **(3)**

Strongly polarized 1,1-difluoro-2-triphenylsilyloxy-1,3-butadiene **(4)** reacted with *captodative* olefins **5a** and **5b** to give [2 + 2] cycloadducts **6a** and **6b**, respectively (equation 2)[3].

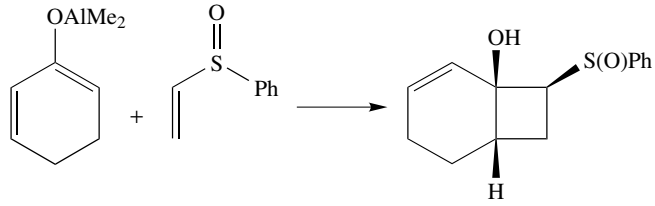
Symmetrically substituted dienophiles such as *p*-benzoquinone and *N*-phenylmaleimide reacted with **4** to give the expected [4 + 2] cycloadducts. No cycloaddition took place, however, in the reaction of 1,1-difluoro-2-triphenylsilyloxy-1-propene with 2-chloroacrylonitrile, which showed the importance of an additional vinyl group for the reactivity of **4** in the [2 + 2] cycloaddition.



(2)

(4) (**5a**; R^1 = CN, R^2 = OMe) (**6a**; R^1 = CN, R^2 = OMe)
(**5b**; R^1 = CO_2Et, R^2 = Br) (**6b**; R^1 = CO_2Et, R^2 = Br)

Another example of a diene undergoing a [2 + 2] cycloaddition reaction with an alkene has been reported recently[4]. 2-Dimethylaluminumoxy-1,3-cyclohexadiene **(7)** reacted with phenyl vinyl sulfoxide **(8)** to afford a diastereomeric mixture of *cis* substituted cyclobutanols **9** (equation 3). The occurrence of a [2 + 2] cycloaddition as well as the high *cis* stereoselectivity observed were explained by a pre-organization of the reactants by complexation of the diene bound aluminum with the sulfoxide oxygen on the olefin.



(3)

(7) **(8)** **(9)**

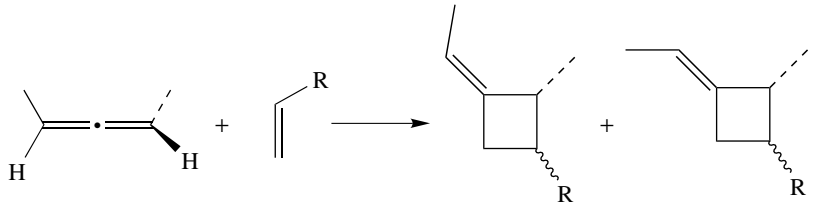
B. Cumulated Dienes (Allenes)

Like ketenes, allenes generally undergo [2 + 2] cycloadditions with alkenes affording methylene cyclobutanes[5]. In reactions with 1,3-butadienes, both Diels–Alder adducts and [2 + 2] cycloadducts are formed. Cyclopentadiene, however, has been reported to react with several allenes to give exclusively Diels–Alder adducts[6]. From the several possible mechanisms by which [2 + 2] cycloaddition reactions of allenes could occur, i.e. [$\pi 2_s + \pi 2_a$], [$\pi 2_s + (\pi 2_s + \pi 2_s)$] or diradical, the diradical mechanism is generally considered to be the most probable one[6–10].

The most recent review[5d] about [2 + 2] cycloadditions of allenes covers the literature up to 1992. This section deals with recent results combined with some representative results from the past decade.

Pasto and colleagues studied the stereochemical features of the [2 + 2] cycloadditions of chiral allenes. The formation of a diradical intermediate in the cycloadditions of enantiomerically enriched 1,3-dimethylallene **(10)** with acrylonitrile **(11a)** and methyl acrylate **(11b)** (equation 4) was shown to be irreversible. 1,3-Dimethylallene recovered from the reaction mixture was shown to have the same ee as the starting material. Interestingly,

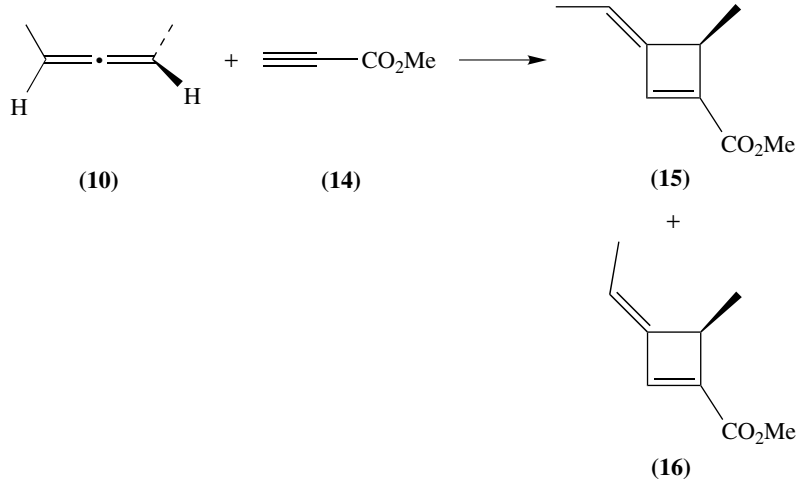
a surprisingly large amount of the ee of **10** was transferred to cycloadducts **12** and **13**. The exact amount proved dependent on the size of the alkene substituent, being larger for methyl acrylate than for acrylonitrile. These results were discussed in terms of preferred conformations of approach adopted by both reactants to form the activated complex leading to the diradical intermediate[7].



(4)

(10) (**11a**; R = CN) (**12a**; R = CN) (**13a**; R = CN)
(**11b**; R = CO_2Me) (**12b**; R = CO_2Me) (**13b**; R = CO_2Me)

In the [2 + 2] cycloadditions of **10** with *N*-phenylmaleimide and dimethyl fumarate, the major cycloadducts were formed with a very high degree of ee transfer from 1,3-dimethylallene[8]. Similar results were obtained in the reaction of **10** with 1,1-dichloro-2,2-difluoroethene. The reaction with less reactive 1,1-diphenylethene did not lead to cycloadduct formation, but resulted in racemization of the chiral 1,3-dimethylallene instead[9], which implies reversible formation of the diradical intermediate in this case. Finally, the cycloaddition of 1,3-dimethylallene to methyl propiolate **(14)** afforded two cycloadducts, **15** and **16**, to which >40% of the initial ee had been transferred (equation 5)[11].



(10) **(14)** **(15)**

(16)

(5)

The reactions of 1-*t*-butyl-3-methylallene with several alkenes, e.g. *N*-phenylmaleimide, acrylonitrile and methyl acrylate, afforded exclusively [4 + 2] cycloadducts of 1-*t*-butyl-1,3-butadiene, which had been formed from 1-*t*-butyl-3-methylallene by a [1,3] sigmatropic rearrangement[12]. The reaction of 1-*t*-butyl-3-methylallene with 1,1-dichloro-2,2-difluoroethene occurred more rapidly than the hydrogen shift, which allowed the

isolation of a mixture of four [2 + 2] cycloadducts, including one to which 91% of the initial ee had been transferred[10].

Introduction of an alkylthio group on the allene system increased the reactivity of the allene moiety in [2 + 2] cycloaddition reactions. It proved possible to conduct reactions of this allene at much lower temperatures. By adding Lewis acids, the reaction temperature could be decreased even more, as was illustrated by the Lewis acid catalyzed [2 + 2] cycloadditions of 1-trimethylsilyl-1-methylthio-1,2-propadiene with a variety of electron-poor alkenes, including cyclic and non-cyclic enones, acrylates, methyl fumarate and acrylonitrile[13]. When a chiral diol **21** based titanium catalyst was employed, the [2 + 2] cycloaddition reactions of *N*-acryloyl-1,3-oxazolidin-2-ones **17a** and **17b** with allenyl sulfides **18** yielded methylenecyclobutanes **19** and **20** with high optical purities (equation 6)[13,14]. The highest yields were obtained with electron-poor allenophile **17b**. The substituent R^2 proved to have a strong effect on the yield, as the yield was quantitative for **18a**, whereas no reaction was observed for **18c**.

Reactions of 3-methylthio-4-trimethylsilyl-1,2-butadiene with electron-poor monosubstituted and disubstituted alkenes were promoted by a catalytic amount of ethylaluminum dichloride, affording the corresponding methylenecyclobutanes with high selectivities and with yields ranging from 37% for methyl crotonate to 97% for methacrylonitrile[15].

Electron-rich 3-methoxy-4-trimethylsilyl-1,2-butadiene **(22)** reacted with several electron-poor alkenes in the presence of diethylaluminum chloride to afford methylene cyclobutanes **23**. Reactions with alkynes were performed in the presence of methylaluminum bis(2,4,6-tri-*t*-butylphenoxide) (equation 7)[16].

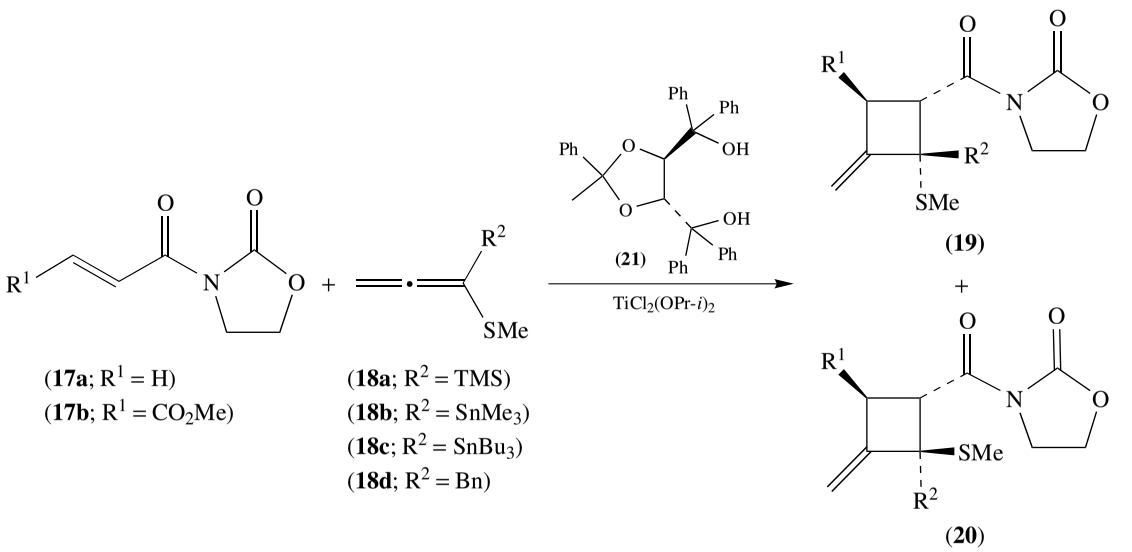
The nature of the substituents on the allene can have an impact on the outcome of a [2 + 2] cycloaddition reaction, as was illustrated by the Lewis acid catalyzed cycloadditions of 1-thioaryl-3,3-dimethylallene **(24)** and 1-methyl-1-trimethylsilylallene to various 2-alkoxy-*p*-benzoquinones **25** (e.g. equation 8)[17]. The reactions were considered to proceed via carbocation intermediates formed by nucleophilic attack of the thioallene on the Lewis acid activated quinone. At lower temperatures, these carbocations closed to cyclobutanes **26**, whereas at higher temperatures, the thermodynamically more stable benzofurans **27** were formed.

Titanium tetrachloride promoted reactions of 1-methyl-1-trimethylsilylallene with quinones **25** afforded products derived from a reaction with one of the carbonyl groups on the quinones. Besides the substitution pattern on the allene, the higher activity of titanium tetrachloride has to be considered to play a role in this abnormal product formation.

Cyclic allenes have improved reactivity due to ring strain. The cycloaddition of 1,2,4-cyclohexatriene **(28)** with styrene **(29)**, for example, afforded exclusively cyclobutane **31** (equation 9)[18]. Semi-empirical calculations (AM1) determined the diradical intermediate **30** to be at an energy minimum[19].

5,6-Didehydro-3,4-dihydro-2*H*-pyran, easily generated from 5-bromo-3,4-dihydro-2*H*-pyran, was trapped with enolates to give mixtures of cyclobutanes[20].

Elliot and coworkers[21] found that cephalosporin triflates **32** reacted with various alkenes and acetylenes via a strained six-membered cyclic allene intermediate to give cyclobutanes **33** and **34** (equation 10). The cycloaddition reaction had a broad scope with **32** reacting with electron-rich as well as electron-poor highly substituted olefins. The most facile cycloadditions (in terms of the highest yield and the lowest required excess of olefin) were found for electron-rich olefins. Close inspection of the products that were obtained indicated a concerted process. For example, vinylcyclopropane reacted to give a mixture of cyclobutane isomers in which the cyclopropyl group was still present. This ruled out a stepwise diradical mechanism, as the intermediate cyclopropylcarbinyl radical, having a very short lifetime, would undergo ring opening rather than bond rotation followed by ring

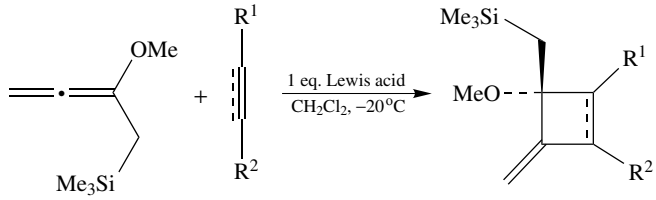


(**17a**; R^1 = H)
(**17b**; R^1 = CO_2Me)

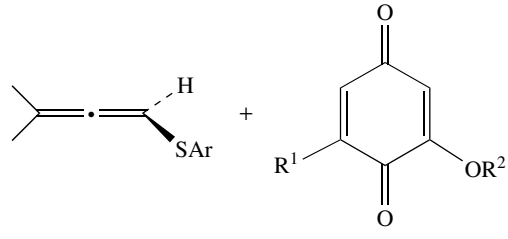
(**18a**; R^2 = TMS)
(**18b**; R^2 = $SnMe_3$)
(**18c**; R^2 = $SnBu_3$)
(**18d**; R^2 = Bn)

(6)

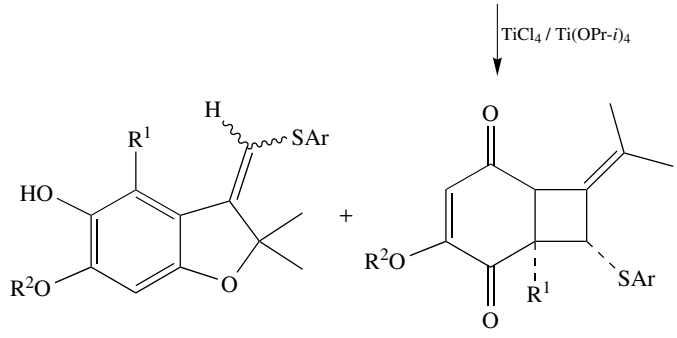
closure. Olefins with electron-donating as well as electron-withdrawing substituents such as ethyl vinyl ether and methyl acrylate all afforded products with the same regiochemistry, which suggested that no zwitterionic intermediates were involved.



(22) (23) (7)

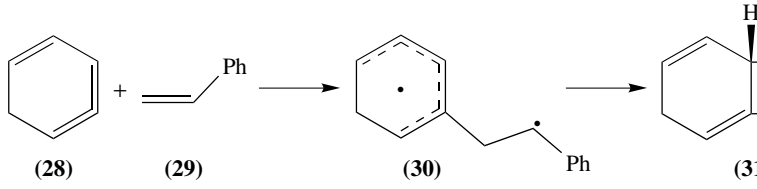


(24) (25)



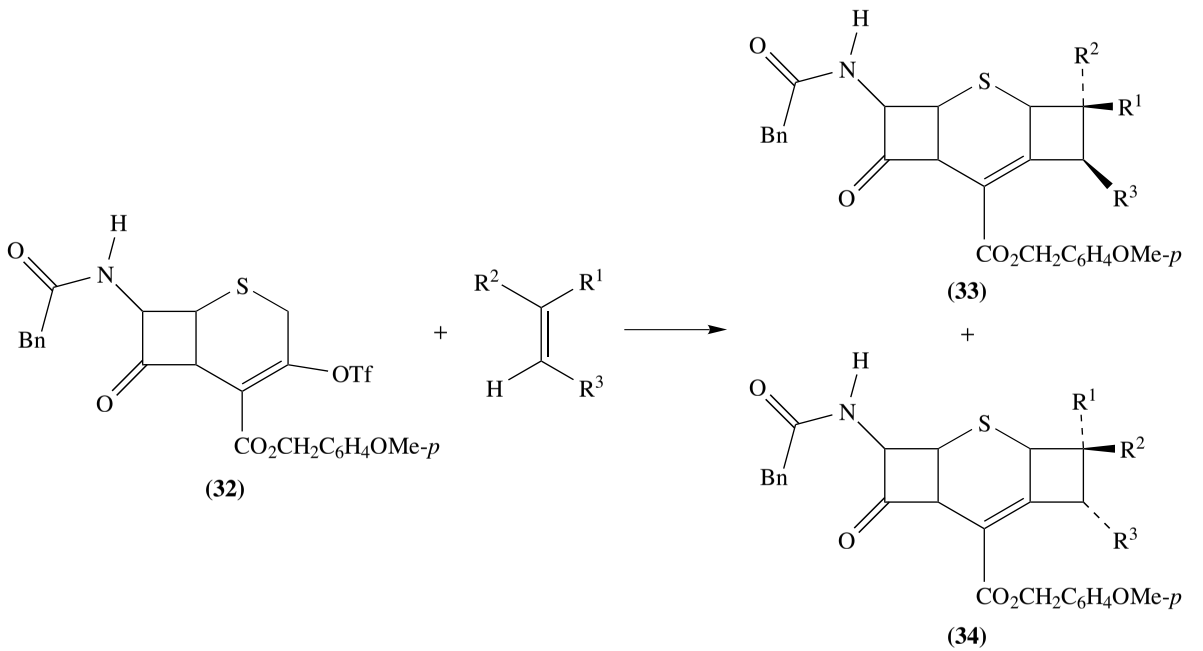
(27) (26) (8)

Ar = Ph, *p*-$MeOC_6H_4$



(28) (29) (30) (31) (9)

In addition to the concerted [2 + 2] cycloadditions of cyclic allenes reported by Elliot and colleagues, Kimura and coworkers[22] reported [2 + 2] cycloadditions of several 4-ethenylidene-1,3-oxazolidin-2-ones **35** with alkenes and alkynes (equation 11). The


H
O
N
Bn
S
OTf
O
CO2CH2C6H4OMe-p
(32)
+
R2
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H
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R2
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CO2CH2C6H4OMe-p
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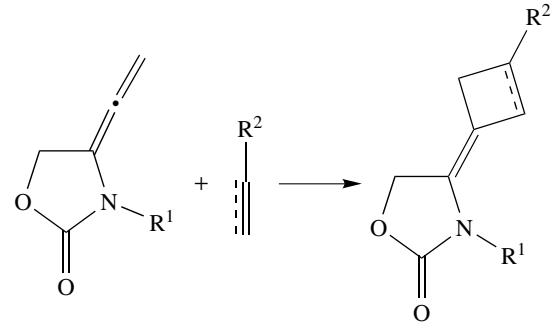
R3
CO2CH2C6H4OMe-p
(34)

(10)



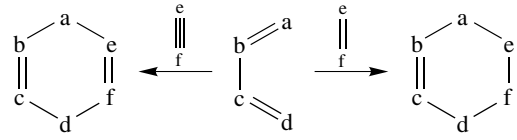
(11)

(**35a**; $R^1 = SO_2Ph$) (**36a**; $R^1 = SO_2Ph$)
(**35b**; $R^1 = COPh$) (**36b**; $R^1 = COPh$)
(**35c**; $R^1 = Tos$) (**36c**; $R^1 = Tos$)

reactions were considered to proceed via a $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ mechanism. The cycloadditions provided **36** as single diastereomers, showing that the alkene or alkyne moieties were introduced *syn* to the *N*-phenylsulfonyl, *N*-tosyl or *N*-benzoyl group. The alkenes employed encompassed electron-attracting, electron-donating and conjugating groups. Even 1,3-dienes exclusively yielded [2 + 2] cycloaddition products.

III. DIELS–ALDER REACTIONS

The formation of compounds with an unsaturated six-membered ring through the addition of a conjugated diene to a double or triple bond is known as the Diels–Alder reaction (equation 12). Such a cycloaddition was already described by Zincke and Günther in 1893[23]. The names of Diels and Alder have, however, been connected to this type of reactions due to the systematic and extensive work which they have performed on these reactions since the 1920s,[24] and for which a Nobel prize was awarded in 1950. Since these early investigations, the Diels–Alder reaction has grown to become probably the most valuable and most applied reaction in synthetic organic chemistry. It has a very broad scope and it allows the stereochemically controlled introduction of up to four chiral centers in the adduct in one synthetic step. Besides all-carbon systems, dienes and dienophiles containing heteroatoms have been widely employed.



(12)

Although this chapter is limited to intermolecular all-carbon reactions, the literature connected to this type of Diels–Alder reactions is still immense. The last general reviews about intermolecular Diels–Alder reactions date from nearly ten years ago[25–27]. During the past decade, several reviews were published dealing with specialized topics such as mechanistic aspects[28–31], specific dienes[32–35] and dienophiles[2,36,37], applications in synthesis[38–40] and introduction of chirality by using chiral auxiliaries[41,42] or chiral Lewis acids[41,43,44].

In this section, the literature about Diels–Alder reactions will be presented in a conceptual and illustrative way. After a profound introduction dealing with the development of mechanistic understanding of the Diels–Alder reaction, some interesting recent synthetic developments and applications will be presented. The reaction types and fields of interest are structured in such a way that they can be easily linked to ongoing research from the past ten years. Special attention will be paid to the application of chiral auxiliaries and chiral Lewis acids in asymmetric Diels–Alder reactions.

A. The Diels–Alder Reaction. A Theoretical Description

1. Development of mechanistic understanding. Mechanistic facts and concepts

Mechanistic and theoretical studies of the Diels–Alder reaction have resulted in the characterization of this reaction as a concerted, although not necessarily synchronous, single-step process[28–31,45]. The parent reaction, the addition of 1,3-butadiene to ethylene yielding cyclohexene, has been the subject of an ongoing mechanistic debate. Experimental results supported a concerted mechanism, whereas results from calculations seemed to be dependent on the method used. Semi-empirical calculations predicted a stepwise mechanism, whereas *ab initio* calculations were in favor of a concerted pathway. At the end of the '80s experimental and theoretical evidence converged on the synchronous mechanism[29–31].

Zwitterionic intermediates have been reported for reactions of strongly electron-rich 1,3-butadienes, e.g. 1,1-dimethoxy-1,3-butadiene, with strongly electron-poor dienophiles[46]. In the reactions of 1,4-bis(dimethylamino)-1,3-butadiene with strongly electron-poor dienophiles, electron transfer from the diene to the dienophile was reported to occur[47].

The following mechanistic aspects have been found to be characteristic of the Diels–Alder reaction[28,45].

(i) *The 'cis principle'*: The steric arrangement of substituents in both addends is preserved in the adduct, i.e. groups which are *cis* or *trans* in the olefin remain *cis* and *trans*, respectively, in the adduct.

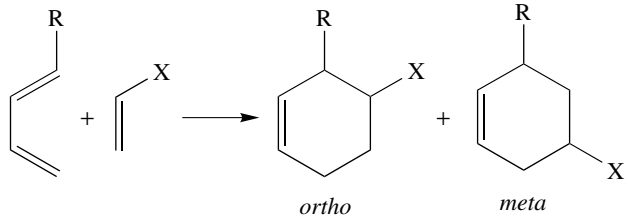
(ii) *Diene conformation*: Open-chain 1,3-dienes undergo [4 + 2] cycloadditions only in their *cisoid* conformation.

(iii) *Solvent effects*: Diels–Alder reactions are only slightly affected by a change of solvent.

(iv) *Activation parameters*: Diels–Alder reactions are accompanied by strong negative entropies of activation, $\Delta S^{\neq}$ (*ca* −35 eu), and large negative volumes of activation, $\Delta V^{\neq}$ (*ca* 30 $cm^3 mol^{-1}$), but only small enthalpies of activation, $\Delta H^{\neq}$.

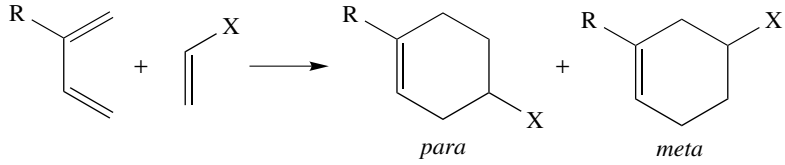
(v) *Isotope effects*: Small inverse secondary isotope effects at both termini undergoing sp^2–sp^3 changes during the cycloaddition are found.

(vi) *Regioselectivity*: Unsymmetrically substituted dienes and dienophiles afford mixtures of both regioisomers, one of which usually predominates. 1-Substituted dienes yield mostly *ortho* substituted adducts with monosubstituted dienophiles (equation 13), while



(13)

2-substituted dienes give predominantly *para* adducts (equation 14). The yield of the predominant isomer is increased by Lewis acid catalysis. The regioselectivity in the reactions of disubstituted and higher substituted dienes depends on the electronic properties and the relative positions of the substituents.



(14)

(vii) *The 'Alder rule', Reactivity*: Three different types of Diels–Alder reactions have been defined with respect to the electronic properties of the diene and dienophile substituents. [4 + 2] Cycloadditions between electron-rich dienes and electron-poor dienophiles are defined as *normal* Diels–Alder reactions. Their reaction rates increase with increasing electron-donating properties of the substituents on the dienes and increasing electron-withdrawing properties of the substituents on the dienophiles.

[4 + 2] Cycloadditions of reactants with opposite electronic properties are defined as Diels–Alder reactions with *inverse electron demand* or *inverse* Diels–Alder reactions.

Neutral Diels–Alder reactions encompass cycloadditions of dienes and dienophiles with intermediate electronic characters.

The *normal* [4 + 2] cycloadditions are most frequently observed and generally proceed more easily than the other reaction types. Recently, Sauer and colleagues[48] demonstrated that each of these three types of Diels–Alder reactions can be observed in the cycloadditions of a series of polyhalogenated cyclopentadienes with aryl substituted dienophiles, the actual reaction type observed depending on the substitution pattern of the reactants.

(viii) *The 'Alder endo rule'*, *Stereochemistry*: Cycloadditions of monosubstituted or disubstituted dienophiles generally lead to the formation of the *endo* isomer as the main product. Assuming a 'sandwich'-like pre-organization of the reactants, the *endo* product arises from that orientation in which the larger substituent is directed towards the double bond to be formed at C(2) of the diene (Figure 1). Formation of the *endo* isomer is promoted by Lewis acid catalysis.

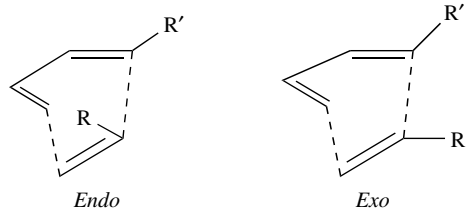


FIGURE 1. *Endo* and *exo* transition states of the Diels–Alder reaction

2. Frontier molecular orbital theory

A fundamental understanding of the mechanistic and stereochemical aspects of the Diels–Alder reaction was unfolded during the 1970s. Several theoretical approaches are available nowadays from which Fukui's Frontier Molecular Orbital theory (FMO theory) is most frequently used because of its simplicity[49–53].

This theory proves to be remarkably useful in rationalizing the whole set of general rules and mechanistic aspects described in the previous section as characteristic features of the Diels–Alder reaction. The application of perturbation molecular orbital theory as an approximate quantum mechanical method forms the theoretical basis of Fukui's FMO theory. Perturbation theory predicts a net stabilization for the intermolecular interaction between a diene and a dienophile as a consequence of the interaction of an occupied molecular orbital of one reaction partner with an unoccupied molecular orbital of the other reaction partner.

In order to simplify mathematical treatment, less important contributions from interactions between orbitals with large energy differences are neglected. The procedure is limited to the interaction of the frontier orbitals, viz. the highest occupied molecular orbitals (HOMOs) and the lowest unoccupied molecular orbitals (LUMOs), as illustrated in Figure 2.

With this simplification in mind, the stabilization energy ΔE can be given by equation 15, E_{HOMO} and E_{LUMO} being orbital energies, $C^i_{\mathrm{A}'}$, C^i_{A} and $C^i_{\mathrm{D}'}$, C^i_{D} being the relevant orbital coefficients at the carbon centers to which the new bonds are being formed; β^i_{AD} and $\beta^i_{\mathrm{A'D'}}$ are the resonance integrals for the overlap at the sites of interaction.

$$\Delta E = 2\frac{\left[\sum_i C^i_{\mathrm{A}} C^i_{\mathrm{D}} \beta^i_{\mathrm{AD}}\right]^2}{E^{\text{diene}}_{\mathrm{HOMO}} - E^{\text{dienophile}}_{\mathrm{LUMO}}} + 2\frac{\left[\sum_i C^i_{\mathrm{A}'} C^i_{\mathrm{D}'} \beta^i_{\mathrm{A'D'}}\right]^2}{E^{\text{dienophile}}_{\mathrm{HOMO}} - E^{\text{diene}}_{\mathrm{LUMO}}} \tag{15}$$

The main stabilization in reactions with activated reaction partners, viz. when one partner is electron-rich and the other electron-poor, arises through interaction between the donor HOMO and the acceptor LUMO which are much closer in energy than the acceptor HOMO and the donor LUMO. Figure 2 illustrates which interactions between the frontier orbitals cause the main stabilization in *normal, neutral* and *inverse* Diels–Alder reactions. For example, the main stabilization in the reaction between an electron-rich diene and an electron-poor dienophile stems from the interaction of the diene HOMO with the dienophile LUMO.

Several quantitative descriptions of [4 + 2] cycloadditions have been reported applying equation 15 or derived equations. HOMO and LUMO energies can be calculated from ionization potentials or electron affinities. Orbital coefficients have been calculated for simple ethenes and dienes using various quantum mechanical methods, e.g. INDO, CNDO/2, AM1 and STO-3G. These different methods may, however, lead to substantially different results[54–56].

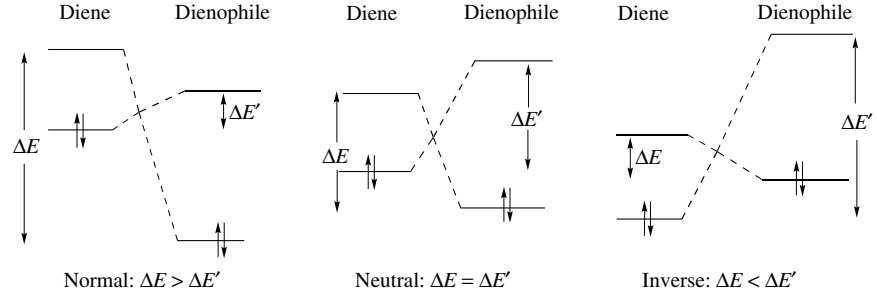


FIGURE 2. Energies of HOMOs and LUMOs as a function of the Diels–Alder reaction type

Discussions about reactivity, regioselectivity and stereoselectivity are mostly based on a more qualitative application of equation 15. To that aim, the following general considerations given by Fleming[51] and Houk[52] can be used to evaluate the influence of substituents on the reacting π systems:

(i) Conjugating substituents compress the frontier orbital separation of both diene and dienophile and lower the coefficients at the site of attachment in both frontier orbitals.

(ii) Electron-donating substituents, e.g. OAlk and $N(Alk)_2$, raise the energy levels of both frontier orbitals of each reactant. The HOMO level is generally raised more than the LUMO level. Electron-donating substituents enlarge the relative magnitude of the coefficients at the remote site in the HOMO [C(2) of the dienophile, C(2) and C(4) of the diene] and at the site of attachment in the LUMO [C(1) of the dienophile, C(1) and C(3) of the diene].

(iii) Electron-withdrawing groups lower both frontier orbital energies of each reactant. Since most electron-withdrawing groups are at the same time conjugating (e.g. CN, NO_2, and CO_2Me), the LUMO energy level is lowered more than the HOMO energy level. Electron-attracting groups reduce the relative magnitudes of the HOMO coefficients at C(2) and C(4). The LUMO coefficients at C(2) and C(4) of the diene and at C(2) of the dienophile are always relatively large in comparison with the coefficients at C(1).

(iv) Substituents at C(2) of the diene have a similar effect on the coefficients in comparison with the same substituents at C(1). They affect the π bond to which they are attached more than the other π bond. Electron-donating substituents cause the highest HOMO coefficient to be at C(1). Electron-withdrawing substituents cause the highest LUMO coefficient to be at C(1).

Application of these qualitative rules allows a simple prediction of the reactivity, regioselectivity and *endo/exo* selectivity. According to equation 15, the net stabilization energy ΔE depends on the frontier orbital energies. The highest stabilization is predicted for transition states derived from reactants of which one has a HOMO energy similar to the LUMO energy of the other. This means that electronically opposite substituents on the diene and the dienophile will increase the Diels–Alder reactivity. The largest increase of cycloaddition rate will be observed, if the electron-releasing substituent is present on the reactant with the higher HOMO energy. This usually is the diene partner because of its higher degree of conjugation.

The differences in stabilization energies for the formation of the various regioisomers are mainly determined by the differences in the largest term of equation 15. Formation of that regioisomer is favored for which the largest term consists of the largest frontier orbital coefficients from both diene and dienophile.

This means, for example, that in *normal* Diels–Alder reactions of 1-substituted dienes with 1-substituted ethenes, bond formation between C(4) of the diene and C(2) of the alkene, which leads to the *ortho* adduct, is favored over the other bond formation leading to the *meta* adduct. Formation of *para* products from 2-substituted dienes can be explained by a similar reasoning.

The *endo* selectivity in many Diels–Alder reactions has been attributed to attractive secondary orbital interactions. In addition to the primary stabilizing HOMO–LUMO interactions, additional stabilizing interactions between the remaining parts of the diene and the dienophile are possible in the *endo* transition state (Figure 3). This secondary orbital interaction was originally proposed for substituents having π orbitals, e.g. CN and CHO, but was later extended to substituents with $\pi(CH_2)$ type of orbitals, as encountered in cyclopropene[57].

There has been, however, an ongoing debate about other factors which may control *endo* selectivity. *Endo* selectivity has been observed when no secondary orbital interactions are possible and have been ascribed to steric effects in these cases[58,59]. Recently, the

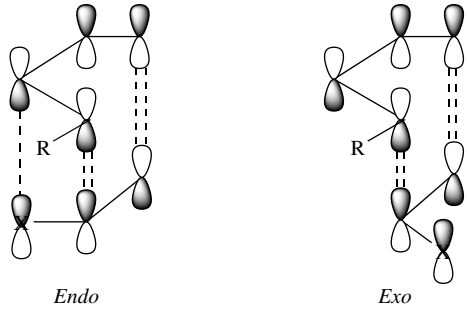


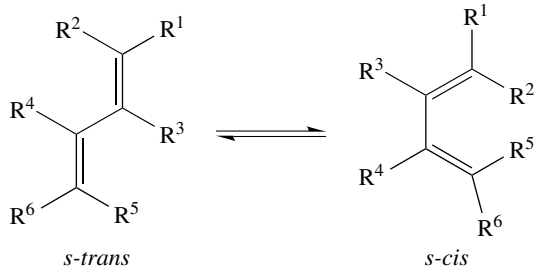
FIGURE 3. Primary and secondary orbital interactions between diene and dienophile

effect of pre-reactive van der Waals intermediates on the *endo/exo* selectivity has been investigated[60].

Secondary orbital interactions may also be involved in controlling the regioselectivity, if the differences between the terminal coefficients of diene and dienophile are small[61].

3. Effect of diene structure on reactivity. The resonance integral β

The reactivity of dienes in Diels–Alder reactions is also controlled by the diene conformation. The two planar conformations of 1,3-butadiene are referred to as *s-trans* and *s-cis* (equation 16). Calculations have shown the *s-trans* conformation to be 2–5 kcal mol^{-1} more stable than the *s-cis* conformation. Open-chain dienes can only react in their *cisoid* conformation. Thus, 2-substituted dienes are generally more reactive than 1,3-butadiene due to their stronger preference for the *s-cis* conformation. 1-*Cis* substituted 1,3-butadienes are almost exclusively in the *s-trans* conformation and are not reactive in Diels–Alder reactions. Highly substituted dienes may, however, be present in the *s-cis* conformation during a sufficient amount of time to participate in Diels–Alder reactions, even if a 1-*cis* substituent is present[62].



(16)

Reactivity may also depend on the C(1)–C(4) distance of the diene[63]. In a concerted [2 + 4] cycloaddition reaction, overlap has to be achieved between the lobes of the π orbital at C(1) and C(2) of the dienophile, lying about 1.3 Å apart, and the lobes of the π-orbital at C(1) and C(4) of the diene, lying about 3 Å apart. This means that the shorter the C(1)–C(4) distance is, the more efficient the overlap will be in the transition state. This is translated into a higher resonance integral β. It was shown for a series of equally substituted rigid 1,3-dienes that their reactivity in the cycloaddition reactions

with dienophiles depended strongly on the C(1)–C(4) distance. The decrease in reactivity toward cycloadditions going from cyclopentadiene to cyclohexadiene to cycloheptadiene can be attributed to increasing C(1)–C(4) distances of the dienes, the distances being 2.35, 2.85 and 3.15 Å, respectively.

4. Limitations of the FMO theory

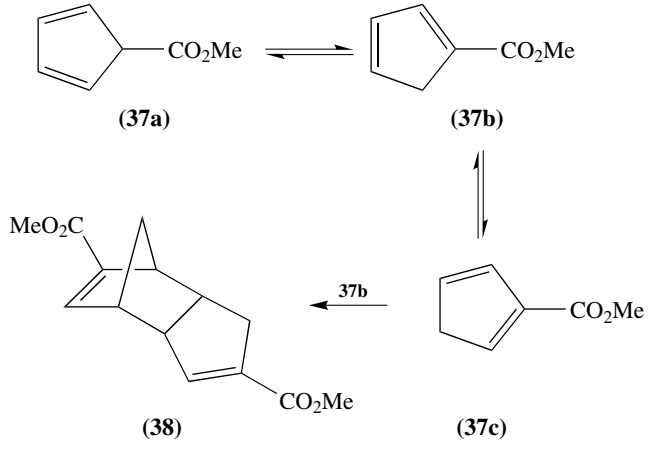
The FMO theory predicts the reactivity and selectivity in Diels–Alder reactions based on one dominant MO interaction. Especially in the last decade, many reactions have been found which disobey the FMO rules concerning reactivity and regiochemistry. For example, dienes having conjugating electron-withdrawing substituents at C(2) or C(3), e.g. CN, SO_2R and COR, are often more reactive toward electron-poor dienophiles than isoprene, 2,3-dimethyl-1,3-butadiene and 1,3-pentadiene[64–66]. This has been explained by taking into account the paralocalization energy of the diene in the transition state. This energy represents more or less the energy needed to reorganize the π-bonds in the cycloaddition reaction. Dienes with a conjugating substituent at C(2) or C(3) change from a cross-conjugated 6π electron system to a 4π electron system, whereas 1,3-butadiene changes from a 4π electron system to a 2π electron system, causing the paralocalization energy for these 2- and 3-substituted dienes to be lower than for 1,3-butadiene. In addition, calculations and experiments support an early reorganization of π electrons which entails an important contribution of this paralocalization energy to the transition state energy[64,65].

A classic example is the dimerization of methyl cyclopentadienylcarboxylate **(37)** to Thiele's ester **(38)**[67]. Although diene **37b** should be more reactive than **37c** according to the FMO theory, it was diene **37c** that reacted with diene **37b** (equation 17).

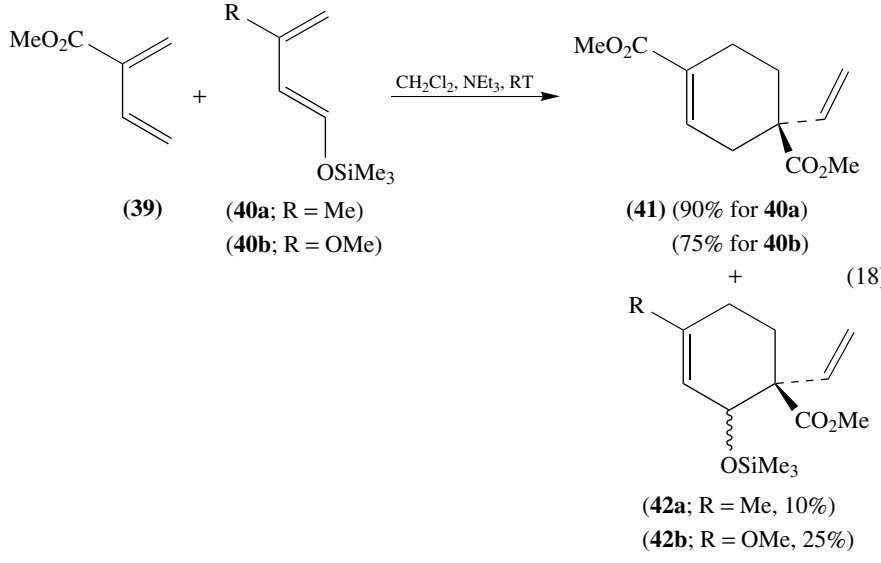
In a similar way, 2-(methoxycarbonyl)-1,3-butadiene **(39)** dimerizes rapidly, even in the presence of electron-rich dienes such as **40a** or **40b**, as illustrated in equation 18[65]. The dimeric adduct **41** and the mixed adduct **42** were obtained in ratios of 90 : 10 and 75 : 25 in the reactions of **39** with **40a** and **40b**, respectively.

The reactivity of **45** towards various dienophiles was similar to that of dienes **43** and **44**, whereas diene **46** was much less reactive[64]. According to the FMO theory, dienes **45** and **46** should have a similar reactivity.

The FMO model is sometimes unable to correctly predict the regioisomer to be obtained from cycloadditions of dienes having either two different substituents or two identical substituents at two different positions. For example, substituents at C(1) have proven to



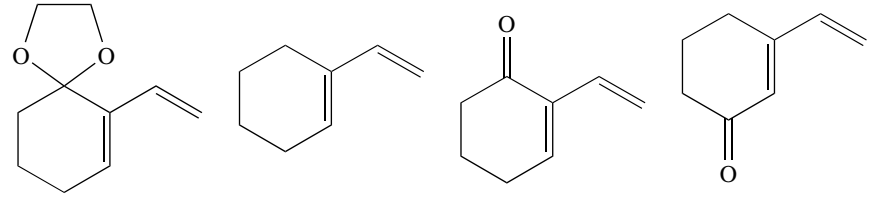
(17)



(39) (**40a**; R = Me) (**40b**; R = OMe) **(41)** (90% for **40a**) (75% for **40b**) + (18)

(**42a**; R = Me, 10%)
(**42b**; R = OMe, 25%)

exert greater control over regiochemistry than the same substituents at C(2), which is not predicted by the FMO theory. An alternative model has been proposed by Hehre and coworkers[68]. This model is based on matching complementary reactivity surfaces for both diene and dienophile. This approach proved more successful in predicting the regioselectivity in the cases mentioned above.



(43) **(44)** **(45)** **(46)**

B. The Diels–Alder Reaction. Recent Developments

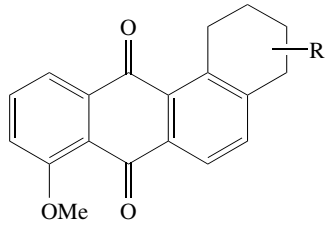
1. Diels–Alder reactions in targeted synthesis

Because the Diels–Alder reaction allows the construction of six-membered rings with the introduction of up to four new stereocenters in a stereocontrolled fashion in one single step, it is a very important tool for the synthesis of six-membered rings containing natural compounds and derivatives. In many synthetic strategies toward these types of compounds, the Diels–Alder reaction is a crucial step, as illustrated by the following examples.

Many groups have employed a Diels–Alder strategy toward the synthesis of the well-known antitumor compound paclitaxel, which has a tetracyclic core containing two

six-membered rings[69]. Nicolaou and colleagues[70] prepared both of these rings by a Diels–Alder approach. Coupling of these ring fragments ultimately led to the second total synthesis of paclitaxel in 1994[71].

The wide range of biological properties associated with the angucycline class of antibiotics has stimulated great interest in these compounds. Several groups reported a Diels–Alder approach toward angucyclinones **(47)**, a simpler subclass devoid of carbohydrate functionalities. The general strategy was to react a naphthoquinone derivative with an *inner–outer* diene which afforded the basic angucyclinone skeleton[72].



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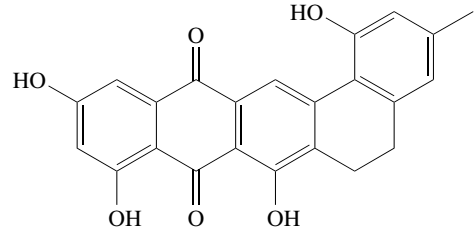

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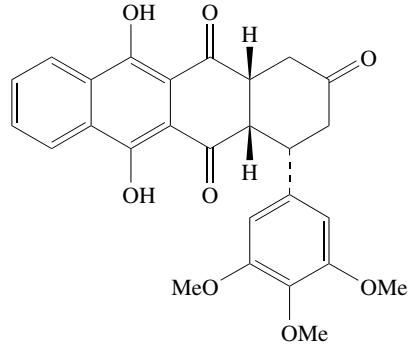


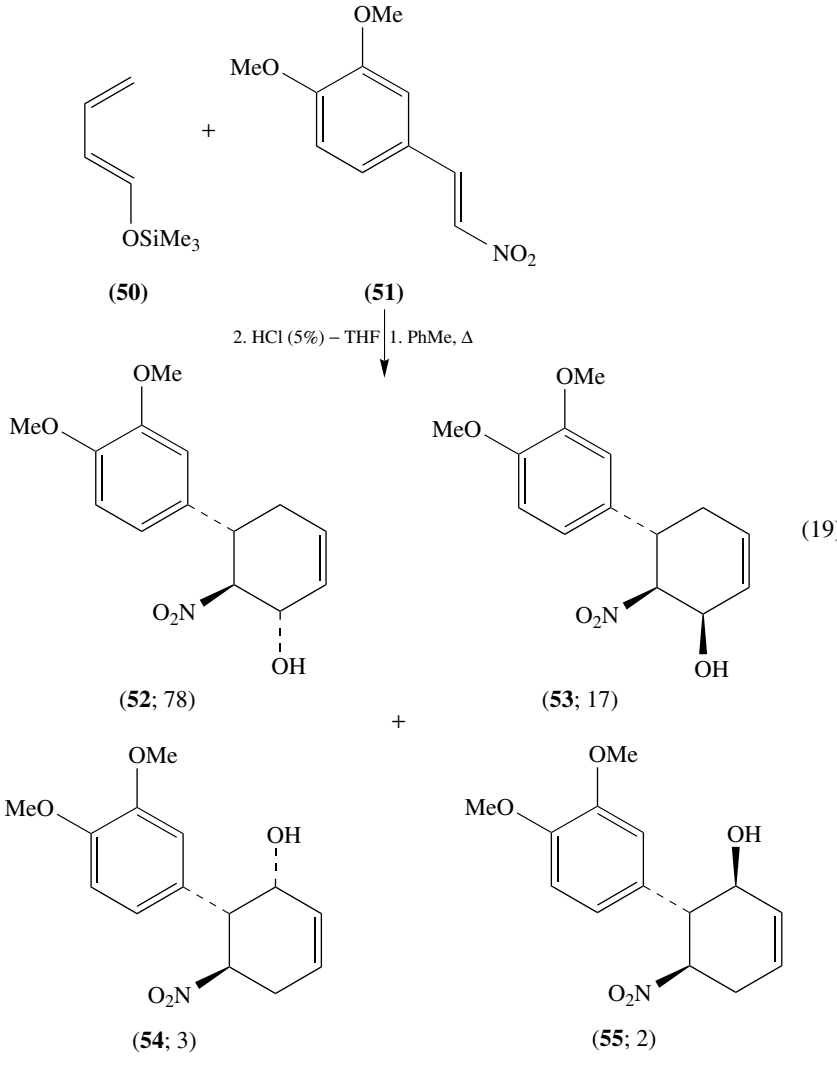
(49)

Kraus and Zhao[73] described the total synthesis of G-2N **(48)**, an angularly fused quinone natural product, using a Diels–Alder reaction between an *outerring* bicyclic diene and a *p*-benzoquinone derivative. Sahagún and colleagues[74] reported the synthesis of tetracyclic ketone **49** using a Diels–Alder approach. Ketone **49** was intended to be used in the synthesis of new anthracycline analogs.

In the course of their research about drugs with oncologic activity, Martinez and Iglesias[75] examined the Diels–Alder reaction between 1-trimethylsilyloxy-1,3-butadiene **(50)** and nitroalkene **51** which afforded, after hydrolytic work-up, a mixture of two regioisomeric pairs of *endo/exo* isomers **52/53** and **54/55** in a ratio of **52**/**53**/**54**/**55** = 78 : 17 : 3 : 2 (equation 19).

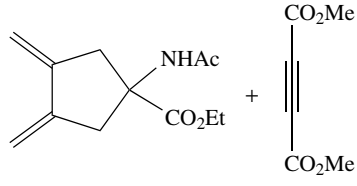
Constrained α-amino acids, which have gained widespread use in peptide design and are important for controlling secondary structures, were prepared by Kotha and colleagues[76] via Diels–Alder reactions of *outerring* diene **56** with several dienophiles, followed by

aromatization of the primary cycloadduct using DDQ. The reaction between **56** and dimethyl acetylenedicarboxylate **(57)**, which gives **58**, has been depicted in equation 20.

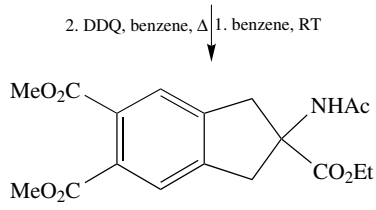


(19)

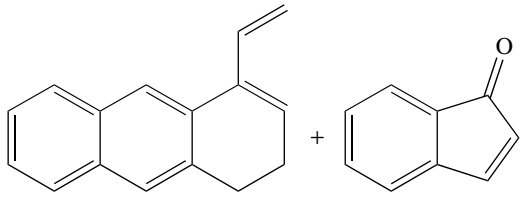
As a part of a broad study dealing with the development of synthetic methods for polycyclic aromatic compounds, Minuti and colleagues[77] prepared some [5]phenacenes and fluorenoanthracenes via Diels–Alder reactions between dienes such as **59** and several activated dienophiles. Oxidation of the primary adducts with DDQ afforded the desired polycyclic aromatic compounds. Equation 21 shows the reaction between 3,4-dihydro-1-vinylanthracene **(59)** and *in situ* generated 2-inden-1-one **(60)** which afforded a 3 : 1 mixture of regioisomers **61** and **62** with 51% overall yield.



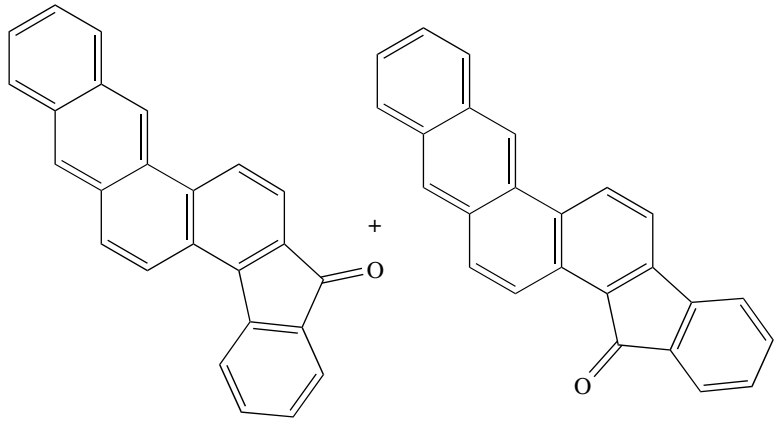
(56) **(57)**



(58) (20)

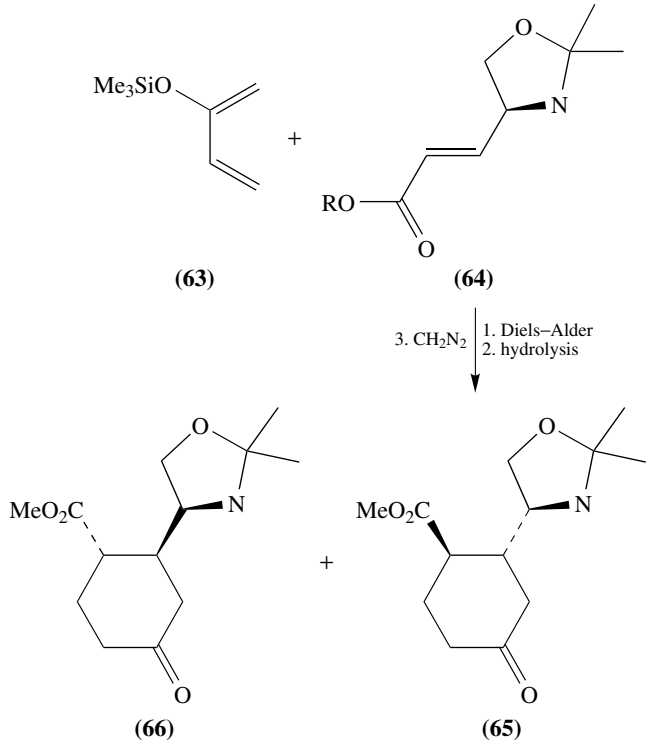


(59) **(60)**



(**62**; 25) (**61**; 75) (21)

Ohfune and coworkers[78] used Diels–Alder reactions between 2-trimethylsilyloxy-1,3-butadiene **(63)** and acrylate esters **64** to synthesize constrained L-glutamates which they intended to use for the determination of the conformational requirements of glutamate receptors. The reactions between **63** and acrylate esters **64a** and **64b** did not proceed. Changing the ethyl and methyl ester moieties into more electron-deficient ester moieties, however, led to formation of Diels–Alder adducts, the yields being moderate to good. In nearly all cases, the cycloadducts were obtained as single diastereomers, which is indicative of a complete facial selectivity (equation 22, Table 1). Other dienes, e.g. cyclopentadiene and isoprene, also showed a markedly enhanced reactivity toward acrylate **64g** in comparison with acrylate **64a**.

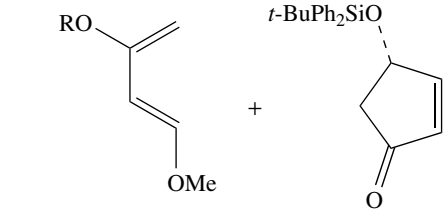


(22)

TABLE 1. Data for reaction 22

Entry	R	Dienophile	T (°C)	Yield (%)	**65/66**
1	Me	**64a**	160	—	
2	Et	**64b**	160	—	
3	CH_2CF_3	**64c**	130	47	80/20
4	$CH(CF_3)_2$	**64d**	130	71	100/0
5	Ph	**64e**	130	—	
6	*p*-$NO_2C_6H_4$	**64f**	130	52	100/0
7	C_6F_5	**64g**	130	84	100/0

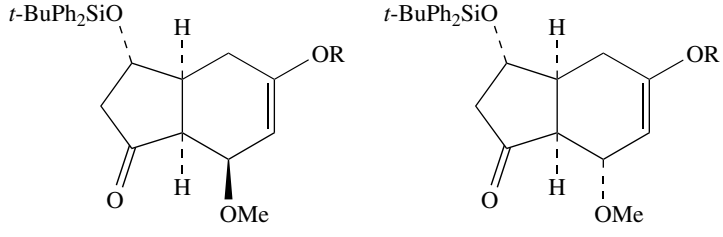
Rokach and colleagues[79] made use of a Diels–Alder approach to synthesize isoprostanes. Starting with dienes **67a/67b** and enantiomerically pure (>99% ee) dienophile **68**, they were able to obtain the desired adducts with high diastereofacial and regioselectivities (equation 23). *Endo* **69** and *exo* **70** were formed by attack of the diene at the less shielded upper face of the dienophile, whereas *exo* **71** resulted from attack at the more shielded lower face of **68**.



(**67a**; R = Me) **(68)**

(**67b**; R = $SiMe_2Bu$-*t*)

toluene, Δ

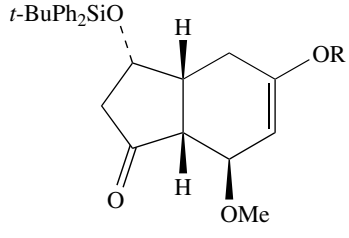


(23)

(**69a**; R = Me, 62) (**70a**; R = Me, 21)

(**69b**; R = $SiMe_2Bu$-*t*, 65) (**70b**; R = $SiMe_2Bu$-*t*, 18)

+

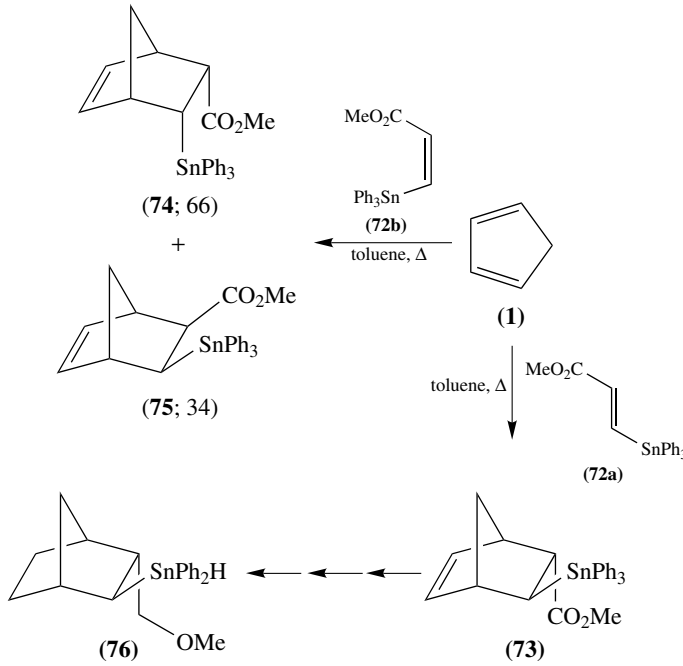


(**71a**; R = Me, 17)

(**71b**; R = $SiMe_2Bu$-*t*, 17)

The Diels–Alder reaction has also been used to prepare special reagents. Thomas and coworkers[80], for instance, studied the Diels–Alder reactions of methyl (*E*)- and (*Z*)-3-(triphenylstannyl)acrylates **72a** and **72b** with cyclopentadiene and converted the organostannanes obtained to tin hydrides. (*E*)-**72a** afforded *endo* **73** exclusively with 99% yield, whereas (*Z*)-**72b** afforded a 2 : 1 mixture of *endo* **74** and *exo* **75** with 77% overall yield (equation 24). Cycloadduct **73** was easily converted to tin hydride **76**. By

extending this strategy to the use of chiral 3-(triphenylstannyl)acrylates, chiral tin hydrides were produced with high enantiomeric excesses[81].



(24)

2. Lewis acid catalyzed Diels–Alder reactions

Lewis acid catalysts are often applied in Diels–Alder chemistry to enhance the reaction rate by co-ordinating to the dienophile, thereby lowering its LUMO energy. The catalyzed Diels–Alder reactions can, and usually *must*, be performed at lower temperatures and generally show an improved regioselectivity in comparison with the corresponding thermal reactions. New types of Lewis acids and Lewis acid mediated Diels–Alder reactions are published regularly, the following reactions being representative recent examples.

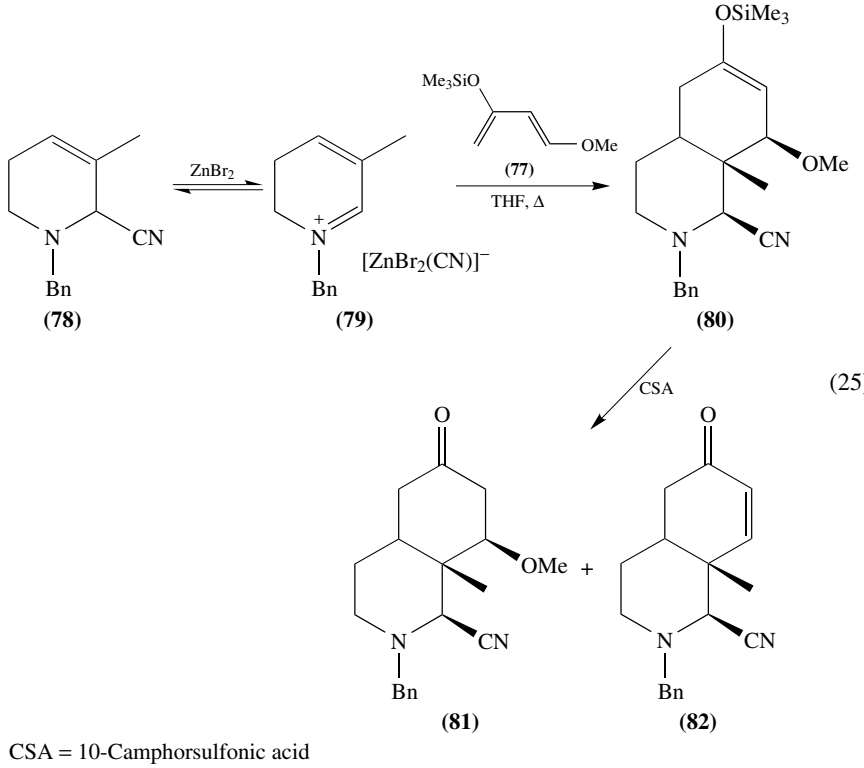
Baldwin and coworkers[82] studied the Diels–Alder reactions between dihydropyridinium ions and diene **77** with the aim to synthesize functionalized hydroisoquinolines. The reaction of diene **77** with dihydropyridinium ion **79**, which was prepared *in situ* by treating **78** with zinc bromide, afforded **80**. After acidic work-up, a mixture of methoxyketone **81** and enone **82** was obtained (equation 25). The reaction proceeded with complete *exo* selectivity. Without the addition of zinc bromide, no Diels–Alder reaction was observed.

Danishefsky and coworkers[83] used a dioxolenium mediated Diels–Alder reaction between **83** and **85**, generated from **84**, in their total synthesis of dysidiolide **(87)** (equation 26). The Diels–Alder reaction, using trimethylsilyl triflate as the dioxolenium generating species, proceeded with high facial, *endo* and regioselectivity affording **86** as the main product, together with 5% of a yet unidentified stereoisomer.

Desimoni and coworkers[84] probed the catalytic effect of metal perchlorate salts on the rate of the Diels–Alder reactions between malonates **88** and cyclopentadiene (equation 27). They found that especially magnesium perchlorate was able to catalyze the reaction by binding two malonates in a bidentate fashion. Reaction times were shortened up to 1000 times. The *endo/exo* selectivity was inverted from **89/90** = 40/60 ($n = 4$) and 17/83 ($n = 5$) for the thermal uncatalyzed reactions to **89/90** = 60/40 ($n = 4$) and 80/20 ($n = 5$) for the magnesium perchlorate catalyzed reactions.

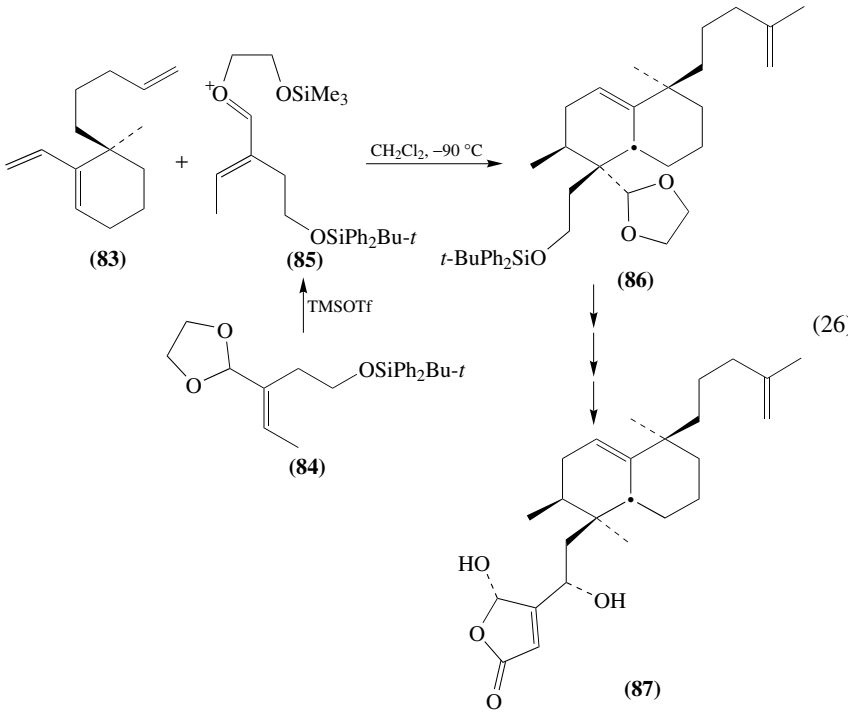
Because of their previous findings that α,β-unsaturated thioesters were more reactive than their ester counterparts in Diels–Alder reactions[85], Hart and coworkers[86] performed a systematic study of the cycloaddition reactions of α,β-unsaturated thioesters and α,β-unsaturated selenoesters with several dienes. Thermal reactions were compared with Lewis acid catalyzed reactions at room temperature (equation 28 and Table 2). The results clearly demonstrated that use of a Lewis acid enhanced the regioselectivity (entries 1 *vs* 2, 3 *vs* 4, 5 *vs* 6 and 7 *vs* 8) as well as the *endo* (with respect to the thioester or selenoester group) selectivity (entries 5 *vs* 6 and 7 *vs* 8).

Hubbard and Miller[87] used a Lewis acid catalyzed Diels–Alder reaction between γ,γ-disubstituted α,β-unsaturated esters and cyclopentadiene in their approach toward oligomeric cyclopentanoids. In order for the reaction to proceed, they needed to add trimethylaluminum as a desiccant prior to addition of the Lewis acid catalyst aluminum trichloride. The *endo/exo* selectivity of the reaction with **97**, depicted in equation 29, increased from **98**/**99** = 75/25 to 88/12 when the reaction temperature was dropped from room temperature to −20 °C.

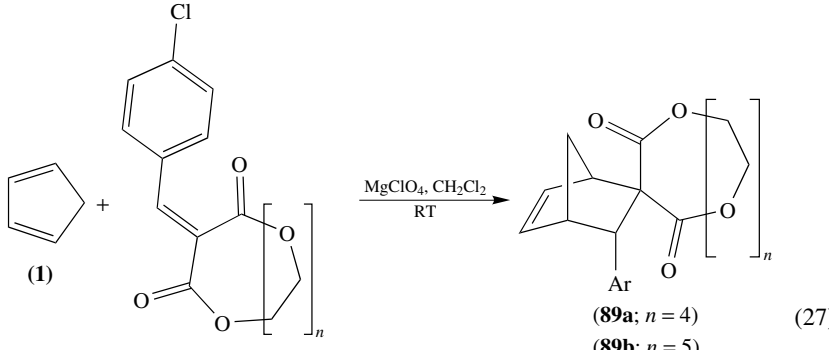


(25)

CSA = 10-Camphorsulfonic acid



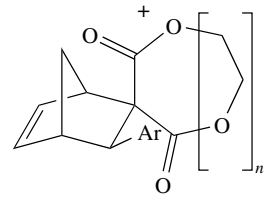
(83) (85) (86) (84) (87) (26)



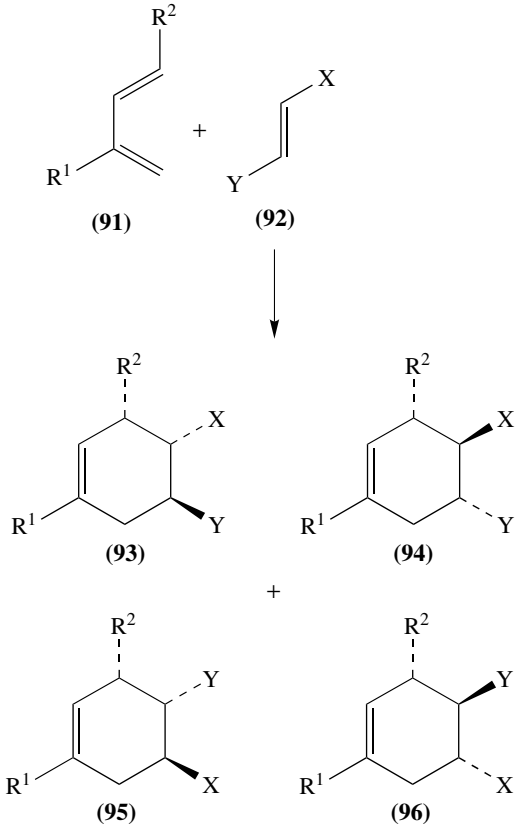
(1) (88a; $n = 4$) (88b; $n = 5$)

Ar = p-ClC_6H_4

(89a; $n = 4$) (89b; $n = 5$) (27)



(90a; $n = 4$)
(90b; $n = 5$)



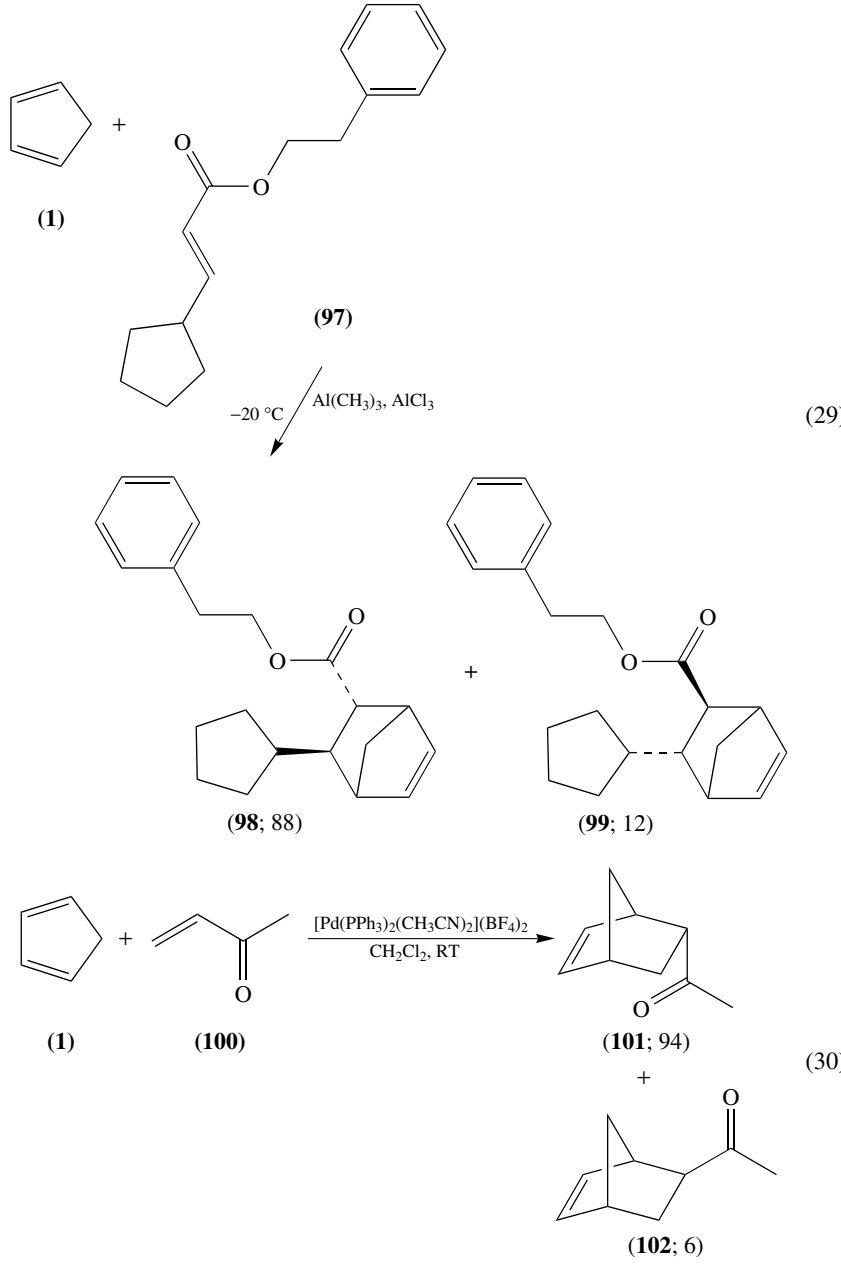
(28)

Oi and coworkers[88] employed a cationic palladium(II) complex to catalyze Diels–Alder reactions. The benefits of such a catalyst compared to traditional catalysts such as boron and aluminum halides were reported to possess better stability to air and moisture,

TABLE 2. Reaction conditions and product distribution for equation 28

Entry	R^1	R^2	Diene	X	Y	Dienophile	Conditions	**93/94/95/96**
1	Me	H	**91a**	COSPh	Me	**92a**	190–195 °C	63/37
2	Me	H	**91a**	COSPh	Me	**92a**	$EtAlCl_2$, RT	88/12
3	Me	H	**91a**	COSePh	CO_2Me	**92b**	190–195 °C	55/45
4	Me	H	**91a**	COSePh	CO_2Me	**92b**	$TiCl_4$, RT	100/0
5	H	Me	**91b**	COSPh	CO_2Me	**92c**	185–195 °C	29/27/24/20
6	H	Me	**91b**	COSPh	CO_2Me	**92c**	$EtAlCl_2$, RT	67/14/16/3
7	H	Me	**91b**	COSePh	Me	**92d**	185–195 °C	34/56/10/0
8	H	Me	**91b**	COSePh	Me	**92d**	$EtAlCl_2$, RT	80/20/0/0
9	$OSiMe_3$	H	**63**	COSPh	Me	**92e**	185–195 °C	>95/<5
10	$OSiMe_3$	H	**63**	COSePh	Me	**92f**	185–195 °C	>95/<5
11	$OSiMe_3$	H	**63**	COSPh	CO_2Me	**92g**	$TiCl_4$, RT	95/5
12	$OSiMe_3$	H	**63**	COSePh	CO_2Me	**92h**	$TiCl_4$, RT	100/0

higher turnover numbers and better-defined structures. A typical example of a reaction catalyzed by Oi's palladium complex is the reaction between methyl vinyl ketone **(100)** and cyclopentadiene (equation 30), which afforded a mixture of *endo/exo* isomers



(29)

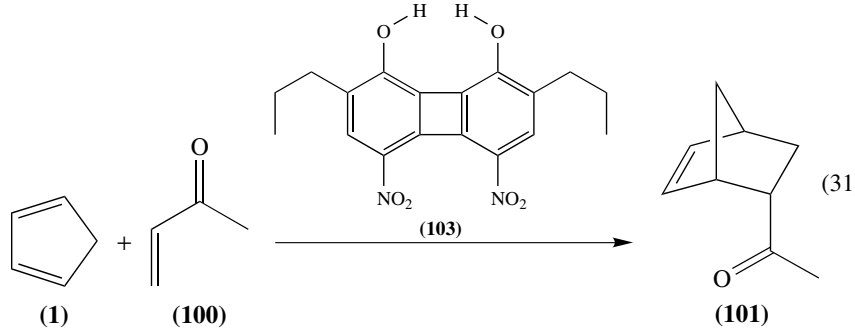
(30)

(**101**/**102** = 94/6) in 94% overall yield. By replacing the two triphenylphosphine ligands by a chiral bidentate ligand, Oi and colleagues were able to conduct enantioselective Diels–Alder reactions.

3. Non-Lewis acid catalyzed Diels–Alder reactions

In recent years, supramolecular chemistry has produced a number of systems which have been shown to be able to effectively catalyze a Diels–Alder reaction. Most systems selectively afforded only one diastereomer because of a pre-organized orientation of the reactants. These systems include cyclodextrines, of which applications in Diels–Alder chemistry have recently been reviewed[89]. Some other kinds of non-Lewis acid catalyzed Diels–Alder reactions, including catalysis by proteins and ultrasound, have been discussed by Pindur and colleagues[90].

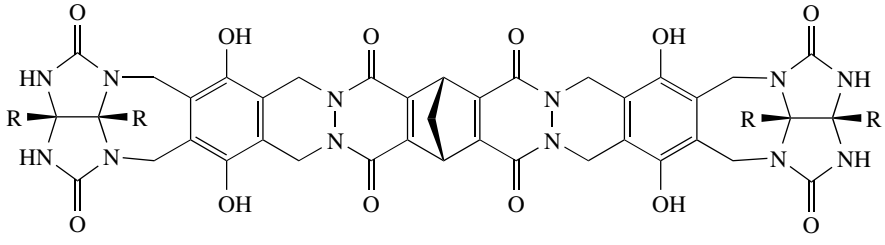
Kelly and colleagues[91] explored the use of bisphenylenediol **103** as a catalyst in Diels–Alder reactions of α,β-unsaturated carbonyl compounds. Activation of the dienophile occurred through double hydrogen bonding of the two hydroxyl functions on **103** to the carbonyl group on the dienophile. The reaction of cyclopentadiene with methyl vinyl ketone (equation 31) at ambient temperature showed, after a reaction time of 10 minutes, 3% of product formation in the absence of **103** against 90% of product formation in the presence of 0.4 equivalents of **103**.



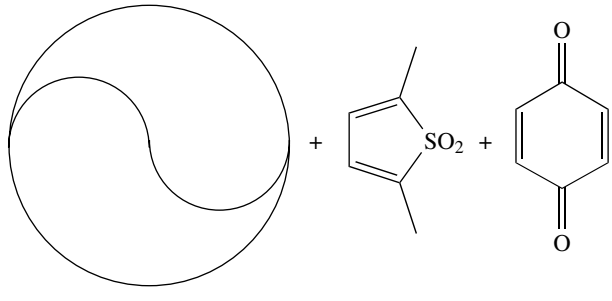
(31)

Rebek and colleagues[92] were able to accelerate the reaction of *p*-benzoquinone with several dienes, e.g. 1,3-cyclohexadiene and cyclopentadiene, by encapsulating the reaction partners into a pseudospherical capsule **105** built up of two self-assembling multiring compounds **104**. The effective molarities of the reaction partners in the reaction of 1,3-cyclohexadiene with *p*-benzoquinone, which afforded exclusively the *endo* cycloadduct, were more than 100 times higher than the corresponding concentrations in the bulk solution. Product inhibition prevented the system from turning over and offering true catalysis. That is why first-order kinetics were only observed till approximately 10% conversion was reached.

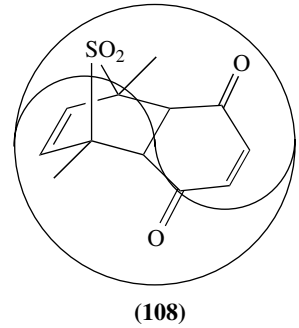
When thiophene dioxide **(106)** was used as the diene component, true catalysis was observed with **107**, affording the capsule bound adduct **108** (equation 32)[93]. The displacement of a single molecule of adduct by two molecules of starting material is, in principle, disfavored on entropic grounds, but turnover took place in this case due to the poorer affinity of the Diels–Alder adduct for the capsule. The rate enhancement of this reaction, based on the ratio of the half-life for the reaction outside *vs* inside the capsule, was 10-fold.



(**104**; R = 4-*n*-heptylphenyl)



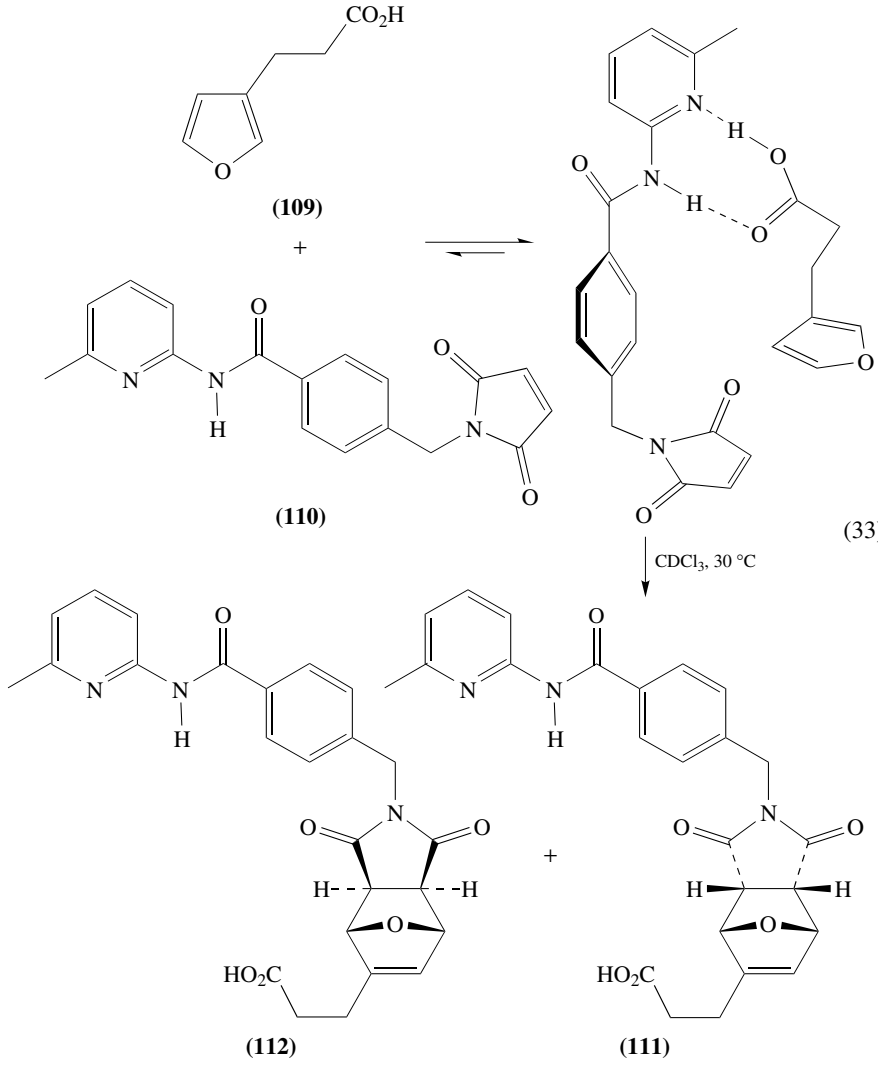
(105) **(106)** **(107)**



(108)

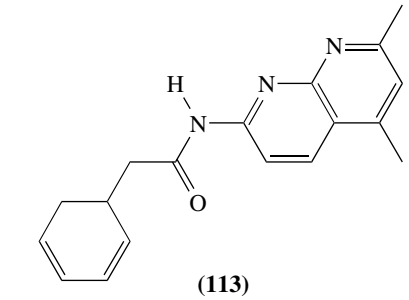
(32)

Philp and Robertson[94] developed a system which is capable of controlling the stereochemical outcome of the Diels–Alder reaction between a maleimide and a furan. By attaching functional groups which can recognize each other to both maleimide and furan, they were able to get a rate acceleration and a much higher *endo* selectivity compared to the control reaction of benzyl maleimide with furan **109**. Whereas the bulk concentrations were 5 mM in both reactants **109** and **110**, effective molarities of 64 mM and 6 mM were achieved within the *endo* and *exo* [**109** : **110**] complexes, respectively (equation 33). This difference, together with the fact that the *endo* adduct **111** is stabilized by an intramolecular hydrogen bond which makes the retro Diels–Alder reaction more difficult, caused the *exo* adduct **112** to be the minor adduct.

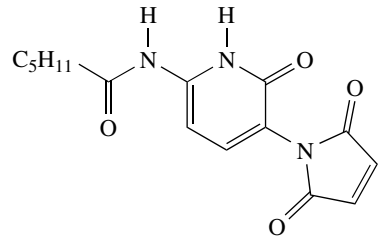


Wang and Sutherland[95] communicated an autocatalytic Diels–Alder reaction in which the adduct of diene **113** and olefin **114** catalyzed its own formation. This was accomplished through binding of both reactants in a pre-organized fashion by means of multiple hydrogen bonding (see complex below structures **113** and **114** overleaf).

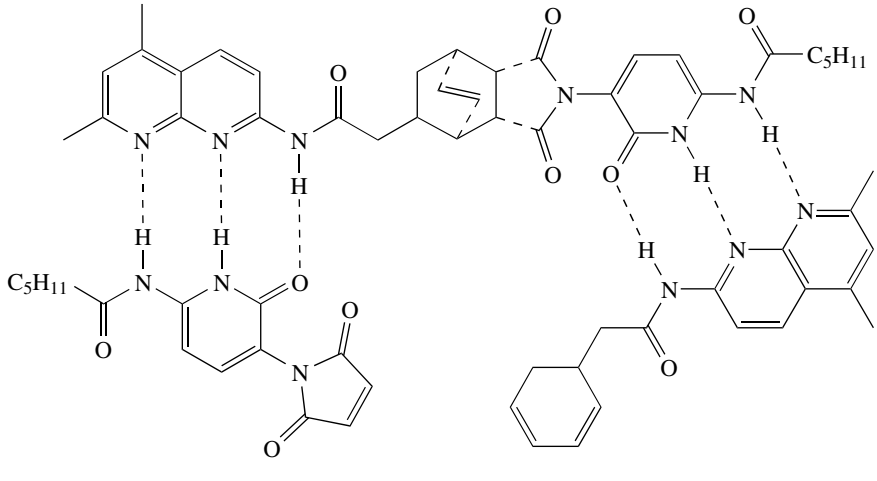
Sanders and coworkers[96,97] catalyzed and directed the Diels–Alder reaction between 4-(maleimidomethyl)pyridine and 4-(3-furyl)pyridine using metalloporphyrin oligomers. When trimer **115a** having three butadiyne linkers was used as the catalyst, the *exo* adduct was the exclusive product isolated at both 30 °C and 60 °C, whereas the uncatalyzed reaction provided an *endo/exo* ratio of 2/1 at 30 °C and a transient trace of *endo* adduct



(113)



(114)

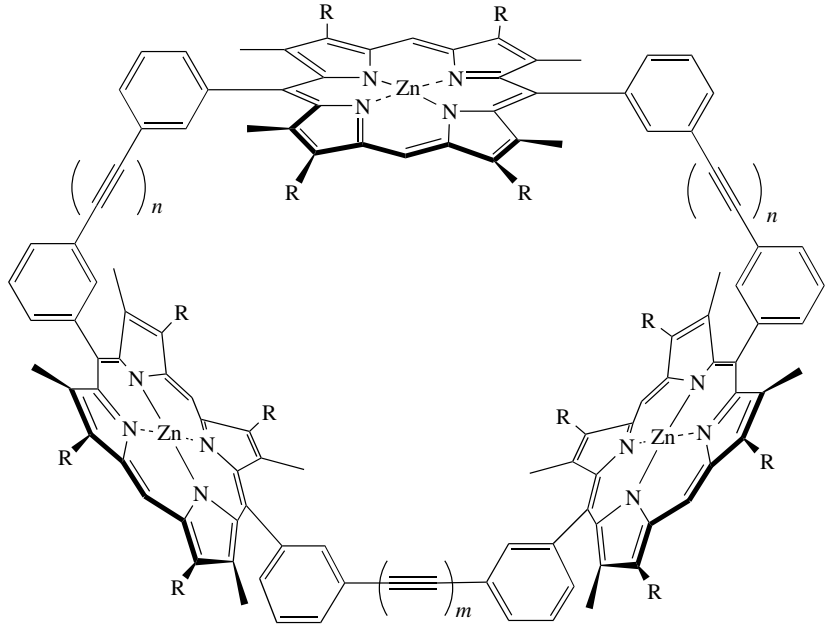


at 60 °C due to cycloreversion. When trimer **115b** was employed, the *endo* adduct was formed exclusively at 30 °C, whereas a mixture of *endo* and *exo* adducts was obtained at 60 °C. These results were considered to result from stabilization of the *exo* transition state by co-ordination of the pyridine nitrogens to two zinc ions in the case of trimer **115a** and stabilization of the *endo* transition state, in which the pyridine nitrogens are closer together, in the case of the smaller trimer **115b**.

Endo and coworkers[98] were able to catalyze the Diels–Alder reaction between acrolein and 1,3-cyclohexadiene by using a novel organic network material built up of anthracene-bisresorcinol derivatives which were held together by intermolecular hydrogen bonds. The suggested catalytic cycle was composed of sorption of the reactants in the cavities of the material, a pre-organized intracavity reaction, and desorption of the adduct.

Harman and colleagues[99] studied the activation of styrenes toward Diels–Alder reactions by application of a pentaammineosmium(II) complex. Cycloaddition reactions between styrenes and dienophiles generally require harsh reaction conditions, low yields and side products being the logical result. By complexing the phenyl ring with a pentaammineosmium(II) complex, thereby partly localizing the π system, it proved possible to perform Diels–Alder reactions with a wide variety of dienophiles under mild conditions. The reactions proceeded with almost complete site selectivity, the *inner–outer* diene system of **116** being the preferred site of attack, as illustrated by the reaction with

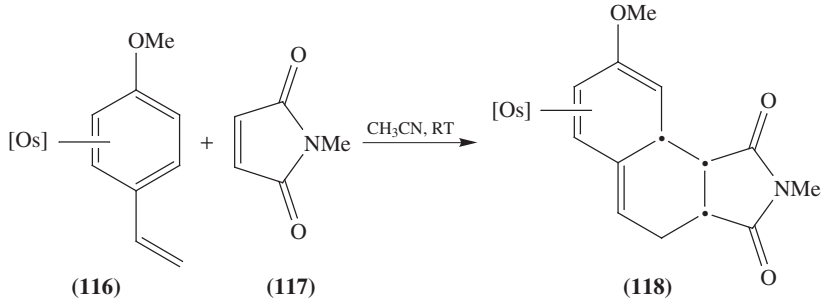
N-methylmaleimide **(117)** depicted in equation 34. Cycloadduct **118** can be decomplexed by a variety of reagents, e.g. silver triflate, affording the free adduct **119**.



(**115a**; $n = m = 2$, R = $CH_2CH_2CO_2Me$)
(**115b**; $m = 2$, $n = 1$, R = $CH_2CH_2CO_2Me$)

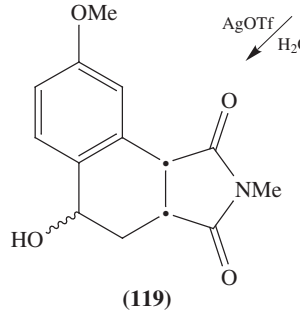
Kita and coworkers[100] reported the strong base catalyzed cycloaddition reactions between 4-phenylthio-substituted homophthalic anhydrides and various sulfinyl substituted dienophiles. The cycloaddition of **120** to **121a** afforded, after elimination of the sulfinyl group and extrusion of carbon dioxide under the reaction conditions employed, **122** as the ultimate reaction product (equation 35). The presence of the sulfinyl group proved essential for a sufficient activity of the 1,2-dicarbonyl substituted double bond of **121**, because substitution of the sulfinyl group by other leaving groups, e.g. Cl or Br (cf **121b** and **121c**), greatly diminished the reaction rate.

A modern method of catalysis is the application of microwave irradiation, which has, however, been used only sparingly to accelerate Diels–Alder reactions. Rao and colleagues[101] studied the differences in reaction rates between thermally and microwave activated Diels–Alder reactions of 1,2-difluoro-1-chlorovinyl phenyl sulfone **(123)** with several cyclic dienes. For example, the thermal reaction between **123** and cyclopentadiene took 10 hours in refluxing toluene for completion, whereas the microwave assisted reaction took only 3 minutes, affording *exo* adducts **124** and **125** in 95% yield and a **124/125** = 40/60 ratio (equation 36). Likewise, the reaction of **123** with furan did not take place under thermal conditions, whereas it proceeded within 7 minutes in the microwave, yielding the *endo* cycloadduct with 40% yield. The *endo* selectivity was considered to originate from secondary orbital interactions between the fluorine atoms and the bridged oxygen atom.

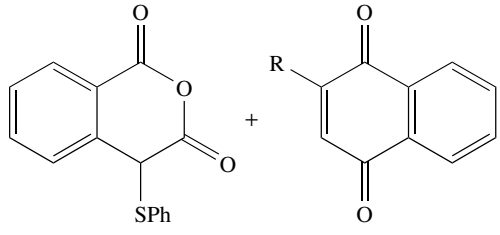


(116) **(117)** **(118)**

(34)

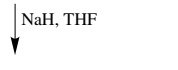


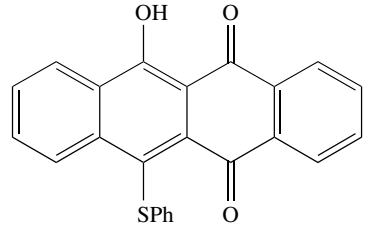
(119)



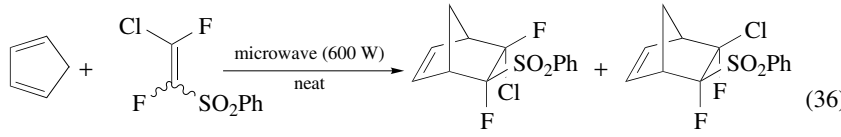
(120) (**121a**; R = S(O)Ph)
(**121b**; R = Cl)
(**121c**; R = Br)

(35)





(122)

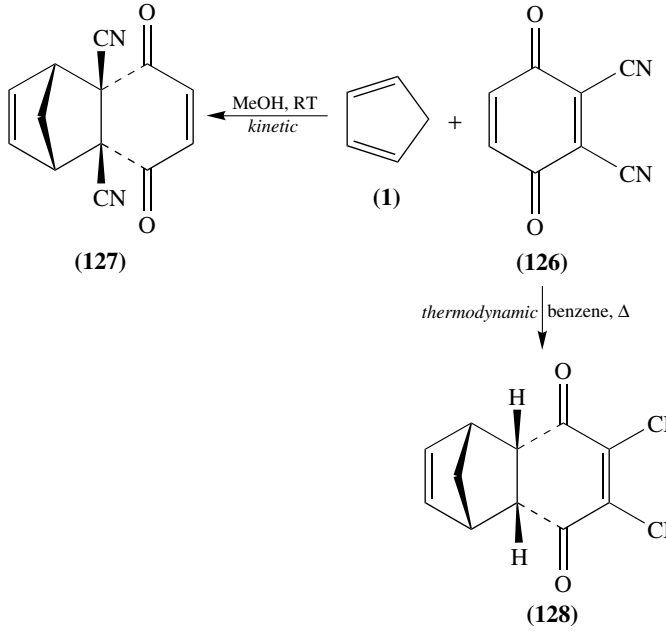


(**1**) (**123**; *E*/*Z* = 40/60) (**124**; 40) (**125**; 60) (36)

4. Site selective reactions

Dienophiles may contain more than one double or triple bond. This might result in multiple product formation, but in most instances the diene will attack one bond with high site specificity. This site selectivity is often controlled by substitution patterns and electronic or steric parameters.

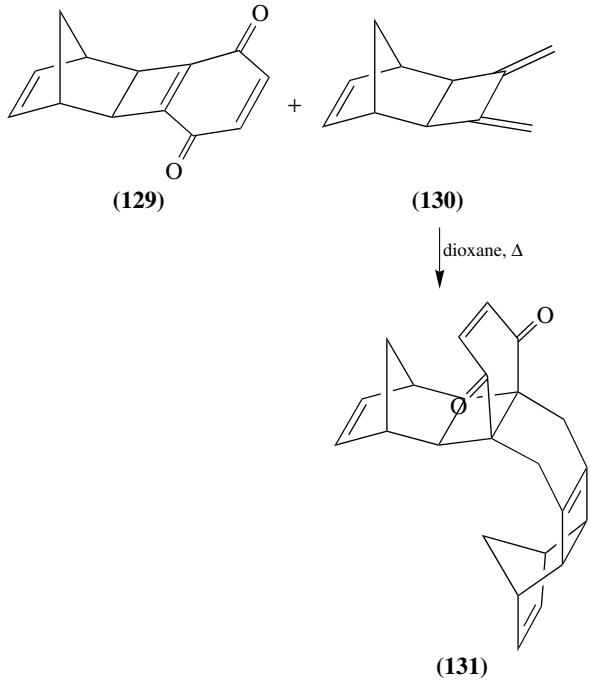
Marchand and coworkers[102] reported a difference in site selectivity between the thermodynamically and kinetically controlled Diels–Alder reactions of cyclopentadiene with 2,3-dicyano-*p*-benzoquinone **(126)** (equation 37). Under kinetic conditions, the more reactive double bond of **126** reacted with cyclopentadiene affording **127**, whereas the less substituted double bond reacted under thermodynamic conditions affording **128**. Both reactions proceeded with complete *endo* selectivity. These findings were in agreement with *ab initio* HF/3–21G* calculations.



(37)

In general, 2,3-dialkyl-*p*-benzoquinones exhibit site selectivity in that they tend to give predominantly Diels–Alder adducts resulting from diene attack on the external rather than the internal double bond. This external site selectivity is, however, dramatically reversed when a (substituted) cyclobutane ring is fused to *p*-benzoquinone. Paddon-Row and coworkers[103] studied the reactions of *p*-benzoquinones such as **129** with several

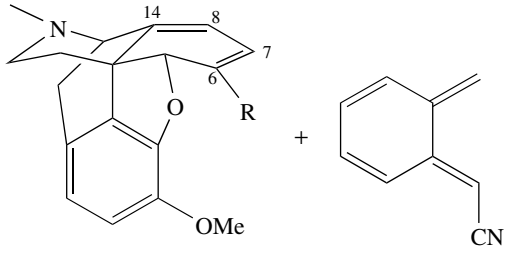
dienes. The reaction with diene **130**, for example, afforded **131** as the exclusive adduct (equation 38). The complete site selectivity was explained by the great relief of strain upon cycloaddition to the internal double bond. This was confirmed by *ab initio* calculations which showed the transition states of the *endo* and *exo* internal cycloadditions to be 3.0 and 4.3 kcal mol^{-1} more stable, respectively, than those of the corresponding external cycloadditions.



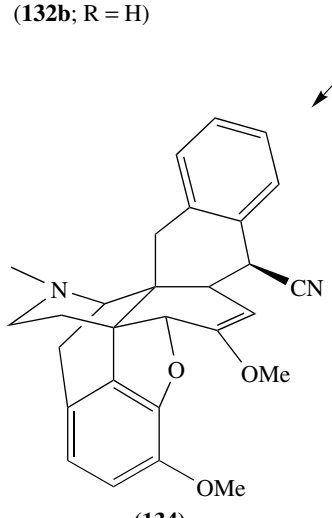
(129) **(130)** **(131)** (38)

Portoghese and colleagues[104] employed opiate dienes **132** as dienophiles in the reactions with *in situ* generated **133** and studied the site selectivity in these reactions. When thebaine **(132a)** was reacted with **133**, the Diels–Alder reaction took place at the 8(14) double bond affording **134**, the diene approaching from the less hindered β face of **132a** (equation 39). According to the authors, the methoxy substituted double bond is too electron-rich to react with **133**. This was confirmed by the non-reactivity of the thebaine derivative obtained by hydrogenation of the 8(14) double bond. When **132b** was employed as the dienophile, the reaction took place at the less substituted double bond at C(6) affording **135**.

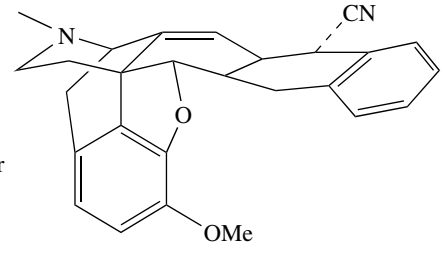
The Diels–Alder reactions of 'dienes' that have two or more pairs of conjugated double bonds may also exhibit site selectivity, as has been demonstrated by several groups[105]. Talamás and coworkers[106] found complete site selectivity when 5-triisopropylsilyl-2-vinylfuran **(136)** was reacted with dimethyl acetylenedicarboxylate, affording **137** (equation 40), and several other dienophiles. The same extra-annular site selectivity was found for 2-triethylsilyl-4-vinylfuran. The large silyl groups apparently block the intra-annular cycloaddition. When the triisopropylsilyl group on **136** was replaced by a tri(*n*-butyl)stannyl group, site selectivity diminished, probably because of a decreased bulkiness and a longer carbon–metal bond.



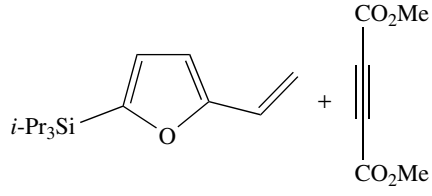
(**132a**; R = OMe) (**133**)
(**132b**; R = H)



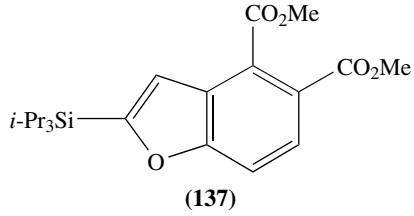
(39)



(**134**) (**135**)



(**136**) (**57**)



(40)

(**137**)

5. Tandem reactions

Tandem pericyclic processes offer the opportunity to synthesize complex highly substituted cyclic molecules in a completely stereocontrolled fashion in a few consecutive steps. As a consequence, tandem processes have been studied extensively. Some tandem processes involving Diels–Alder reactions have recently been reviewed[38,40,107].

Seitz and colleagues[108] made 10-ethylcolchicide **(138)**, a colchicine derivative, react with several dienophiles. The reaction of **138** with dimethyl acetylenedicarboxylate **(57)** afforded a single Diels–Alder adduct **(139)** which underwent a consecutive [3 + 2] cycloaddition with another equivalent of dimethyl acetylenedicarboxylate to give **140**. The formal elimination of C_2H_6 afforded **141**, whereas fragmentation led to **142** (equation 41).

Dailey and colleagues[109] employed a 'domino' Diels–Alder reaction to synthesize the complex hexacycle **146**. The intermolecular reaction of tetracycle **143** with maleic anhydride **144** afforded a single adduct **(145)** which immediately underwent an intramolecular Diels–Alder reaction to give **146** (equation 42). This reaction is similar to a reaction performed previously by Prinzbach and colleagues[110]. Prinzbach observed that when alkynes were used as dienophiles, either 'domino' or 'pincer' Diels–Alder reactions occurred. In the latter type, the triple bond reacts with both diene units.

Itoh and coworkers[111] carried out tandem [2 + 2 + 2]/[4 + 2] cycloadditions catalyzed by a ruthenium catalyst. The reaction of diyne **147** with excess norbornene **148** in the presence of ruthenium catalyst **153**, for example, afforded **149**. Adduct **150** either dissociated from the catalyst or reacted with another equivalent of norbornene. In the latter case, a ruthenium catalyzed Diels–Alder reaction occurred, affording hexacyclic adduct **152** via **151** (equation 43). Compounds **150** and **152** were obtained in yields of 78% and 10%, respectively. Both cycloaddition reactions proceeded with complete stereoselectivity. When 1,6-heptadiyne was used instead of **147**, only trace amounts of a cycloadduct were obtained. Replacing norbornene by norbornadiene, which was expected to result in polymer formation, did not afford any adduct at all.

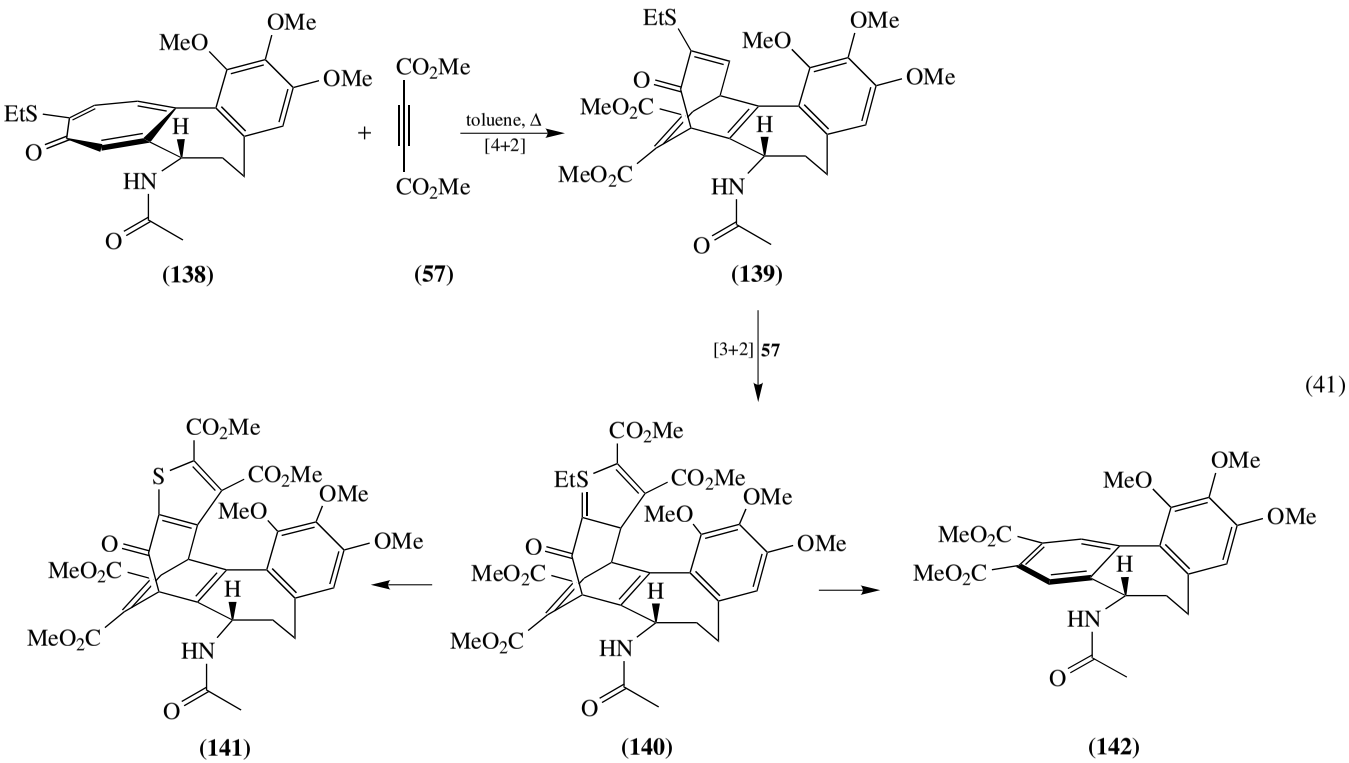
6. Diels–Alder polymerizations

Diels–Alder reactions have been used to synthesize and functionalize polymers, as reported by several groups. Rotello and coworkers[112], for example, covalently attached [60]fullerene to furan and cyclopentadiene substituted resins. The reaction with the furan substituted resin proved reversible. The resin was recovered by heating the fullerene functionalized resin.

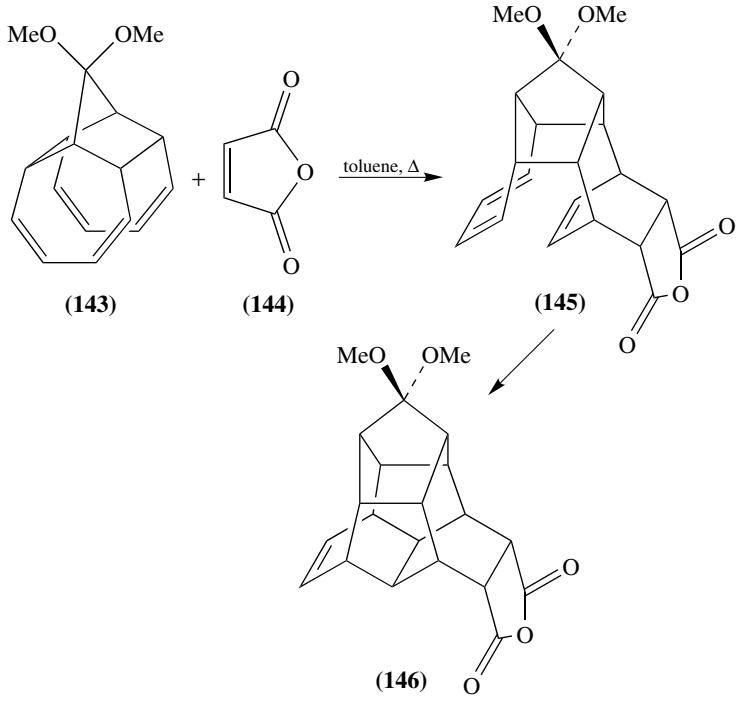
Stranix and Darling[113] functionalized divinylbenzene-rich copolymers **154** by Diels–Alder reactions with both dienophiles and dienes. Treating polymer **154** with maleic anhydride (**144**) afforded polymer **155**. Re-aromatization to give **156** occurred by means of an ene reaction with another equivalent of **144** (equation 44).

Copolymers of [60]fullerene and *in situ* generated bis-*o*-quinodimethanes were prepared by Gügel and colleagues[114]. In order to get soluble polymers, it proved necessary to introduce flexible groups on the bis-*o*-quinodimethanes. A maximum of 10 [60]fullerene units were incorporated into oligomers when [60]fullerene was reacted with a 7 : 3 mixture of **157** and **158** (i.e. with *o*-quinodimethanes **159** and **160**). Monosulfone **158** was added to induce the formation of triple cycloadducts of [60]fullerene. This prevented polymerization of the oligomer (quadruple cycloadditions to [60]fullerene are hard to accomplish) and enhanced its solubility.

Kottner and Klemm[115] studied the Diels–Alder polymerization of bismaleimides with 4,4′-dimethyl-6,6′-(octamethylene)di-2-pyrone. When the maleimide units were connected


EtS
O
H
HN
O
MeO
OMe
OMe
(138)
+
CO2Me
CO2Me
(57)
toluene, Δ
[4+2]
EtS
O
MeO2C
MeO2C
H
HN
O
MeO
OMe
OMe
(139)
[3+2] 57
(41)
CO2Me
S
CO2Me
MeO
OMe
O
MeO2C
H
MeO2C
HN
O
OMe
(141)
CO2Me
EtS
CO2Me
MeO
OMe
O
MeO2C
H
MeO2C
HN
O
OMe
(140)
MeO
OMe
MeO2C
MeO2C
H
HN
O
OMe
(142)

via a flexible spacer group, polymers with a coronand structure were formed, together with some cyclic oligomers.



(143) **(144)** **(145)** **(146)** (42)

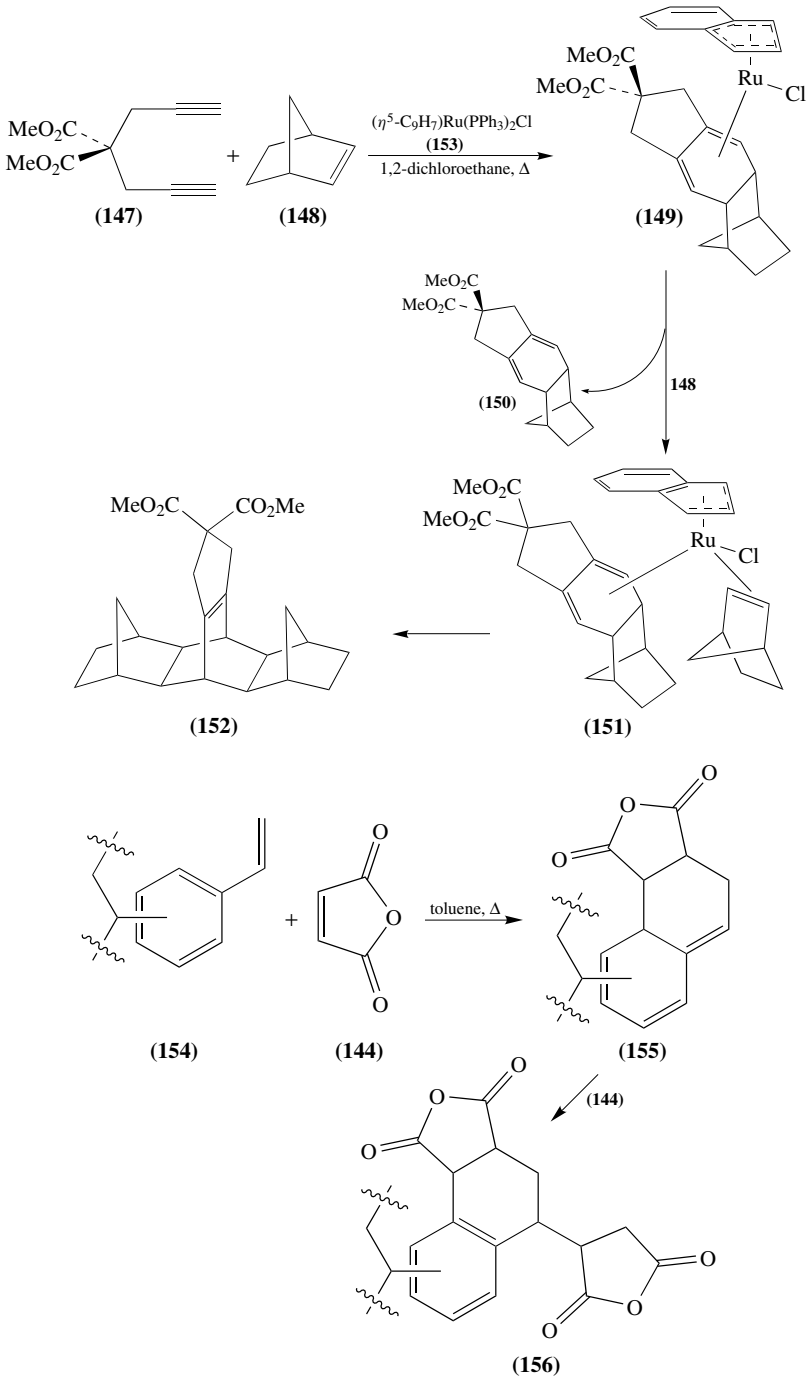
A rather novel application of the Diels–Alder reaction is the synthesis of dendrimers. Müllen and coworkers[116] made cyclopentadienone **161** react with 3,3′,5,5′-tetraethynylbiphenyl **162**. This afforded, after extrusion of carbon monoxide, a first generation dendrimer **163** containing 22 phenyl rings (equation 45). Cyclopentadienone **161** reacted only as a diene, since the bulky triisopropyl groups prevented the ethynyl functions from reacting.

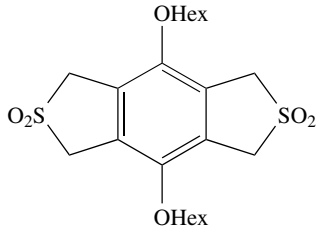
7. Diels–Alder reactions of furans

Despite their aromatic character, furans have found widespread use as dienes in Diels–Alder reactions[33]. The following examples have been intended to demonstrate the wide applicability of and the ongoing interest in Diels–Alder reactions of this diene.

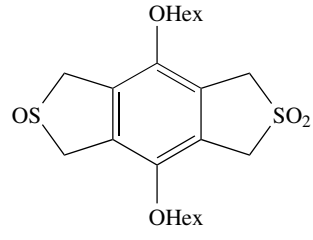
Copolymers with pendant furan moieties have been used to synthesize new polymer structures by exploiting the reactivity of this heterocycle toward various dienophiles[117], e.g. [60]fullerene[112b].

Gandini and coworkers[118] investigated the Diels–Alder reactions of furan rings attached to a polymer with a polystyrene backbone. When copolymers **164a** and **164b** were treated with excess *N*-phenylmaleimide (**165**), about 70% of the furan rings underwent a Diels–Alder reaction to give **166a** and **166b**, respectively. When bismaleimide **167** was used, cross-linking occurred to a high extent (equation 46). On heating polymer **168a** in the presence of 2-methylfuran, **164a** was fully recovered by a sequence of retro Diels–Alder/Diels–Alder reactions. Polymer **164b** was only partly regenerated using this same method.

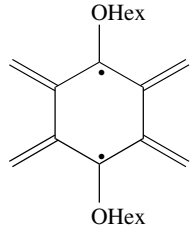

MeO2C
MeO2C
(147)
(148)
(η5-C9H7)Ru(PPh3)2Cl
(153)
1,2-dichloroethane, Δ
Ru
Cl
(149)
(150)
148
(43)
CO2Me
(152)
(151)
toluene, Δ
(154)
(144)
(155)
(156)
(44)



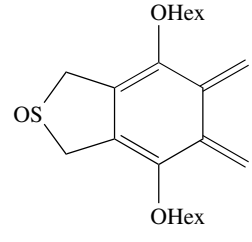
(157)



(158)



(159)



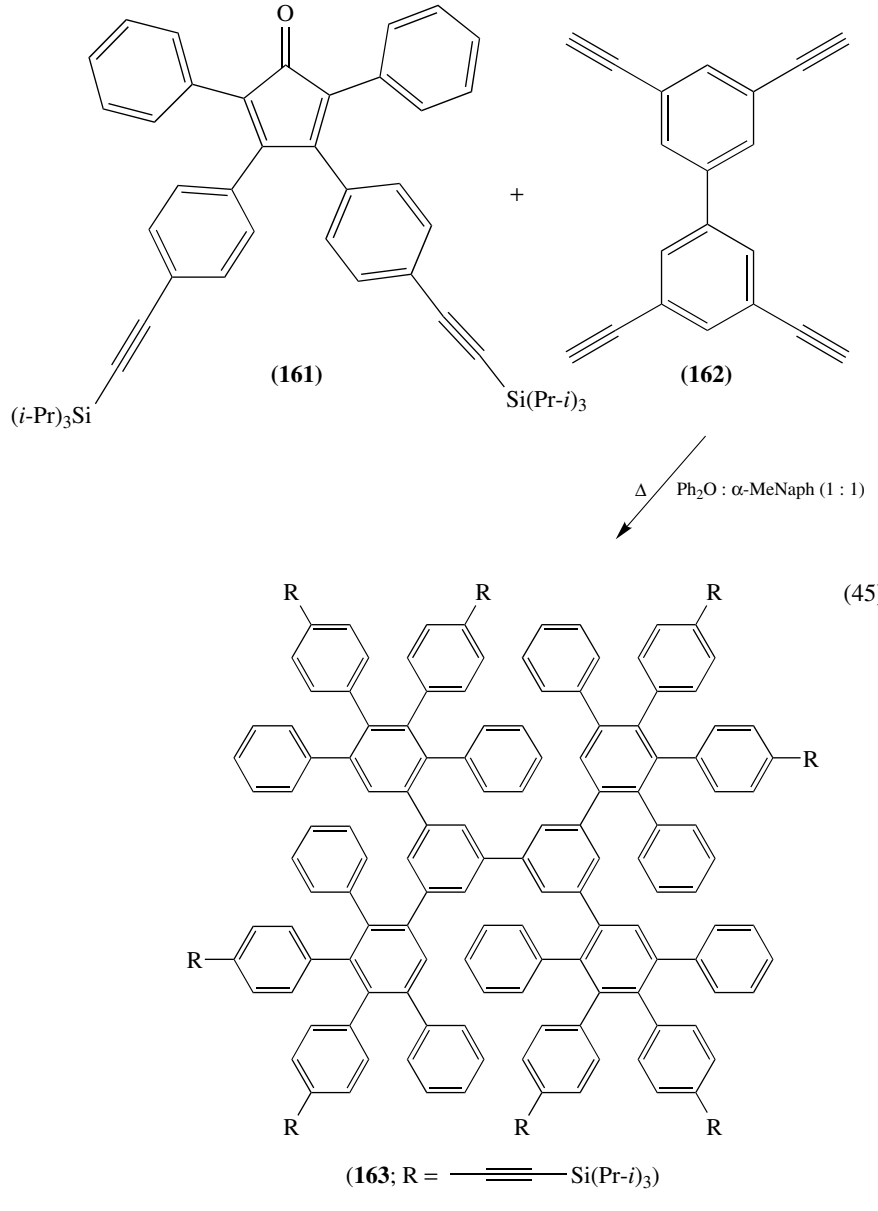
(160)

Berson and colleagues[119] re-examined the Diels–Alder reaction between 1,3-diphenylisobenzofuran and cyclopropenone. They selectively obtained the *exo* adduct, as was confirmed by X-ray analysis. *Ab initio* calculations indicated a kinetic preference for the *exo* isomer due to stabilizing interactions between the ether oxygen and the carbonyl carbon in the *exo* transition state[120].

The Lewis acid catalyzed reaction of furan **(169)** with ketovinylphosphonate **170** produced a mixture of adducts, both of which slowly underwent retro Diels–Alder reactions at room temperature[121]. When diethylaluminum chloride was used as the catalyst, the *endo* selectivity (with respect to the keto functionality) was enhanced from **171**/**172** = 58/42 to 78/22 by raising the reaction temperature from −25 °C to 0 °C (equation 47). This is in agreement with the FMO theory, since initial Lewis acid complexation is with the phosphonate group.

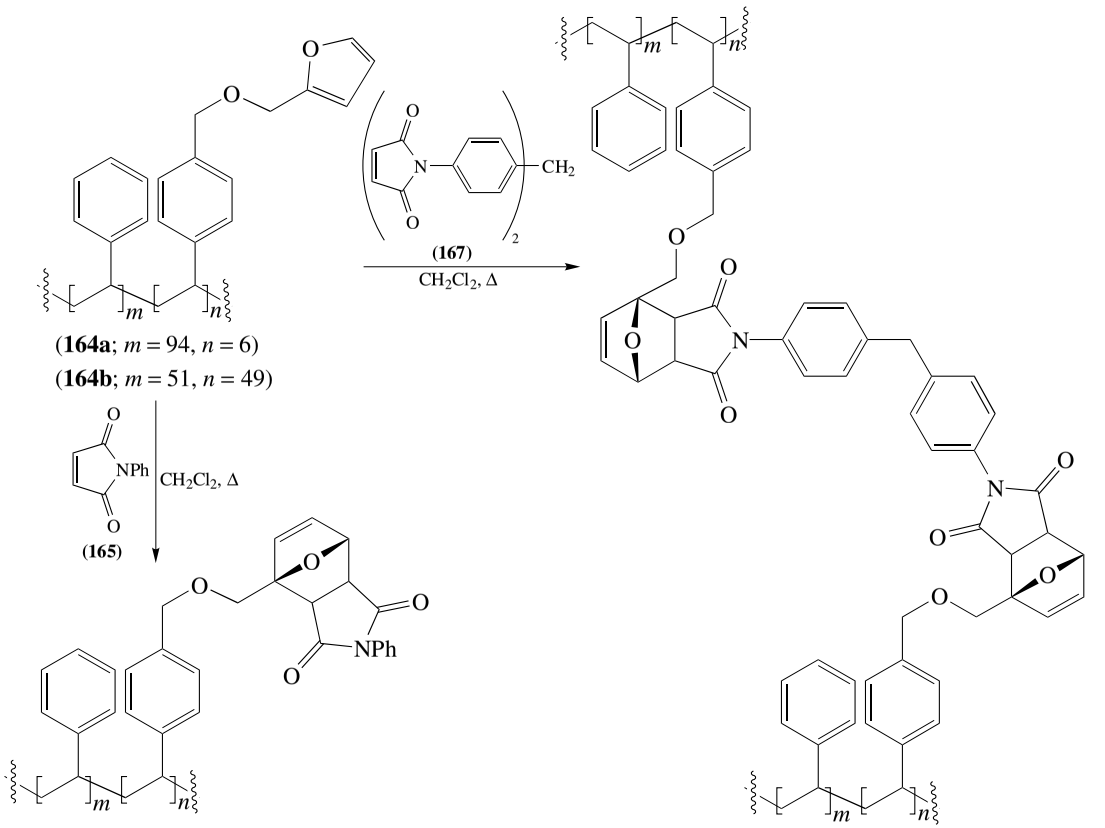
Arjona and coworkers[122] studied the Diels–Alder reactions between some substituted furans **173** and (*E*)-1,2-bis(phenylsulfonyl)ethylene (**174**) (equation 48). The results depicted in Table 3 show that all reactions of 2-substituted furans afforded **175** as the exclusive adduct, the reaction of furan **173c** being an exception. These findings were explained by unfavorable interactions of the 2-substituent with the *cis* sulfonyl group (steric repulsions) and by long-range favorable interactions with the *trans* sulfonyl group (electrostatic, dipolar, van der Waals). The reactions of **174** with 3-substituted furans **173f** and **173g** did not show any stereoselectivity.

Padwa and colleagues[123] reported Diels–Alder reactions of several 2-amino substituted furans. These dienes reacted smoothly with monoactivated olefins in the absence of Lewis acids to give the corresponding adducts with complete regioselectivity. In most cases, the 7-oxabicyclo[2.2.1]hept-5-enes ring-opened under the reaction conditions. In the case of 2-morpholino-5-nitrofuran **(177)**, consecutive ring-opening and elimination of HNO_2 afforded *p*-aminophenol **178** (equation 49). Phenol **179** was considered to be formed by ring-opening of the primary adduct followed by migration of the nitro group and consecutive aromatization. An additional [1,5] hydrogen shift was proposed to explain the formation of **180**.

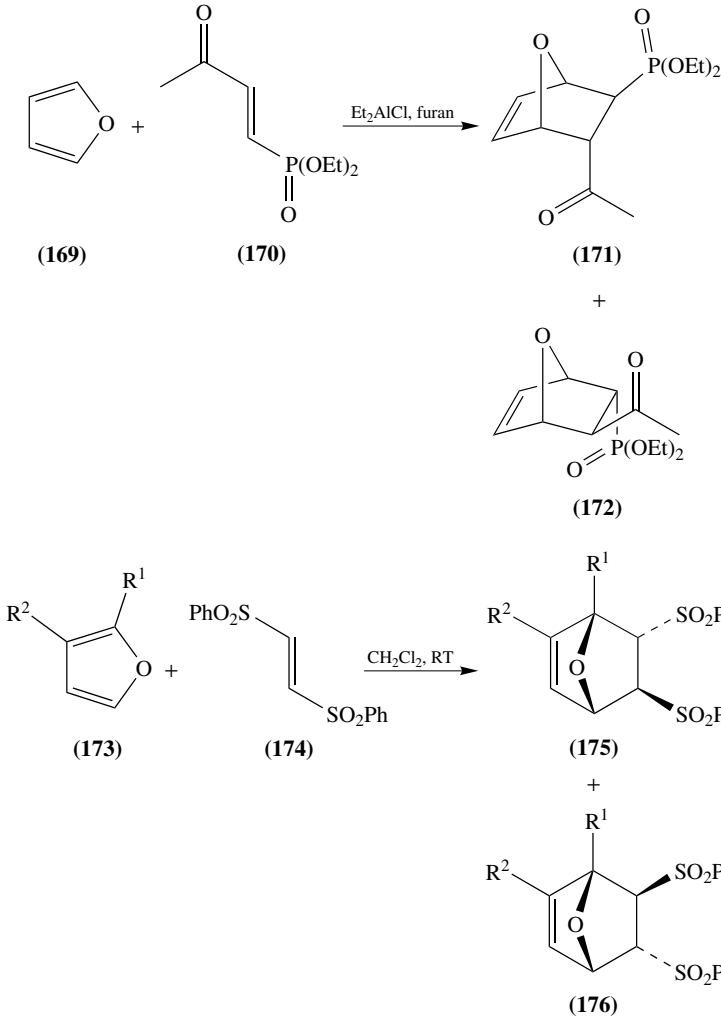


(45)

Liao and coworkers[124] studied the Diels–Alder reactions of substituted furans, now acting as dienophiles, with masked *o*-benzoquinones. A representative reaction has been depicted in equation 50. The masked *o*-benzoquinones such as **181** reacted with unactivated, electron-rich as well as electron-poor furans such as **182**. The substitution pattern of the masked *o*-benzoquinones proved, however, more important. An electron-withdrawing


(167)
CH2Cl2, Δ
(164a; m = 94, n = 6)
(164b; m = 51, n = 49)
(165)
CH2Cl2, Δ
(166a; m = 94, n = 6)
(166b; m = 51, n = 49)
(168a; m = 94, n = 6)
(168b; m = 51, n = 49)

(46)



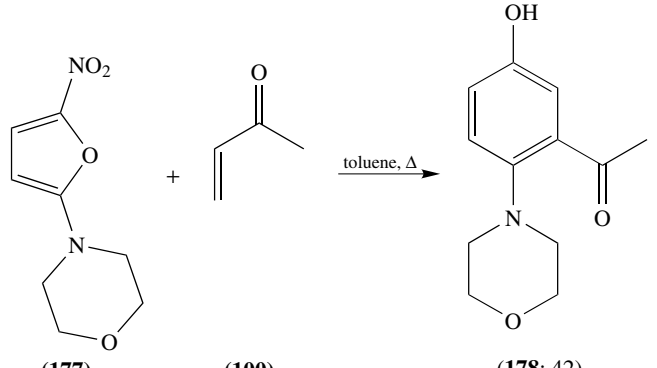
(47)

(48)

TABLE 3. Product distributions for equation 48

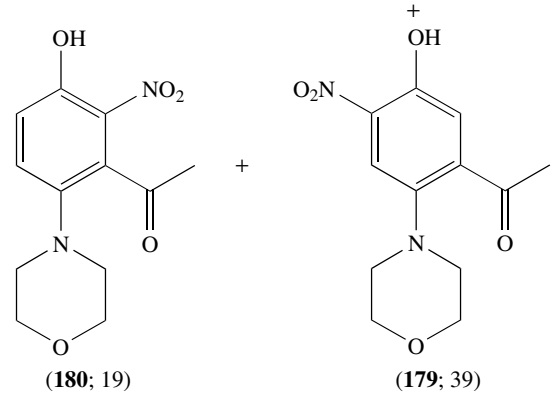
Entry	R^1	R^2	Furan	**175/176**
1	Me	H	**173a**	100/0
2	OMe	H	**173b**	100/0
3	CH_2OH	H	**173c**	70/30
4	CH_2OBn	H	**173d**	100/0
5	CH_2SH	H	**173e**	100/0
6	H	CH_2OH	**173f**	50/50
7	H	CH_2OBn	**173g**	50/50

group at C(3) or an electron-releasing group at C(2) greatly diminished reactivity. The reactions were completely site selective, i.e. the unsubstituted double bond of the substituted furans reacted in every instance to give adducts like **183**.

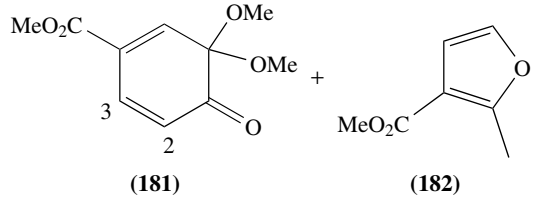


(**177**) (**100**) (**178**; 42)

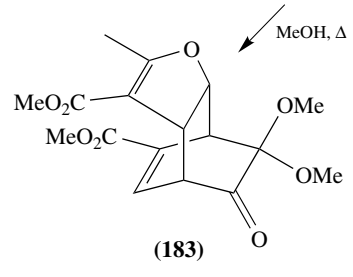
(49)



(**180**; 19) (**179**; 39)



(**181**) (**182**)



(**183**)

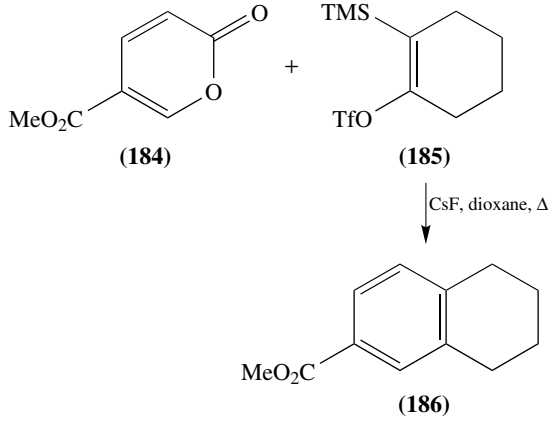
(50)

8. Diels–Alder reactions of pyrones and pyridones

Because α-pyrones and α-pyridones have some aromatic character, like furans, they undergo Diels–Alder reactions less easily than most cyclic dienes do. Nevertheless, suitable reaction conditions have been developed and their Diels–Alder reactions have been used intensively to generate useful synthetic intermediates[35]. Unsubstituted α-pyrones and α-pyridones generally react with electron-poor dienophiles in *normal electron demand* Diels–Alder reactions. The regioselectivity, determined by the weakly directing endocyclic heteroatom, is often poor. To improve regioselectivity, either electron-releasing or electron-withdrawing substituents must be present. The reaction becomes an *inverse electron demand* Diels–Alder reaction in the latter case.

By using electron-withdrawing *N*-substituents, the aromatic character of α-pyridones can be reduced and the efficiency as well as the stereoselectivity of the Diels–Alder reaction increased. The efficiency of the reactions of α-pyridones can be further improved by using bulky electron-withdrawing *N*-sulfonyl substituents, as was shown by Afarinkia and Mahmood[125]. *N*-Sulfonyl 2-pyridones generally rearrange easily to the thermodynamically more stable 2-(sulfonyloxy)pyridines. The authors found that use of the large 2,4,6-triisopropylbenzenesulfonyl group and solvents of low polarity suppressed this rearrangement, thereby improving the yields of the cycloaddition.

Guitián and colleagues[126] performed some Diels–Alder reactions between *in situ* generated cyclohexyne and several α-pyrones. The reactions were performed at 100 °C which resulted in immediate loss of carbon dioxide from the primary cycloadducts. Reaction yields were generally above 80%. The reaction between **184** and cyclohexyne, derived from **185**, to give **186** has been depicted in equation 51.

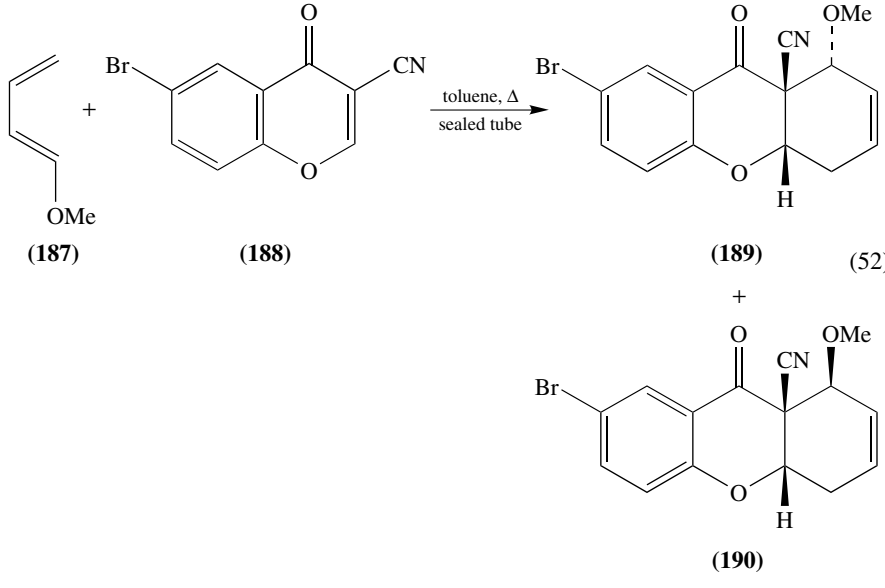


(184) **(185)** **(186)** (51)

Hsung[127] used a [4 + 2] cycloaddition reaction of a γ-pyrone to synthesize the tetracyclic core of arisugacin, a novel inhibitor of acetylcholinesterase. He noticed an unexpected concentration effect on the stereoselectivity in the reactions of 3-cyano-γ-benzopyrone derivatives with electron-rich dienes[128]. When 1-methoxybutadiene **(187)** reacted with γ-benzopyrone **188**, for example, the ratio between *endo* adduct **189** and *exo* adduct **190** depended on the concentration of **188**, as demonstrated by the data given in Table 4 (equation 52). Raising the concentration of **188**, while keeping the diene concentration twice as high, caused the reaction to become less *endo* selective. Variation of the diene concentration, while keeping the γ-benzopyrone concentration constant, did not demonstrate a clear trend.

TABLE 4. Reaction data for equation 52

Entry	**[188]** (M)	Equiv. **187**	Time (h)	Yield (%)	*endo/exo*
1	0.10	2	30	74	90/10
2	0.45	2	48	79	50/50
3	0.10	17	24	71	96/4
4	0.10	29	26	67	95/5

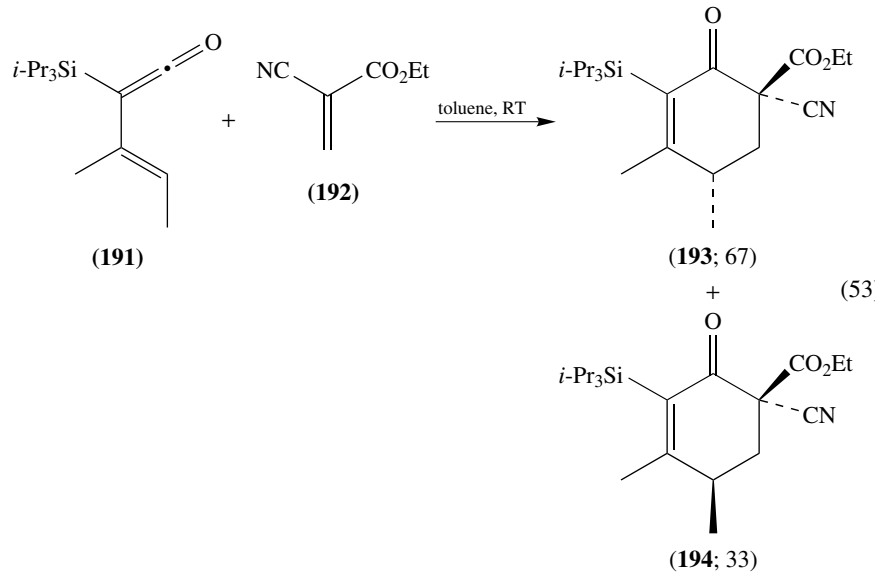


9. Diels–Alder reactions of dienes/dienophiles with cumulated double bonds

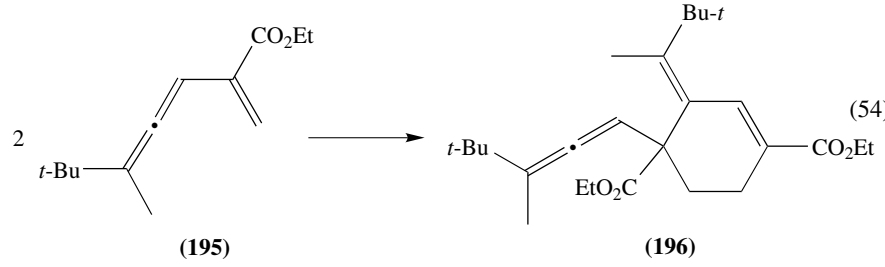
Ketenes generally dimerize easily to afford cyclobutanediones, but when silyl substituents are present, [2 + 2] cycloadditions are remarkably suppressed. This allows the application of silyl substituted vinylketenes as electron-rich dienes in Diels–Alder reactions. Danheiser and colleagues[129] showed that reactions of silyl substituted vinylketenes with reactive olefinic and acetylenic dienophiles proceed with high regioselectivity. For example, the reaction between vinylketene **191** and dienophile **192** afforded diastereomeric regioisomers **193** and **194** (equation 53). The carbonyl oxygen, acting as an electron-donor substituent, was considered to be the directing group.

Compared to the application of ordinary conjugated dienes, the use of vinylallenes as diene components is advantageous from the viewpoint of both reactivity and stereoselectivity. The equilibrium between the *s-trans* and *s-cis* conformers is more on the side of the *s-cis* isomer for vinylallenes than it is for 1,3-dienes. Consequently, vinylallenes exhibit a higher reactivity.

Reich and coworkers[130] demonstrated that the reactions of vinylallenes with unsymmetrical dienophiles proceed predominantly via a transition state in which the largest substituents on both the allene moiety and the olefin are furthest apart. The regiochemistry is governed by these steric interactions, because the HOMO coefficients of the vinylallene at the sites of bond formation are very similar.



Krause and colleagues[131] reported the cycloadditions of several substituted vinylallenes with symmetrically as well as asymmetrically substituted olefins. The reactions proceeded at a reasonable rate at room temperature, affording adducts with high to complete facial, *endo* and regioselectivities. Vinylallene **195** proved highly reactive, even at 5 °C, affording dimer **196** as a 70 : 30 mixture of two isomers (equation 54). The regiochemistry was contrary to that generally observed (see above).



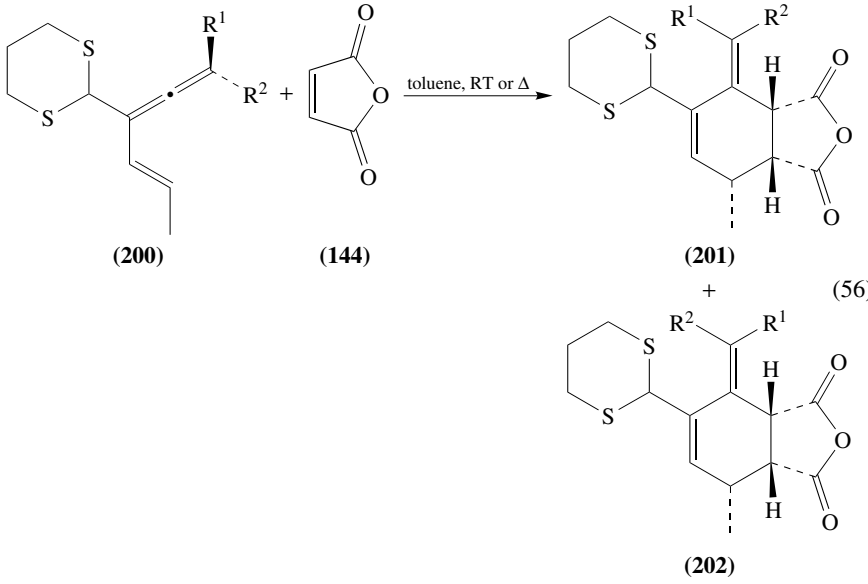
Murakami and colleagues[132] studied the Diels–Alder reactions of vinylallenes with alkynes catalyzed by a rhodium complex. When a vinylallene lacking substituents at the vinylic terminus was reacted with a terminal alkyne, 1,3,5-trisubstituted benzenes were obtained, the reaction between vinylallene **197** and 1-hexyne (**198**) being a representative example (equation 55). The reaction was proposed to proceed via a rhodacycle which afforded the primary Diels–Alder adduct via reductive elimination. Aromatization via isomerization of the exocyclic double bond led to the isolation of **199**.

The palladium catalyzed reactions of substituted vinylallenes with unactivated 1,3-butadienes proceeded with high selectivity[133]. A multistep mechanism, involving several palladacycles, was proposed to explain the high selectivities observed.

(55)

(197) **(198)** **(199)**

Spino and colleagues[134] studied the Diels–Alder reactions of vinylallenes aiming to synthesize six-membered rings with a tetrasubstituted exocyclic double bond, which were to be employed as precursors of quassinoids. Some representative results of their investigations have been summarized in Table 5 (equation 56). Due to the presence of two different substituents at the allene terminus of **200**, facial differentiation occurred, which resulted in non-equivalent amounts of geometrical isomers **201** and **202**. The major isomers obtained in each case were formed by *endo* attack of maleic anhydride **144** at the less hindered face of the diene.



(56)

(200) **(144)** **(201)** **(202)**

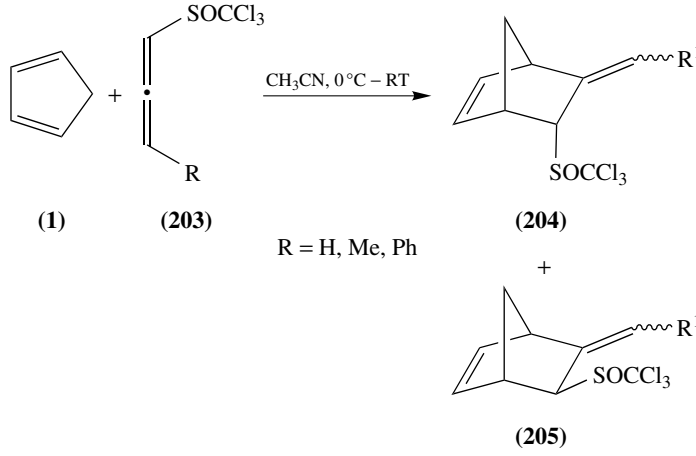
TABLE 5. Isomer distribution for equation 56

Entry	R^1	R^2	**201/202**
1	*n*-pentyl	Me	75/25
2	*n*-pentyl	$SiMe_3$	<1/>49
3	2-(Methoxymethyloxy)pent-1-yl	Me	90/10

Allenes generally react with conjugated dienes to give [4 + 2] type of adducts in contrast with ketenes which generally react with dienes in a [2 + 2] kind of way. Some enhancement of reactivity is expected in comparison with olefins because of the significant amount of strain that allenes have. Semi-empirical calculations, however, have shown allene to be less reactive than ethylene due to higher deformation energies[135].

Gedanken and colleagues[136] investigated the Diels–Alder reactions of trichloromethyl allenyl sulfoxides **203** and cyclopentadiene under ultrasound irradiation. Allenes **203** are generally very sluggish in reactivity. However, when ultrasound was applied, the reactions of allenes **203** with cyclopentadiene were completed within 2 hours (equation 57). Mixtures of *endo* **(204)** and *exo* **(205)** isomers were obtained in all instances. When the γ-position of the allenyl sulfoxides was substituted, additional mixtures of *E* and *Z* isomers were obtained.

Kanematsu and coworkers studied the reactions of optically pure allene-1,3-dicarboxylates with furan[137] and cyclopentadiene[138]. The aluminum trichloride catalyzed reaction of **206** with cyclopentadiene proceeded at −78 °C with virtually complete *endo* selectivity and complete facial selectivity to afford **207** and **208** in a ratio of 98 : 2 (equation 58), cyclopentadiene approaching the double bond from the face opposite to the perpendicular carboxylate group.



(1) **(203)** **(204)** (57)

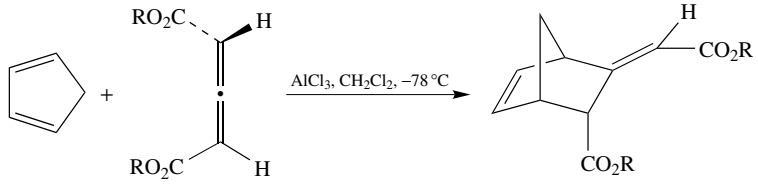
R = H, Me, Ph

+

(205)

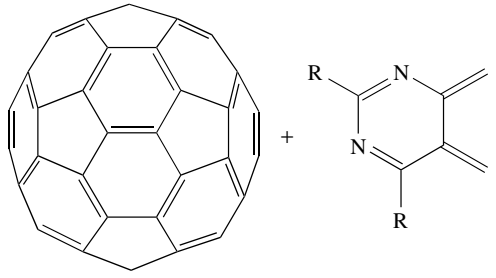
10. Diels–Alder reactions of fullerenes

The Diels–Alder chemistry of fullerenes has proven to be an important method for the preparation of novel organofullerenes. Consequently, a wide variety of cycloadducts have been reported[36]. In spite of the presence of 30 conjugated double bonds in [60]fullerene, it does not behave as a diene in Diels–Alder reactions. Instead, the carbon–carbon double bonds across two six-membered rings in [60]fullerene serve as dienophiles in reactions with predominantly electron-rich dienes. Although the strain of the π-orbitals and the electron-withdrawing ability of [60]fullerene make it reactive toward dienes, the loss of aromaticity of the two six-membered rings involved generally leads to retro Diels–Alder reactions at low temperatures. The well-explored reactions of [60]fullerene with *o*-quinodimethanes provide especially stable adducts as a consequence of the aromatization process which takes place during product formation. The reactions with heterocyclic *o*-quinodimethanes have been investigated much less[139].



(**1**) (**206**) R = (−)-menthyl (**207**; 98) + (**208**; 2) (58)

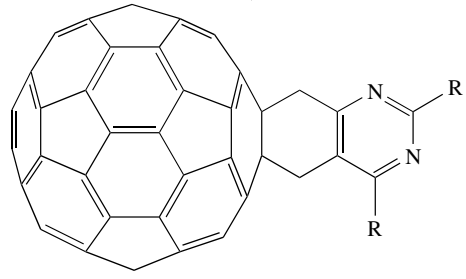
The trapping of *in situ* generated pyrimidine *o*-quinodimethanes **210a–d** with [60]fullerene **(209)** was investigated by Herrera and colleagues[140]. The reactions were conducted in refluxing *o*-dichlorobenzene and yielded adducts **211a–d** in yields ranging from 54% to 96%, based on the amount of consumed [60]fullerene (equation 59). According to



(**209**)

(**210a**; R = Me)
(**210b**; R = Ph)
(**210c**; R = *p*-MeC_6H_4)
(**210d**; R = *p*-ClC_6H_4)

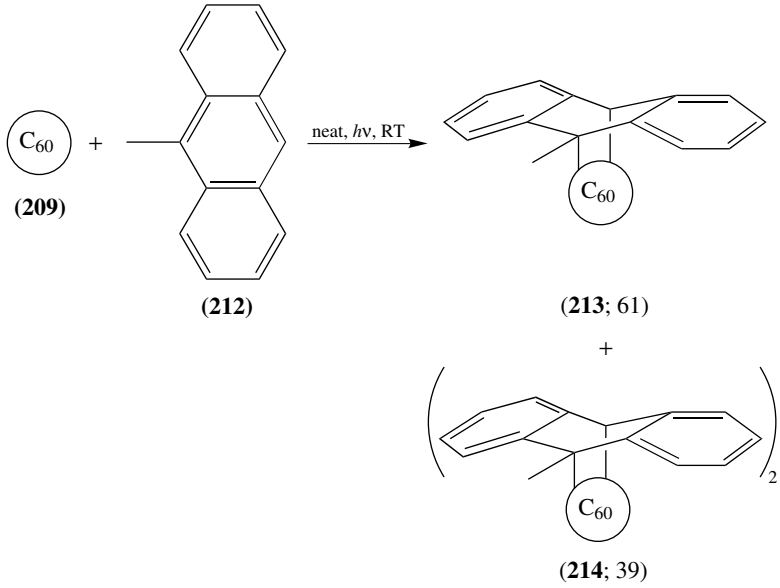
o-dichlorobenzene, Δ



(**211a–d**) (59)

semi-empirical AM1 and PM3 calculations, these cycloadditions were controlled by the HOMOs of **210**.

The photo-induced single and double Diels–Alder reactions between [60]fullerene and 9-methylanthracene **(212)** which gave **213** and **214** were performed in the solid state by Mikami and colleagues (equation 60)[141]. The Diels–Alder reaction was considered to proceed following a photo-induced electron transfer from 9-methylanthracene to fullerene. The higher ionization potential of anthracene should explain its inreactivity toward the cycloaddition reaction with [60]fullerene.



(**209**) (**212**) (**213**; 61) + (**214**; 39) (60)

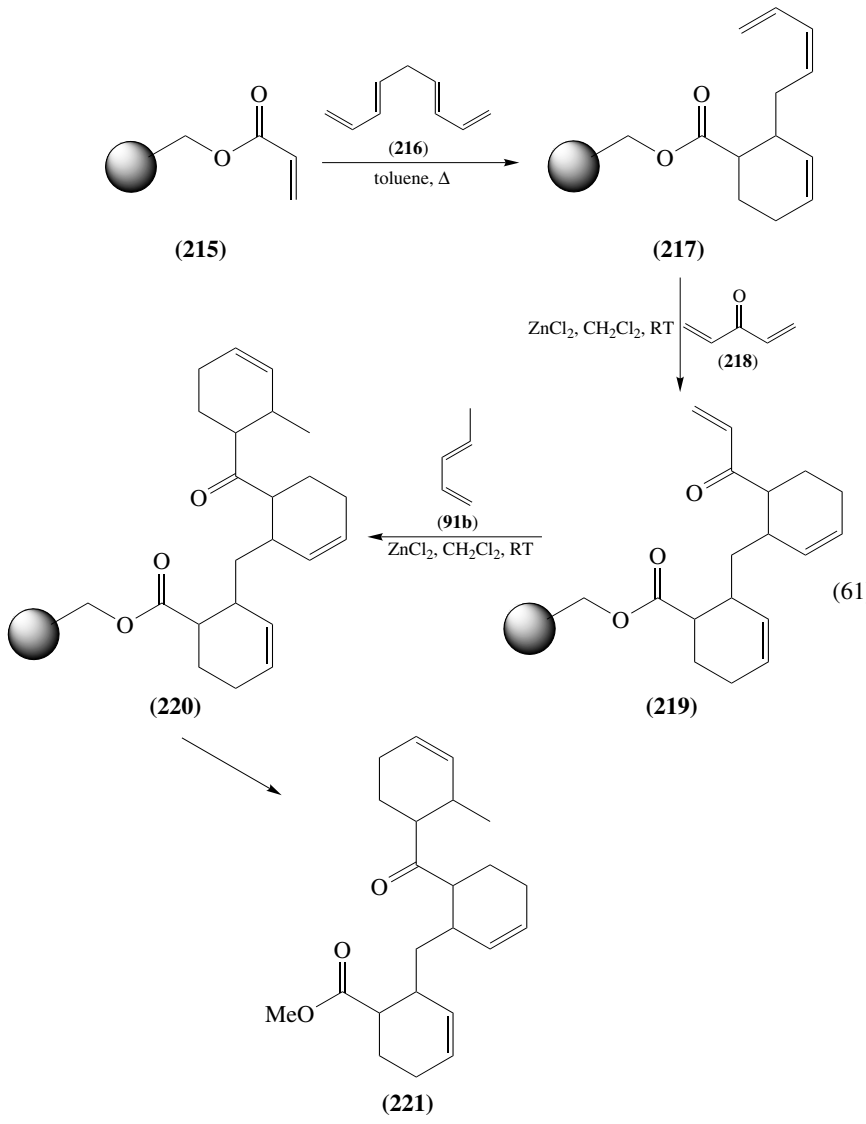
Cheng and coworkers[142] reported the first Diels–Alder reactions of fullerenes with dienes having an electron-withdrawing group at C(1). The reactions with [60]fullerene proceeded at elevated temperatures to afford the corresponding adducts with moderate yields. The adducts appeared to be more stable than the adducts of electron-rich dienes.

11. Diels–Alder reactions of resin-bound reagents

Solid phase chemistry has gained widespread use in recent years. Among the immense number of reactions that can be performed on the resin nowadays, the all-carbon Diels–Alder reaction still takes a minor place. The resin-bound Diels–Alder reactions reported in the literature between 1992 and 1997 have been reviewed recently[143].

Winkler and Kwak[144] recently prepared tricyclic ester **221** from **215** by means of three consecutive Diels–Alder reactions with **216**, **218** and **91b** to give **217**, **219** and **220**, respectively, followed by cleavage of the triple adduct **221** from the resin (equation 61). The overall yield was almost three times higher than when the same reaction sequence was performed in solution, thereby demonstrating the efficiency of resin-bound reactions in this case.

On the other hand, Hird and colleagues[145] studied the Diels–Alder reactions of resin-bound 2-amino-1,3-butadienes with several *N*-substituted maleimides and nitrostyrenes.



(61)

These reactions generally proceeded with lower *endo/exo* selectivities than the corresponding reactions in solution. In some cases, Michael adducts were isolated in minor amounts, possibly indicating a stepwise reaction.

Schlessinger and Bergstrom[146] reported some asymmetric Diels–Alder reactions of several polystyrene bound furans to which a chiral auxiliary had been attached with methyl acrylate. The adducts were obtained with de values of more than 99%, as was determined after cleavage of the adducts from the resin.

C. Chiral Auxiliaries

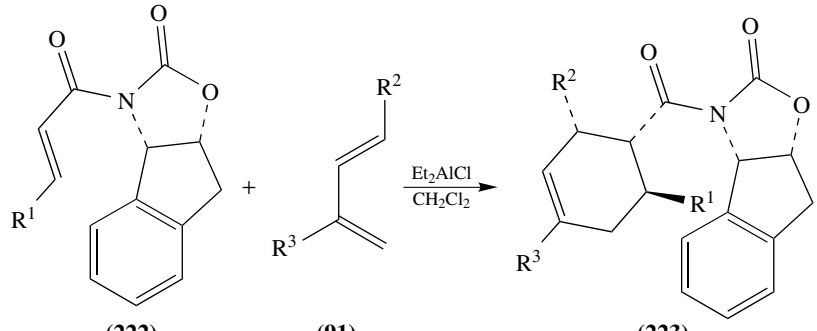
The synthesis of enantiomerically enriched compounds can be accomplished by application of chiral Lewis acids or chiral auxiliaries attached to either one of the reactants. The latter application[41,42] will be discussed in this section.

In most reported cases, the covalently bound chiral auxiliary has been attached to the dienophile via an acyl linkage, but there are also many examples known in which the auxiliary has been attached to the diene via an acyl, alkyl or heteroatom linkage, the first example of the latter being Trost's diene[147]. Lewis acids are often added to the reaction mixtures when the chiral auxiliary attached to the dienophile contains an additional Lewis basic site. This is not only to enhance the reaction rate, but especially to enhance the diastereofacial selectivity by complexing to the dienophile in a bidentate fashion. This makes the dienophile more conformationally rigid.

1. 1,3-Oxazolidin-2-ones as chiral auxiliaries

1,3-Oxazolidin-2-ones, introduced by Evans and coworkers[148] and usually synthesized from α-amino acids[149], have been applied in asymmetric syntheses with success, producing the target compounds with high de values.

Davies and coworkers[150], for example, used *N*-enoyl derivatives of a *cis*-1-aminoindan-2-ol based 1,3-oxazolidin-2-one **(222)** as chiral dienophiles in the Diels–Alder reactions with isoprene **(91a)** and piperylene **(91b)** which give **223** (equation 62). Their results have been summarized in Table 6. The reactions proceeded with high *endo/exo* and regioselectivities. Bidentate co-ordination of the catalyst to both carbonyl groups kept the dienophile in a rigid conformation, which gave rise to the high de values observed.



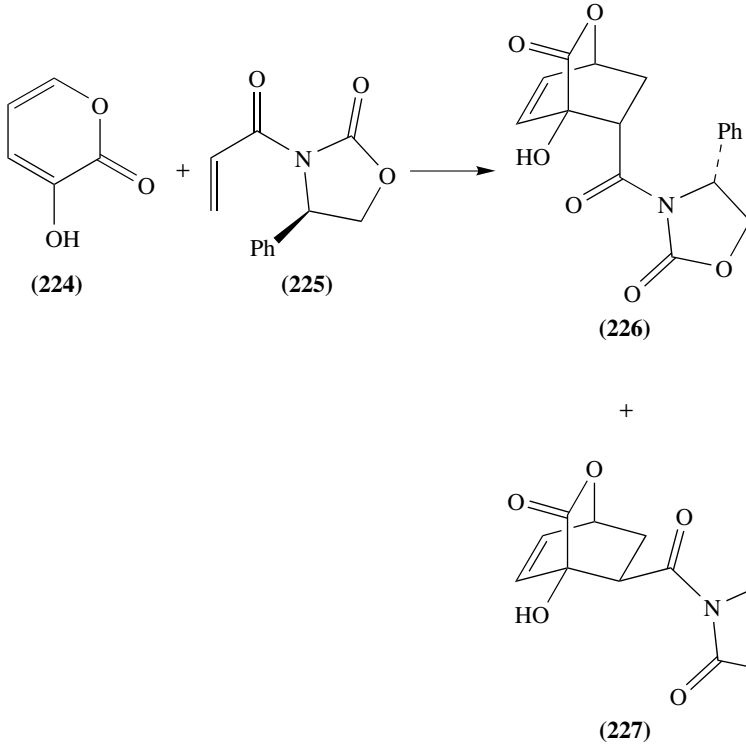
(222) **(91)** **(223)** (62)

TABLE 6. Reaction data for equation 62

Entry	R^1	R^2	R^3	Diene	T (°C)	Yield (%)	*endo/exo*	de (%)
1	H	H	Me	**91a**	−70	85	—	87.5
2	H	Me	H	**91b**	−70	69	98/2	98.4
3	Me	H	Me	**91a**	−35	—	—	93.4
4	Me	H	Me	**91a**	−15	88	—	92.9
5	Me	Me	H	**91b**	−35	—	97/3	98.4
6	Me	Me	H	**91b**	−15	77	96/4	93.7

Okamura and coworkers[151] studied the base catalyzed Diels–Alder reactions between 3-hydroxy-2-pyrone **(224)** and chiral 1,3-oxazolidin-2-one based acrylate derivatives. Catalysis of the reaction between **224** and **225** by triethylamine gave fair to good de values, somewhat dependent on the solvent system used (equation 63, Table 7). Addition of 5% of water to the solvent isopropanol, for example, increased the de of the *endo* adduct **226** substantially. When the amount of water was increased, however, the triethylamine catalyzed reaction became less *endo* and diastereofacially selective, a small amount of *exo* **227** being obtained. Replacing triethylamine by the chiral base cinchonidine also improved the de, but now independently of the solvent system used.

Hintermann and Seebach[152] studied the reaction between cyclopentadiene and *N*-crotonyl-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one (**228**) using dimethylaluminum

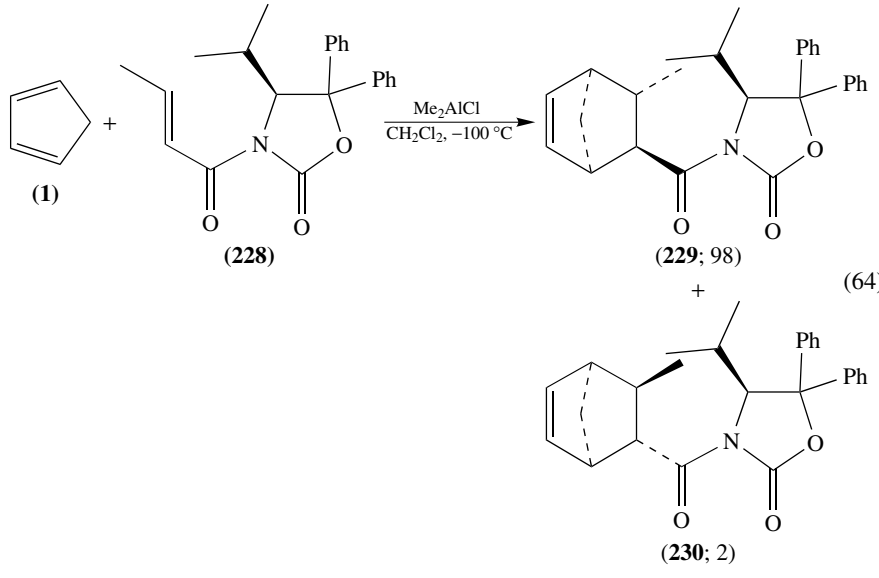


(63)

TABLE 7. Reaction data for equation 63

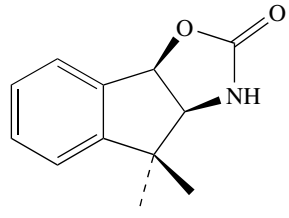
Entry	Base	Solvent	Yield (%)	**226/227**	% de **226**
1	Et_3N	CH_2Cl_2	97	100/0	53
2	Et_3N	*i*-PrOH	100	100/0	69
3	Et_3N	*i*-PrOH : H_2O = 95 : 5	99	100/0	82
4	Et_3N	*i*-PrOH : H_2O = 80 : 20	87	88/12	61
5	Cinchonidine	*i*-PrOH	100	100/0	89
6	Cinchonidine	*i*-PrOH : H_2O = 95 : 5	93	100/0	95

chloride as the Lewis acid catalyst. The reaction proceeded with good yield (87%), almost complete *endo* selectivity (**229/230** = 98/2) and high diastereomeric selectivity (>90% de for **229**) (equation 64). Because the chiral dienophiles as well as the cycloadducts were generally more prone to crystallization than those containing Evans' chiral auxiliaries, use of **228** as a chiral auxiliary was stated to offer some advantages.



(**1**) (**228**) (**229**; 98) + (**230**; 2) (64)

Sudo and Saigo[153] reported the application of *cis*-2-amino-3,3-dimethyl-1-indanol derived 1,3-oxazolidin-2-one **231** as a chiral auxiliary in asymmetric Diels–Alder reactions. The *N*-crotonyl and *N*-acryloyl derivatives were reacted with cyclopentadiene, 1,3-cyclohexadiene, isoprene and 2,3-dimethyl-1,3-butadiene, using diethylaluminum chloride as the Lewis acid catalyst. The reactions afforded the expected cycloadducts in moderate to high yields (33–97%) with high *endo* selectivities and high de values (92% to >98%).

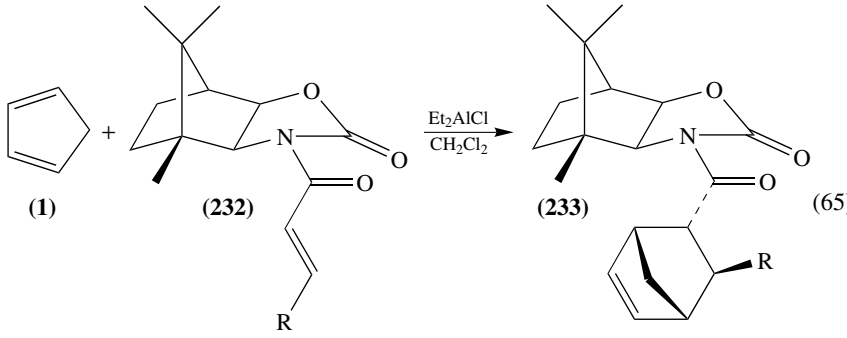


(**231**)

Cadogan and coworkers[154] employed camphor-derived 1,3-oxazolidin-2-ones **232** as chiral auxiliaries in Diels–Alder reactions between their *N*-enoyl derivatives and cyclopentadiene. The diethylaluminum chloride catalyzed reactions proceeded to give **233** with complete *endo* selectivities and high diastereofacial selectivities (Table 8, equation 65). When the angular methyl group in the chiral auxiliary was substituted by an ethyl group, the de increased to more than 95% for the adduct analogous to **233a**.

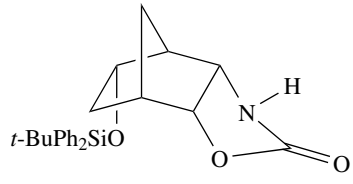
TABLE 8. Yields and de of adducts **233**

Entry	R	Dienophile	T (°C)	Yield (%)	% de **233**
1	H	**232a**	−78	100	81
2	Me	**232b**	−78	92	>99
3	Ph	**232c**	−20	100	>99



(1) **(232)** **(233)** (65)

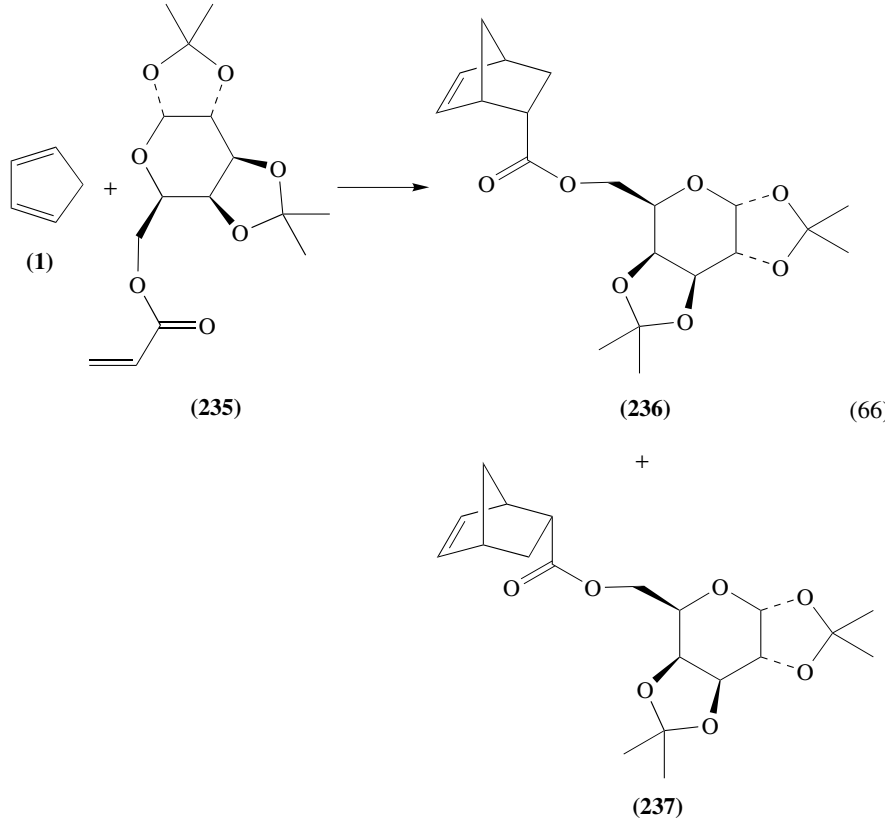
Kunieda and colleagues[155] used a similar kind of 1,3-oxazolidin-2-one **(234)** and studied the diethylaluminum chloride and boron trifluoride etherate catalyzed Diels–Alder reactions of its *N*-acryloyl and *N*-crotonyl derivatives with cyclopentadiene. The yields were high (80–100%), the reactions being almost completely *endo* selective. The diastereomeric excesses obtained ranged from 71% to more than 99%.



(234)

2. Carbohydrate based chiral auxiliaries

Carbohydrates have found widespread use as chiral auxiliaries in asymmetric Diels–Alder reactions[156]. A recent example is a study conducted by Ferreira and colleagues[157] who used carbohydrate based chiral auxiliaries in the Lewis acid catalyzed Diels–Alder reactions of their acrylate esters **235** with cyclopentadiene (equation 66). Some representative results of their findings, including the ratios of products **236** and **237**, have been summarized in Table 9. The formation of **236** as the main product when diethylaluminum chloride was used in dichloromethane (entry 3) was considered to be the result of an equilibrium between a bidentate and monodentate catalyst–dienophile complex. The bidentate complex would, upon attack by the diene, lead to **236**, whereas the monodentate complex would afford **236** and **237** in approximately equal amounts. The reversal of selectivity on changing the solvent from dichloromethane to toluene (entry 2 *vs* 3) remained unexplained by the authors.

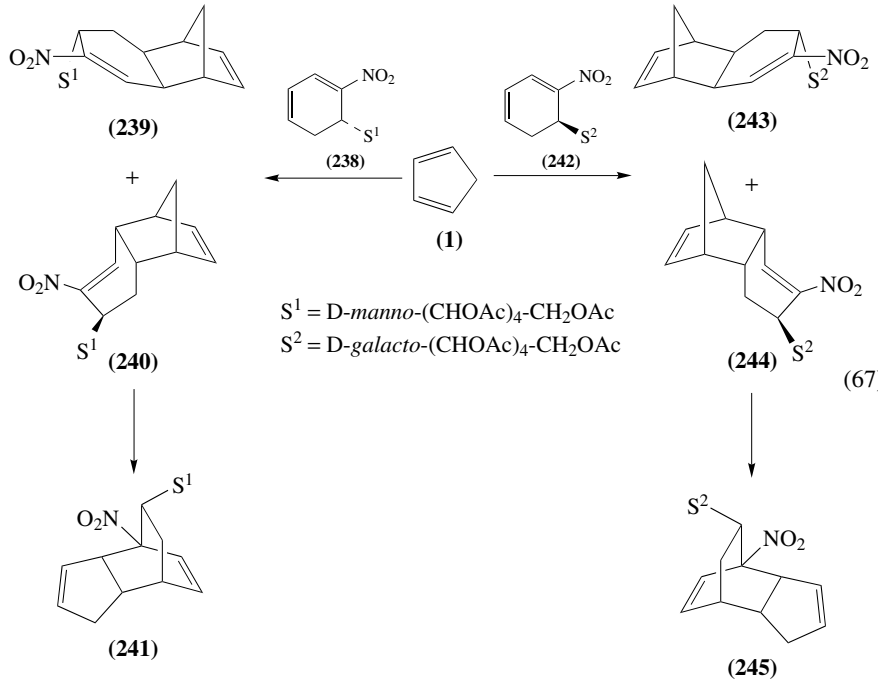


(66)

TABLE 9. Reaction data for equation 66

Entry	Solvent	Catalyst	T(°C)	Yield (%)	*endo/exo*	**236/237**
1	CH_2Cl_2	none	0	85	85/15	60/40
2	Toluene	Et_2AlCl	−78	37	>98/<2	30/70
3	CH_2Cl_2	Et_2AlCl	−78	11	>98/<2	70/30
4	CH_2Cl_2	$EtAlCl_2$	−78	38	>98/<2	50/50
5	Toluene	$MgBr_2$	−78	78	83/17	50/50

Serrano and coworkers[158] reported some enantioselective syntheses of norbornene and cyclohexene nitroaldehydes via asymmetric Diels–Alder reactions with sugar-derived nitrodienes acting as chiral dienophiles. Dienes **238** and **242**, which were prepared from sugar-derived nitroalkenes and 1-acetoxy-1,3-butadiene, were employed in cycloaddition reactions with cyclopentadiene and gave **239** and **240**, and **243** and **244**, respectively (equation 67)[159]. Both reactions proceeded with complete site and diastereofacial selectivities and with almost complete *endo* selectivity. Cyclopentadiene approached the dienophiles from the face opposite to the sugar moiety. Under the reaction conditions applied, the *endo* adducts **240** and **244** rearranged to give the Cope rearranged products **241** and **245**, respectively.



(67)

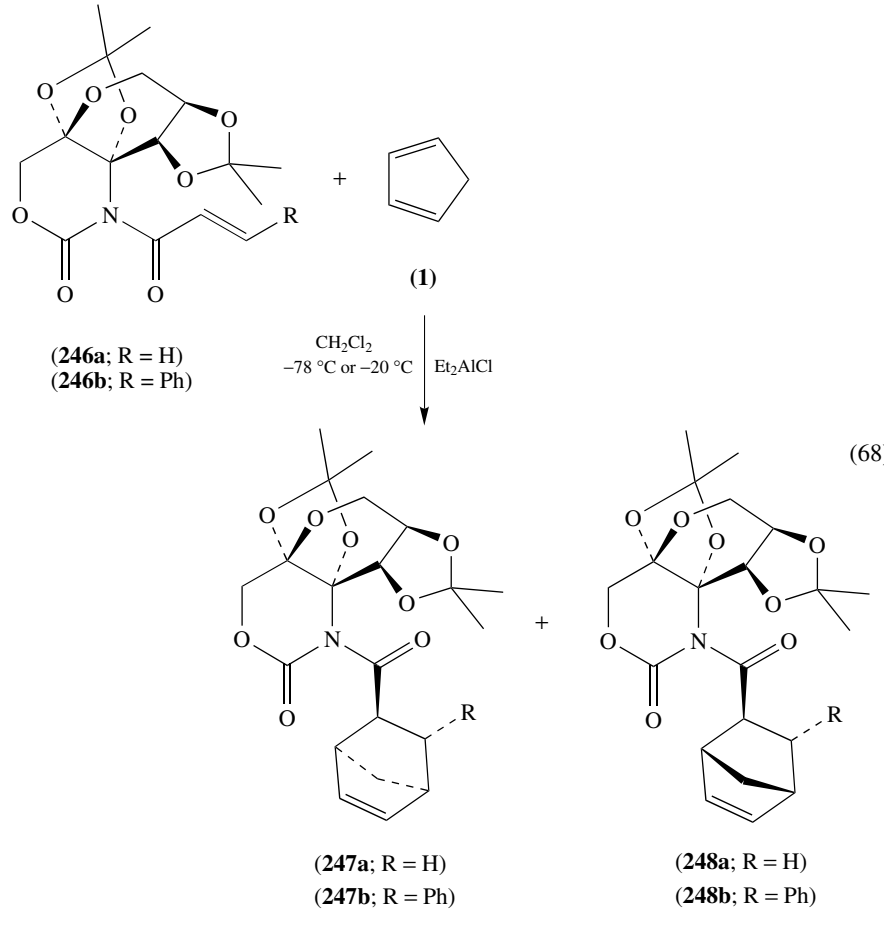
Cadogan and coworkers[160] developed a fructose-derived 1,3-oxazin-2-one chiral auxiliary which they applied in the Diels–Alder reactions of its *N*-enoyl derivatives **246** with cyclopentadiene using diethylaluminum chloride as the Lewis acid catalyst. The reactions afforded mixtures of *endo* **247** and *exo* **248** (equation 68). The catalyst binds to the chiral dienophile in a bidentate fashion (co-ordination to both carbonyl groups). As a consequence, the dienophile is constrained to a rigid conformation which accounts for the almost complete diastereofacial selectivities observed.

Stoodley and coworkers[161] studied the Diels–Alder reactions of substituted dienes having a chiral sugar moiety attached to C(1) via an *O*-glycosidic linkage with *N*-phenylmaleimide and tetracyanoethylene. They were able to reverse the diastereofacial selectivities of these reactions by anomerization of the sugar moiety. The β-anomers generally provided higher diastereofacial selectivities. The degree of facial selectivity was shown to be dependent on the steric bulk of the 2′ and 6′ hydroxyl protecting groups on the sugar moiety.

3. Sulfoxides as chiral auxiliaries

A wide variety of chiral sulfinyl substituents have been employed as chiral auxiliaries on both dienes[162] and dienophiles[163] in asymmetric Diels–Alder reactions. Carreño and colleagues[164], for example, used Diels–Alder reactions of (S_S)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone **(249)** to separate racemic mixtures of a wide variety of diene enatiomers **250a** and **250b** via kinetic resolution and to obtain enantiomerically enriched

tetracyclic quinones **251** and **252** after thermal elimination of the sulfoxide auxiliary group (equation 69). A representative overview of their work with *inner–outer* dienes has been given in Table 10.



(68)

García Ruano and colleagues[165] studied the asymmetric Diels–Alder reactions of α-sulfinyl α,β-unsaturated esters with several dienes. In the reactions with cyclopentadiene, both reactivity and stereoselectivity were increased in the presence of zinc dihalides acting as catalysts. $TiCl_4$ was found to be the most efficient catalyst, however, allowing reactions to be conducted at low temperatures. Different models were proposed to explain the diastereofacial selectivities observed.

Diels–Alder reactions of chiral 1-sulfinyl-1,3-butadienes generally proceed very slowly, which requires the use of either long reaction times or high pressure to complete the reactions[166]. The reaction between diene **253** and *N*-methylmaleimide **117** (equation 70), for example, took 20 days in the absence of a Lewis acid and still 6 days when catalyzed

by $SnCl_4$. In the uncatalyzed reaction, the primary adduct **254** partially underwent a [2,3] sigmatropic rearrangement to **255**.

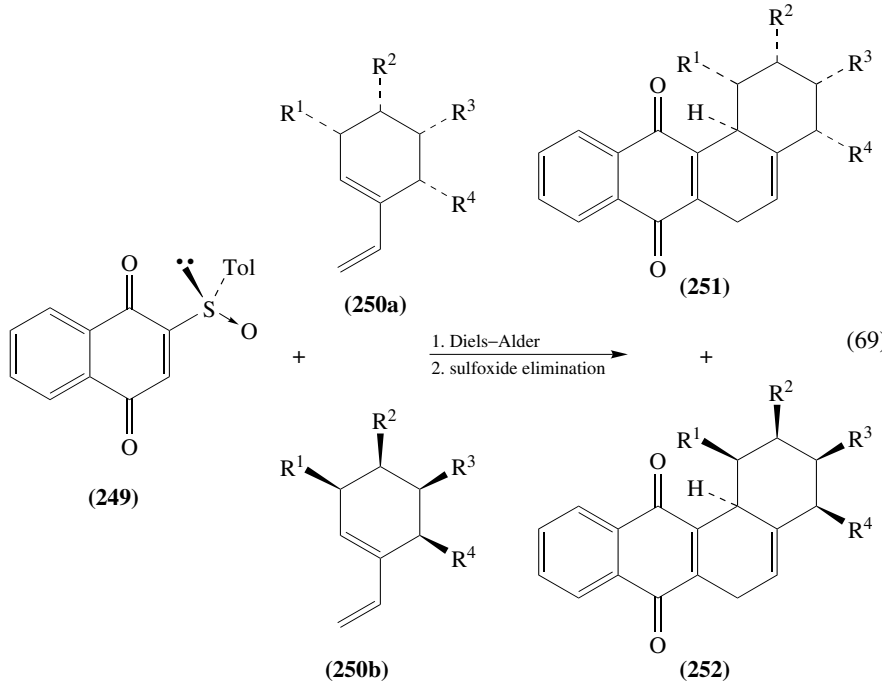


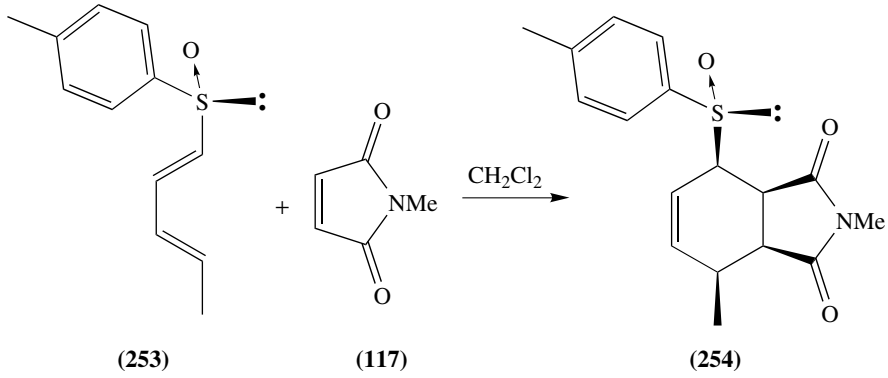
TABLE 10. Reaction data for equation 69

Entry	R^1	R^2	R^3	R^4	Yield (%)	**251/252**	% ee **251**	% ee **252**
1	H	H	H	OH	73	100/0	20	—
2	H	H	H	OTBS	75	100/0	94	—
3	H	H	H	OMOM	61	100/0	92	—
4	H	Me	H	OH	69	100/0	20	—
5	OH	H	H	H	62	72/28	76	50
6	OMOM	H	H	H	61	100/0	94	—
7	H	H	OH	H	55	60/40	78	n.d.[a]
8	H	H	OMOM	H	53	70/30	86	n.d.[a]

[a] n.d. = not determined.

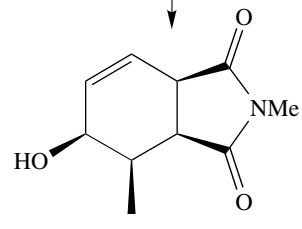
Fernández de la Pradilla and coworkers[167] studied the reactions of chiral sulfinyl and sulfonyl dienes such as **256** and **257** with *N*-phenylmaleimide. They found that the sulfinyl dienes showed facial selectivities opposite to those of the corresponding sulfonyl dienes, indicative of the powerful stereocontrol exerted by the sulfinyl moiety.

Aversa and colleagues[168] studied the facial selectivities in the reactions of (S_S)- and (R_S)-3-alkylsulfinyl-1-methoxy-1,3-butadienes with several dienophiles. Table 11 summarizes the results of the completely *endo* selective reaction of **258** with *N*-phenylmaleimide (**165**) and the effects of different catalysts on the diastereofacial selectivity of this reaction (equation 71)[168e]. In the case of the uncatalyzed reaction, the dienophile attacked the

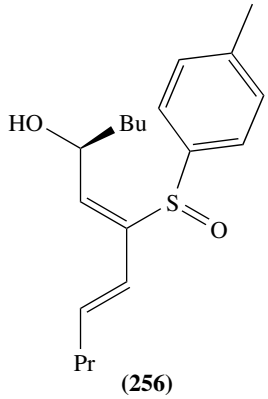


(253) **(117)** **(254)**

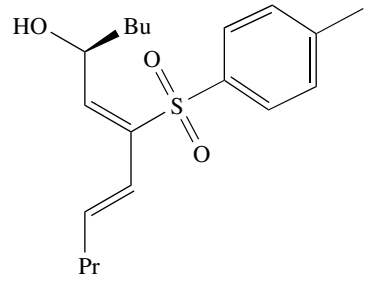
(70)



(255)



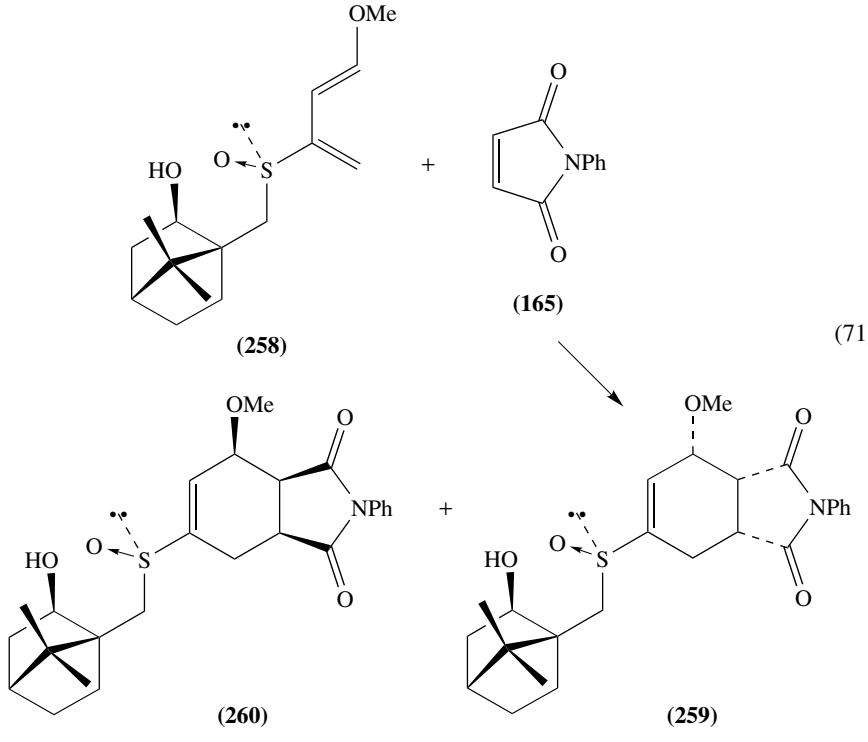
(256)



(257)

diene predominantly from the more electron-rich *re* face, opposite to the sulfinyl oxygen, the diene adopting the less sterically hindered conformation along the C−S bond. In the case of the Lewis acid catalyzed reactions, in which the Lewis acid co-ordinated to both the sulfinyl oxygen and one carbonyl oxygen on the dienophile, an additional diene conformation was stated to play a role. Depending on the size of the catalyst and the steric

requirements of the dienophile, the dienophile was now able to approach the diene from the *re* as well as the *si* face, which led to lower diastereofacial selectivities.



(71)

TABLE 11. Reaction data for equation 71

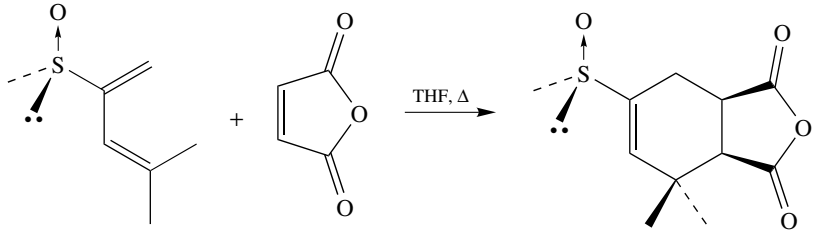
Entry	Catalyst	T (°C)	Yield (%)	**259/260**
1	none	25	80	85/15
2	none	−20	80	87/13
3	$MgBr_2$	0	83	80/20
4	$BF_3{\cdot}Et_2O$	25	63	75/25
5	$ZnCl_2$	0	90	73/27
6	$LiClO_4$	−20	86	60/40
7	$Eu(fod)_3$	−20	90	36/64

Gosselin and colleagues[169] prepared Karahana ether **(264)**, starting with an asymmetric Diels–Alder reaction between chiral diene **261** and maleic anhydride. This reaction yielded diastereomers **262** and **263** in a 1 : 4 ratio (equation 72).

4. Cyclohexyl based chiral auxiliaries

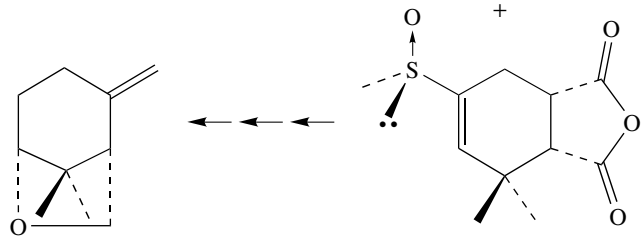
Cyclohexyl based chiral auxiliaries have been widely employed in asymmetric syntheses[170]. Barluenga and coworkers[171] reported the first chiral 2-alkoxy-1,3-butadienes of

which the chiral auxiliary was either a *trans*-2-phenylcyclohexyl or a *trans*-2-mesitylcyclohexyl group. The reactions with *N*-phenylmaleimide and tetracyanoethene proceeded with moderate to high de values (60–90%). The auxiliary groups were stated to achieve better facial selectivities than menthol derived chiral auxiliaries.



(261) **(144)** (**262**; 20)

(72)

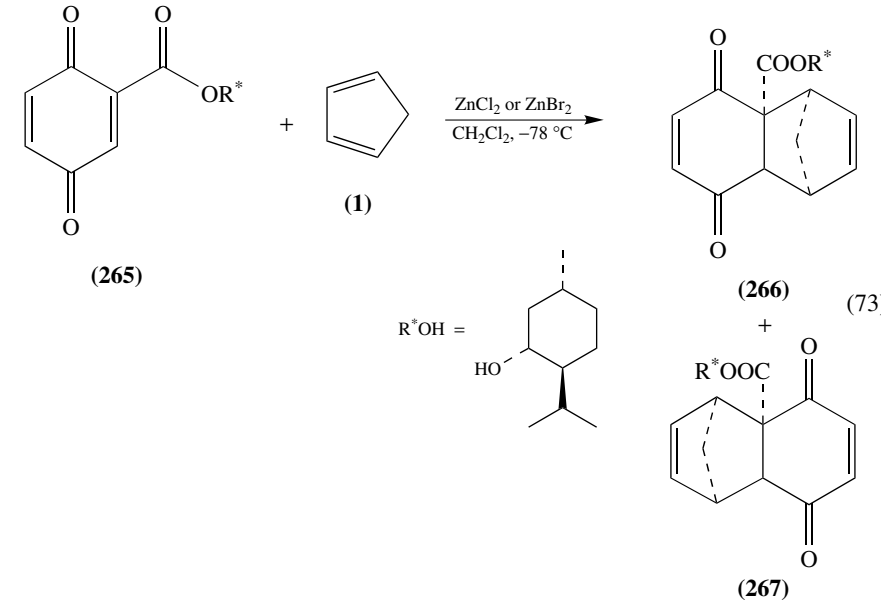


(264) (**263**; 80)

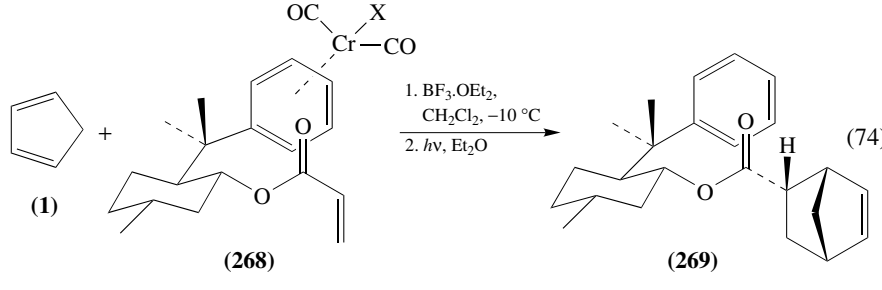
Brimble and coworkers[172] reported the asymmetric Diels–Alder reactions between quinones **265** bearing a menthol chiral auxiliary and cyclopentadiene (equation 73). When zinc dichloride or zinc dibromide was employed as the Lewis acid catalyst, the reaction proceeded with complete *endo* selectivity, but with only moderate diastereofacial selectivity affording 3 : 1 and 2 : 1 mixtures of **266** and **267** (dominant diastereomer unknown), respectively. The use of stronger Lewis acids, such as titanium tetrachloride, led to the formation of fragmentation products. Due to the inseparability of the two diastereomeric adducts, it proved impossible to determine which one had been formed in excess.

Pericàs and coworkers[173] studied the *endo* selective reactions of 1-alkoxy-1,3-butadienes and 1-alkoxy-1,3-octadienes with maleic anhydride. They found that the *trans*-2-phenylcyclohexan-1-ol and 3-*exo*-(neopentyloxy)isobornan-1-ol based chiral dienes induced the highest facial selectivities. The relative transition state energies for the formation of the different diastereomers were calculated using semi-empirical methods (AM1).

Jones and colleagues[174] studied the influence of ligand substitution on the rates and diastereofacial selectivities of the Diels–Alder reactions between cyclopentadiene and 8-phenylmenthol based chiral acrylate-chromium complexes **268** (equation 74, Table 12). When the ligand co-ordinated to chromium was changed from CO to $P(OPh)_3$ to PPh_3, the diastereomeric excess of **269** was enhanced with concomitant increase of the reaction rate. This phenomenon was attributed to $\pi-\pi$ interactions between the aryl group and the enone system. These $\pi-\pi$ interactions were regarded as dipole–dipole interactions rather than $\pi-\pi$ stacking interactions because of the rate enhancement that was observed on changing the ligand.



(73)



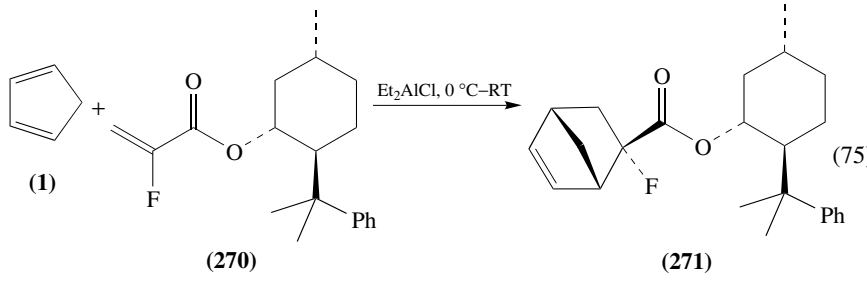
(74)

TABLE 12. *Endo/exo* ratio and % de of **269**

Entry	X	Dienophile	*endo/exo*	% de **269**
1	-(uncomplexed)	**268a**	92/8	93.9
2	CO	**268b**	90/10	90.2
3	$P(OPh)_3$	**268c**	92/8	92.7
4	$P(OEt)_3$	**268d**	92/8	92.3
5	PPh_3	**268e**	93/7	99.1

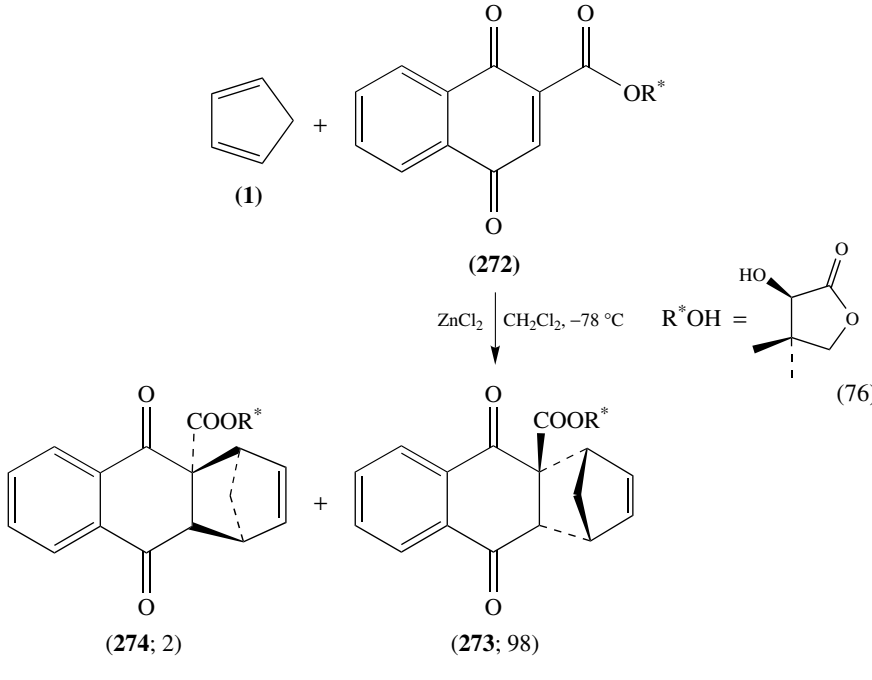
Taguchi and coworkers[175] studied the Lewis acid catalyzed asymmetric Diels–Alder reactions of chiral 2-fluoroacrylic acid derivatives with isoprene and cyclopentadiene. When a chiral 1,3-oxazolidin-2-one and diethylaluminum chloride were used as the chiral auxiliary and the Lewis acid catalyst, respectively, a de of 90% was observed for the reaction with isoprene. The reaction with cyclopentadiene afforded a 1 : 1 mixture of *endo* and *exo* isomers with de values of 95% and 96%, respectively. The *endo/exo* selectivity was improved by using 8-phenylmenthol as the chiral auxiliary. Thus, the reaction

of cyclopentadiene with **270** afforded **271** with complete *exo* selectivity and 95% de (equation 75). The diastereoselectivity dropped when the fluoro atom was substituted by a chloro atom or a methyl group. The high de observed in the case of the fluoro substituent was tentatively attributed to bidentate chelation of the Lewis acid catalyst to both the acrylate carbonyl and the fluoro atom.

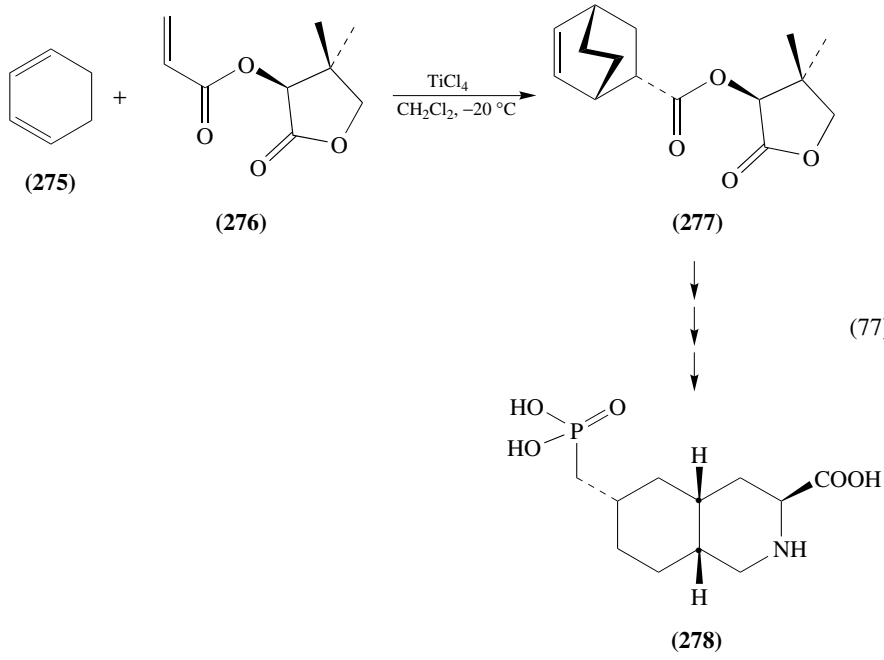


5. Pantolactone based chiral auxiliaries

Brimble and coworkers[176] studied the asymmetric Diels–Alder reactions of cyclopentadiene with chiral naphthoquinones **272** bearing different chiral auxiliaries. The highest *endo* and facial selectivities were obtained using zinc dichloride as the Lewis acid catalyst and (−)-pantolactone as the chiral auxiliary. Thus, the reaction between cyclopentadiene and **272** afforded a 98 : 2 mixture of **273** and **274** (equation 76). The chiral auxiliary was removed easily by lithium borohydride reduction.

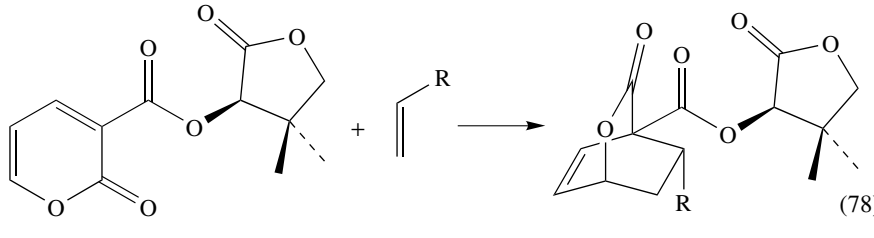


Hansen and colleagues[177] used (+)-pantolactone as a chiral auxiliary to achieve asymmetric induction in the first step toward their synthesis of *cis*-perhydroisoquinoline **278**. The titanium tetrachloride catalyzed reaction between 1,3-cyclohexadiene **(275)** and chiral acrylate **276** proceeded with high diastereofacial selectivity to give **277** (94% de) in 75% yield (equation 77).



(275) **(276)** **(277)** **(278)** (77)

Markó and colleagues[178] studied the Eu(hfc)$_3$ catalyzed *inverse electron demand* Diels–Alder reactions between (−)-pantolactone derived chiral α-pyrones **279** and vinyl ethers and thio ethers **280**. This auxiliary proved superior to other auxiliaries in these reactions. The reactions generally proceeded with high yields, affording the *endo* adducts **281** with de values generally above 95%. The de proved independent of the chirality or achirality of the Lewis acid employed, as (+)-Eu(hfc)$_3$, (−)-Eu(hfc)$_3$ and Eu(fod)$_3$ all afforded the same diastereomer with >95% de (equation 78, Table 13).



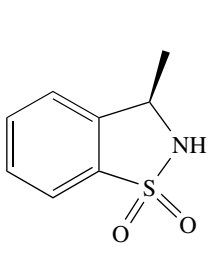
(279) **(280)** **(281)** (78)

TABLE 13. Reaction data for equation 78

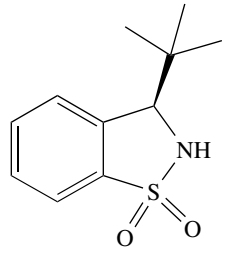
Entry	R	Dienophile	Catalyst	Yield (%)	% de **281**
1	OEt	**280a**	(+)-Eu(hfc)$_3$	97	>95
2	OEt	**280a**	(−)-Eu(hfc)$_3$	91	>95
3	OEt	**280a**	Eu(fod)$_3$	94	>95
4	OBu	**280b**	(+)-Eu(hfc)$_3$	84	>95
5	OBu	**280b**	Eu(fod)$_3$	95	>95
6	SBu	**280c**	(+)-Eu(hfc)$_3$	87	>95
7	SPh	**280d**	(+)-Eu(hfc)$_3$	91	75

6. Sultam based chiral auxiliaries

Oppolzer and colleagues performed pioneering work on the application of chiral sultam based dienophiles in asymmetric Diels–Alder reactions. The bornanesultam based dienophiles provided excellent de values in the Lewis acid mediated Diels–Alder reactions with a wide variety of dienes[179]. The efficiency of the simpler toluene-2,α-sultam based dienophiles was also studied[180]. Chiral auxiliary **282** proved superior to **283** and **284** in the aluminum Lewis acid catalyzed Diels–Alder reactions of its *N*-acryloyl derivative with cyclopentadiene, 1,3-butadiene and isoprene, affording the adducts with >90% de.



(282)



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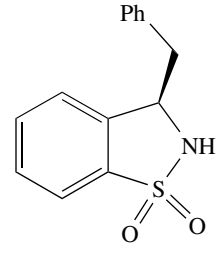
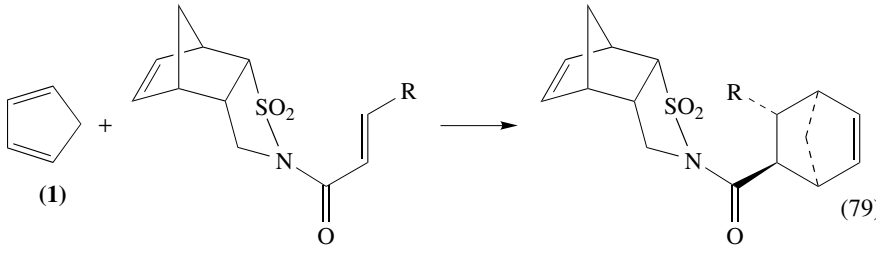


(284)

Chan and colleagues[181] studied the efficiency of tricyclic sultam **285** in asymmetric Diels–Alder reactions which gave adducts like **286** (equation 79). Some of their results have been summarized in Table 14. The *endo* selectivities were high in all cases, whereas the diastereofacial selectivities depended on the catalyst and the reaction conditions employed.



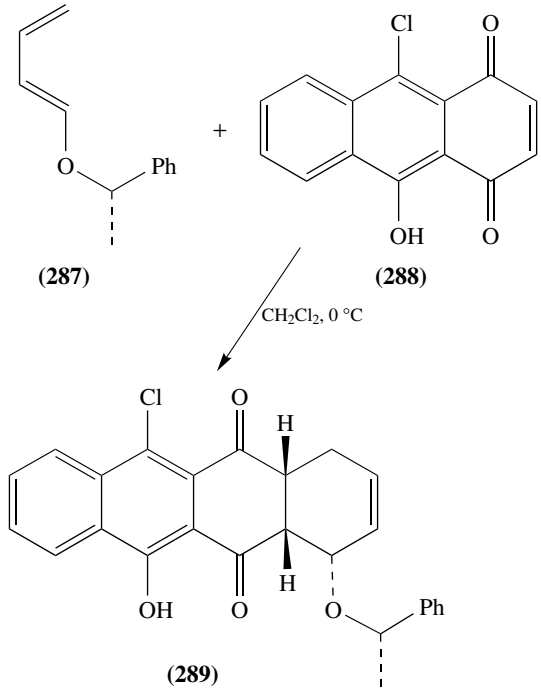
(1) **(285)** **(286)** (79)

TABLE 14. Reaction data for equation 79

Entry	R	Dienophile	Lewis acid (equiv.)	T (°C)	Yield (%)	*endo/exo*	% de **286**
1	H	**285a**	—	−20	80	>90/<10	0
2	H	**285a**	$SnCl_4$ (0.5)	−78	87	98/2	88
3	Me	**285b**	$ZnBr_2$ (10)	20	88	91/8	24
4	Me	**285b**	$TiCl_4$ (0.8)	−78	90	97/3	88

7. Other chiral auxiliaries

Breitmaier and colleagues[182] used asymmetric Diels–Alder reactions between chiral dienes such as **287** and anthraquinone **288** to synthesize anthracycline precursors such as **289** (equation 80). The reactions generally proceeded with high yields and excellent de values (>98%). The high facial selectivity was attributed to $\pi-\pi$ stacking between the phenyl ring and the diene unit, because replacement of the phenyl ring by a cyclohexane ring induced a dramatic drop in the facial selectivity.



(80)

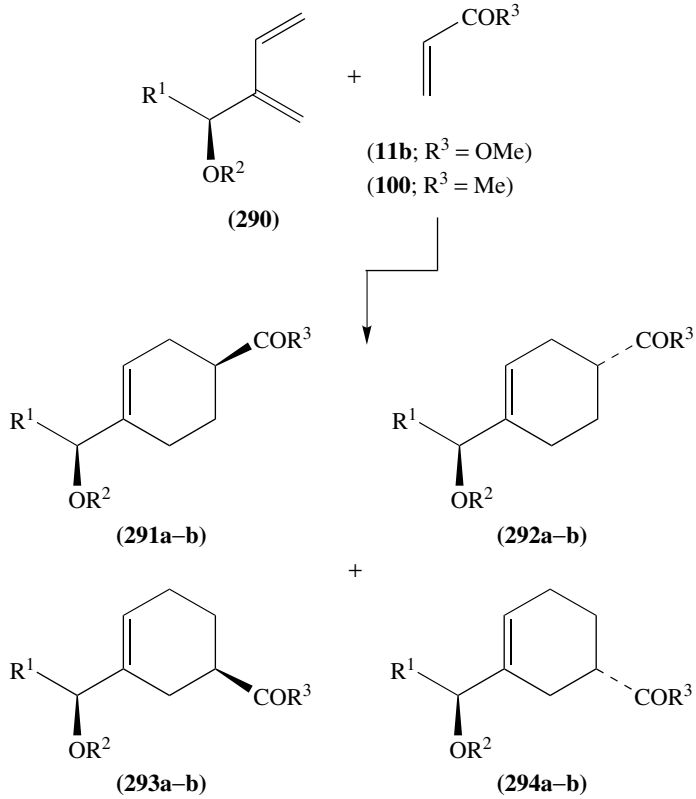
The $\pi-\pi$ stacking model has originally been used by Trost and colleagues to explain the stereoselectivity found in cycloadditions of chiral 1,3-butadien-1-yl *O*-methylmandelate[147]. In a more recent paper[183a], they retreated from this model because of a molecular mechanics study of the Diels–Alder reactions of this diene. Their results supported an earlier statement of Siegel and Thornton[183b] based on experimental results indicating that the orientation of the phenyl group is perpendicular to the diene plane in the transition state. In the sterically favored perpendicular conformation, the dienophile (quinone) will

approach the diene from the side opposite to the perpendicular phenyl group for steric reasons and also to avoid electrostatic repulsions between the electron-rich phenyl ring and one of the oxygen atoms on the quinone. This explanation seems more appropriate to explain the stereochemical results[184].

Vogel[185] used 3-aza-6,8-dioxabicyclo[3.2.1]octane based chiral dienophiles to prepare anthracyclines and anthracycline derivatives.

Bloch and Chaptal-Gradoz[186] studied the diastereofacial selectivities of the thermal and Lewis acid catalyzed Diels–Alder reactions of chiral 2-substituted 1,3-butadienes **290** with methyl acrylate and methyl vinyl ketone which gave adducts **291**–**294**) (equation 81). The allylic stereocenter contained either a free or protected hydroxyl group. The unprotected dienes afforded the "para" adducts with high de values, probably due to hydrogen bonding of the hydroxyl group to the carbonyl group on the dienophile which approached the diene from the face opposite to the phenyl group. The absence of this interaction caused the de values to be low for the protected dienes. The sharp increase in de observed when boron trifluoride etherate was added to the reaction mixture was proposed to originate from selective attack on the diene conformer which minimized the interaction between the co-ordinated Lewis acid and the protective group R^3 (Table 15).

Crisp and Gebauer[187] studied the *endo* selective Diels–Alder reactions of chiral dienes **295** with maleic anhydride. They found that the diastereofacial selectivity was dependent

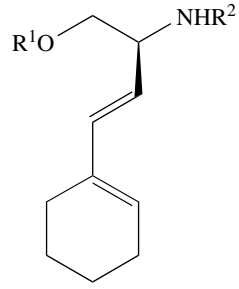


(81)

TABLE 15. Reaction data for equation 81

Entry	R^1	R^2	R^3	Catalyst	Yield (%)	"para"/"meta"	**291/292**
1	n-C_6H_{13}	H	OMe	—	83	67/33	80/20
2	n-C_6H_{13}	TBDMS	OMe	—	87	70/30	45/55
3	n-C_6H_{13}	TBDMS	Me	$BF_3 \cdot Et_2O$	66	100/0	12/88
4	Ph	H	OMe	—	72	69/31	80/20
5	Ph	TMS	Me	—	70	67/33	45/55
6	Ph	TMS	Me	$BF_3 \cdot Et_2O$	78	100/0	>5/<95

on the size of R^1 and independent of the size of R^2. A transition state conformation was proposed in which the 1,2- and 1,3-eclipsing interactions were minimized. This conformation involved a perpendicular orientation of the R^1OCH_2 unit with respect to the diene system, thereby shielding one face of the diene. A maximum de of 76% was obtained for $R^1 = SiPh_2Bu$-t.



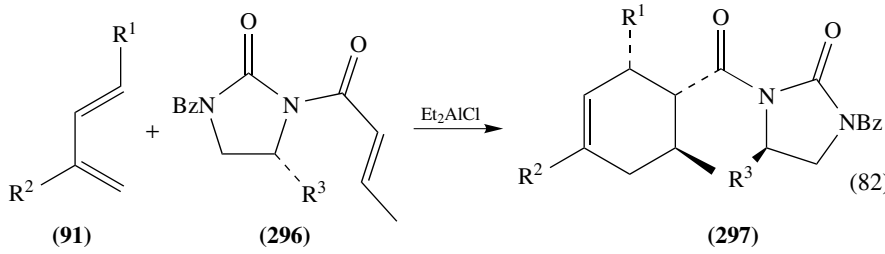
(295)

Roos and Balasubramaniam[188] tuned imidazolidin-2-one chiral auxiliaries in order to obtain reasonable reactivities in the Diels–Alder reactions of their 3-*N*-enoyl derivatives with relatively unreactive acyclic dienes. When 1-*N*-methyl substituted imidazolidin-2-ones were used as chiral auxiliaries, the corresponding 3-*N*-enoyl derivatives proved to lack sufficient reactivity to react with dienes beyond the highly reactive cyclic variants, irrespective of the reaction conditions applied. It was rationalized that the probable reason for this is the donor capacity of the 1-*N*-methyl group and it was therefore 'replaced' by a benzoyl group. The reactions of 3-*N*-enoyl derivatives **296a** and **296b** with cyclopentadiene afforded adducts with excellent *endo/exo* selectivities and high diastereomeric excesses (*endo*/*exo* = 90/10 and 98/2, respectively; >99 de in both cases) and moderate to good diastereomeric excesses in the reactions with isoprene and piperylene (**91a–b**) leading to **297** (equation 82, Table 16). *Endo* attack of the diene occurred at the C_α-*si* face of the dienophile having adopted a preferred *s-cis* conformation.

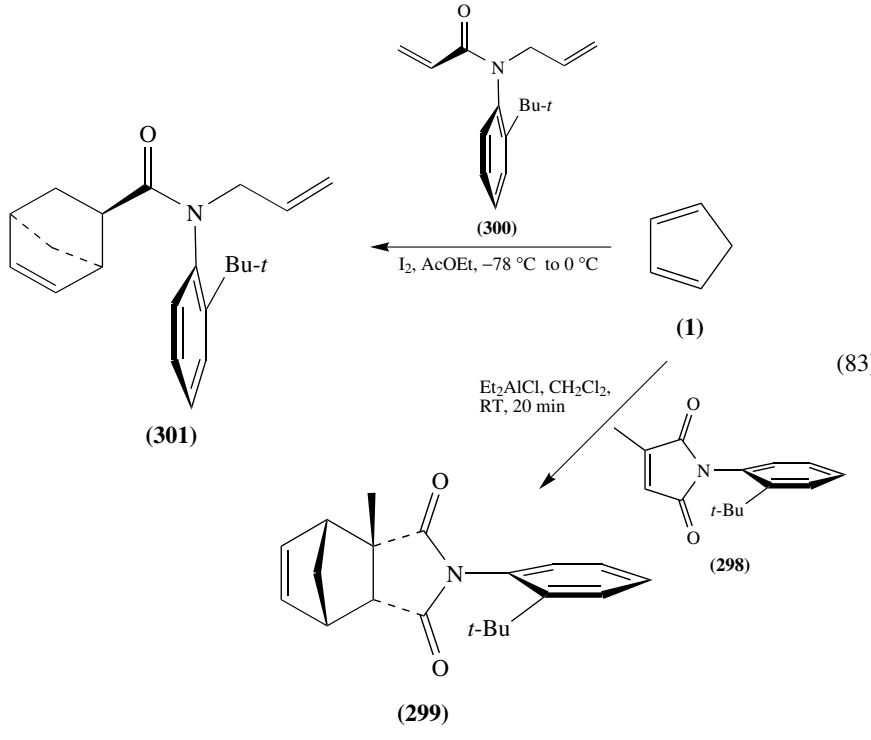
Taguchi and colleagues[189] studied the reactions of axially chiral maleimide and anilide derivatives **298** and **300** with cyclopentadiene (equation 83). The reaction of **298** with cyclopentadiene, catalyzed by diethylaluminum chloride, proceeded quantitatively with almost complete *endo* and diastereofacial selectivities to give **299** and **301**, respectively. The reaction of **300** with cyclopentadiene was catalyzed by iodine and proceeded via a cationic iodocyclization intermediate. The reaction afforded a mixture of *endo* and *exo* isomers in a ratio of *endo*/*exo* = 97/3, the *endo* isomer being obtained with 97% de.

TABLE 16. Yields and de of **297**

Entry	R^1	R^2	Diene	R^3	Dienophile	Yield (%)	% de **297**
1	Me	H	**91b**	CO_2Bu-*t*	**296a**	68	66
2	H	Me	**91a**	CO_2Bu-*t*	**296a**	50	64
3	H	Me	**91a**	CO_2Me	**296b**	61	38



(91) **(296)** **(297)** (82)

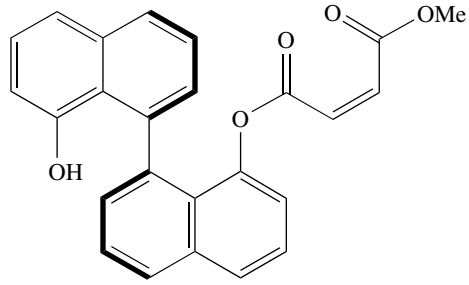


(83)

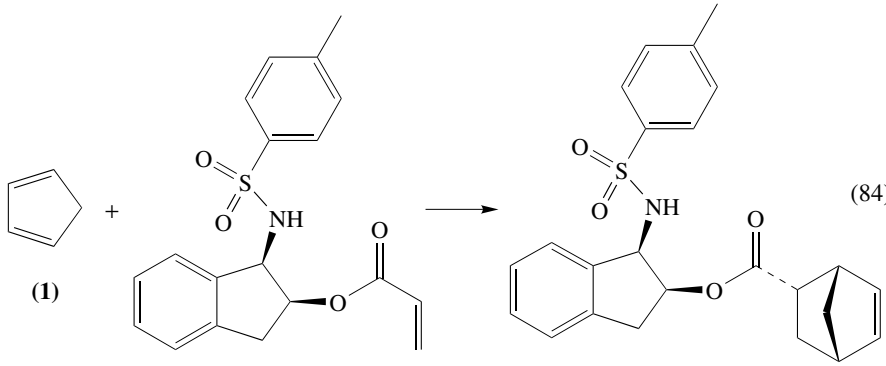
The applicability of axially chiral 1,1′-binaphthalene-8,8′-diol in asymmetric Diels–Alder reactions was studied by Fuji and colleagues[190]. They studied the Lewis acid catalyzed reaction of the unsymmetrically substituted maleate ester of 1,1′-binaphthalene-8,8′-diol **302** with cyclopentadiene. The diastereoselectivity proved to depend strongly on the Lewis

acid used. Diethylaluminum chloride and tin(IV) tetrachloride, for example, induced opposite diastereoselectivities. The best results were obtained using titanium catalysts (78–100% de for the *endo* adducts). It was proposed that these catalysts bind to **302** via tridentate co-ordination to both carbonyl groups and the hydroxyl group, thereby keeping the dienophile in a rigid conformation.

Cis-1-(arylsulfonamido)indan-2-ols have been shown to be excellent chiral auxiliaries for asymmetric Diels–Alder reactions[191]. Some results obtained in the Lewis acid catalyzed Diels–Alder reaction of 1-(*p*-toluene sulfonamido)indan-2-yl acrylate **(303)** with cyclopentadiene (equation 84) have been depicted in Table 17. The reaction conducted in the absence of a Lewis acid did not afford any facial selectivity and only moderate *endo/exo* selectivity. However, when a Lewis acid was added, excellent de values and almost complete *endo* selectivities (cf. **304**) were observed, almost independent of the type and amount of Lewis acid added.



(302)



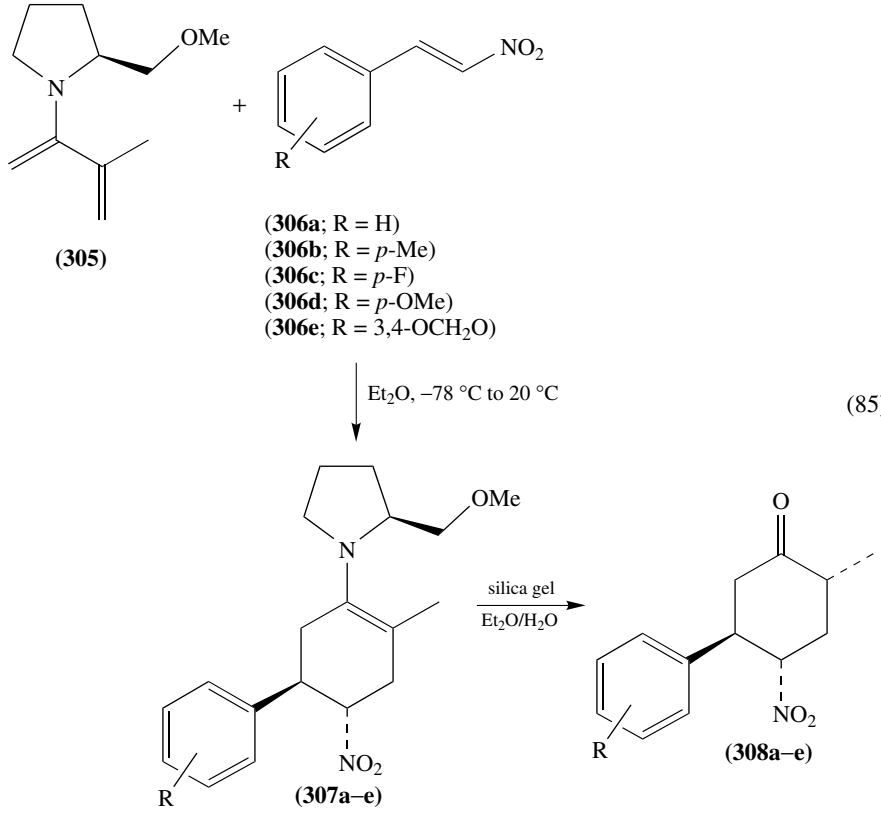
(84)

(1) **(303)** **(304)**

The Diels–Alder chemistry of chiral amino-1,3-butadienes has recently been reviewed[34] and has been the subject of several studies since. For instance, Enders and Klatt studied the reactions between chiral diene **305** carrying (*S*)-2-methoxymethylpyrrolidine as the chiral auxiliary[192] and substituted (*E*)-β-nitrostyrenes **306a–e**[193]. The reactions proceeded with moderate yields (26–60%). Hydrolysis of the intermediate enamines **307a–e** through diastereoselective protonation afforded ketones **308a–e** with high enantiomeric purities (95–99% ee) and high diastereoselectivities (75–95%) (equation 85).

TABLE 17. Reaction data for equation 84

Entry	Lewis acid (equiv.)	T (°C)	Yield (%)	*endo/exo*	% de **304**
1	none	0	85	80/20	0
2	$BF_3 \cdot OEt_2$ (1.0)	−78	85	>99/<1	76
3	$BF_3 \cdot OEt_2$ (2.0)	−78	91	>99/<1	80
4	$TiCl_4$ (1.0)	−78	83	>99/<1	76
5	$TiCl_4$ (2.0)	−78	87	>99/<1	86
6	Et_2AlCl (2.0)	−78	80	>99/<1	54
7	$SnCl_4$ (2.0)	−78	85	>99/<1	72

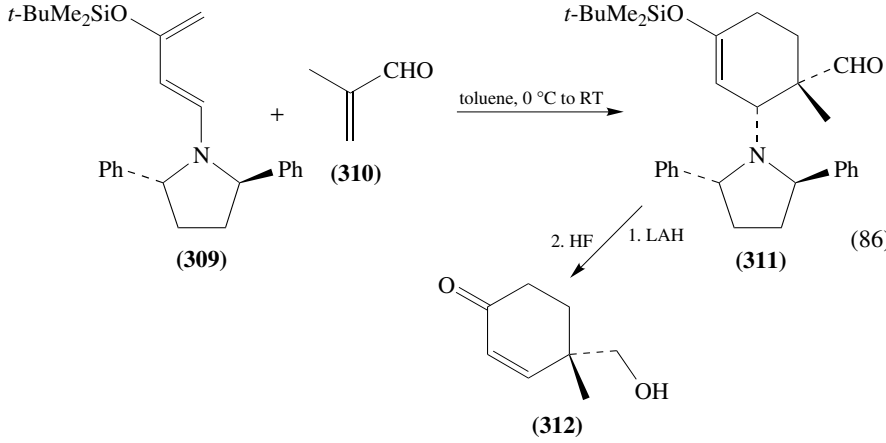


(85)

Barluenga and coworkers[194] recently extended the scope of the reaction between nitroalkenes and dienes like **305** by varying the substituents on the nitroalkene as well as on the diene. The 4-nitrocyclohexanone derivatives were generally obtained with good yields and very high enantiomeric excesses. This Diels–Alder strategy was used to synthesize cyclic β-amino acids[195].

Kozmin and Rawal[196] examined the reactions of chiral diene **309** with various dienophiles. Using this strategy, cyclohexenones were obtained with very high ee values (86–98%). Thus, the reaction of **309** with methacrolein **(310)** afforded adduct **311**, which

was converted in two steps to enantiomerically enriched **312** (equation 86). The major adduct was said to arise through a transition state in which the larger group on the dienophile was placed in the open pocket of the chiral pyrrolidine.



(86)

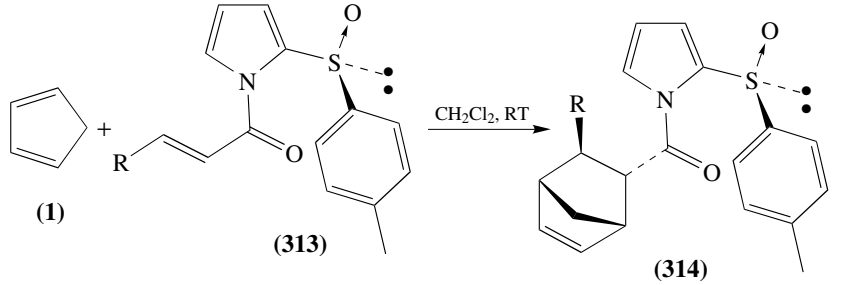
Arai and coworkers[197] reported the utilization of a chiral pyrrole sulfoxide as a chiral auxiliary in the asymmetric Diels–Alder reactions of its *N*-cinnamoyl and *N*-crotonyl derivatives **313** with cyclopentadiene which gave **314**–**317** (equation 87). The results have been summarized in Table 18. The yield as well as the *endo/exo* selectivity and the de proved to depend on the type and amount of Lewis acid used.

Nieman and Keay[198] reported the use of *cis,cis*-spiro[4,4]nonane-1,6-diol as a new chiral auxiliary to be used in asymmetric Diels–Alder reactions. Their best results in a series of reactions between chiral acrylates and cyclopentadiene were obtained when the pivalate ester of *cis,cis*-spiro[4,4]nonane-1,6-diol was used as the chiral auxiliary. When **318** was treated with cyclopentadiene, the expected *endo* adduct **319** was obtained with more than 97% de (equation 88).

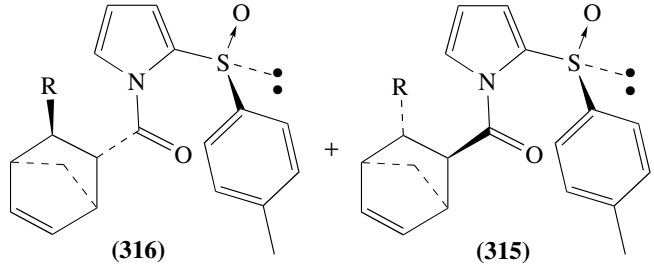
Murray and colleagues[199] developed some 2,5-diketopiperazines as new chiral auxiliaries and examined their asymmetric induction in the Diels–Alder reactions of their *N*-acryloyl derivatives with several dienes. Some of their results with dienophile **320** have been summarized in Table 19 (equation 89). When the benzyl group on **320** was substituted by an isopropyl or *t*-butyl group, the diastereofacial selectivity dropped dramatically. It was proposed that $\pi-\pi$ stacking between the phenyl group and the electron-poor double bond provided a more selective shielding of one face of the double bond in this special case.

TABLE 18. Reaction data for equation 87

Entry	R	Dienophile	Lewis acid (equiv.)	Yield (%)	*endo/exo*	% de **314**
1	Ph	**313a**	$BF_3 \cdot Et_2O$ (1.0)	0	—	—
2	Ph	**313a**	$ZnCl_2$ (1.0)	60	77/23	38
3	Ph	**313a**	$AlCl_3$ (1.0)	99	95/5	>99
4	Ph	**313a**	$AlCl_3$ (2.0)	84	59/41	11
5	Ph	**313a**	$Yb(OTf)_3$ (0.2)	33	80/20	80
6	Ph	**313a**	$Yb(OTf)_3$ (1.0)	61	69/31	89
7	Me	**313b**	$Yb(OTf)_3$ (1.0)	93	92/8	93
8	Me	**313b**	$AlCl_3$ (1.0)	100	91/9	92

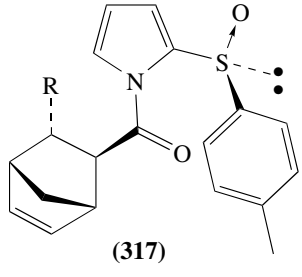

(1)
+
R
N
O
S
O
O
(313)
CH2Cl2, RT
R
N
O
S
O
O
(314)

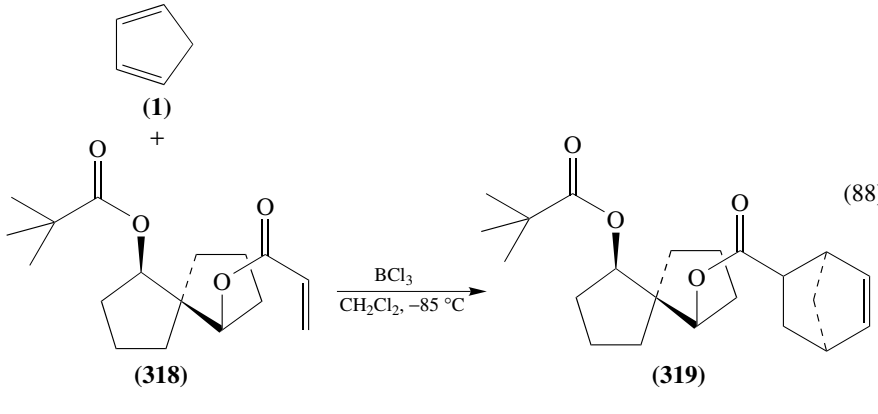
+


R
N
O
S
O
O
(316)
+
R
N
O
S
O
O
(315)

(87)

+

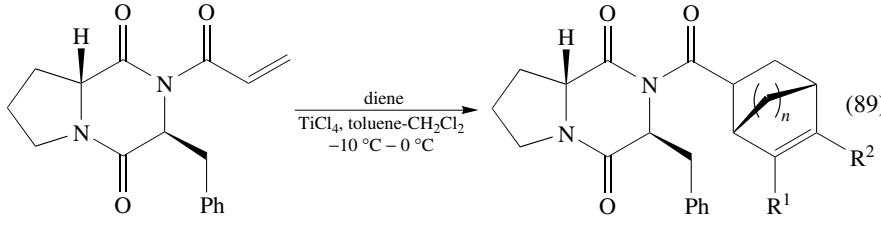

R
N
O
S
O
O
(317)


(1)
+
O
O
O
O
O
(318)
BCl3
CH2Cl2, −85 °C
O
O
O
O
O
(319)

(88)

TABLE 19. Reaction data for equation 89

Entry	*n*	R^1	R^2	Yield (%)	*endo/exo*	% de **321**
1	1	H	H	78	90/10	98
2	2	H	H	88	99/1	97
3	0	Me	Me	92	—	92
4	0	H	Me	94	—	100



(89)

(320) **(321)**

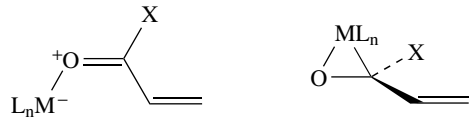
D. Chiral Lewis Acid Catalysts

The most important development within the field of Diels–Alder chemistry during the past two decades must be considered to be the design and application of chiral Lewis acid catalysts. From the mid '80s on, the number of literature reports about the design and application of chiral Lewis acids in the synthesis of chiral Diels–Alder adducts from achiral precursors grew exponentially, but it started to level off and decrease again in the mid '90s. Several excellent reviews about the application of chiral Lewis acids in Diels–Alder reactions have been published[41,43,44]. In this section, the recent literature about the chiral Lewis acid catalyzed all-carbon Diels–Alder reactions of dienes with dienophiles is reviewed, which, as such, has not been reviewed before.

In order to undergo Lewis acid catalysis, the dienophile or diene reacting in the Diels–Alder reaction must be conjugated with a group which can be complexed by a Lewis acid. In nearly all cases, this is a carbonyl functionality on the dienophile. This complexation leads to a lowering of the LUMO energy of the dienophile and to a relative increase of the LUMO coefficient at the β-carbon atom. This results in higher *endo* and regioselectivities.

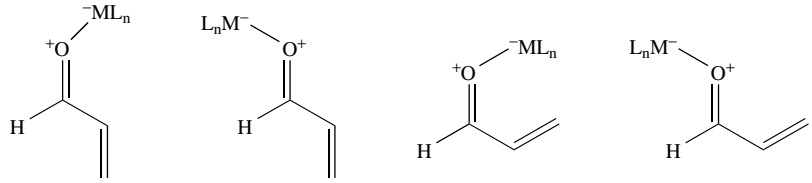
High enantioselectivities can only be obtained if the chiral Lewis acid–carbonyl complex adopts a well-defined rigid conformation in the transition state. Lewis acid–carbonyl complexes exist as either σ or π complexes (Figure 4)[200]. Main group, early transition metal and lanthanide types of Lewis acids are believed to co-ordinate in a σ fashion. Electron-rich transition metal complexes prefer to give π-type of complexes with electron-poor carbonyl groups. The overwhelming majority of Lewis acids which catalyze Diels–Alder reactions belong to the former category.

α,β-Unsaturated carbonyl compounds to which a Lewis acid has been complexed in an η^1 fashion can adopt four conformations, as depicted for aldehydes in Figure 5. The terms *syn* and *anti* refer to the relative orientation of the Lewis acid with respect to the carbonyl substituent with the highest priority. In the case of aldehydes, the *anti* conformations are preferred. This has been shown for several BF_3–aldehyde complexes which proved to have a B–O–C–C dihedral angle of about 180°[201]. The stereoelectronic control in the



η^1 complex (σ bonding) η^2 complex (π bonding)

FIGURE 4. η^1 and η^2 types of co-ordination of a Lewis acid to a carbonyl group



syn s-trans *anti s-trans* *syn s-cis* *anti s-cis*

FIGURE 5. Important conformations of Lewis acid complexed aldehydes

formation of η^1 Lewis acid–carbonyl complexes has recently been discussed by Fu and colleagues[202]. In the case of esters, complexation of the Lewis acid occurs preferentially *anti* to the alkoxy group, as was demonstrated by X-ray crystallographic studies[202,203]. Lewis acids complex to amide carbonyls in an *anti* fashion with respect to the R_2N moiety, because *syn* complexation is strongly disfavored by allylic strain[200].

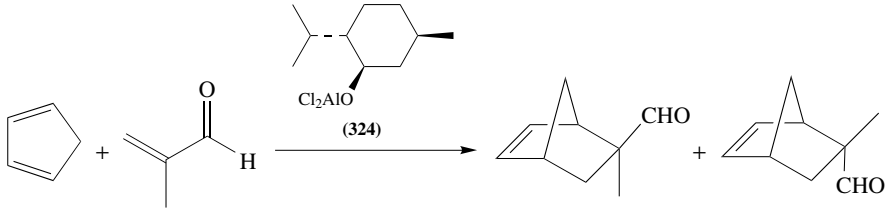
The enone system has to preferably adopt an *s-cis* or *s-trans* conformation in the transition state. Which one is favored may depend on the nature of the Lewis acid. It is generally accepted that Lewis acid complexation dramatically stabilizes the *s-trans* conformation[204]. The *s-cis* conformation, however, may be the more reactive conformation. The dienophile may react selectively in this conformation, if the *s-trans* and *s-cis* conformations are in equilibrium.

Stereoselective complexation of the chiral Lewis acid together with a preferred *s-cis* or *s-trans* conformation of the dienophile generally cause selective shielding of one face of the dienophile. Corey and coworkers[205] explained the high enantioselectivities observed with their chiral Lewis acid by hydrogen bridge formation between a formyl hydrogen and a chiral alkoxy ligand, based on X-ray crystallographic results.

The types of dienophiles which have been studied most are acrylic aldehydes, acrylates and 3-acryloyl-1,3-oxazolidines. The latter have been used predominantly in copper, magnesium, zinc and lanthanide catalyzed reactions in which the chiral Lewis acid binds in an η^2 fashion to the dienophile (complexation to both carbonyls).

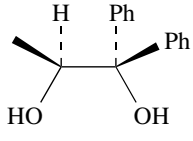
1. Chiral aluminum catalysts

The chiral Lewis acid catalyzed cycloaddition of methacrolein **310** to cyclopentadiene predominantly affording *exo* cycloadduct **322** together with some **323** has been extensively investigated. The application of menthoxyaluminum dichloride **(324)** as the chiral catalyst in this reaction represents one of the earliest examples of a chiral Lewis acid catalyzed Diels–Alder reaction[206] (equation 90). The authors confirmed their results in 1987, but the ee was revised from 72% to 57%[207].

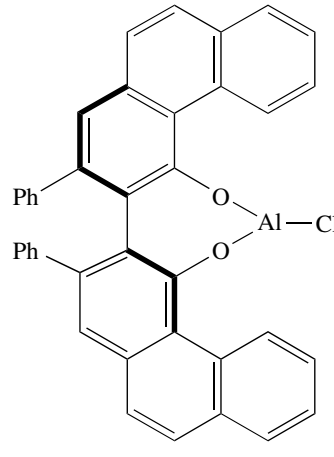


(1) (310) (2*S*-322) (2*R*-323) (90)

Kagan and coworkers studied the reaction between cyclopentadiene and **310** in the presence of aluminum alcoholates of chiral diols and their chiral mono ethers[208]. Among the various diols studied, only 1,1-diphenyl-1,2-propanediol **(325)** gave satisfactory results. Optimization by variation of the dienophile/catalyst ratio, aging of the catalyst and variation of the temperature ultimately resulted in a maximum of 86% ee at −100 °C.



(325)



(326)

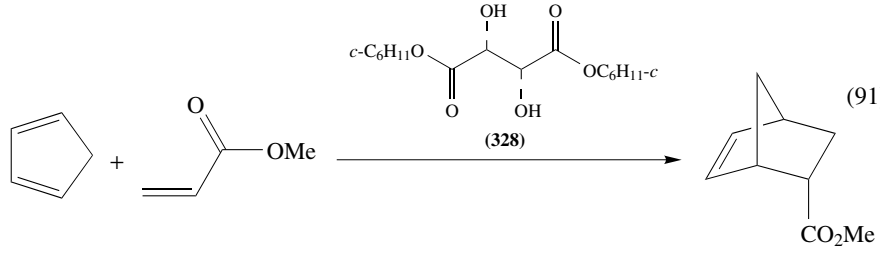
A very high asymmetric induction was observed when the reaction between cyclopentadiene and methacrolein was performed using 0.5 mol% of binaphthol catalyst **326**[209]. Diels–Alder adduct (2*R*)-**322** was formed with up to 97.8% ee within 4 h at −80 °C.

Mayoral and colleagues[210] studied the same reaction catalyzed by a menthoxyaluminum catalyst supported on silica gel and alumina. The catalyst was prepared by treatment of the solid support with diethylaluminum chloride and (−)-menthol. The silica-supported catalyst proved more active than the alumina-supported catalyst. The reaction rates and enantioselectivities depended strongly on the amount of (−)-menthol used. The highest ee obtained was 31% at 81% conversion (*endo*/*exo* = 10/90).

Recently, Diels–Alder reactions between cyclopentadiene and menthoxyaluminum dichloride–acrolein complexes were investigated by means of combined AM1/AM3 calculations and the results were compared to full AM1 results[211].

The asymmetric Diels–Alder reaction of cyclopentadiene with methyl acrylate **11b** has been studied using several types of catalysts. The asymmetric induction of various

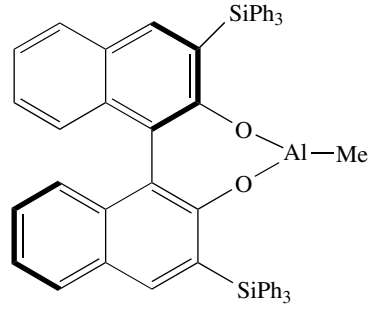
dialkoxyaluminum chloride catalysts was studied by Hermann and coworkers, who also showed the dependence of the composition of the catalyst in solution on aging time. The best results were obtained employing ligand **328**, the reaction affording **327** with an ee of 70% in a yield of 49% (equation 91)[212].



(91)

(1) **(11b)** (2*S*-**327**)

Catalyst **329**, prepared from trimethylaluminum and 3,3′-bis(triphenylsilyl)-1,1′-bi-2-naphthol, allowed the preparation of the *endo* cycloadduct (2*S*)-**327** with 67% ee. The use of non-polar solvents raised the ee, but lowered the chemical yield[213]. Recently, it was reported that the reaction to form **327** exhibited autoinduction when mediated by catalyst **326**[214]. This was attributed to a co-operative interaction of the cycloadduct with the catalyst, generating a more selective catalytic species. A wide variety of carbonyl ligands were tested for their co-operative effect on enantioselectivity. Sterically crowded aldehydes such as pivaldehyde provided the best results. Surprisingly, 1,3-dicarbonyl compounds were even more effective than monocarbonyl compounds. The asymmetric induction increased from 82 to 92% ee when di(1-adamantyl)-2,2-dimethylmalonate was added while at the same time the reaction temperature was allowed to increase by 80 °C, from −80 °C to 0 °C.

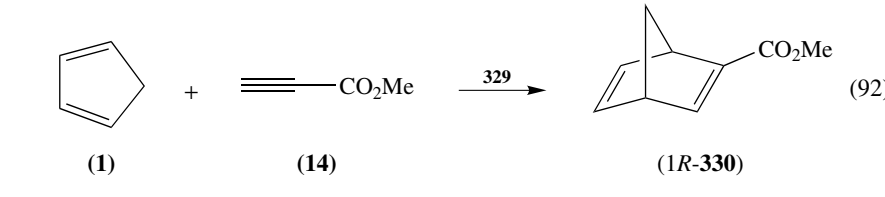


(329)

Catalyst **329** was also applied in the asymmetric Diels–Alder reaction of methyl propiolate **14** with cyclopentadiene, yielding cycloadduct **330** with 55% ee (equation 92)[213].

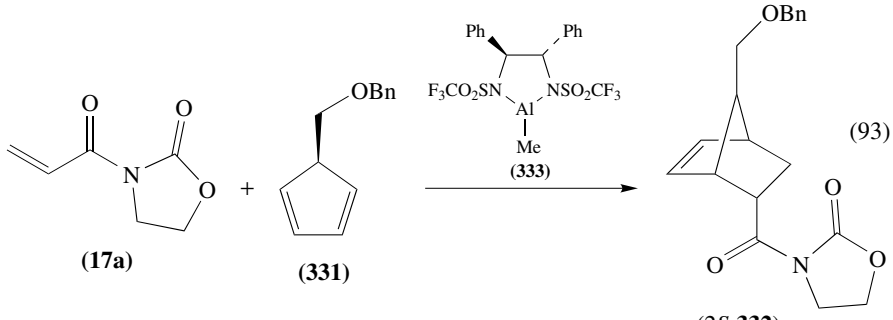
Corey and colleagues[215] prepared chiral aluminum complexes from chiral bis(sulfonamides) and trimethylaluminum. These were successfully applied in the cycloadditions of 3-acryloyl-1,3-oxazolidin-2-one **(17a)** with substituted cyclopentadienes. Thus, the reaction of 3-acryloyl-1,3-oxazolidin-2-one with 5-(benzyloxymethyl)cyclopentadiene **(331)** afforded **332** with 94% ee (equation 93). A transition state was proposed based on the X-ray structure of the chiral catalyst and on NMR data of the 1 : 1 complex between **333**

and **17a**[216]. The cycloaddition was the first step in the enantioselective synthesis of a key intermediate used to synthesize prostanoids[217].



(92)

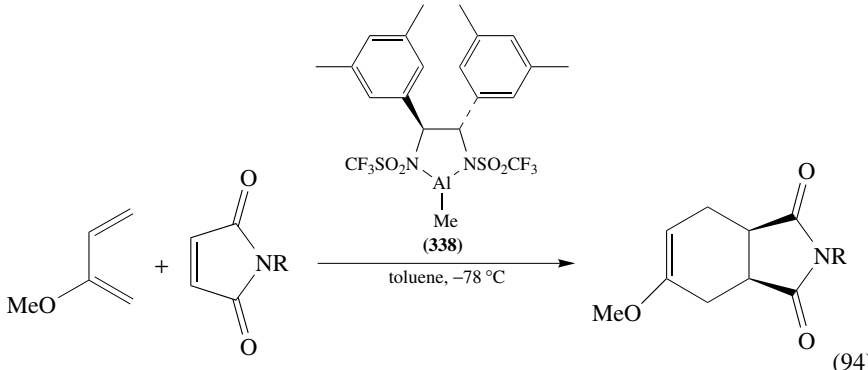
(1) **(14)** (1*R*-**330**)



(93)

(17a) **(331)** (2*S*-**332**)

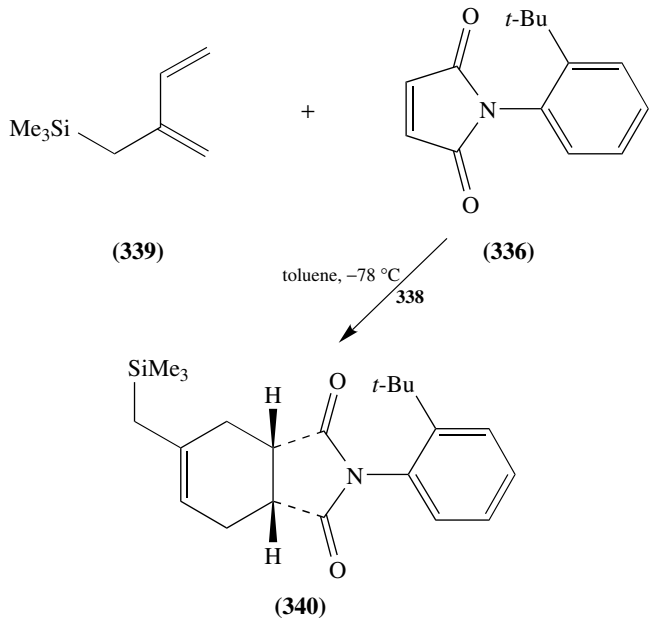
When catalyst **333** was applied in the cycloaddition reaction of 2-methoxy-1,3-butadiene **(334)** with *N*-(*o*-tolyl)maleimide **(335)**, the corresponding cycloadduct **337a** was obtained with only 58% ee. However, an ee of 95% was observed when catalyst **338** and *N*-(*o*-*t*-butylphenyl)maleimide **(336)** were employed (equation 94). The *meta* methyl substituents on the phenyl groups of catalyst **338** proved crucial for producing **337** with high enantioselectivity. In contrast, the Diels–Alder reaction of maleic anhydride with 2-methoxy-1,3-butadiene using catalyst **338** afforded a racemic adduct. These results were considered to result from a different complexation behavior of the catalyst in the case of maleic anhydride in comparison with *N*-arylmaleimides[218].



(94)

(334) (**335**; R = *o*-tolyl) (**337a**; R = *o*-tolyl)
(**336**; R = *o*-*t*-butylphenyl) (**337b**; R = *o*-*t*-butylphenyl)

The reaction between diene **339** and **336** afforded cycloadduct **340** with 95% ee when catalyst **338** was used (equation 95). Adduct **340** was used as a precursor for the marine natural products gracillins B and C[219].



(95)

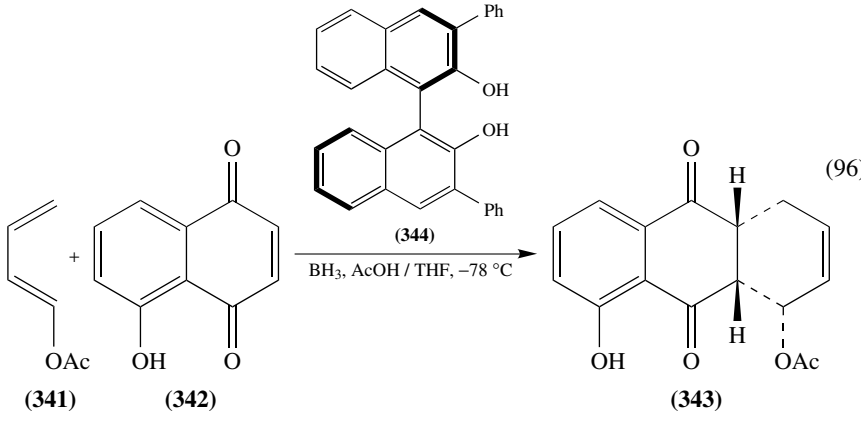
2. Chiral boron catalysts

Chiral boron catalysts had already been widely used in a variety of reactions before they were applied in Diels–Alder reactions[220]. Boron catalysts were first employed in the Diels–Alder reactions of quinones with electron-rich dienes. Kelly and coworkers[221] found that stoichiometric amounts of a catalyst prepared from BH_3, acetic acid and 3,3′-diphenyl-1,1′-bi-2-naphthol **(344)** catalyzed the reaction of 1-acetoxy-1,3-butadiene **(341)** with juglone **(342)** to afford cycloadduct **343** with 98% ee (equation 96). The reaction was supposed to proceed via a spirocyclic borate complex in which one face of the double bond of juglone was effectively shielded from attack by the diene.

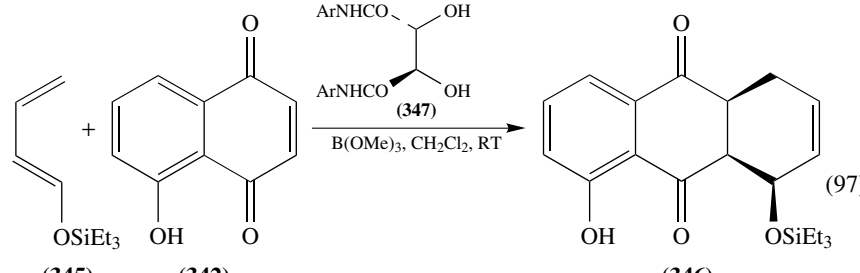
A similar approach was followed by Yamamoto and colleagues[222]. A chiral boron catalyst prepared from trimethyl borate and various (*R*,*R*)-tartaric diamides **347** effectively catalyzed the cycloaddition of juglone to 1-triethylsilyloxy-1,3-butadiene **(345)** to give cycloadduct **346** with high enantioselectivity (equation 97).

The application of chiral boron catalysts in the cycloadditions of α,β-unsaturated aldehydes and acrylic acid derivatives has been investigated most.

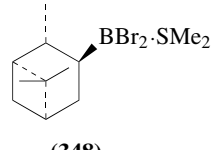
Kaufmann and colleagues examined the asymmetric induction of chiral boron complexes **348** and **349**, obtained through reaction of $HBBr_2$. SMe_2 with pinene[223] and 1,1′-bi-2-naphthol[224], respectively, in the cycloaddition of cyclopentadiene with methacrolein (equation 98). A low ee (28%) was found when employing catalyst **348**, but the ee was greatly improved to 90% using catalyst **349**. The X-ray structure of **349** showed the molecule to have a propeller-like shape with an interesting C_3 symmetry.



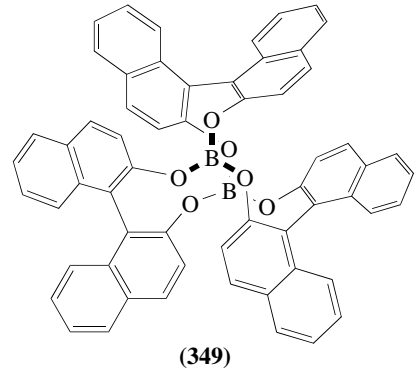
(341) (342) (343) (96)



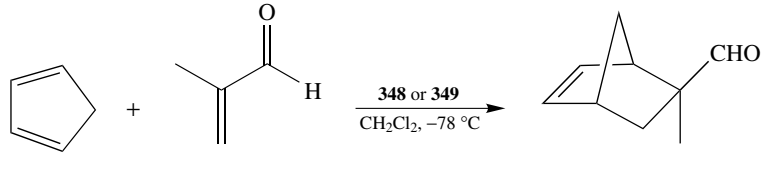
(345) (342) (346) (97)



(348)

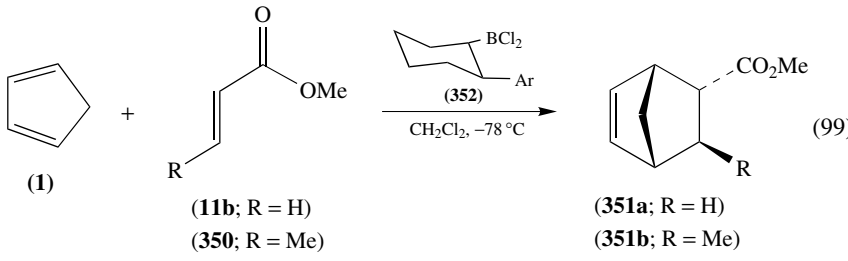


(349)



(1) (310) (2*S*-322) (98)

Hawkins and Loren[225] reported simple chiral arylalkyldichloroborane catalysts **352** which were effectively used in the cycloadditions of acrylates **11b** and **350** to cyclopentadiene, affording adducts **351a** and **351b**, respectively (equation 99). A crystal structure of the molecular complex between methyl crotonate and the catalyst allowed the authors to rationalize the outcome of the reaction. One face of methyl crotonate is blocked by $\pi-\pi$ donor–acceptor interactions, as becomes clear from the structure of complex **353**. The cycloadduct of methyl acrylate and cyclopentadiene (5 equivalents) was obtained with 97% ee, using the same catalyst. Three years later, the authors reported that the cycloadduct was obtained with 99.5% ee in the presence of 10 equivalents of cyclopentadiene[226].

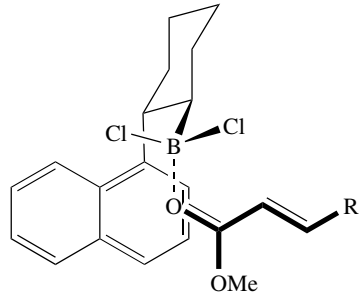


(99)

(**1**)

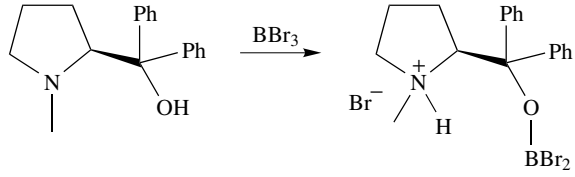
(**11b**; R = H)
(**350**; R = Me)

(**351a**; R = H)
(**351b**; R = Me)



(**353**)

Kobayashi and colleagues[227] prepared chiral boron reagent **355** from BBr_3 and chiral prolinol derivative **354** (equation 100). This catalyst afforded the *exo* Diels–Alder adduct of cyclopentadiene and methacrolein with 97% ee (equation 101). In the same way, norbornene (2*R*)-**357** was obtained from **356** and cyclopentadiene.

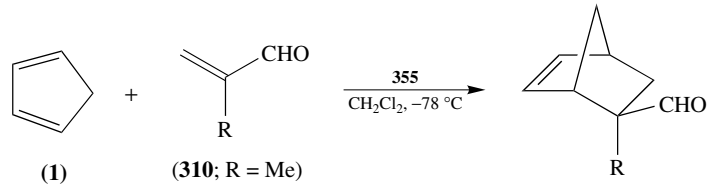


(100)

(**354**) (**355**)

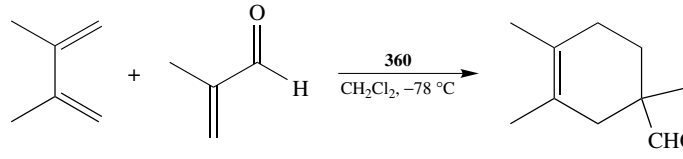
Chiral 1,2,3-oxazaborolidines simply obtained from α-amino acid derived sulfonamides and borane were first applied in Diels–Alder reactions by Taliasu and Yamamoto[228], and Helmchen and colleagues[229]. Yamamoto prepared catalysts from α-aminobutyric acid derived arylsulfonamides and found that the enantioselectivity of the reaction between

methacrolein and 2,3-dimethyl-1,3-butadiene **(358)** increased with increasing bulkiness of the arylsulfonyl group. Cycloadduct **359** was obtained with a maximum of 74% ee using catalyst **360** (equation 102).



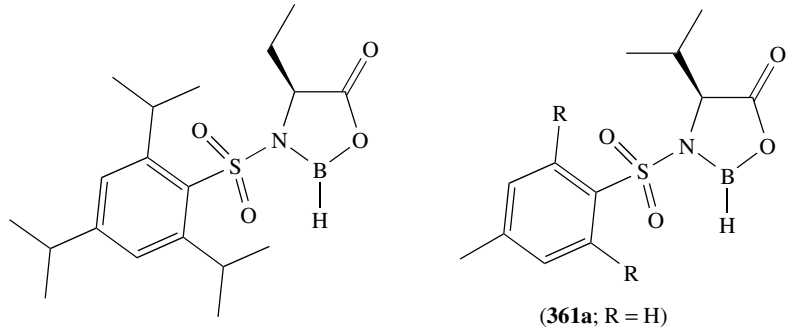
(101)

(1) (**310**; R = Me) (**356**; R = Et) (2*R*-**322**; R = Me, 97% ee) (2*R*-**357**; R = Et, 73% ee)



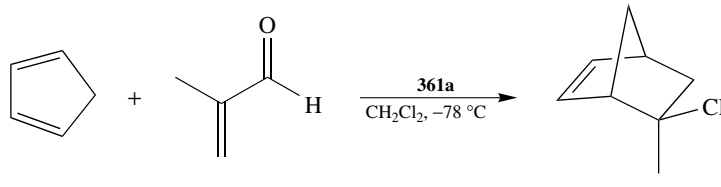
(102)

(358) **(310)** (**359**; 74% ee)



(360) (**361a**; R = H) (**361b**; R = Me)

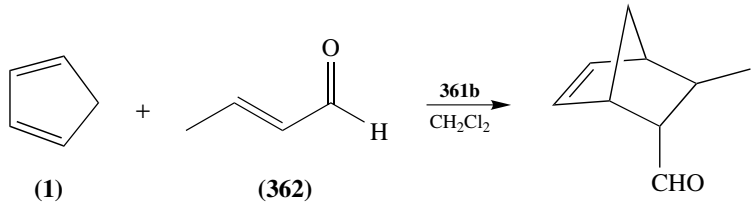
Helmchen and colleagues used equimolar amounts of L-valine derived oxazaborolidine **361a** to catalyze the reaction of methacrolein with cyclopentadiene (equation 103). Cycloadduct **322** was obtained with 64% ee[229]. The enantioselectivity was increased to 86% ee by using 60 mo1% of **361a** and donor solvents like THF. The same catalyst afforded the *endo* cycloadduct of crotonaldehyde and cyclopentadiene with 76% ee.



(103)

(1) **(310)** (2*R*-**322**; 64–86% ee)

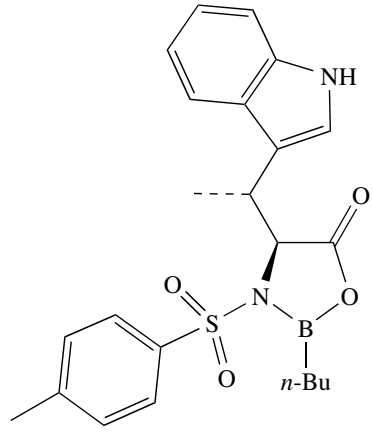
The cycloaddition reaction of crotonaldehyde (**362**) with cyclopentadiene in the presence of 20 mo1% of catalyst **361b** afforded cycloadduct **363** with 58% yield (*endo*/*exo* = 97/3) and 72% ee (equation 104)[230].



(104)

(1) **(362)** (2*S*-**363**; 72% ee)

Interestingly, Corey and coworkers[231] showed that the main adduct in the reaction of methacrolein with cyclopentadiene was (2*S*)-**322** (92% ee) when catalyst **364**, derived from (α*S*,β*R*)-β-methyltryptophan and *n*-butylboric acid, was used.

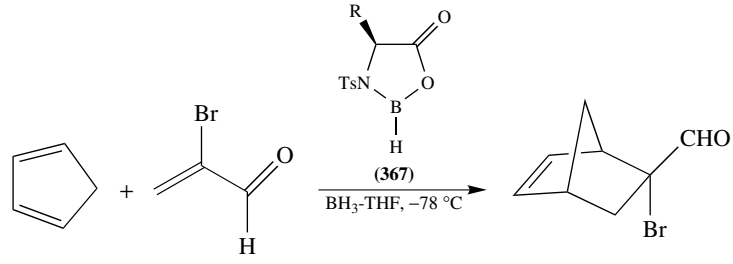


(364)

The effect of changing the position of the electron-donating atom in the side chain R of oxazaborolidine catalysts **367** was studied systematically for the reaction between cyclopentadiene and methacrolein. The enantioselectivity proved to be controlled by the presence of electron-donor atoms at positions 2 and 4 of the side chain. The effect was especially apparent in the formation of **366** from cyclopentadiene with α-bromoacrolein **(365)** (equation 105, Table 20), which is more electron-poor than methacrolein[232].

These results were rationalized by application of a transition state model for the reaction catalyzed by **367d** (Figure 6). A strong donor–acceptor interaction was envisaged between the oxygen atom of the benzyloxymethyl group and the carbonyl carbon of the complexed dienophile. In addition, a $\pi-\pi$ stacking interaction between the aromatic ring and the olefinic double bond was proposed. Because of these interactions, one of the dienophile faces is selectively blocked for approach by cyclopentadiene.

Very high enantioselectivities were obtained in the reaction between cyclopentadiene and α-bromoacrolein using (*S*)-tryptophan derived oxazaborolidine catalyst (*S*)-**369b**. The Diels–Alder adduct (2*R*)-**366** was obtained with at least 99% enantiomeric excess[233].



(105)

(1) **(365)** (2*R*-**366**)

TABLE 20. Reaction data for equation 105

Entry	R	Catalyst	*endo/exo*	% ee
1	Bn	**367a**	5/95	55
2	*p*-$MeOC_6H_4CH_2$	**367b**	4/96	72
3	*p*-$PhCH_2OC_6H_4CH_2$	**367c**	4/96	81
4	$PhCH_2OCH_2$	**367d**	4/96	81

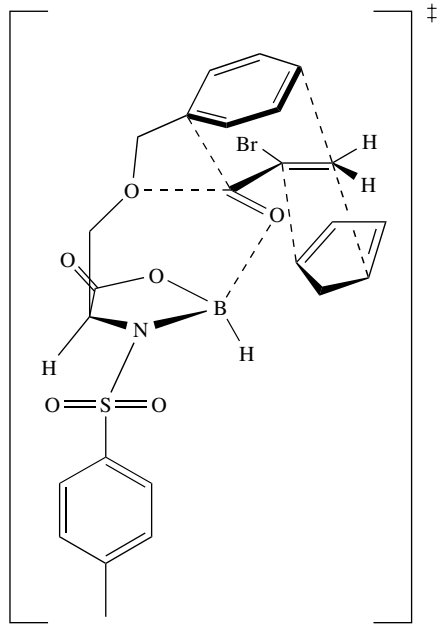
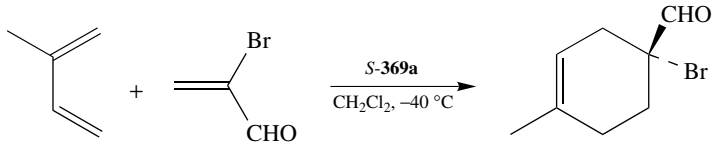


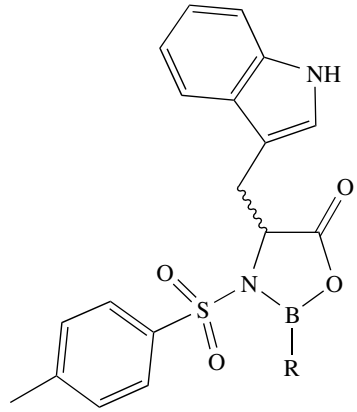
FIGURE 6. Model of the *exo* transition state to form **366** using **367d** as the catalyst

Catalyst (*S*)-**369a** was applied in the cycloaddition of isoprene to α-bromoacrolein to yield cycloadduct **368** with 76% yield and 92% ee (equation 106).



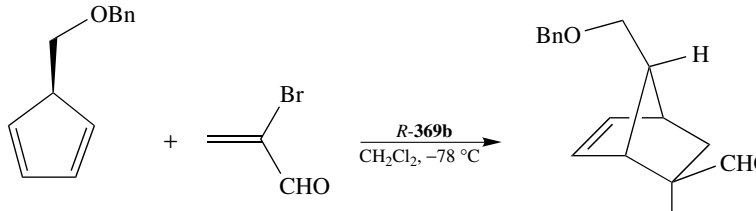
(106)

(91a) **(365)** (*S*-**368**)



(**369a**; R = H)
(**369b**; R = *n*-Bu)

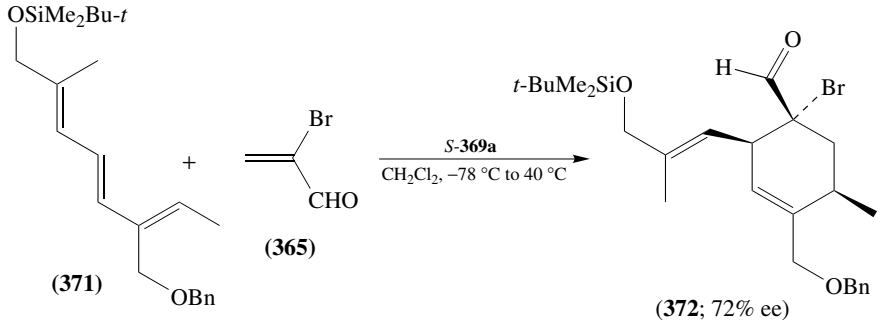
Catalyst (*R*)-**369b** catalyzed the cycloaddition of α-bromoacrolein to 5-(benzyloxymethyl)cyclopentadiene (**331**) to give adduct **370** with 82% yield and 92% ee (equation 107)[231,233]. Cycloadduct **370** has been used in prostaglandin synthesis.



(107)

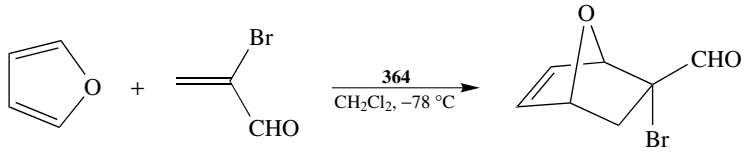
(331) **(365)** (2*S*-**370**)

Marshall and Xie[234] used equimolar amounts of (*S*)-**369a** in the cycloaddition of α-bromoacrolein to diene **371** to prepare adduct **372**, a precursor for a subunit of the antitumor antibiotic kijanimycin. In this cycloaddition, the *endo* adduct was formed exclusively with 88% yield and 72% ee (equation 108).



(108)

Furan reacted with α-bromoacrolein in the presence of 10 mol% of catalyst **364** to give the Diels–Alder adduct **373** in 98% yield with 92% ee (equation 109)[235]. Cycloadduct **373** has been applied in further synthesis[236]. The related catalyst (*S*)-**369b** proved much less effective in this reaction.

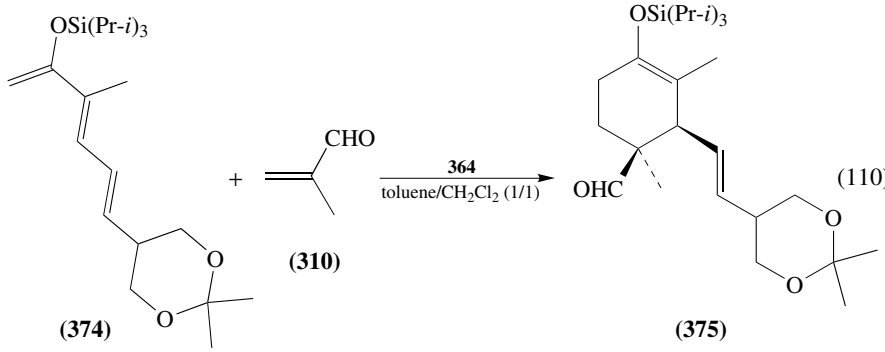


(109)

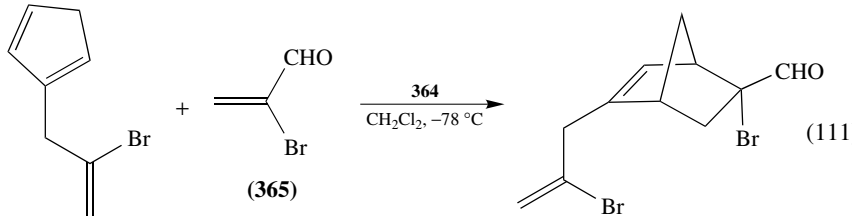
(169) **(365)** (2*R*-**373**; 92% ee)

Two other applications of catalyst **364**, i.e. in cycloaddition reactions of α-substituted acroleins with dienes **374** and **376**, have been depicted in equations 110 and 111[237]. Cycloadducts **375** and **377** have been used as precursors in the syntheses of cassiol and gibberellic acid, respectively. The use of catalysts **364** and **369b** in cycloadditions with acrolein resulted in low enantioselectivities with opposite face selectivities.

Cross-linked polymers bearing *N*-sulfonyl amino acids as chiral ligands were converted to polymer bound oxazaborolidine catalysts by treatment with borane or bromoborane. In the cycloaddition of cyclopentadiene with methacrolein, these catalysts afforded the same enantioselectivities as their non-polymeric counterparts[238].

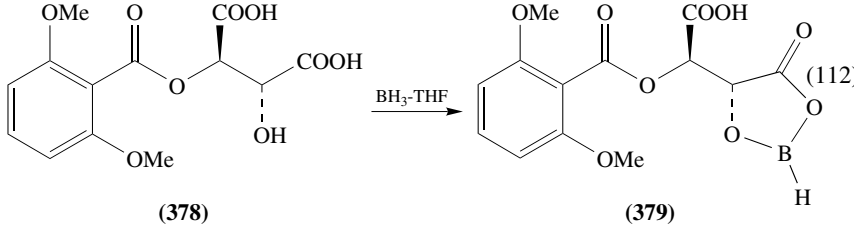


(110)

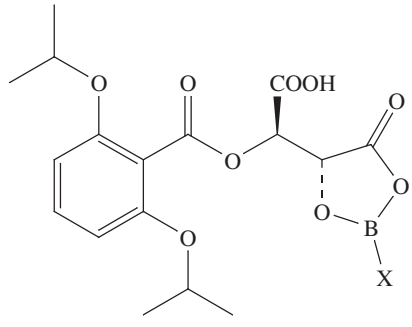


(376) (365) (2*R*-**377**; 99% ee) (111)

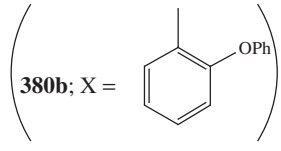
Yamamoto and colleagues developed achiral boron catalysts **379** and **380a–b** derived from monoacylated tartaric acid and BH_3–THF as shown for **379** in equation 112. The cycloaddition of cyclopentadiene to acrylic acid **(381)** afforded *endo* **382** with 78% ee and 93% yield when catalyst **379** was employed (equation 113)[239].

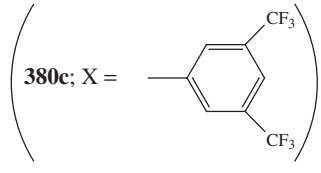


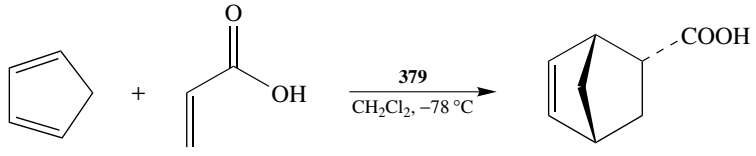
(378) **(379)** (112)



(**380a**; X = H)





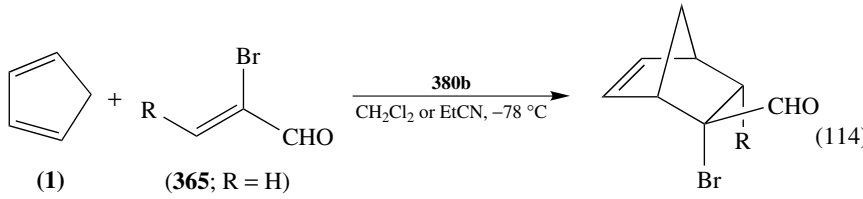


(113)

(1) **(381)** (2*R*-**382**; 78% ee)

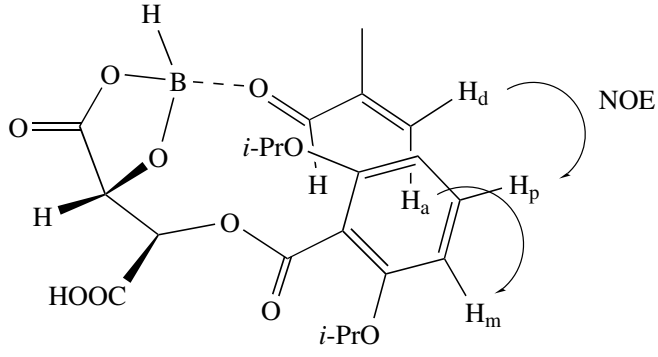
The asymmetric induction by catalyst **379** was extensively studied in the cycloadditions of simple dienes with substituted α,β-unsaturated aldehydes. It proved that α-substitution on the dienophile increased the enantioselectivity, whereas β-substitution dramatically decreased it. In the case of substrates having both α- and β-substituents, high enantioselectivities were observed[240].

Yamamoto and coworkers found that the Diels–Alder reactions of α-bromo-α,β-enals with dienes were also efficiently catalyzed by catalysts **380a** and **380b**[241]. The highest enantioselectivity and yield (98% ee, 100% yield) were obtained in the reaction of cyclopentadiene with α-bromoacrolein using 10 mol% of **380b** (equation 114). The same enantioselectivity was observed in the reaction between cyclopentadiene and **383**, which afforded adduct **384**. Catalyst **380a**, having a hydrogen substituted boron atom, afforded high ee values with other dienes. A model of the catalyst–dienophile complex **(385)** was proposed in which effective shielding of the *si* face of the co-ordinated unsaturated aldehyde arose from $\pi-\pi$ stacking of the 2,6-diisopropoxybenzene ring with the double bond of the unsaturated aldehyde[242].



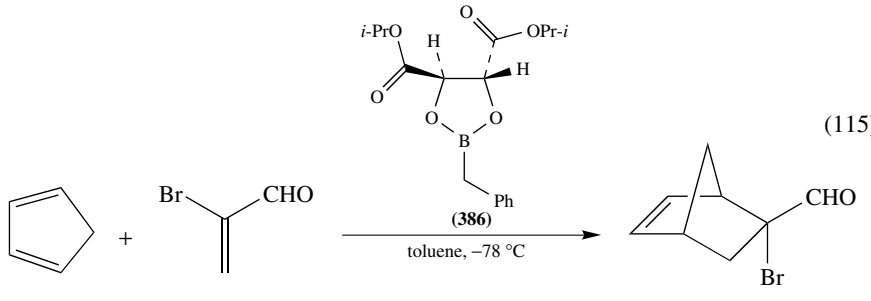
(114)

(1) (**365**; R = H) (**383**; R = Me) (2*S*-**366**; R = H, 98% ee) (2*S*-**384**; R = Me, 98% ee)



(385)

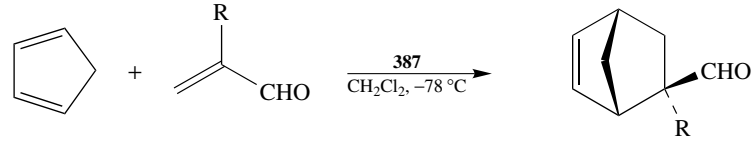
Simple chiral tartrate derived dioxaborolidine **386** induced a moderate enantioselectivity in the cycloaddition reaction of cyclopentadiene with α-bromoacrolein (equation 115)[243].



(115)

(1) **(365)** (2*R*-**366**)

Yamamoto and colleagues showed that very high enantioselectivities and yields were obtained in the cycloadditions of cyclopentadiene with several α-substituted acrylic aldehydes using binaphthol catalyst **387** (equation 116).



(116)

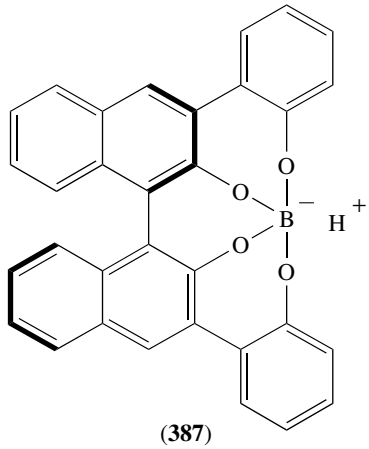
(1) (**310**; R = Me) (2*R*-**322**; R = Me, >99% ee)
(**365**; R = Br) (2*R*-**366**; R = Br, >99% ee)
(**356**; R = Et) (2*R*-**357**; R = Et, 92% ee)

The high stereopreference was rationalized by considering complex **388** in which an attractive $\pi-\pi$ donor–acceptor interaction favors co-ordination of the dienophile to the face of the boron center which is *cis* to the 2-hydroxyphenyl substituent. Hydrogen bonding of the hydroxyl proton of the 2-hydroxyphenyl group to an oxygen of the adjacent B–O bond played an important role in the asymmetric induction. Protection of this hydroxy functionality with a benzyl group caused reversal of enantioselectivity in the cycloaddition of cyclopentadiene with methacrolein (model **389**)[244].

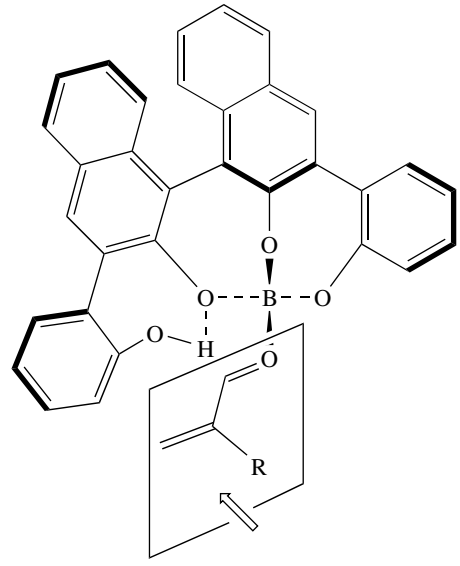
Further improvement of catalyst **387** resulted in the development of catalyst **393**, as demonstrated by the formation of **391** and **392** from dienophiles **390** and cyclic dienes which gave good results with less reactive dienes and dienophiles (equation 117, Table 21)[245].

Reilly and Oh explored the asymmetric induction of chiral catalysts derived from bis(dichloroborane) **397** in the cycloaddition of cyclopentadiene with α-bromoacrolein and methacrolein. *N*-Tosyltryptophan (**394**) and chiral diols **395** and **396** were employed as chiral ligands[246,247]. The application of chiral *N*-tosyltryptophan afforded the best results (equation 118, Table 22).

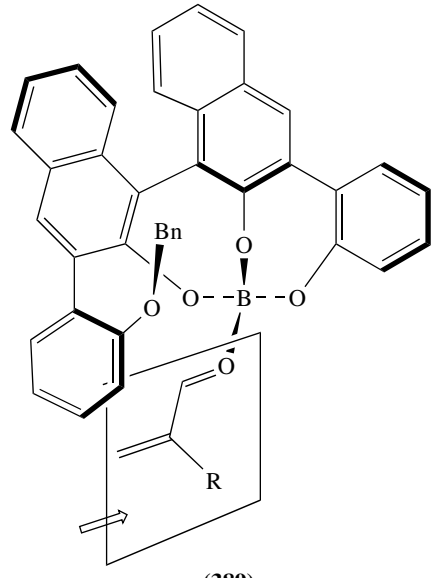
Corey and coworkers[205b,c,248] reported the reactive cationic oxazaborinane catalyst and afforded **398a** which promoted cycloadditions between cyclopentadiene and several α,β-enals good enantioselectivities. Excellent results were obtained in cycloadditions of several modestly reactive dienes to α-bromoacrolein in the presence of catalyst **398b** having tetra[3,5-bis(trifluoromethyl)phenyl]borate as the counterion (Table 23).



(**387**)



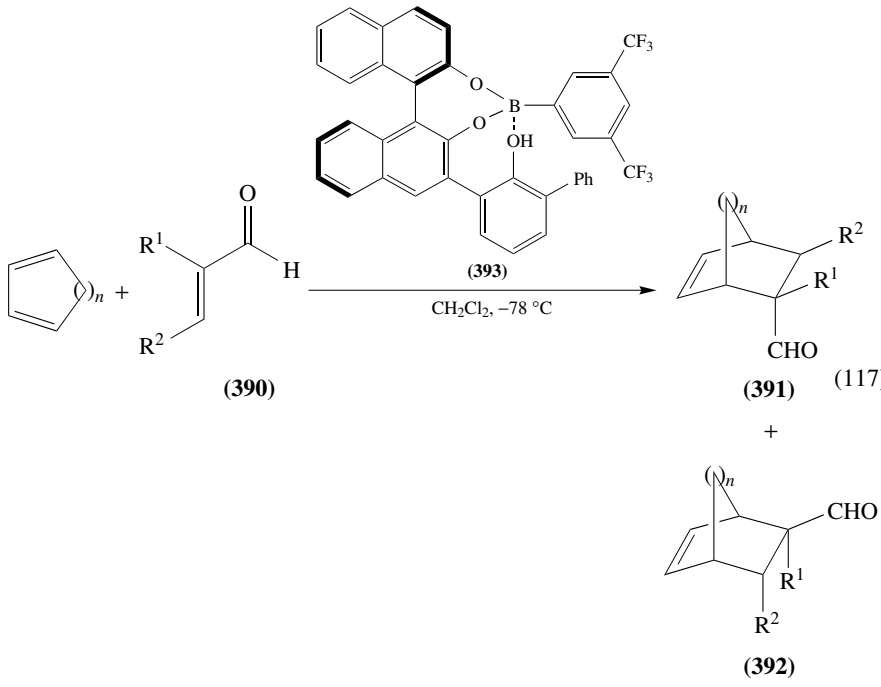
(**388**)



(**389**)

Recently, Yamamoto and coworkers[249] reported the first examples of chiral induction in the cycloadditions of cyclopentadiene to propargylic aldehydes **402** using catalysts **380c, 387** and **393** (equation 119). The cycloadditions were stated to proceed via *exo* transition states and were accelerated by coordination of the Lewis acid to the carbonyl group.

Later, Corey and colleagues reported that this reaction (with R = TMS, TES, Me_2PhSi and Bu_3Sn) was effectively catalyzed by **398b**, with which ee values of 80–87% were obtained[250].



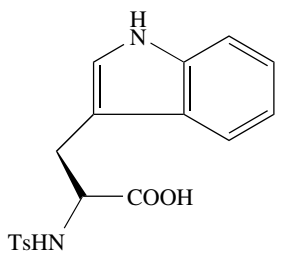
(117)

TABLE 21. Reaction data for equation 117

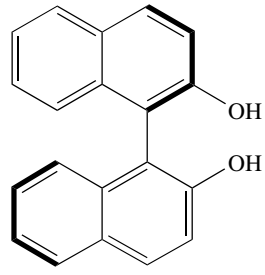
Entry	*n*	R^1	R^2	Dienophile	**391/392**	% ee (major)
1	1	Me	H	**310**	—	99 (S)
2	1	Br	H	**365**	10/90	>99 (R)
3	2	Br	H	**365**	90/10	95
4	1	Me	Me	**390a**	2/98	96
5	1	H	H	**390b**	97/3	95 (S)
6	2	H	H	**390b**	100/0	96 (S)
7	1	H	Me	**362**	90/10	95 (S)
8	1	H	CO_2Et	**390c**	98/2	95 (R)

3. Chiral titanium catalysts

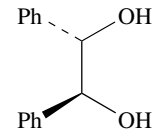
Chiral titanium catalysts have generally been derived from chiral diols. Narasaka and colleagues[251] developed an efficient catalyst, **406**, prepared from $TiCl_2(OPr\text{-}i)_2$ and a (+)-tartaric acid derived 1,4-diol. These authors found that *N*-crotonyl-1,3-oxazolidin-2-one (**404**) reacted with cyclopentadiene in the presence of 10 mol% of **406** to give cycloadduct **405** with up to 91% ee (equation 120)[252].



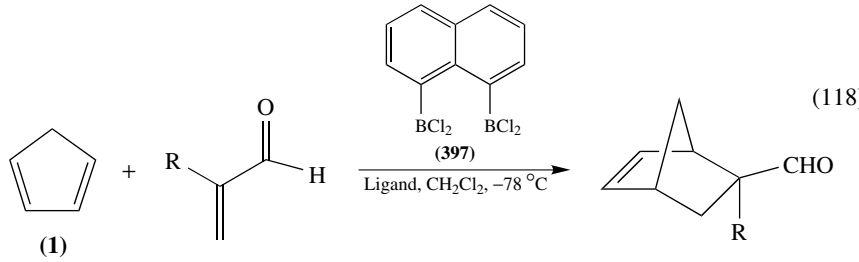
(394)



(395)



(396)

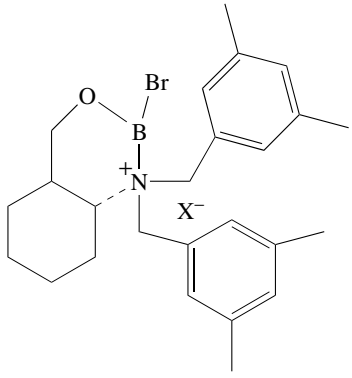


(1)

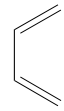
(118)

TABLE 22. Reaction data for equation 118

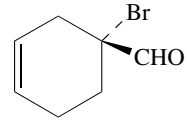
Entry	R	Dienophile	Ligand	Ligand/**397**	Yield (%)	*endo/exo*	% ee
1	Br	**365**	**394**	1	84	8/92	22 *(exo)*
2	Me	**310**	**394**	1	46	37/63	100 *(endo)*
3	H	**390b**	**394**	1	53	94/6	62 *(endo)*
4	Br	**365**	**395**	1	81	14/86	36 *(exo)*
5	Br	**365**	**395**	2	81	20/80	28 *(exo)*
6	Br	**365**	**396**	2	83	20/80	—



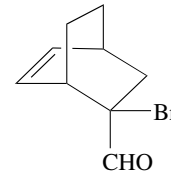
(**398a**; X = BBr_4)
(**398b**; X = $B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4$)



(399)



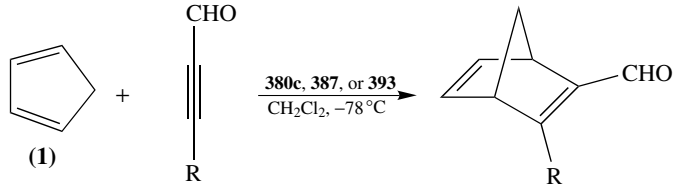
(*R*-**400**)



(2*R*-**401**)

TABLE 23. Reaction data for the cycloaddition reactions between α-bromoacrolein and several dienes

Entry	Diene	Product	Yield (%)	*endo/exo*	% ee
1	**399**	**400**	99	—	94
2	**91a**	**369**	99	—	96
3	**275**	**401**	99	4/96	93
4	**1**	**366**	99	9/91	98



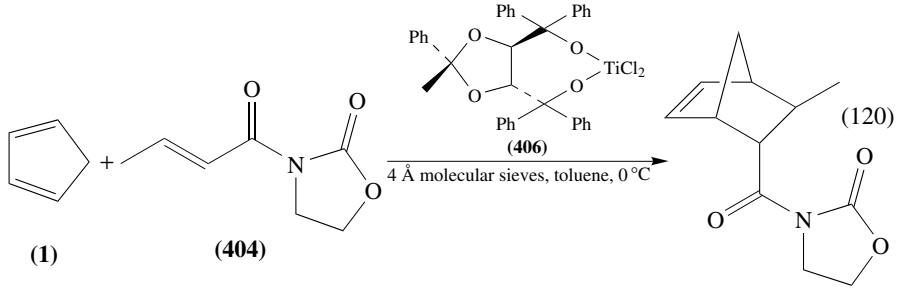
(**1**)

(**402a**; R = H) (**403a**; R = H)

(**402b**; R = Me) (**403b**; R = Me)

(**402c**; R = CO_2Et) (**403c**; R = CO_2Et)

(119)



(**1**) (**404**)

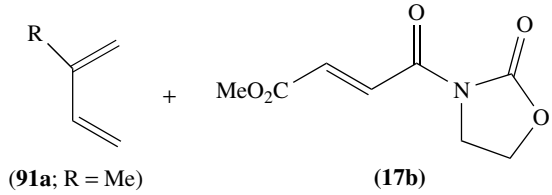
(120)

(2*S*-**405**; 91% ee)

The catalyst was prepared from the corresponding chiral diol and $TiCl_2(OPr\text{-}i)_2$ at room temperature in the presence of 4 Å molecular sieves. Without molecular sieves, stoichiometric amounts of the titanium complex were required to obtain an equally high enantioselectivity. A remarkable solvent effect was observed. Various cycloadducts were only obtained with high optical yields when non-polar solvents were employed[252,253]. For example, 4-substituted 4-cyclohexene-1,2-dicarboxylate derivatives **408** were obtained with ee values ranging from 91 to 94% in the reactions of **91a**, **399** and **407** with **17b** in toluene/
petroleum ether (equation 121).

Narasaka and Yamamoto applied catalyst **406** in the cycloaddition of 1-acetoxy-3-methyl-1,3-butadiene **(409)** to 3-boryl propenoic acid derivative **410** (equation 122). Cycloadduct **411** was employed in the total synthesis of (+)-paniculide[254].

Corey and colleagues studied the chiral induction of various analogs of **406** in which the phenyl groups on the tertiary carbinol unit were replaced by other aromatic groups. The use of 3,5-xylyl groups (catalyst **412**) gave the best results. Cycloadduct **413**, for example, was obtained with 95% ee in the presence of this catalyst[255].

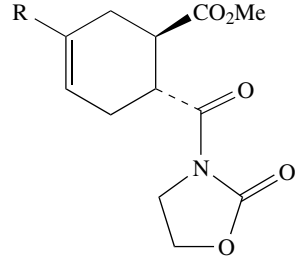


(**91a**; R = Me)
(**399**; R = H)
(**407**; R = SEt)

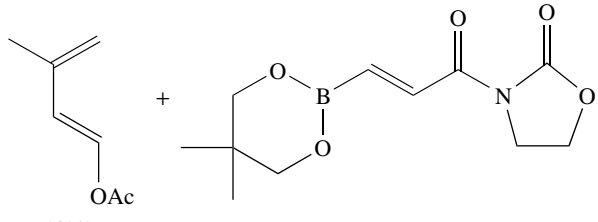
(**17b**)

4 Å mol. sieves,
toluene, petroleum ether **406**

(121)



(**408**; R = H, Me, SEt; 91–94% ee)

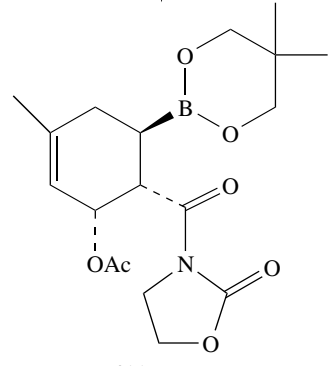


(**409**)

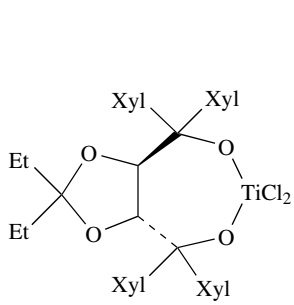
(**410**)

4 Å mol. sieves, RT **406**

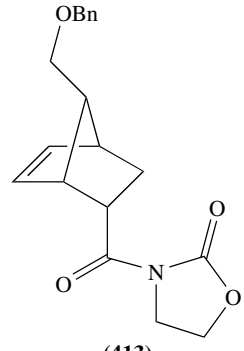
(122)



(**411**; 94% ee)

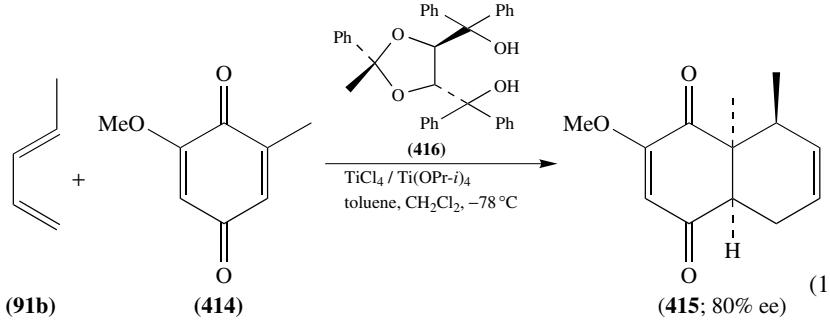


(412)



(413)

Engler and colleagues[256] demonstrated that the way in which catalyst **406** is prepared has a strong effect on the regioselectivity and enantioselectivity of quinone Diels–Alder reactions. The most effective catalyst was prepared from a 1 : 1 : 1 mixture of titanium tetrachloride, titanium tetraisopropoxide and chiral diol **416**. The cycloadditions of 2-methoxy-1,4-benzoquinones such as **414** with simple dienes to give adducts like **415** proceeded with high yields and enantioselectivities of up to 80% ee using this catalytic system (equation 123).

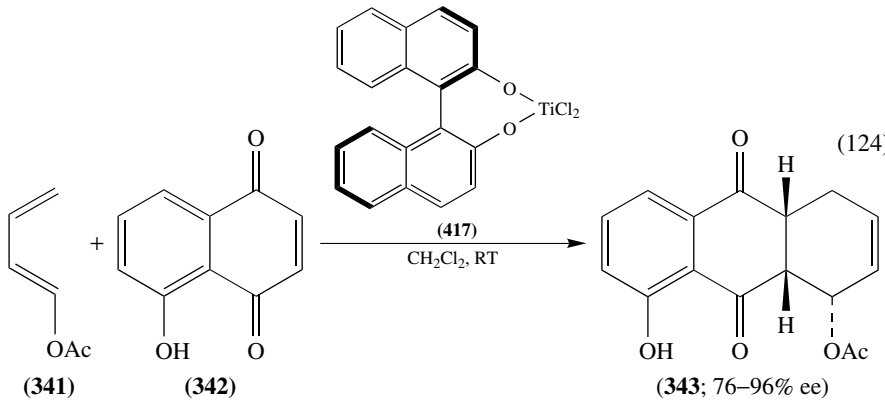


(91b) **(414)** **(415**; 80% ee) (123)

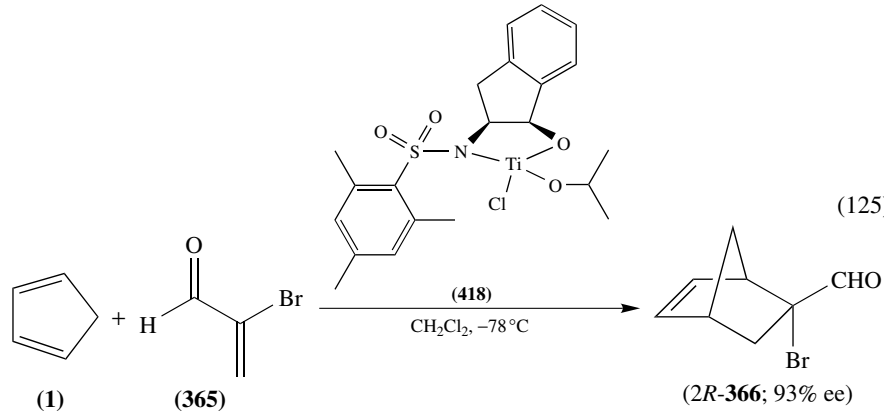
Binaphthol catalyst **417** proved effective in the cycloadditions of 1-alkoxy-1,3-butadienes with methacrolein and 1,4-naphthoquinone[257]. More recently, it was found that the use of molecular sieves was essential for the *in situ* preparation of the catalyst, but also that this had dramatic effects on the enantioselectivity[258]. In the presence of molecular sieves, the cycloaddition of juglone **(342)** with 1-acetoxy-1,3-butadiene was catalyzed by 10 mol% of **417** to give cycloadduct **343** with only 9% ee. In the absence of molecular sieves, the enantiomeric excess increased to 76–96% (equation 124).

Monochlorotitanium complex **418**, prepared from (1*R*,2*S*)-*N*-(2,4,6-trimethylbenzenesulfonyl)-2-amino-1-indanol and titanium tetraisopropoxide followed by treatment with titanium tetrachloride effectively catalyzed the cycloaddition of α-bromoacrolein to cyclopentadiene, affording **366** with 93% ee (equation 125)[259]. Catalyst **418** induced an ee of 90% in the reaction of isoprene with α-bromoacrolein.

Yamamoto and colleagues prepared chiral titanium catalyst **420** from titanium tetraisopropoxide and chiral binaphthol **419** (equation 126). This catalyst gave high asymmetric inductions in various Diels–Alder reactions of α,β-unsaturated aldehydes with cyclopentadiene and 1,3-cyclohexadiene[260].



(124)



(125)

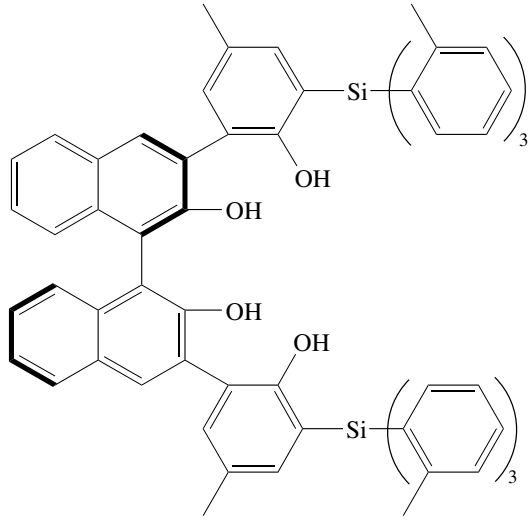
Chiral metallocene complex [(*S*)-1,2-ethylenebis(η^5-tetrahydroindenoyl)]Ti(OTf)$_2$ **422a** and its zirconium analog **422b** efficiently catalyzed the cycloadditions of 1,3-oxazolidin-2-one based dienophiles **17a** and **404** with cyclopentadiene which gave **421** and **405**, respectively[261]. The *endo* selectivity was highest in dichloromethane, whereas the enantioselectivity was higher in nitroalkane solvents (equation 127, Table 24).

4. Chiral copper(II) catalysts

Evans and coworkers[262] demonstrated the utility of bis(oxazolidine)copper(II) complexes **425** as Lewis acid catalysts in Diels–Alder reactions of *N*-enoyl-1,3-oxazolidin-2-ones **423** with cyclopentadiene, which gave adducts **424** (equation 128, Table 25). Their best results were obtained using catalyst **425c**. Surprisingly, only 30% ee was obtained in the reaction between cyclopentadiene and **17a** when catalyzed by **425a**. Similar results were obtained for the thiazolidine-2-thione analogs of the *N*-enoyl-1,3-oxazolidin-2-ones.

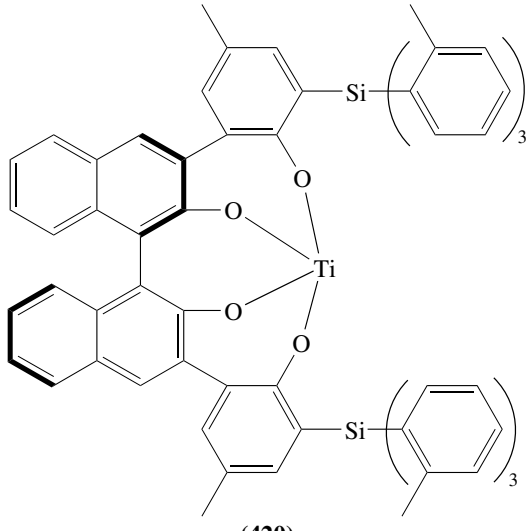
The enantioselectivities observed were rationalized by the transition state depicted in Figure 7. Copper(II) has a high propensity for 4-co-ordinacy. In this case, two co-ordination sites are occupied by the bidentate ligand, the substrate binding to the two remaining binding sites. Cyclopentadiene approaches the dienophile from the side opposite

to the *t*-butyl group. The transition state model was supported by results from stereodifferentiating experiments using chiral (*R*)- and (*S*)-1,3-oxazolidin-2-ones[262,263].



(419)

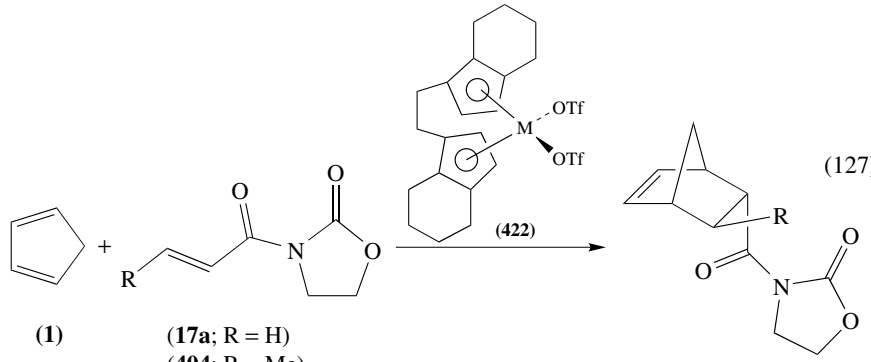
azeotropic removal of *i*-PrOH, $Ti(OPr\text{-}i)_4$, CH_2Cl_2 (126)



(420)

Afterwards, the authors found that catalyst **426** with SbF_6^- as the counterion demonstrated higher inductions in the reactions of substituted *N*-acryloyl-1,3-oxazolidin-2-ones

428 with several dienes, e.g. with cyclopentadiene to form **429** (equation 129, Table 26)[264]. This counterion effect had already been observed in the utilization of tridentate bis(oxazolidinyl)pyridine based copper(II) complexes **427** in Diels–Alder reactions of α-substituted acroleins. Catalyst **427d**, for example, proved about 20 times more reactive and induced higher ee values than catalyst **427a** (equation 130, Table 27)[264,265]. Catalysts **425c** and **427** were compared with their Zn(II) analogs[265]. It was concluded that they are superior to their Zn(II) counterparts as chiral Lewis acids in the Diels–Alder reactions of cyclopentadiene with substituted *N*-acryloyl-1,3-oxazolidin-2-ones.



(127)

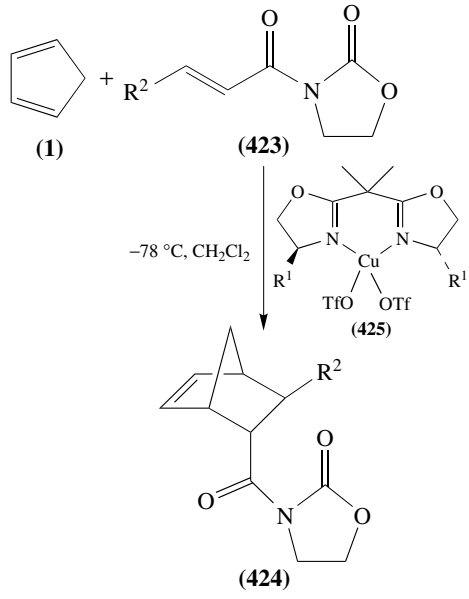
(1) (**17a**; R = H) (**404**; R = Me) (2*R*-**421**; R = H) (2*R*-**405**; R = Me)

TABLE 24. Reaction data for equation 127

Entry	M (mol%)	Catalyst	R	Solvent	T (°C)	*endo/exo*	% ee
1	Ti (10)	**422a**	H	CH_2Cl_2	0	90/10	0
2	Ti (10)	**422a**	H	CH_3NO_2	0	88/12	88
3	Ti (5)	**422a**	H	CH_3NO_2	−30	88/12	89
4	Zr (1)	**422b**	H	CH_2Cl_2	−78	97/3	30
5	Zr (5)	**422b**	H	$(CH_3)_2CHNO_2$	−78	86/14	92
6	Zr (5)	**422b**	Me	$(CH_3)_2CHNO_2$	−78	94/6	95

Davies and colleagues[266] studied the use of copper(II) complexes of chiral bis(oxazolidine) **430** as catalysts in the cycloadditions of cyclopentadiene to substituted *N*-acryloyl-1,3-oxazolidin-2-ones. They observed high *endo* and enantioselectivities. Again, the highest enantioselectivities were observed using SbF_6^- as the counterion, although differences were small this time: ee values of 92 and 95% were obtained for the triflate and SbF_6^- based catalysts, respectively.

The effect of the ligand bite angle on the enantioselectivity in the copper(II) catalyzed Diels–Alder reaction of cyclopentadiene with *N*-acryloyl-1,3-oxazolidin-2-one was studied using *spiro* bis(oxazolidine) based complexes **431a–d** (Table 28)[267,268]. The data show that the enantioselectivity and *endo* selectivity increase with increasing bite angle θ which is related to the angle Φ and n. Substitution of the dimethyl moiety on **430** with a cyclopropyl moiety **(431a)** induced an increase in enantioselectivity, which is in agreement with the expected increase in bite angle.



(128)

TABLE 25. Reaction data for equation 128

Entry	R^1	Catalyst	R^2	Dienophile	Adduct	*endo/exo*	% ee
1	Ph	**425a**	H	**17a**	**421**	—	30
2	*i*-Pr	**425b**	H	**17a**	**421**	—	58
3	*t*-Bu	**425c**	H	**17a**	**421**	—	98
4	*t*-Bu	**425c**	Me	**404**	**405**	96/4	97
5	*t*-Bu	**425c**	CO_2Et	**423a**	**424a**	94/6	95
6	*t*-Bu	**425c**	Ph	**423b**	**424b**	90/10	90

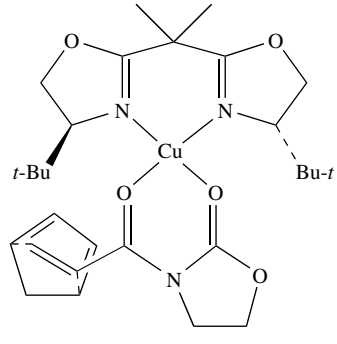
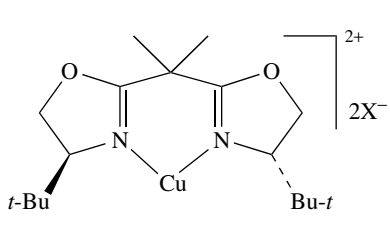
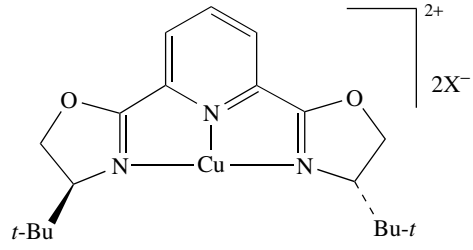


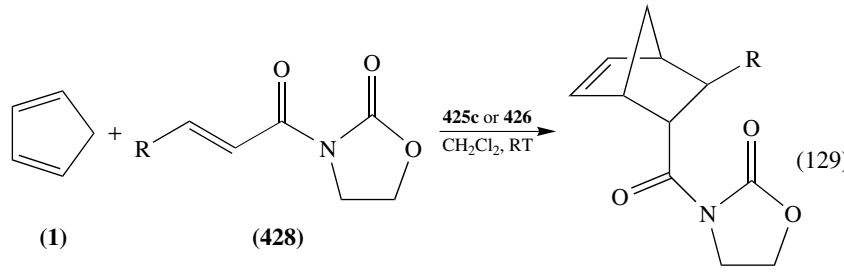
FIGURE 7. Transition state model for the reaction between cyclopentadiene and **17a** catalyzed by **425c**



(**425c**; X = OTf)
(**426**; X = SbF_6)



(**427a**; X = OTf)
(**427b**; X = BF_4)
(**427c**; X = PF_6)
(**427d**; X = SbF_6)



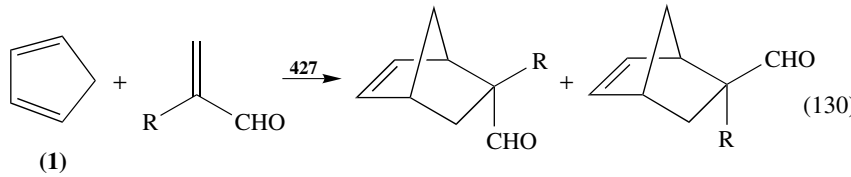
(129)

(1) **(428)** **(429)**

TABLE 26. Reaction data for equation 129

Entry	R	Dienophile	Catalyst	Time (h)	Yield (%)	% ee
1	Me	**404**	**425c**	8	95	94
2	Me	**404**	**426**	8	98	96
3	Ph	**423b**	**425c**	24	85	99
4	Ph	**423b**	**426**	24	96	96
5	Cl	**428**	**425c**	24	10	53
6	Cl	**428**	**426**	24	96	95

Ghosh and coworkers[269] reported high enantioselectivities using catalyst **432** in the cycloadditions of cyclopentadiene to several *N*-enoyl-1,3-oxazolidin-2-ones (equation 131). Recently, complex **425c** was successfully applied in the cycloaddition of *N*-acryloyl-1,3-oxazolidin-2-one to furan (equation 132)[270,271] and 1-acetoxy-2-methyl-1,3-butadiene[272].

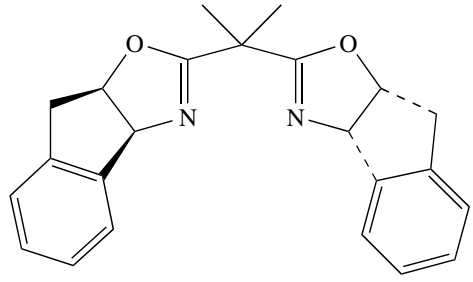


(130)

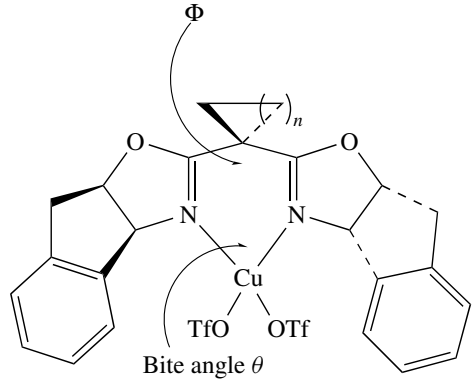
(1)

TABLE 27. Reaction data for equation 130

Entry	Catalyst	R	Dienophile	Time (h)	T (°C)	*endo/exo*	% ee (major)
1	**427a**	H	**390b**	116	−20	97/3	85
2	**427a**	Br	**365**	60	−40	3/97	87
3	**427a**	Me	**310**	120	−20	4/96	85
4	**427d**	H	**390b**	18	−20	94/6	85
5	**427d**	Br	**365**	12	−78	2/98	96
6	**427d**	Me	**310**	8	−40	3/97	92



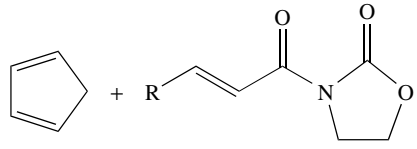
(430)



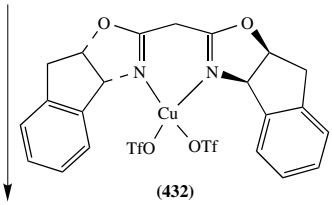
(**431a**; $n = 1$)
(**431b**; $n = 2$)
(**431c**; $n = 3$)
(**431d**; $n = 4$)

TABLE 28. Influence of bite angle θ of catalyst **431** on the *endo* selectivity and enantioselectivity of the cycloaddition reaction between cyclopentadiene and *N*-acryloyl-1,3-oxazolidin-2-one

Entry	Complex	ϕ (°)	*endo/exo*	% ee (*endo*)
1	**431a**	110.6	98/2	96.3
2	**431b**	108.0	97/3	92.0
3	**431c**	105.8	97/3	89.5
4	**431d**	103.7	96/4	83.0
5	**430.Cu(OTf)$_2$**	104.7	98/2	82.5

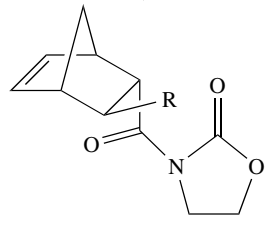


(1) (**17a**; R = H)
(**404**; R = Me)
(**423a**; R = CO_2Et)

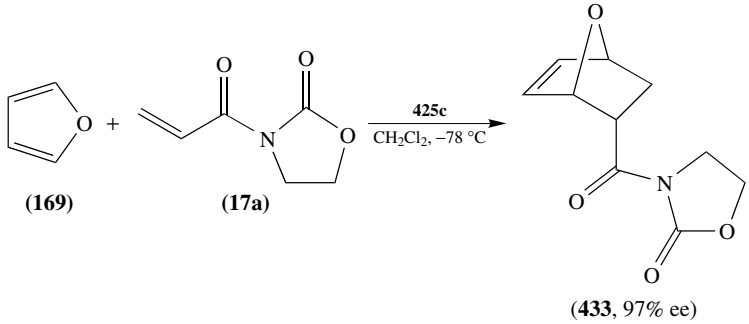


(432)

(131)



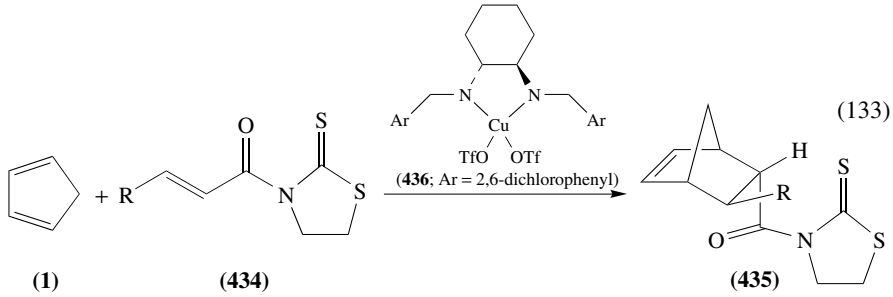
(*R*-**421**; R = H, 99% ee)
(*R*-**405**; R = Me, 84% ee)
(*S*-**424a**; R = CO_2Et, 94% ee)



(169) **(17a)** **(433**, 97% ee)

(132)

Evans and colleagues[263] demonstrated the effectiveness of copper(II) catalyst **436** in the Diels–Alder reactions of cyclopentadiene with several *N*-enoyl-1,3-oxazolidin-2-ones and their dithio analogs **434** (equation 133). The adducts **435** were obtained with good yields (83–98%) and high ee values (83–94%).



(133)

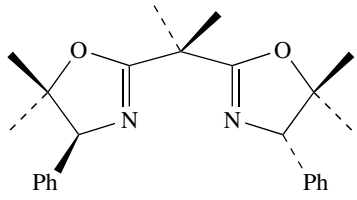
(1) **(434)** **(435)**

Copper(II) complexes of amino acids have been explored as chiral Lewis acid catalysts in the Diels–Alder reaction of 3-phenyl-1-(2-pyridyl)-2-propen-1-one with cyclopentadiene. The best results were obtained using *N*-methyl-*L*-tryptophan, but more interestingly, the highest ee values for the major *endo* adduct were achieved in aqueous solution[273].

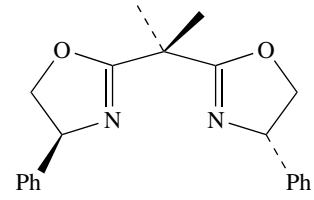
5. Other chiral Lewis acids

Chiral magnesium(II) Lewis acids with chiral bis(oxazolidine) ligands **437** and **438** induced high enantioselectivities in the cycloaddition reactions of cyclopentadiene with several β-substituted *N*-acryloyl-1,3-oxazolidin-2-ones[274]. Interestingly, the enantioselectivities observed when employing the catalyst derived from **437** were opposite to those observed when employing the corresponding Cu(II) catalyst. Moderate to high enantioselectivities in the same cycloadditions were obtained using a magnesium(II) complex derived from oxazolidine **439**[275] and several other magnesium(II) catalysts[276,277] derived from ligands **438** and **440**. Recently, the magnesium triflate and magnesium perchlorate complexes of ligands **438, 441** and **442** were examined in the presence and absence of achiral auxiliaries (water, tetramethylurea), which can co-ordinate to the Lewis acid. Interestingly, the magnesium perchlorate based intermediates were tetrahedral in the absence of an achiral auxiliary, but became octahedral after the addition of two equivalents of the achiral ligand. The reaction of cyclopentadiene with *N*-acryloyl-1,3-oxazolidin-2-one afforded *endo* (2*S*)-**421** in the absence of an achiral auxiliary, and *endo* (2*R*)-**421** in the presence of an achiral auxiliary. Thus, by tuning the chiral ligand and achiral auxiliary, both enantiomers were obtained with ee values of more than 90%[278].

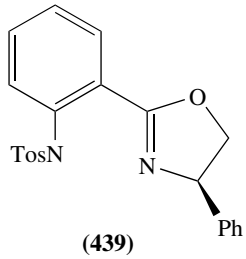
Takacs and colleagues[279] investigated a series of zinc, magnesium and copper catalysts of 1,2- 1,3- and 1,4-bis(oxazolidine) ligands **443–445** in the reaction of cyclopentadiene with *N*-acryloyl-1,3-oxazolidin-2-one. It was demonstrated that the different metal catalysts required different distances between the oxazolidine moieties to induce the highest enantioselectivities. Ligand **445**, a 1,4-bis(oxazolidine), proved best for zinc triflate, whereas 1,3-bis(oxazolidine) ligand **444** gave the best results with magnesium triflate and copper triflate. On account of these results, five chiral 1,4-bis(oxazolidine) ligands, each bearing a bicyclic backbone, were examined in the zinc and copper triflate catalyzed Diels–Alder reaction between cyclopentadiene and *N*-acryloyl-1,3-oxazolidin-2-one. At room temperature, ee values of up to 80% were achieved. Surprisingly, the non-C_2-symmetric bis(oxazolidine) **446**, bearing a *meso* backbone, belonged to the more efficient ligands[280].



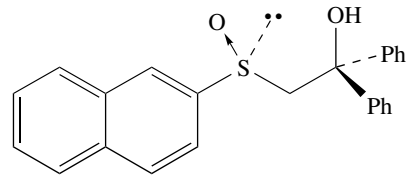
(437)



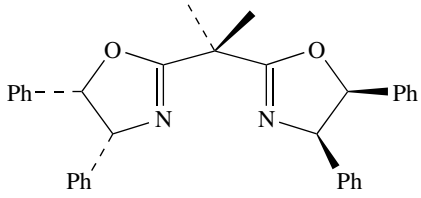
(438)



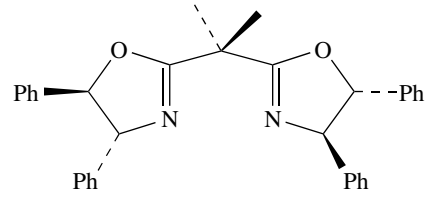
(439)



(440)



(441)



(442)

The cationic aqua complexes of the C_2-symmetric *trans*-chelating tridentate ligand **447** proved also highly effective chiral catalysts. The complexes involving the metal(II) perchlorates of iron, cobalt, nickel, copper and zinc produced the main *endo* adduct of cyclopentadiene and *N*-acryloyl-1,3-oxazolidin-2-one with very high ee values[281].

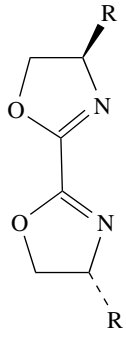
The Diels–Alder reaction of ethyl 2-benzoylacrylate **(450)** with cyclopentadiene was effectively catalyzed by magnesium(II) complexes of bis(oxazolidine) **448** and oxazolidine **449** (equation 134). When the catalysts were prepared in refluxing acetonitrile, adduct **451** was obtained with virtually complete *endo* selectivity for the ethoxycarbonyl group and up to 87% ee[282].

High ee values were achieved in the cycloadditions of α-bromoacrolein to various dienes using iron catalyst **452**[283].

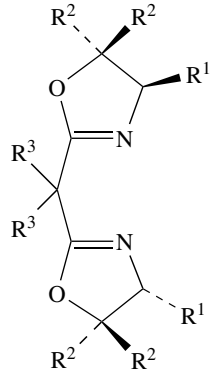
Chiral rhodium[284] and ruthenium catalysts[285,286] have been reported to catalyze the Diels–Alder reaction of methacrolein with cyclopentadiene. Several bis(oxazolidine) and 2-pyridyl-1,3-oxazolidine ligands were used as chiral ligands. The adducts were obtained with only moderate enantioselectivities.

Recently, a palladium(II) complex with a chiral (*S*)-BINAP ligand was shown to induce an excellent enantioselectivity in the model reaction of *N*-acryloyl-1,3-oxazolidin-2-one with cyclopentadiene[88].

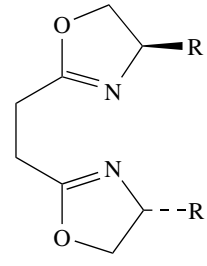
Several chiral lanthanide(III) Lewis acid catalysts, derived from chiral binaphthols, have been used in the cycloaddition reactions of cyclopentadiene with substituted *N*-acryloyl-1,3-oxazolidin-2-ones. A catalyst derived from ytterbium triflate, (*R*)-binaphthol



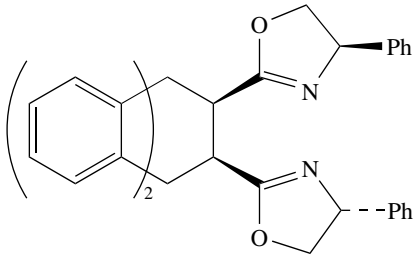
(**443**)



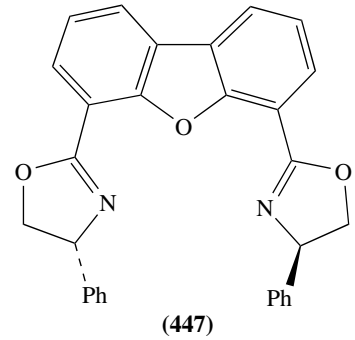
(**444**)



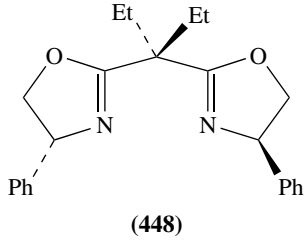
(**445**)



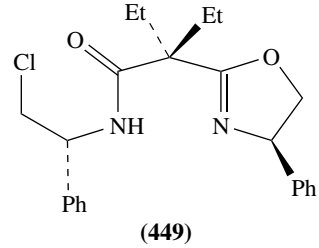
(**446**)



(**447**)



(**448**)

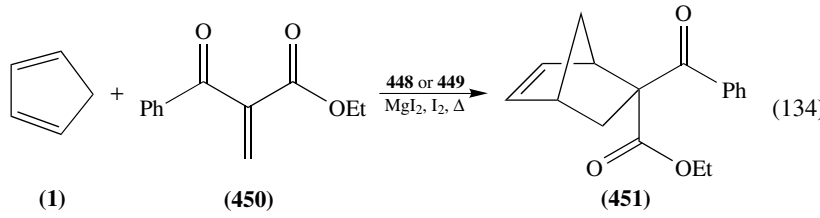


(**449**)

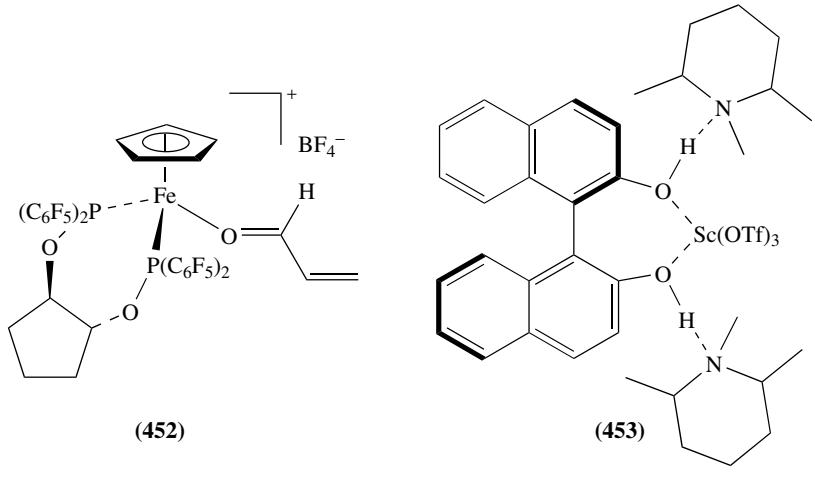
R, R^1 = Bn, $CHPh_2$, Ph, *t*-Bu
R^2, R^3 = H, Me

and *cis*-1,2,6-trimethylpiperidine demonstrated high chiral inductions[287]. The analogous scandium catalyst **453**, the structure of which has been proposed on account of spectroscopic data, also demonstrated high ee values in these cycloadditions[288].

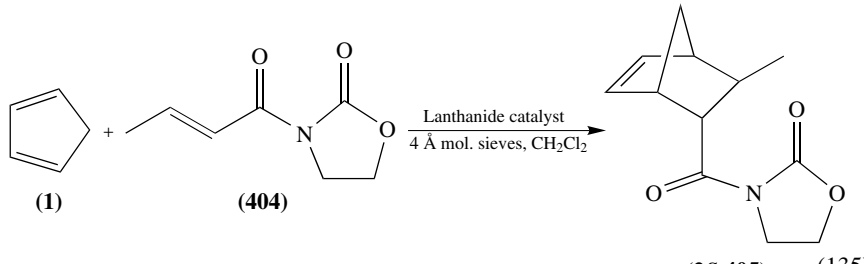
Kobayashi and colleagues[289] showed that the selectivity of other lanthanide (Ln) triflates diminished with the increase of the ionic radius, as has been illustrated in Table 29 (equation 135). It was also found that the activity of the catalysts in solution diminished in time and with increasing temperature. Aging was prevented in the presence of the



(1) (450) (451) (134)



(452) (453)



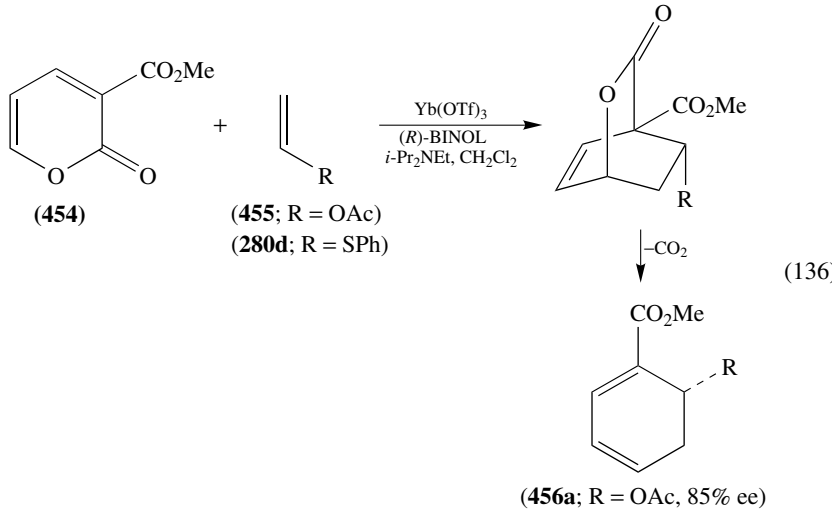
(1) (404) (2*S*-**405**) (135)

TABLE 29. Reaction data for equation 135

Entry	Ln	Ionic radius (Ln^{+3}) (pm)	Yield (%)	*endo/exo*	% ee *(endo)*
1	Lu	85	60	89/11	93
2	Yb	85.8	77	89/11	93
3	Tm	87	46	86/14	75
4	Er	88.1	24	83/17	69
5	Ho	89.4	12	73/27	25
6	Y	89.3	6	70/30	20
7	Gd	93.8	0	—	—

dienophile. Interestingly, the enantioselectivity was reversed by adding diketonic achiral ligands like acetylacetone and 3-phenylacetylacetone to the reaction mixture.

An ytterbium binaphthol catalyst was successfully applied in the cycloaddition reactions of 3-carbomethoxy-2-pyrone **(454)** with *O*- and *S*-substituted olefins like **455** and **280d**. Upon heating, the products lost carbon dioxide to yield chiral cyclohexadienes **456** (equation 136). *S*-substituted olefins generally gave higher ee values than the corresponding *O*-substituted ones.



(136)

IV. [6 + 4] CYCLOADDITION REACTIONS

Thermally allowed [6 + 4] cycloadditions offer the attractive features of high stereoselectivity and rapid increase of molecular complexity. The limiting feature of many higher-order processes, however, is a lack of periselectivity that translates directly into the relatively low chemical yields of the desired cycloadducts.

Due to the high conformational demands which are imposed on higher-order cycloadditions, fulvenes, heptafulvenes and tropones have been mostly applied in uncatalyzed [6 + 4] cycloadditions. The scope of metal-promoted cycloadditions, however, is much broader due to the preorganized orientation of the reactants which are both co-ordinated to the metal center.

Fulvenes can participate as either 6π or 2π reactants in reactions with dienes. The controlling orbitals in the reaction of a fulvene with an electron-deficient diene are the fulvene HOMO, having a nodal plane through the exocyclic double bond, and the diene LUMO (Figure 8). This dictates the participation of fulvenes merely as 2π partners. When an electron-donating substituent is present at C(6), however, the NHOMO (Next Highest Occupied Molecular Orbital) energy (Figure 8) is raised sufficiently to permit a [6 + 4] cycloaddition to prevail[291]. LUMO controlled reactions with electron-rich dienes will produce [6 + 4] adducts because of the large LUMO coefficients at C(2) and C(6).

These phenomena can be illustrated by the cycloaddition reactions of fulvenes with electron-deficient α-pyrones. In general, the Diels–Alder reactions of electron-deficient dienes such as **458** with 6-alkyl substituted fulvenes favor addition across one of the endocyclic

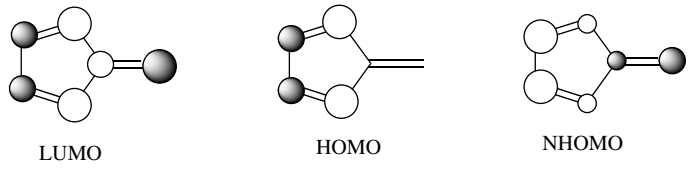
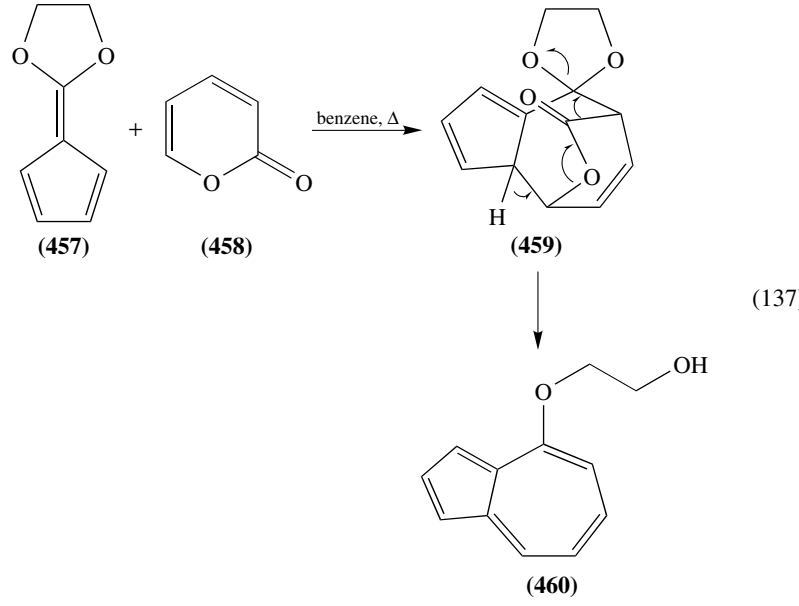


FIGURE 8. Relative frontier orbital coefficients of fulvene

double bonds of the fulvene unit to yield the [4 + 2] adduct[292]. When **458** was reacted with electron-rich fulvene acetal **457**, however, [6 + 4] cycloadduct **460** was obtained in 54% yield by elimination of carbon dioxide from the intermediate cycloadduct **459** (equation 137)[293].

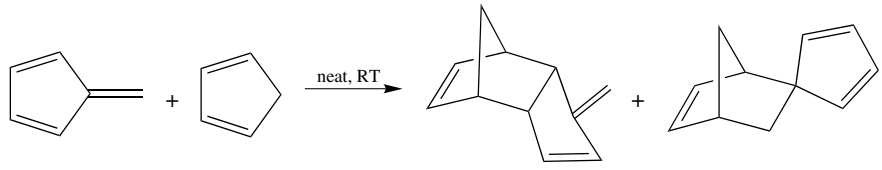


(137)

Niggli and Neuenschwander[294] studied the reaction of fulvene **(461)** with cyclopentadiene. The main product fraction consisted of three 1 : 1 adducts, as illustrated in equation 138. Diels–Alder Adducts **462** and **463** resulted from attack of cyclopentadiene at the endocyclic and exocyclic double bonds of fulvene, respectively. The formation of **464** was rationalized by a [6 + 4] cycloaddition reaction followed by two [1,5] hydrogen shifts. It was stated that due to the absence of electron-donating and electron-withdrawing groups on both triene and diene, fulvene may have reacted via its HOMO as well as its LUMO.

Liu and colleagues[295,296] studied the cycloaddition reactions between electron-deficient 8,8-disubstituted heptafulvenes **466** and electron-rich 6,6-disubstituted fulvenes. The substituted heptafulvene reacted as the trienophile in this case. Only when 6,6-dimethylfulvene **(465)** and heptafulvenes **466a–b** were used as the triene and trienophiles, respectively,

and the reactions were performed at ambient temperature, were [6 + 4] cycloadducts **467** and **470** obtained along with [8 + 2] cycloadducts **468** and **469b** (equation 139). At higher temperatures, the [8 + 2] and [4 + 2] adducts were the only adducts isolated. When 8,8-diphenylfulvene was used, no [6 + 4] adducts were isolated, even when the reaction was performed at room temperature. This is probably due to insurmountable steric hindrance in the transition state. The reaction produced predominantly [8 + 2] and [4 + 2] adducts, the latter becoming more significant at higher reaction temperatures.



(461) **(1)** (**462**; 47) (**463**; 41) (138)

(**464**; 13)

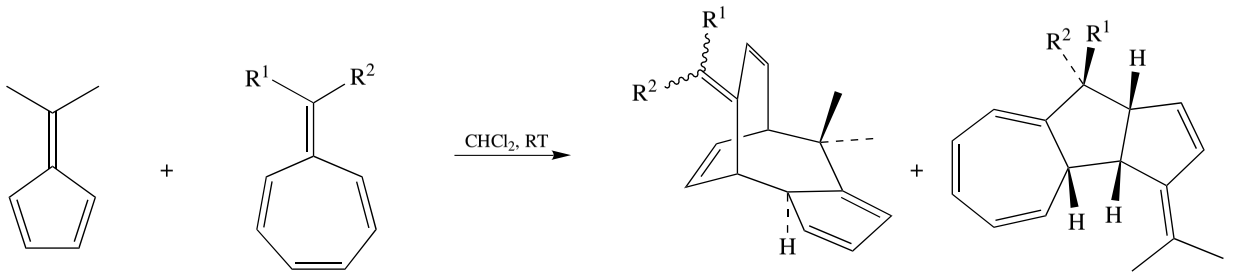
[6 + 4] Cycloaddition reactions using tropone or another cyclic triene as the 6π partner have been abundantly described in the literature. It has been found that virtually all metal-free [6 + 4] cycloadditions of cyclic trienes afford predominantly *exo* adducts. This has been rationalized by consideration of the HOMO–LUMO interactions between the diene and triene partners. An unfavorable repulsive secondary orbital interaction between the remaining lobes of the diene HOMO and those of the triene LUMO develops during an *endo* approach. The *exo* transition state is devoid of this interaction (Figure 9).

The periselectivity of the tropone–diene cycloaddition is dependent on the reaction temperature. The *exo* [6 + 4] cycloadduct is considered to be the *kinetic* product, the *endo* [4 + 2] cycloadduct being the *thermodynamic* product[291].

Mahon and colleagues[297] studied the cycloaddition reactions of substituted *cis*-1,2-isopropylidenedioxycyclohexadienes. The reaction of tropone **(471)** with cyclohexadiene **472**, for example, afforded the expected *exo* cycloadduct **473** with good yield (equation 140).

Hisano and coworkers[298] prepared tricycle **476** by reaction of cyclopentadienone **475** with cyclooctatetraene **(474)** in refluxing benzene (equation 141). Cyclized [4 + 2] cycloadduct **477** was isolated as a by-product.

Takeshita and colleagues[299] studied the reactions of 3-bromo-1,5-azulenequinone **(478)** and 3-bromo-1,7-azulenequinone **(484)** with benzo[*c*]furan **(479)** and 1,3-diphenylbenzo [*c*]furan **(485)** by analogy with the reactions previously described by Scott and Adams[300]. The reaction of **478** with **479** afforded a mixture of four cycloadducts (equation 142), three stereoisomeric [2 + 4]/[6 + 4] tandem adducts **(480–482)** and one [2 + 4]/[2 + 4]/[6 + 4] triple adduct **(483)**. No mono adduct was isolated, indicative of a fast follow-up cycloaddition. The [6 + 4] cycloadditions all proceeded in an *exo* fashion, whereas the [4 + 2] cycloaddition proceeded in an *endo* fashion for **480** and **483**, and in an *exo* fashion for **481** and **482**. The reaction of **478** with **485** afforded a mixture of [4 + 2] adducts and [4 + 2]/[8 + 4] tandem adducts.



(**465**)

(**466a**; $R^1 = R^2 = CN$)
(**466b**; $R^1 = CN$, $R^2 = CO_2Me$)

(**467a**; 5)
(**467b**; 0)

(**468a**; 46)
(**468b**; 24)

(**470a**; 49)
(**470b**; 26)

(**469b**; 50)

(139)

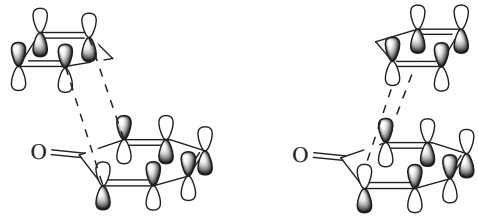
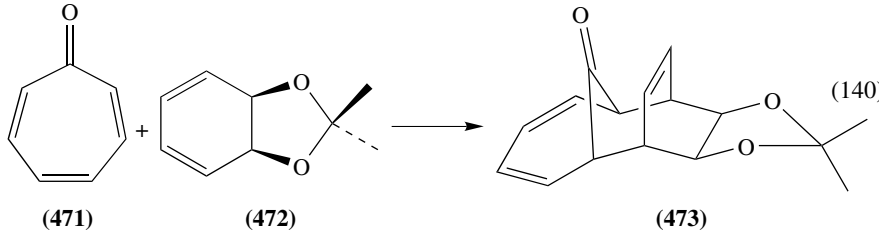
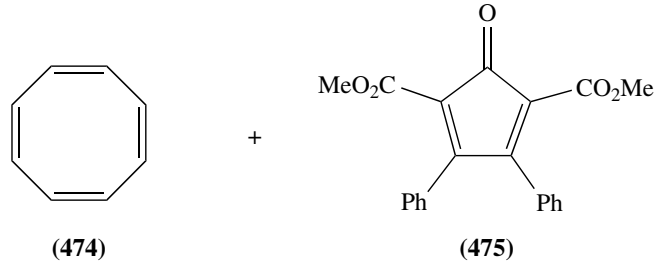


FIGURE 9. *Endo* and *exo* approach of cyclopentadiene to tropone

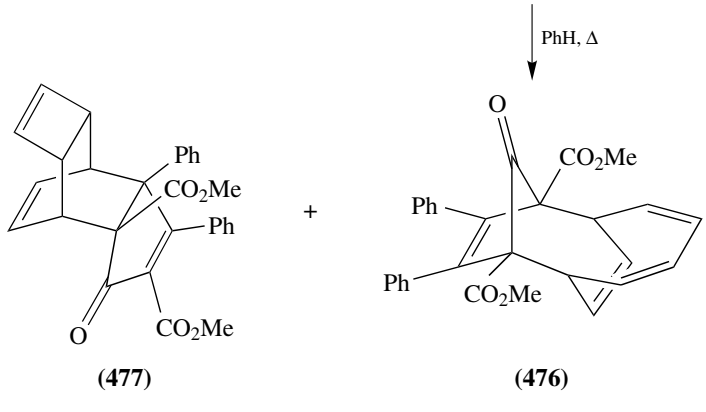


(140)

(471) **(472)** **(473)**

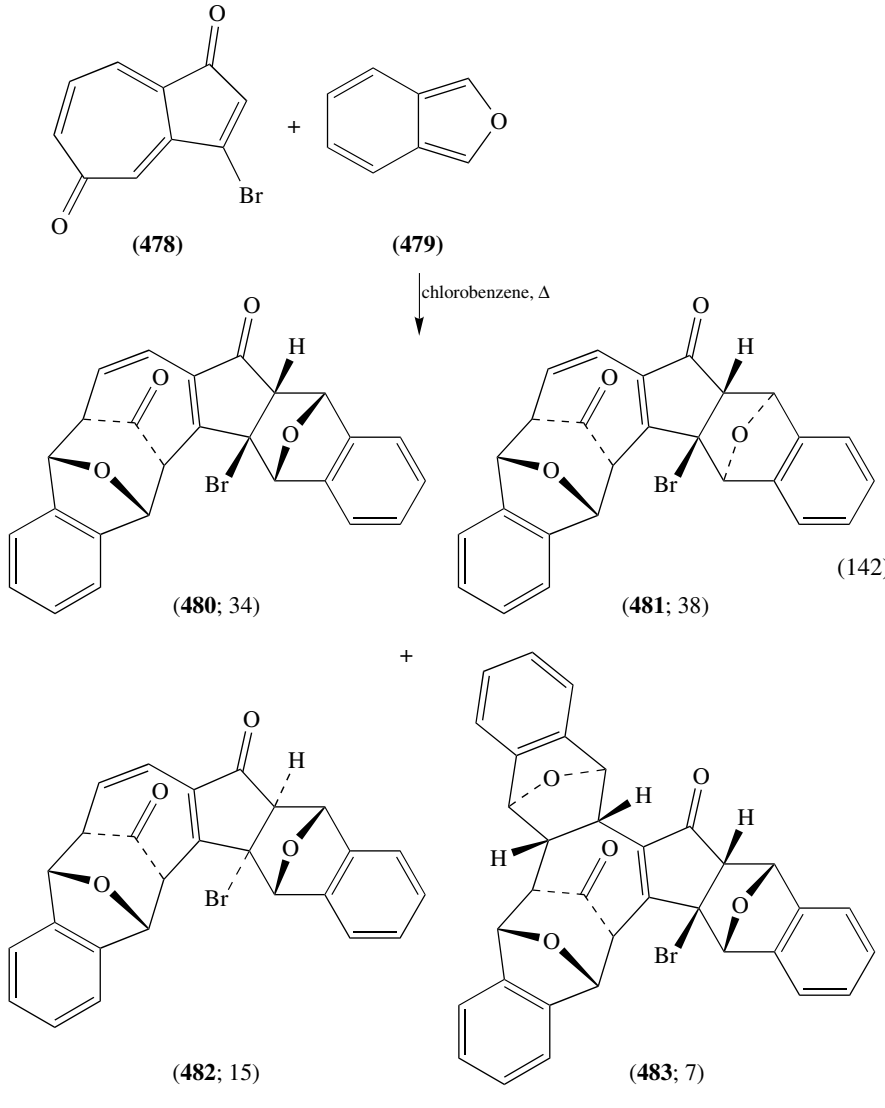


(474) **(475)**



(141)

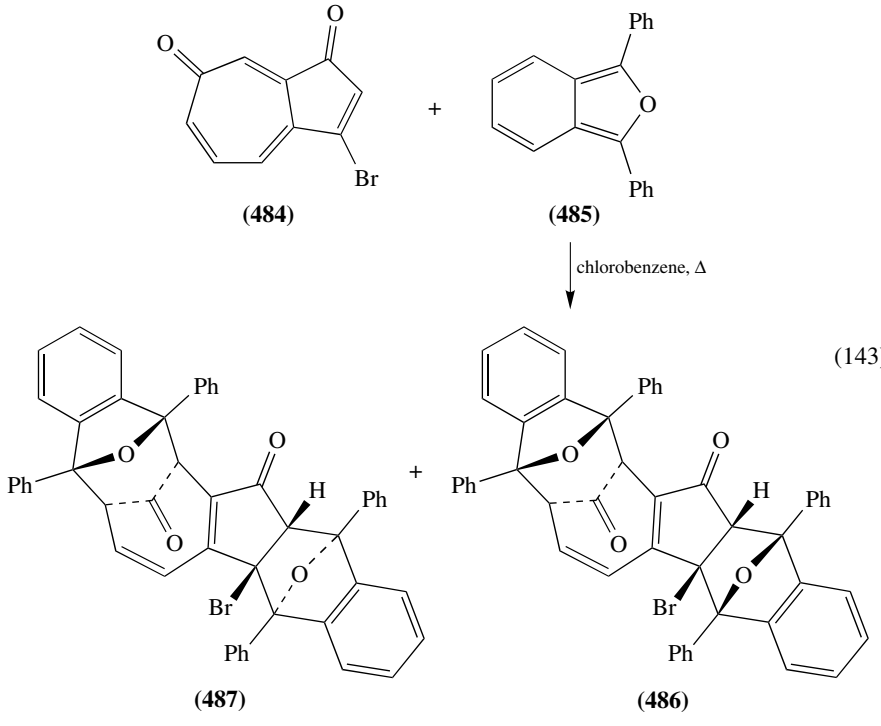
(477) **(476)**



The reactions of **484** with **479** and **485** produced two tandem [4 + 2]/[6 + 4] adducts in both cases. The [6 + 4] cycloadditions proceeded in an *exo* fashion. The Diels–Alder reaction proceeded in an *endo* fashion for **479**, whereas *endo* and *exo* Diels–Alder adducts **486** and **487** were observed for **485** (equation 143).

Gandolfi and coworkers[301] studied the periselectivity in the reactions of substituted cyclopentadienones with *N*-aryl-8-azaheptafulvenes. The reactions proved to produce mainly [6 + 4] cycloadducts, along with some [8 + 2] and [4 + 2] cycloadducts, as illustrated by the reaction between azaheptafulvene **488** and cyclopentadienone **489** which

afforded adducts **490**–**493** (equation 144). By means of cycloreversion experiments, Gandolfi and colleagues were able to determine that the formal [8 + 2] cycloadduct **491** was formed by a [3,3] sigmatropic rearrangement of the [6 + 4] adduct **490**.



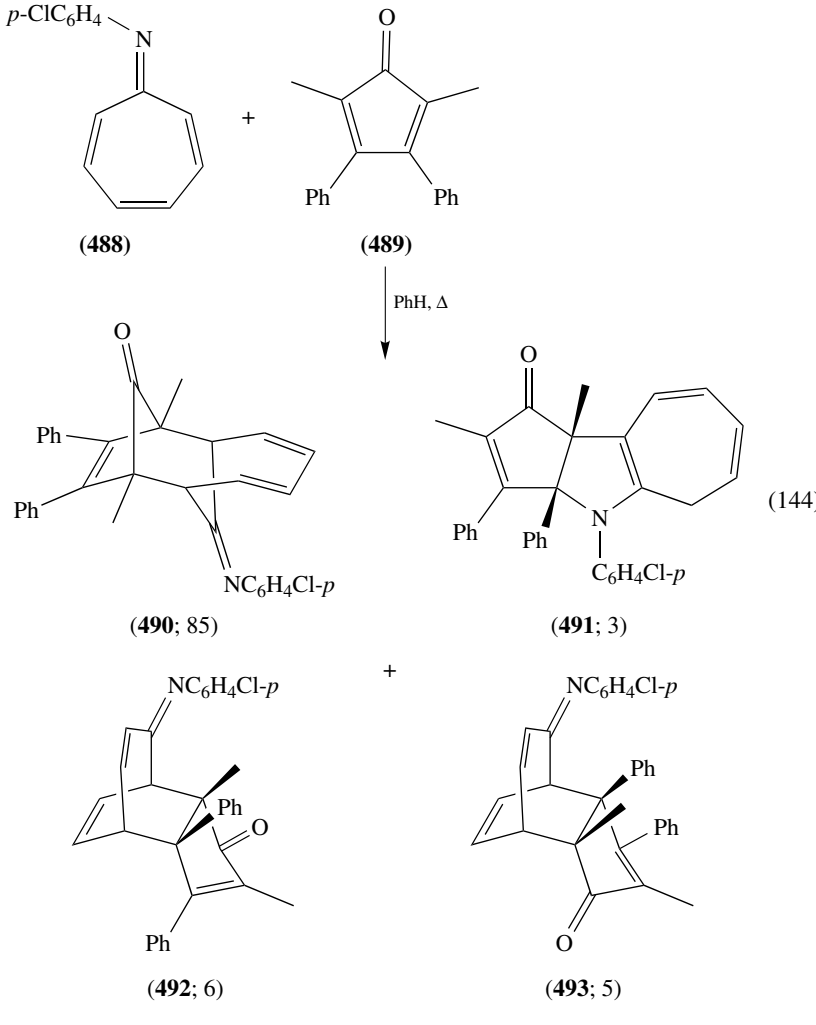
(143)

The use of transition metal templates represents a particularly intriguing strategy to selectively accomplish [6 + 4] cycloadditions, as was shown first in the Kreiter laboratories[302]. Chromium(0) has emerged as the metal of choice in this kind of cycloaddition reaction which is either thermally or photochemically activated[291].

Two mechanisms have been proposed which primarily differ in the way in which the initial co-ordinatively unsaturated intermediates are generated. In mechanism 1, a light-induced CO dissociation from **494** to **495** occurs, whereas a light-induced hapticity slippage from η^6 **(494)** to η^4 **(499)** occurs in mechanism 2 (equation 145). Co-ordination of a diene to **495** or **499** affords complexes **496** and **500**, respectively, which then undergo an intramolecular reaction to give **497** and **501**, respectively. Ring closure finally affords the complexed adduct **498**. Stufkens and coworkers[303] have demonstrated that mechanism 1 is the likely pathway for these processes in low-temperature matrices and in liquid noble gas solutions. Kreiter and colleagues[304] demonstrated that this mechanism also holds in THF at 203 K.

Rigby and coworkers obtained some conflicting results. When electron-rich dienes were employed, exposure of the reaction mixtures to a blanket of CO after photolysis led to increased yields, which is in support of mechanism 1 (the **497** to **498** step).

When electron-deficient dienes were used, however, it proved that vigorously flushing the solution with an inert gas during photolysis resulted in higher reaction yields. This may indicate that the reaction can also proceed according to mechanism 2. A pathway according to **494** → **499** → **500** → **501** → **497** → **498** could then explain the positive effect of a CO blanket in the case of electron-rich dienes[305].

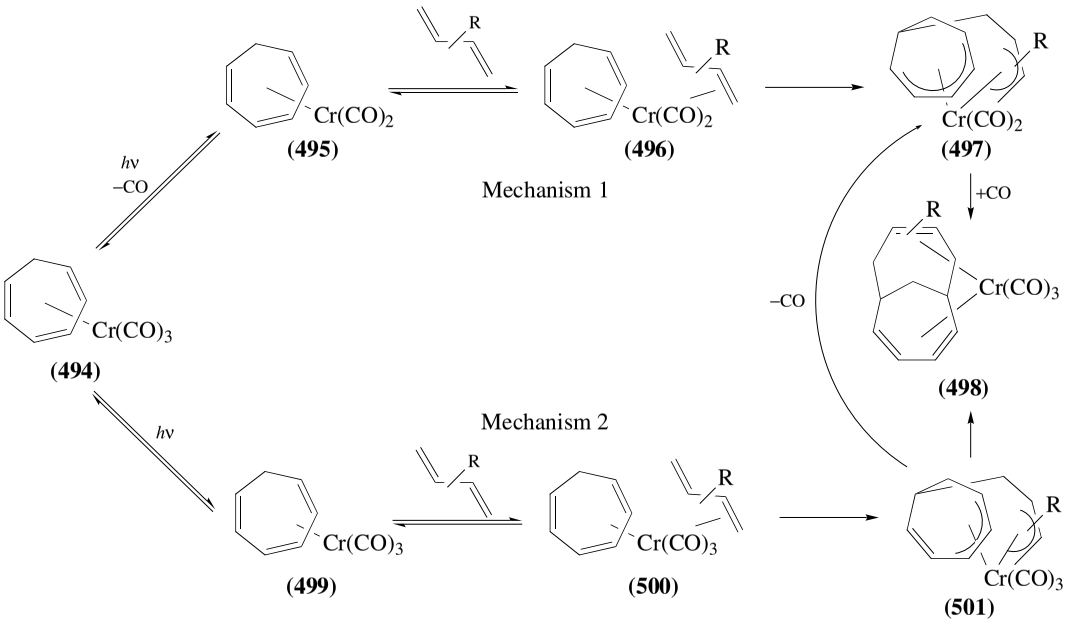


(**488**) (**489**)

(**490**; 85) (**491**; 3) (144)

(**492**; 6) (**493**; 5)

In concurrence with the thermal metal-free version, diastereoselection is virtually complete in the metal mediated cycloaddition. In contrast to thermal, metal-free [6 + 4] cycloaddition reactions, however, the metal mediated reactions of trienes are known to furnish exclusively *endo* products. This is in agreement with both mechanisms,

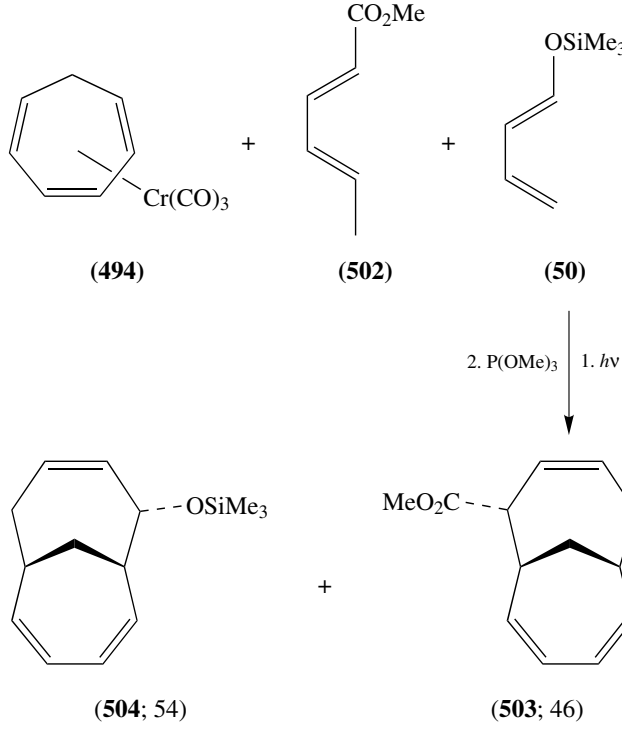

R
Cr(CO)2
(495)
R
Cr(CO)2
(496)
R
Cr(CO)2
(497)
hν
–CO
Mechanism 1
+CO
R
Cr(CO)3
(498)
–CO
Cr(CO)3
(494)
hν
Mechanism 2
R
Cr(CO)3
(499)
R
Cr(CO)3
(500)
R
Cr(CO)3
(501)

(145)

because neither **497** nor **501** is capable of accommodating an *exo* orientated diene component.

In contrast with the metal-free cycloaddition again, the efficiency of metal mediated cycloaddition reactions is relatively insensitive to the electronic nature of the reactants. This has been nicely demonstrated by Rigby and colleagues[305] who treated complex **494** with a 1 : 1 mixture of methyl sorbate **(502)** and 1-trimethylsilyloxy-1,3-butadiene **(50)**. The reaction proceeded in 90% yield and afforded **503** and **504** in a 46 : 54 ratio (equation 146).

Rigby and colleagues also demonstrated that the regioselectivities in the reactions of 1- and 2-substituted dienes with 1-substituted cycloheptatrienes, which do not proceed under metal-free conditions, were generally high. In the case of 1-substituted dienes, this may be completely attributed to steric hindrance. 2- And 3-substituted cycloheptatrienes hardly showed any regioselectivity[305].

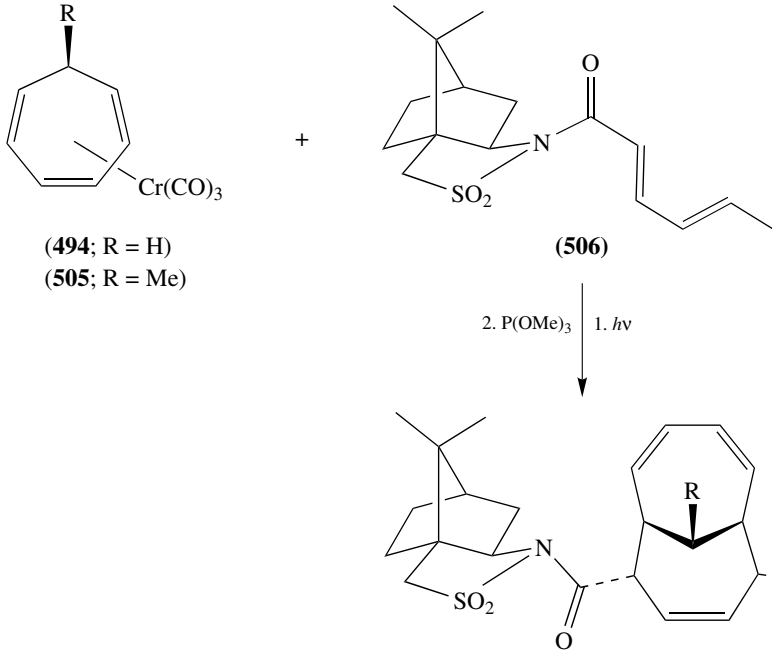


(146)

By attaching a chiral auxiliary to the diene unit, Rigby and colleagues[305] were able to obtain cycloadducts with high diastereomeric excesses. Their best results were obtained using chiral camphorsultam based sorbate **506**. The reaction with **494** afforded **507a** with 74% yield and 84% de (equation 147). The analogous reaction using **505** as the triene component afforded **507b** (equation 147) with 75% yield and 75% de. Adduct **507b** was used to prepare the C5–C11 segment of streptovaricin D[306].

A diastereoselectivity of 85% was obtained in the reaction of **494** with chiral diene **508** (equation 148)[307]. This reaction showed once again the high reactivity of two unactivated reactants toward cycloaddition in the presence of chromium(0). Cycloadduct **509** was considered to be a model precursor for the convergent synthesis of the unusual sesterpene cerorubenol **(510)**.

When the reactions of **494** with some dienes were carried out under thermal conditions, the adducts were obtained metal-free. This suggested the possibility of effecting these transformations using a catalytic amount of an appropriate Cr(0) source. Rigby and colleagues showed that the reaction between cycloheptatriene **511** and 1-acetoxy-1,3-butadiene **(341)** can be catalyzed by employing a catalytic amount of **513** (equation 149). The yield of **512** was 36% in this instance, whereas a yield of 20% was obtained when a catalytic amount (10 mol%) of **494** was used as the catalyst[305,308].



(**494**; R = H)
(**505**; R = Me)

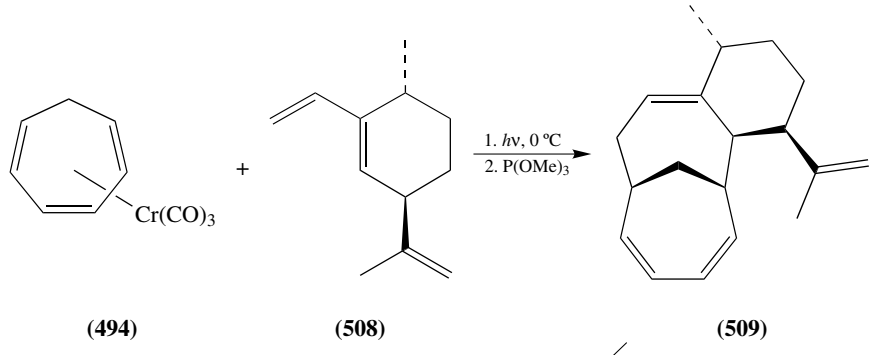
(506)

(147)

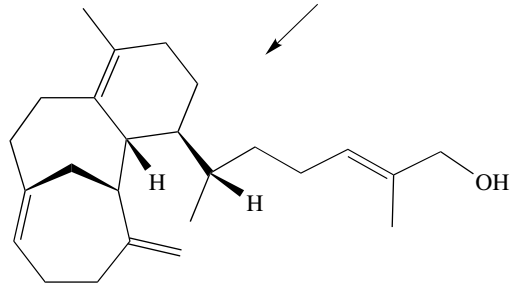
(**507a**; R = H)
(**507b**; R = Me)

Rigby and coworkers[305,309] also performed metal mediated [6 + 4] cycloadditions of heterocyclic trienes and tropones with various dienes. In concurrence with the all-carbon trienes, the electronic nature of the diene partners generally had little influence on the cycloaddition efficiency. The only reported exceptions are the reactions of thiepin-1,1-dioxides. Lower yields were observed in the reactions involving electron-deficient dienes in comparison with the reactions with electron-rich dienes. The reaction of complex **514**

with diene **50** to give **516,** for example, proceeded with a yield of 78%, whereas the reaction with diene **515** afforded adduct **517** with only 38% yield (equation 150).

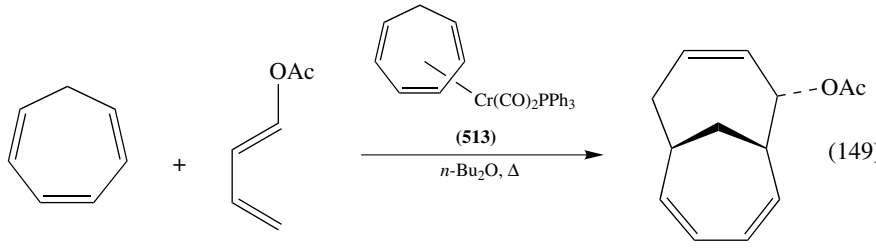


(494) **(508)** **(509)**



(510)

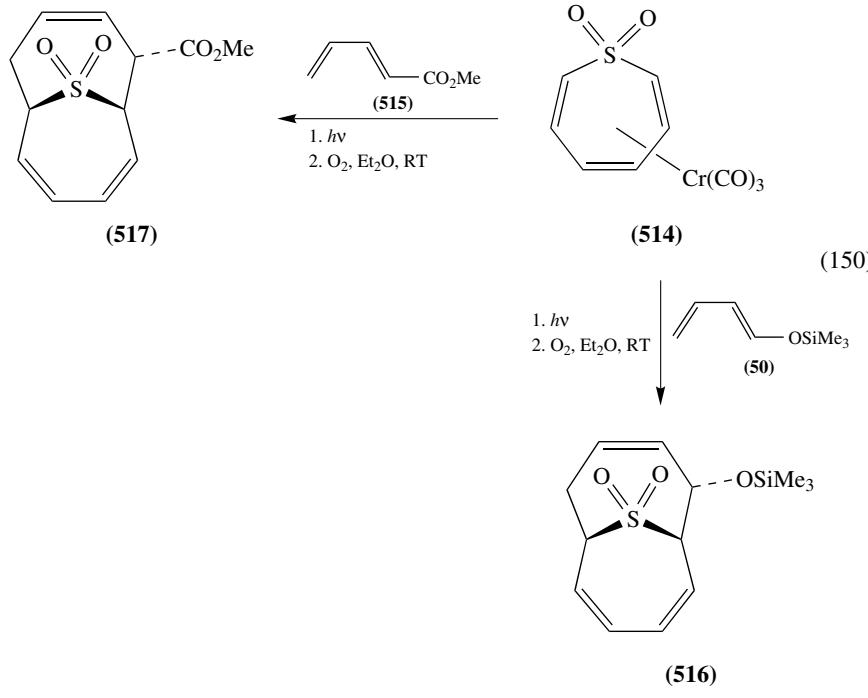
(148)



(511) **(341)** **(512)**

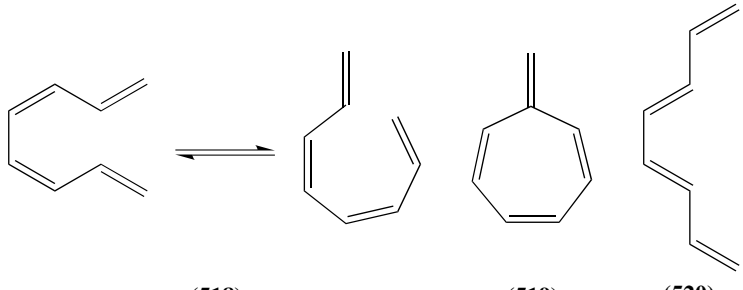
(149)

A recent application of the metal mediated [6 + 4] cycloaddition reaction is the synthesis of nine-membered carbocycles by a sequential [6 + 4] cycloaddition-pinacol rearrangement, as employed by Rigby and Fales[310].



V. [8 + 2] CYCLOADDITION REACTIONS

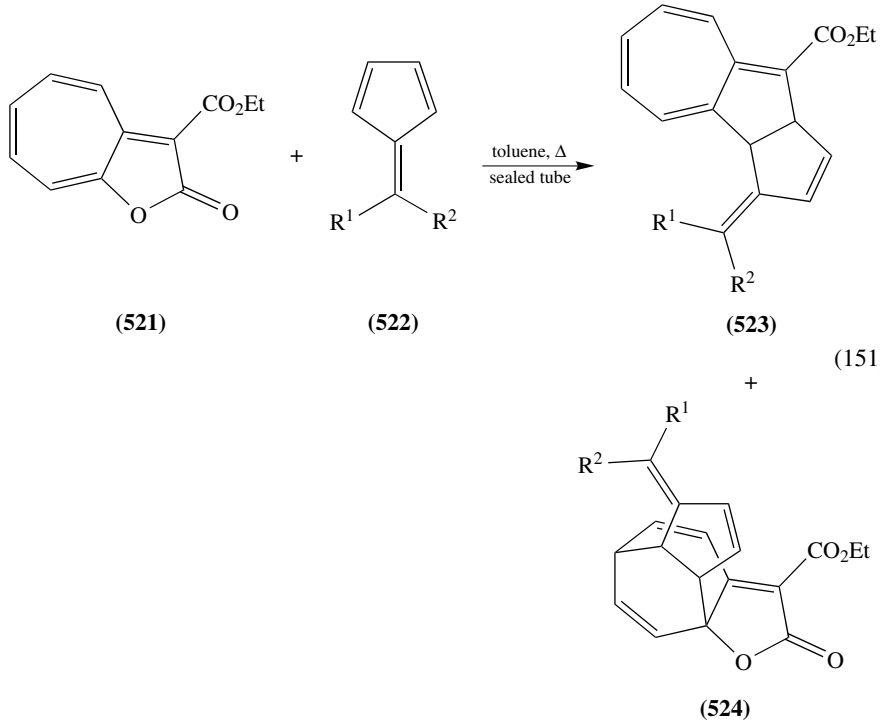
The thermally allowed [8 + 2] cycloaddition reactions may be considered as the 10π analogs of the Diels–Alder reaction in which the diene component has been replaced by a tetraene component. Like trienes in the [6 + 4] cycloaddition reactions, the 8π tetraenes must satisfy certain requirements concerning geometry in order to be able to participate in an [8 + 2] cycloaddition. For example, tetraenes **518** and **519** can undergo an [8 + 2] cycloaddition, whereas an [8 + 2] cycloaddition with **520** is virtually impossible. Due to its fixed π-system, **519** is more reactive in cycloaddition reactions than **518** and is therefore more often encountered in the literature. [8 + 2] Cycloadditions have been applied only



(518) **(519)** **(520)**

occasionally in organic synthesis. The reaction often proceeds with accompanying [4 + 2] and, in the case of a diene being the tetraenophile, [6 + 4] cycloaddition reactions.

Nair and coworkers have described the [8 + 2] cycloaddition reactions of 2H-cyclohepta[*b*]furan-2-ones such as **521** in several reports[311]. The reactions of **521** with alkenes yield azulene derivatives upon extrusion of carbon dioxide. Table 30 summarizes the results of the reactions between **521** and some 6,6-disubstituted fulvenes **522** (equation 151)[311b]. In the case of 6,6-dialkyl fulvenes **522a–c**, the [8 + 2] cycloadducts **523** were the major adducts obtained, the Diels–Alder adducts **524** only being formed in trace amounts.



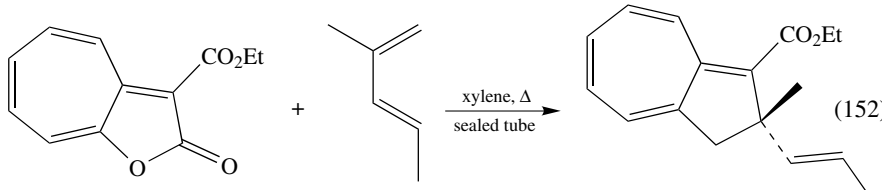
When cycloalkyl pentafulvenes **522e–g** were employed, [8 + 2] and [4 + 2] cycloadducts were produced in approximately equal amounts. The [4 + 2] cycloadduct became the major cycloadduct in the reaction of **521** with 6,6-diphenylfulvene **522d**. Semi-empirical

TABLE 30. Yields of products in the reaction of **521** with **522**

Entry	R^1	R^2	Fulvene	Yield **523** (%)	Yield **524** (%)
1	Et	Et	**522a**	87	trace
2	Me	Et	**522b**	68	trace
3	Me	*i*-Bu	**522c**	80	trace
4	Ph	Ph	**522d**	16	60
5	$-(CH_2)_4-$		**522e**	46	43
6	$-(CH_2)_5-$		**522f**	39	31
7	$-(CH_2)_6-$		**522g**	37	31

calculations indicated that the [8 + 2] adduct is probably formed via a reaction of the HOMO of **521** with the LUMO of fulvene **522**, whereas the Diels–Alder adduct is produced via interaction of the NLUMO of **521** with the fulvene HOMO. The Diels–Alder reactions must therefore be classified as being *inverse electron demand* Diels–Alder reactions.

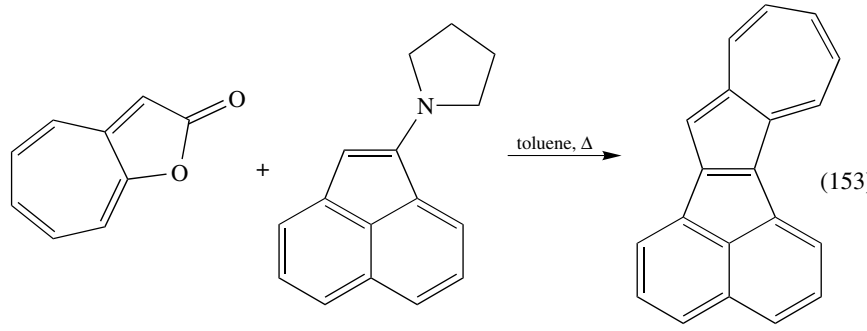
The reactions of **521** with 1,3-dienes were found to proceed exclusively in an [8 + 2] addition mode. The reactions were completely site and regioselective, as exemplified by the reaction between **521** and 2-methyl-1,3-pentadiene **(525)** which gave **526** after loss of CO_2 (equation 152). The regiochemistry observed was in agreement with the frontier orbital coefficients calculated with semi-empirical methods.



(152)

(521) **(525)** **(526)**

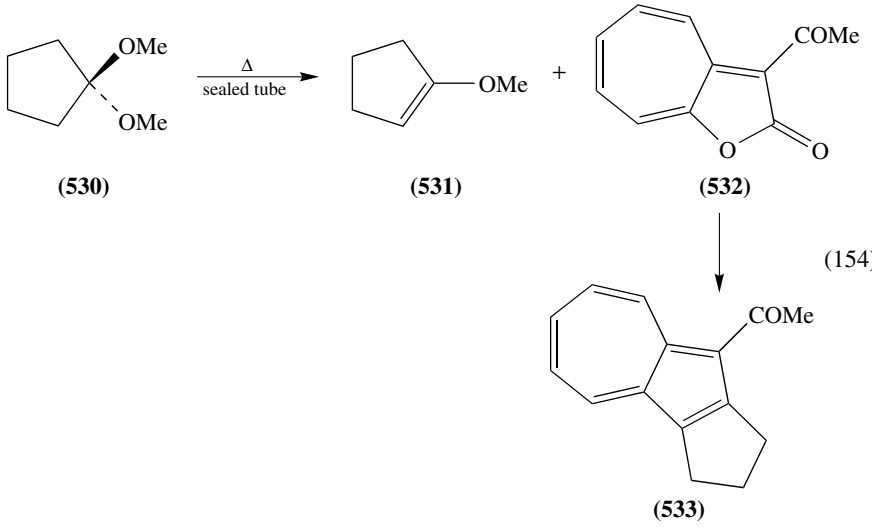
The [8 + 2] cycloaddition reactions between substituted cyclohepta[*b*]furan-2-ones and enamines have been described by Kuroda and coworkers[312]. The cycloaddition reactions proceeded with concomitant elimination of carbon dioxide and amine. Thus, the reaction between **527** and enamine **528** afforded [8 + 2] cycloadduct **529** with good yield (equation 153)[312c].



(153)

(527) **(528)** **(529)**

Nozoe and colleagues[313] performed [8 + 2] cycloaddition reactions between substituted cyclohepta[*b*]furan-2-ones and vinyl ethers, vinyl acetates, dihydrofurans and dihydropyrans, which resulted in the formation of various substituted azulenes. They also investigated the reactions with acetals. These afforded the corresponding vinyl ethers at high reaction temperatures by elimination of one mole of alcohol[314]. For example, acetal **530** gave enol **531** upon heating, which reacted with cyclohepta[*b*]furan-2-ones **532** to give **533** (equation 154). In the same way, Nozoe and colleagues[315] prepared 2-alkoxyazulene derivatives by reacting orthoesters, which generate ketene acetals upon heating, with cyclohepta[*b*]furan-2-ones.



(530) **(531)** **(532)** **(533)** (154)

Daub and colleagues studied the [8 + 2] cycloaddition reactions of electron-rich 8-substituted heptafulvenes with a wide variety of acceptor substituted alkenes. 8-Methoxyheptafulvene **(534)** proved to give the best results, the more electron-rich heptafulvenes being less reactive toward [8 + 2] cycloaddition reactions and more prone to oxidative dimerization[316]. The reactions of 8-methoxyheptafulvene with acceptor substituted polyenophiles **535** can in principle produce up to 8 diastereomers. The reactions proved, however, highly regioselective, the *exo* and site selectivities being moderate to good, and afforded mixtures of **536**, **537** and **538** (equation 155, Table 31)[317].

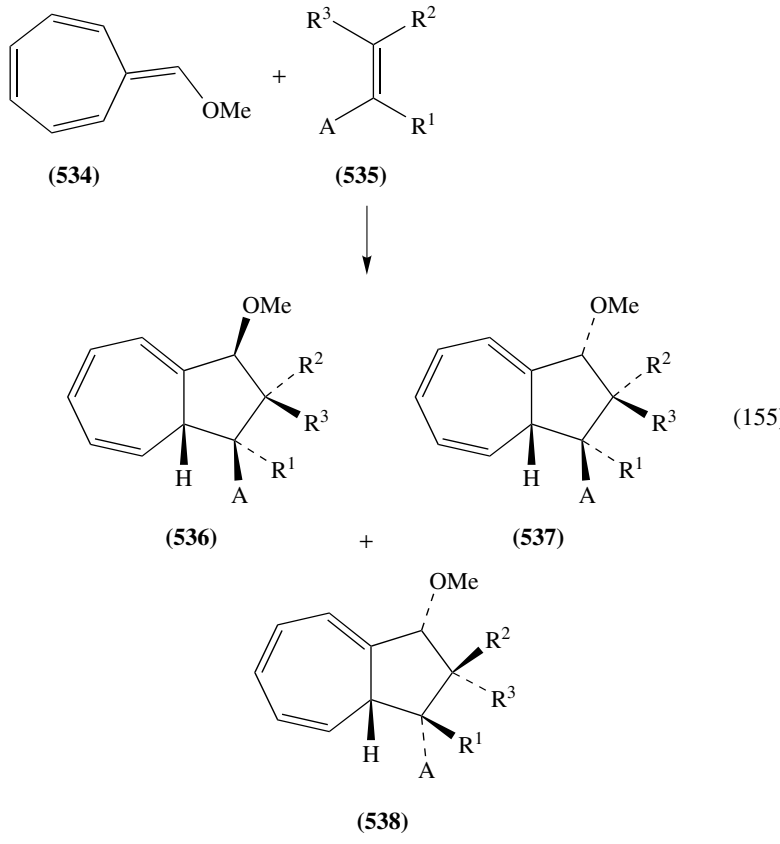
The regioselectivity observed was in agreement with the calculated orbital coefficients for the HOMO of heptafulvene **534** and the LUMOs of the polyenophiles. The largest coefficient in the HOMO of **534** is at C(8). The reactions of nitroethene and (*E*)-*β*-nitrostyrene with **533** (entries 4 and 5) afforded merely *exo* adducts, the two isomers arising from attack of the polyenophile at the two different sites of **534**.

The reactions of **534** with substituted quinones produced mixtures of regioisomers. The substituent effect on the regioselectivity of the [8 + 2] cycloaddition reactions was said to be dependent on steric as well as electronic effects. Equation 156 shows the reaction between **534** and 2-methylbenzoquinone **(539)**. The reaction afforded a mixture of two regioisomeric adducts **540** and **541**, which were transformed to azulenes **542–545** under the reaction conditions applied[318].

Daub and colleagues have also described the cycloaddition reaction of **534** with [60]fullerene **(209)** (equation 157)[319] and [70]fullerene[320], which were the first [8 + 2] cycloaddition reactions with fullerenes described in the literature. Reaction with [60]fullerene afforded **546** as the main product with a yield of more than 90%. On the basis of the results of previous cycloadditions performed with fullerenes, it was assumed that it was a 6,6-double bond which had reacted with **533**, [60]fullerene adding to the less hindered site of **534**.

[8 + 2] Cycloaddition reactions of indolizines such as **547** can generally be performed with moderately electron-poor alkenes only, because alkenes with strong acceptor substituents predominantly give Michael adducts. The cycloaddition of 2-methylindolizine

(547) with 1-cyclobutene-1,2-dicarbonitrile **(548)**, for example, proceeded to give the dehydrogenated adduct **549**, whereas the reaction with *cis*-3-hexene-2,5-dione **(550)** afforded solely the Michael adduct (equation 158)[321].

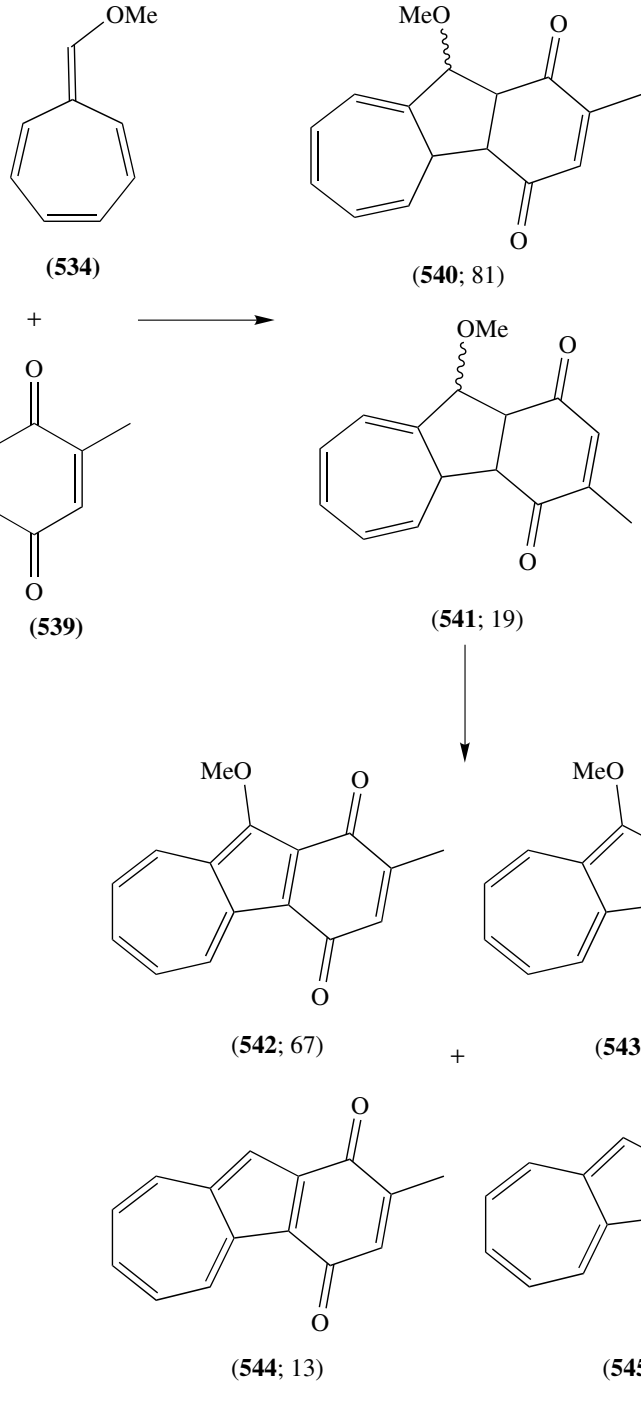


(155)

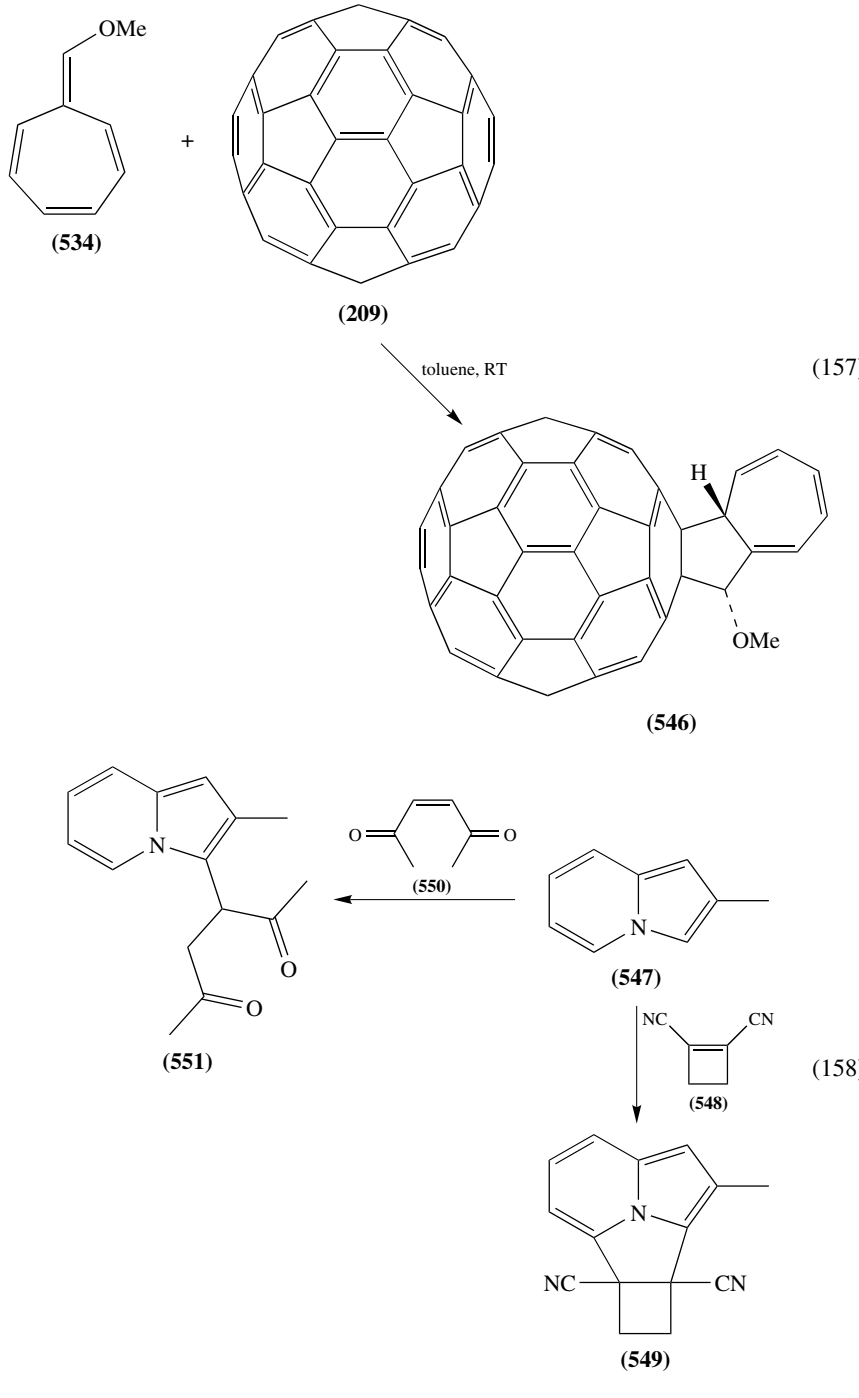
TABLE 31. Yields and product distributions in the reaction of **534** with **535**

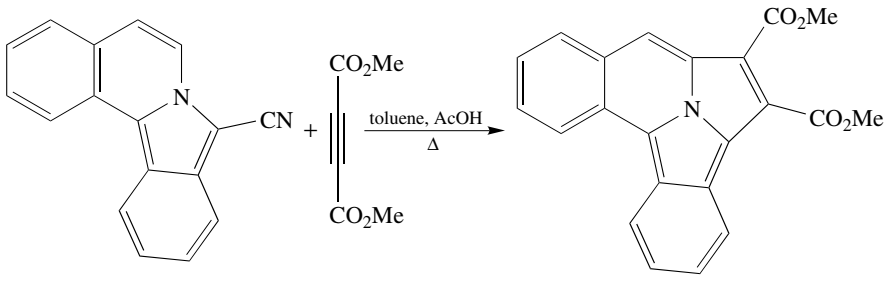
Entry	A	R^1	R^2	R^3	Yield (%)	**536/537/538**
1	CN	CN	CF_3	CF_3	85	33/67/0
2	CN	CN	Ph	H	100	12/68/20
3	CN	CN	*p*-$O_2NC_6H_4$	H	94	12/65/23
4	NO_2	H	Ph	H	98	10/90/0
5	NO_2	H	H	H	100	28/72/0

Tominaga and coworkers[322] prepared dimethyl dibenzo[*a*,*h*]cycl[3.2.2]azine-1,2-dicarboxylate **(553)** by an [8 + 2] cycloaddition reaction of 1-cyanoisoindolo[2,1-*a*]isoquinoline **(552)** with dimethyl acetylenedicarboxylate **(57)**, followed by elimination of HCN. A small amount of acetic acid was added to improve the yield of the reaction from 1% to 26%. The double adduct **554** was isolated in minor amounts (equation 159).


OMe
MeO
O
O
(534)
(540; 81)
+
O
O
OMe
O
O
(539)
(541; 19)
MeO
O
O
MeO
O
O
(542; 67)
+
(543; 13)
O
O
O
O
(544; 13)
(545; 7)

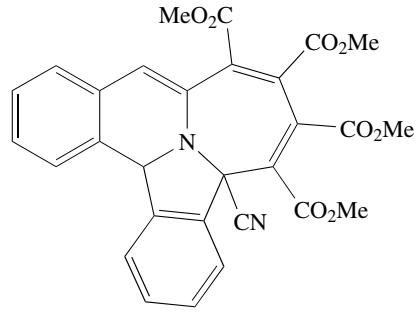
(156)


OMe
(534)
+
(209)
toluene, RT
(157)
H
OMe
(546)
N
O
O
O
O
(550)
(551)
N
(547)
NC
CN
(548)
(158)
N
NC
CN
(549)



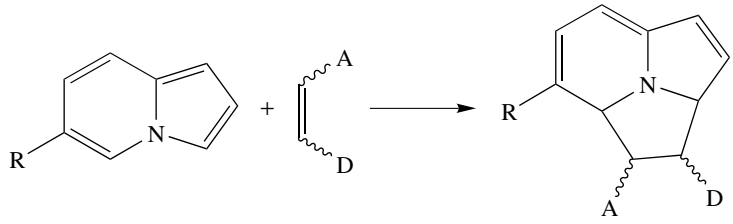
(552) **(57)** **(553)**

(159)



(554)

Jug and colleagues performed quantum mechanical SINDO1 and AM1 calculations of the transition states for the, in some cases experimentally still unknown, [8 + 2] cycloaddition reactions of indolizine **(555a)** and 6-nitroindolizine **(555b)** with nitroethene, methyl acrylate, acrylonitrile, ethene and dimethylvinylamine to give **556a** and **556b**, respectively (equation 160)[323]. They found that most [8 + 2] cycloaddition reactions should proceed concertedly, i.e. no intermediate and second transition state were found. Only the reactions of nitroethene (D = H, A = NO_2) with **555a** and **555b**, and the reaction of dimethylvinylamine (D = NMe_2, A = H) with **555b** were classified as being two-step processes. The experimentally observed reactions of nitroalkenes with indolizines, however, were Michael additions, which corresponds to only the first step of the two-step process.



(160)

(**555a**; R = H)
(**555b**; R = NO_2)

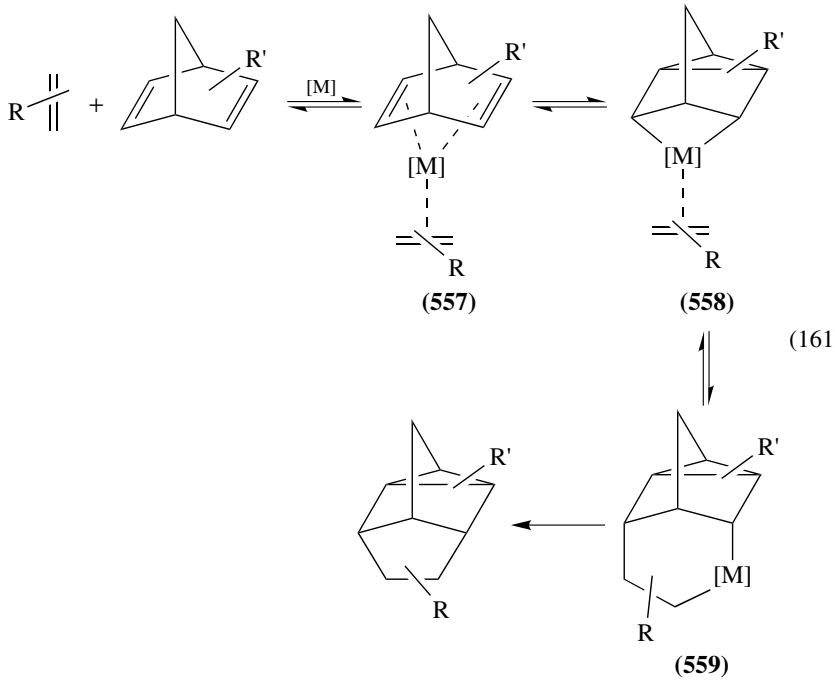
(**556a**; R = H)
(**556b**; R = NO_2)

VI. [2 + 2 + 2] CYCLOADDITION REACTIONS

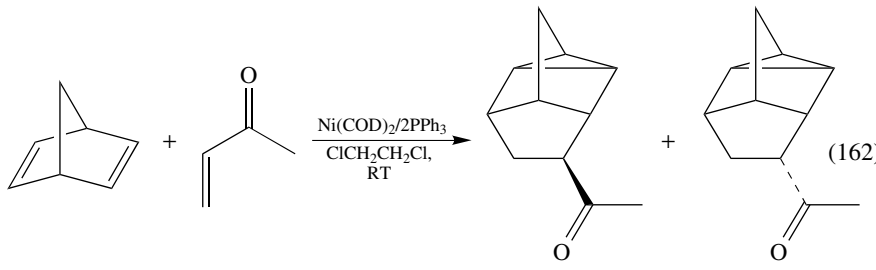
Even more than [6 + 4] and [8 + 2] cycloaddition reactions, the [2 + 2 + 2] cycloaddition reactions require a very well preorganized orientation of the three multiple bonds with respect to each other. In most cases, this kind of cycloaddition reaction is catalyzed by transition metal complexes which preorientate and activate the reacting multiple bonds[111,324]. The rarity of thermal [2 + 2 + 2] cycloadditions, which are symmetry allowed and usually strongly exothermic, is due to unfavorable entropic factors. High temperatures are required to induce a reaction, as was demonstrated by Berthelot, who described the synthesis of benzene from acetylene in 1866[325], and Ullman, who described the reaction between norbornadiene and maleic anhydride in 1958[326]. As a consequence of the limiting scope of this chapter, this section only describes those reactions in which two of the participating multiple bonds are within the same molecule.

Most metal mediated [2 + 2 + 2] cycloadditions involve two triple bonds which coordinate to a metal center to form a reactive metallocyclopentadiene species (*vide infra*). The corresponding reactions involving at least two double bonds and an intermediate metallocyclopentane species are almost completely limited to norbornadiene systems. These reactions can be considered as homo Diels–Alder reactions.

The most efficient catalysts for the homo Diels–Alder reactions of norbornadiene were found to be cobalt[327] and nickel[328] complexes. The general mechanistic pathway that has been proposed for these reactions has been depicted in equation 161[329]. According to this mechanism, co-ordination of norbornadiene and the olefin or acetylene to the metal center gives **557**, which is in equilibrium with metallocyclopentane complex **558**. Then, insertion of the olefin or acetylene in the metal–carbon bond takes place to form **559**. Reductive elimination finally liberates the deltacyclane species.



Lautens and colleagues[328] found 5 mol% $Ni(COD)_2/2PPh_3$ to be the most efficient catalytic system for the cycloaddition between methyl vinyl ketone **(100)** and norbornadiene **(560)**. The adducts **561** and **562** were obtained with 99% overall yield and with an *exo/endo* ratio of >95/<5 (equation 162).



(162)

(560) **(100)** (**561**; >95) (**562**; <5)

Unlike thermal homo Diels–Alder reactions in which *endo* adducts predominate[330], the nickel catalyzed reactions of acyclic electron-deficient dienophiles afford the *exo* isomers as the major cycloadducts. This has been explained by unfavorable steric interactions within intermediate **559** leading to the *endo* adduct. Cyclic dienophiles, on the contrary, give predominantly the *endo* isomer, which has again been explained by unfavorable steric interactions within *exo* **559**. The preferred conformation of the dienophile, *s-cis* or *s-trans*, has also been suggested to play a role[328].

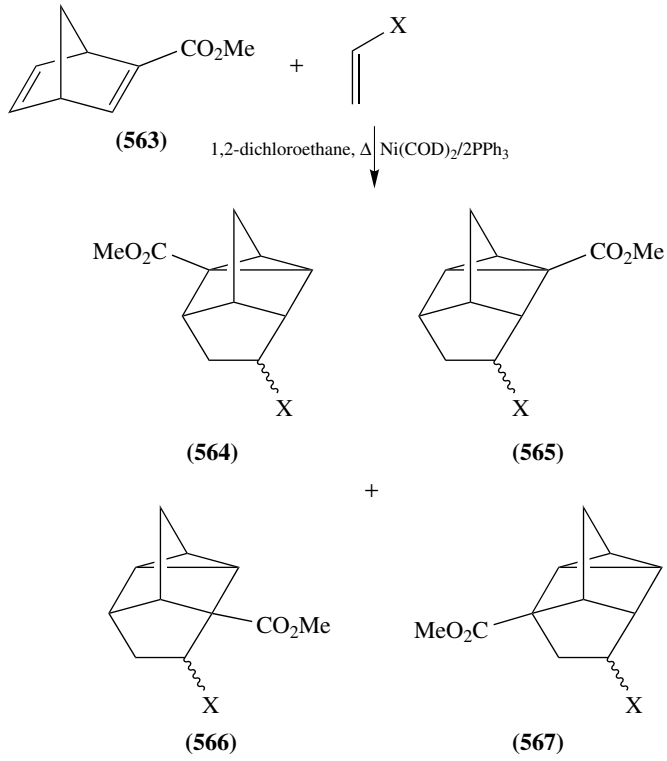
The regiochemistry of nickel mediated cycloadditions of substituted norbornadienes has been investigated in detail. The regioselectivity, *exo/endo* selectivity and site selectivity seem to depend strongly on the substituents on both diene and dienophile. Tetracyanoethene, for example, reacted with 2-acetyloxymethyl substituted norbornadiene on the distal side[331].

The reactions between norbornadiene **563** and unsymmetrical dienophiles can, in principle, produce up to 8 cycloadducts. Lautens and colleagues[328] reported that **564** was the main regioisomer found in the reactions of **563** with the range of dienophiles examined (equation 163, Table 32). When the PPh_3 ligand was replaced by $P(OPr\text{-}i)_3$, however, **566** became the main product in the reaction of **563** with methyl vinyl ketone. The *endo/exo* selectivity depended strongly on the olefinic substituent and the regiochemical course of the reaction. The reaction of methyl vinyl ketone with 2-methoxynorbornadiene, which proceeded more slowly than the reaction with **563**, gave the regioisomer analogous to **566** as the major isomer, whereas the reaction with 2-trimethylsilylnorbornadiene afforded the adduct analogous to **565** as the major product. An adduct analogous to **567** was not obtained in any instance.

[2 + 2] Adducts were obtained as exclusive adducts or as by-products in the nickel mediated reactions of some substituted norbornadienes with various dienophiles. The formation of these products was considered to result from an intermediate metallocyclopentane species built up of the metal center, the dienophilic double bond and one of the double bonds of the norbornadiene moiety.

The cobalt mediated homo Diels–Alder reaction of norbornadiene **(560)** with phenyl acetylene **(568a)**, affording a phenyl substituted deltacyclene, demonstrated the potential of low-valent cobalt complexes as catalysts[332]. Lautens and coworkers[327] extended the scope of this reaction and were able to synthesize a wide range of substituted deltacyclenes from alkynes **568** (equation 164, Table 33). The low-valent cobalt(I) or cobalt(0) species to be used was prepared *in situ* by reduction of $Co(acac)_3$ with Et_2AlCl. Monosubstituted

acetylenes **568a–e** and **198** were more reactive than disubstituted acetylenes **568f–h**. The reactions between diphenylacetylene **(568g)** and norbornadiene did not take place at room temperature. Bis(trimethylsilyl)acetylene **(568h)** did not react, not even on prolonged heating at 60 °C. Dimers of norbornadiene were obtained instead.



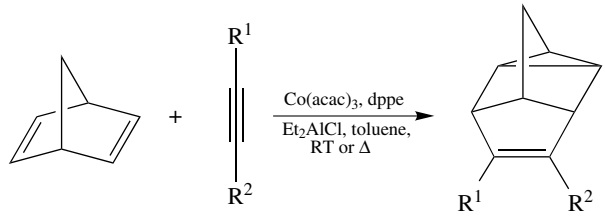
(163)

TABLE 32. Reaction data for equation 163

Entry	X	Yield (%)	Relative yield (*exo/endo*)			
			564	**565**	**566**	**567**
1	CN	94	100 (30/70)	—	—	—
2	SO_2Ph	75	66 (>95/<5)	33 (>95/<5)	—	—
3	COMe	84	70 (75/25)	10 (42/58)	20 (0/100)	—

The possibility of asymmetric induction in these reactions was probed by adding chiral phosphine ligands to the cobalt complex. Brunner and colleagues[333] found an ee of 98.4% for the adduct of norbornadiene and phenylacetylene using a cobalt complex based on the chiral bidentate phosphine NORPHOS **(570)**. They extended their studies to include a variety of other bidentate phosphines and different acetylenes, reaching enantioselectivities of more than 99%[334]. Buono and coworkers[335] obtained high enantioselectivities (up to 97% ee) using a cobalt(II) iodide complex and amino acid based chiral phosphine ligand **571**. Chiral phosphine **572** induced an ee of 82% in the reaction of norbornadiene

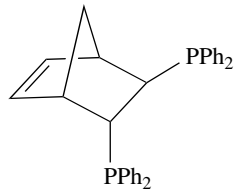
with phenylacetylene, as reported by Lautens and coworkers[327,336]. The highest enantioselectivity (91% ee) with 1-hexyne was found when phosphine **573** was employed as the chiral ligand.



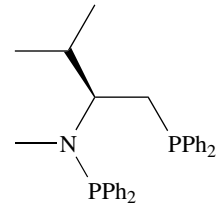
(560) **(568)** **(569)** (164)

TABLE 33. Reaction data for equation 164

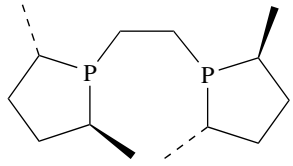
Entry	R^1	R^2	Alkyne	T(°C)	Yield (%)
1	Ph	H	**568a**	RT	100
2	*n*-Bu	H	**198**	RT	91
3	*i*-Pr	H	**568b**	RT	58
4	*i*-Bu	H	**568c**	RT	50
5	$(CH_2)_3$OTBDMS	H	**568d**	RT	90
6	$SiMe_3$	H	**568e**	RT	50
7	Et	Et	**568f**	60	65
8	Ph	Ph	**568g**	60	58
9	TMS	TMS	**568h**	60	0



(570)



(571)



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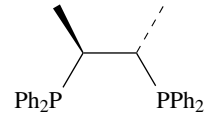
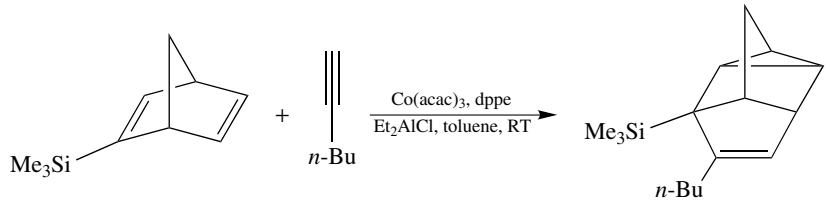


(573)

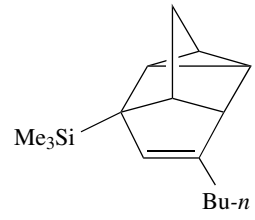
The regioselectivity in the reactions of 7-substituted norbornadienes with substituted acetylenes generally proved low. The reactions of **563** and 2-methoxynorbornadiene with 1-hexyne (**198**) did not proceed. With 2-trimethylsilylnorbornadiene (**574**), adducts **575** and **576** were obtained, albeit in low to moderate yields (equation 165). The best regioselectivity (**575**/**576** = 92/8) was obtained when the reaction was performed at room

temperature and $Co(acac)_3$ was used as the pre-catalyst[327]. The low yields and the formation of acetylene trimers suggested that 2-substituted norbornadienes do not co-ordinate well to the active cobalt complex.



(574) **(198)** **(575)**

\+ (165)



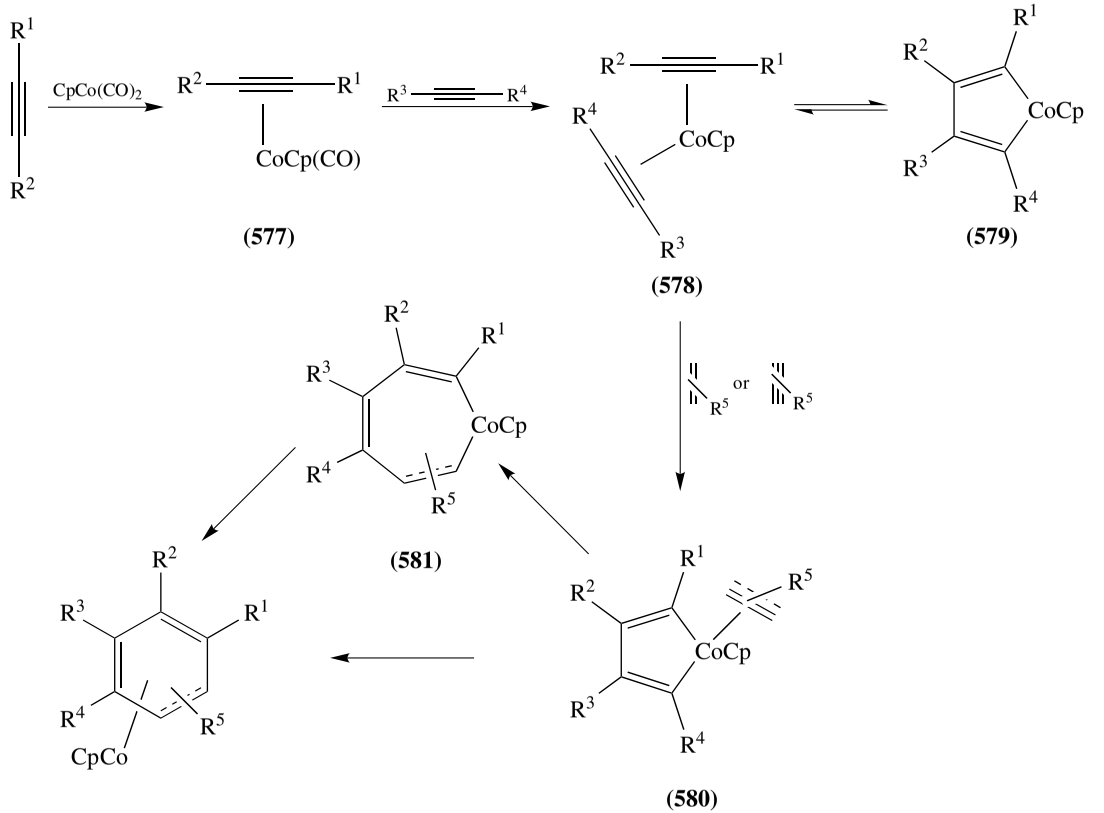
(576)

Cobalt, as its $CpCo(CO)_2$ complex, has proven to be especially suited to catalyze [2 + 2 + 2] cycloadditions of two alkyne units with an alkyne or alkene. These cobalt-mediated [2 + 2 + 2] cycloaddition reactions have been studied in great detail by Vollhardt[337]. The generally accepted mechanism for these cobalt mediated cycloadditions, and similar transition metal mediated cycloadditions in general, has been depicted in equation 166. Consecutive co-ordination of two triple bonds to $CpCo(CO)_2$ with concomitant extrusion of two molecules of carbon monoxide leads to intermediates **578** and **579** via monoalkyne complex **577**. These react with another multiple bond to form intermediate **580**. The conversion of **578** to **580** is said to be kinetically favored over that of **579** to **580**. Because intermediates like **580** have never been isolated, it is still unclear whether the next step is a Diels–Alder reaction to form the final product or an insertion to form **581**. The exact circumstances might determine which pathway is followed.

Vollhardt and colleagues have explored the reactions between diynes and enamines[338–341]. The reactions between symmetrically substituted alkynes and alkyne tethered uracil derivatives proceeded in moderate yields, producing adducts with predominant *anti* configurations[342–343]. On the other hand, the reactions between diynes and uracil derivatives produced predominantly *syn* isomers.

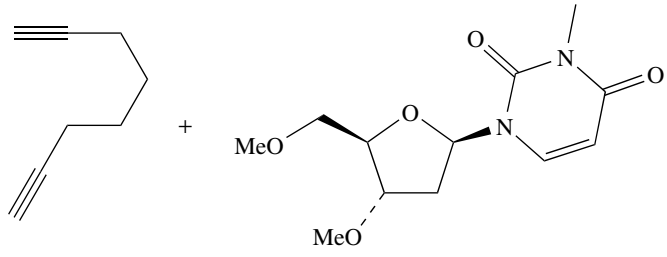
The attachment of chiral sugar-derived auxiliaries to the uracil unit generally induced low diastereoselectivities. Only in the reaction between diyne **582** and uracil **583** was a high *syn* and diastereoselectivity observed, complex **584** being obtained as the major diastereomer (equation 167).

The cobalt mediated [2 + 2 + 2] cycloadditions of α,ω-diynes with indole were only accomplished when the nitrogen atom was substituted with an electron-withdrawing

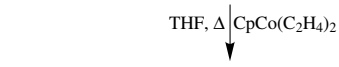


(166)

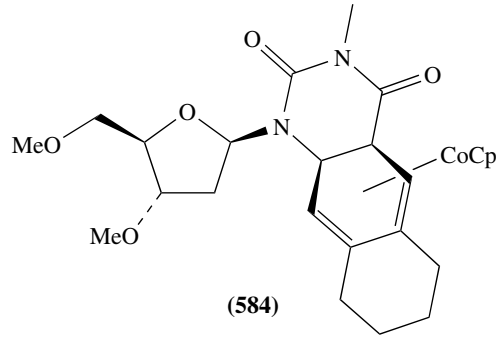
group[338a]. Furthermore, the $CpCo(CO)_2$ complex proved inefficient in these reactions. When $CpCo(C_2H_4)_2$ was used, however, the reactions proceeded well.



(582) **(583)**



(167)



(584)

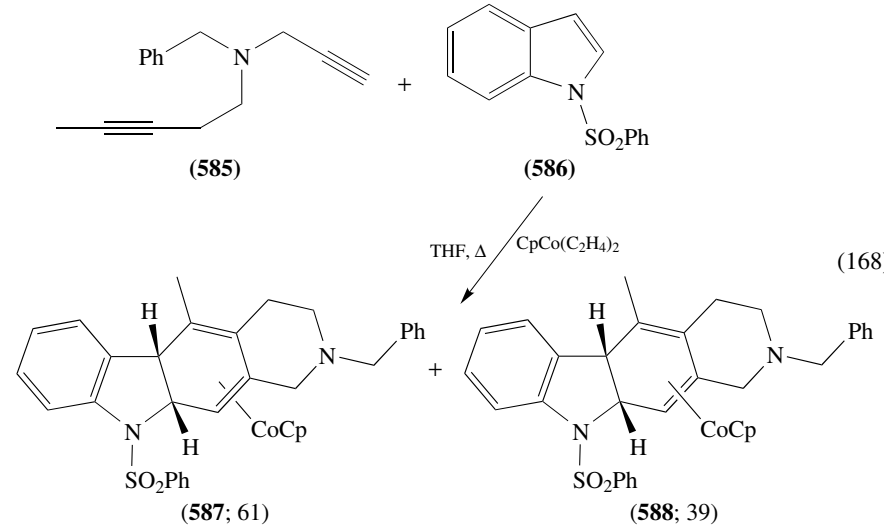
Vollhardt and colleagues[338b] studied the regiochemistry in these cycloaddition reactions. When the α,ω-diynes had large substituents at both termini, the reaction with *N*-phenylsulfonylindole did not afford any adduct due to steric hindrance. When smaller substituents were present, the cycloaddition proceeded in such a way that the larger substituent was distant from the phenylsulfonamide moiety, as illustrated for the reaction of **585** with **586** (equation 168). *Anti* **587** and *syn* **588** were obtained in a 61 : 39 ratio.

A formal synthesis of γ-lycorane was accomplished by Vollhardt and colleagues by employing a $[2 + 2 + 2]$ cycloaddition between enyne **589** and **568h** (equation 169)[344]. The reaction afforded a mixture of *syn* and *anti* adducts **590** and **591** in a 80 : 20 ratio when the reaction was conducted at room temperature. When the reaction was conducted in refluxing **568h**/THF (1 : 1, v/v), a *syn:anti* ratio of 60 : 40 was obtained. A small amount of $[2 + 2]$ adduct **592** was also isolated. This product became the dominant product when the enamide double bond was substituted. The additional steric hindrance probably prevented the enamide double bond from participating in the cycloaddition reaction.

Vollhardt and colleagues also investigated the $[2 + 2 + 2]$ cycloadditions of alkyne tethered furans **593a** and thiophenes **593b** with alkynes[345]. The reactions with **568h** proceeded to generate the expected cycloadducts **594a** and **594b** (equation 170). These species,

however, underwent heterolytic ring opening in most cases and provided the rearranged compounds **595a** and **595b** through a series of ring-closure/ring-opening sequences.

Malacria and coworkers[346] prepared phyllocladane and kaurane types of diterpenes by means of [3 + 2]/[2 + 2 + 2]/[4 + 2] cascade reaction sequences. A representative example of such a reaction sequence has been outlined in equation 171. The five-membered ring of **598** was built by a 1,3-dipolar cycloaddition between **596** and an all-carbon 1,3-dipole generated from **597**. The reaction of **598b** with **568h** afforded benzocyclobutene **599**. The intramolecular [4 + 2] cycloaddition afforded diastereomers **600** and **601** in a 5 : 1 ratio. It is noteworthy that the exocyclic double bond in **598b** neither participates in the [2 + 2 + 2] cycloaddition reaction nor isomerizes under the reaction conditions applied.

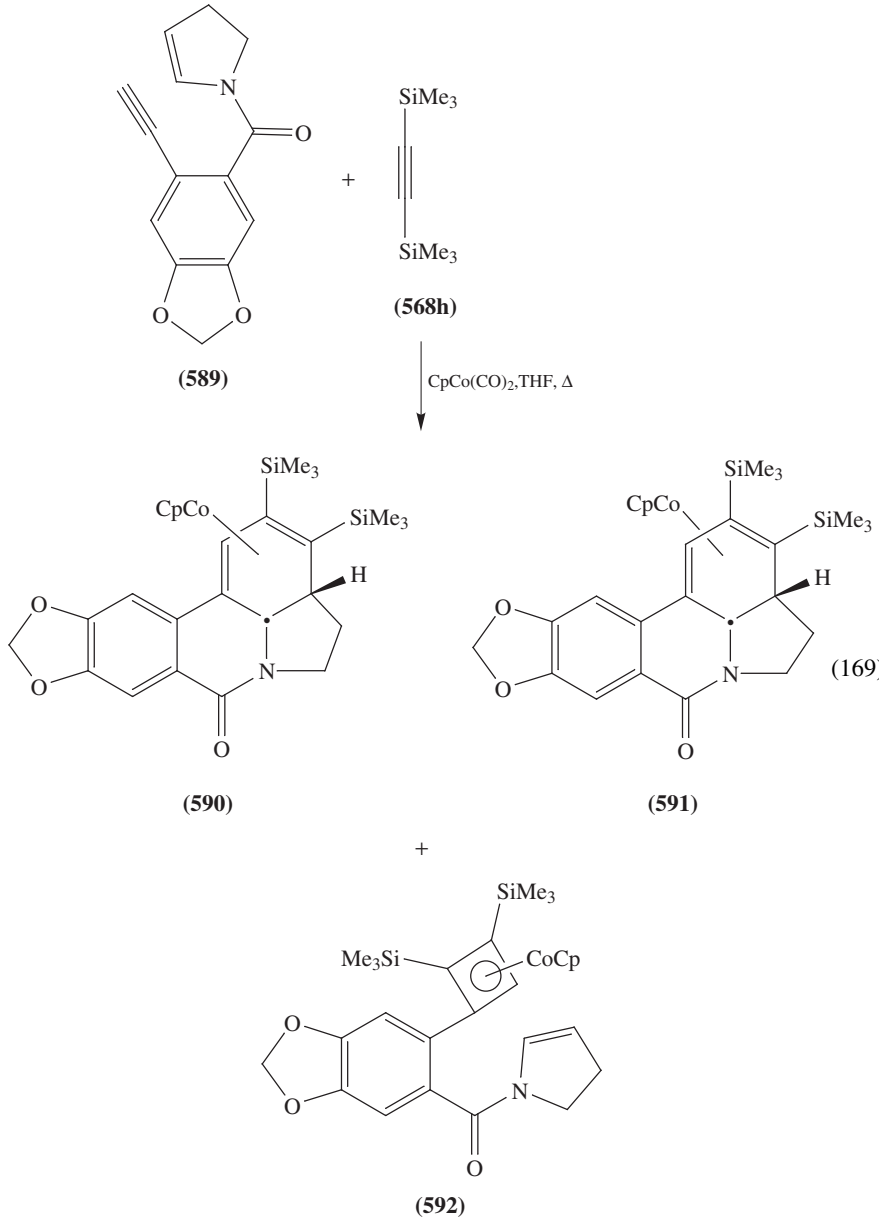


The kaurane type of adduct **601** became the major product when the methylene group at C(12) was replaced by a carbonyl group and substituents were present at C(15). Repulsive steric interactions between the substituents at C(15) and H(1) prevented the formation of phyllocladane type of compounds like **600**[347].

In a similar way, Malacria and colleagues accomplished the formation of the stemodan skeleton by a tandem [2 + 2 + 2]/[4 + 2] cycloaddition process[348].

Apart from cobalt, other metals have also been shown to be able to catalyze [2 + 2 + 2] cycloaddition reactions. Grigg and coworkers[349], for example, used a Pd(0) complex to catalyze [2 + 2 + 2] cycloadditions.

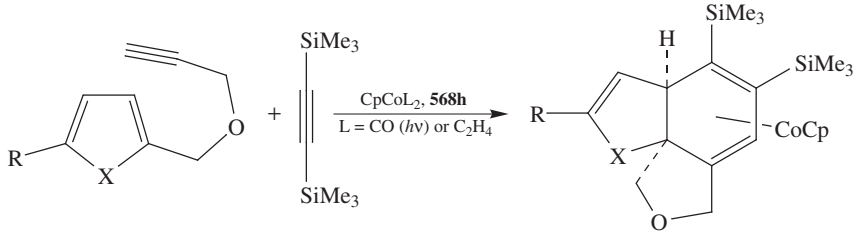
Tsuda and coworkers[350] used nickel(0) complexes to effect the [2 + 2 + 2] cycloadditions between two alkyne units and one alkene unit and employed this strategy to synthesize copolymers. Thus, the reaction of diyne **602** with *N*-octylmaleimide (**603**) catalyzed by $Ni(CO)_2(PPh_3)_2$ afforded copolymer **604** with a maximum yield of 60% and a GPC molecular weight of as high as 35,000, which corresponds to $n = 64$ (equation 172). The *exo,exo*-bicyclo[2.2.2]oct-7-ene moiety of **604** arises through the reaction of the initially formed [2 + 2 + 2] adduct with another equivalent of *N*-octylmaleimide.



Ikeda and coworkers[351] performed [2 + 2 + 2] cycloadditions of diynes with α,β-enones using $NiCl_2$/Zn (1 : 10) as the catalytic couple. In these reactions, nickel dichloride

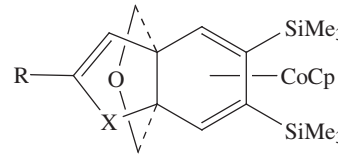
reacts with zinc to afford a Ni(0) species and zinc dichloride. The best catalytic results were obtained when 1.5 equivalents of zinc dichloride and triethylamine were added to the reaction mixture. Thus, methyl vinyl ketone (**100**) reacted with diyne **605** to afford the aromatized adduct **606** as the exclusive product (equation 173). The two abstracted hydrogen atoms proved to be incorporated into another molecule of methyl vinyl ketone.

When trimethylsilyl substituted diyne **607** was reacted with methyl vinyl ketone, the reaction proceeded with complete regioselectivity and without aromatization to afford **608** with 56% yield (equation 174). The regioselectivity observed was considered to result from a metallacyclopentene intermediate which was built up of the nickel atom, the double bond of methyl vinyl ketone and the less substituted triple bond of **607**.



(**593a**; X = O) (**568h**) (**594a**; X = O)
(**593b**; X = S) (**594b**; X = S)

(170)

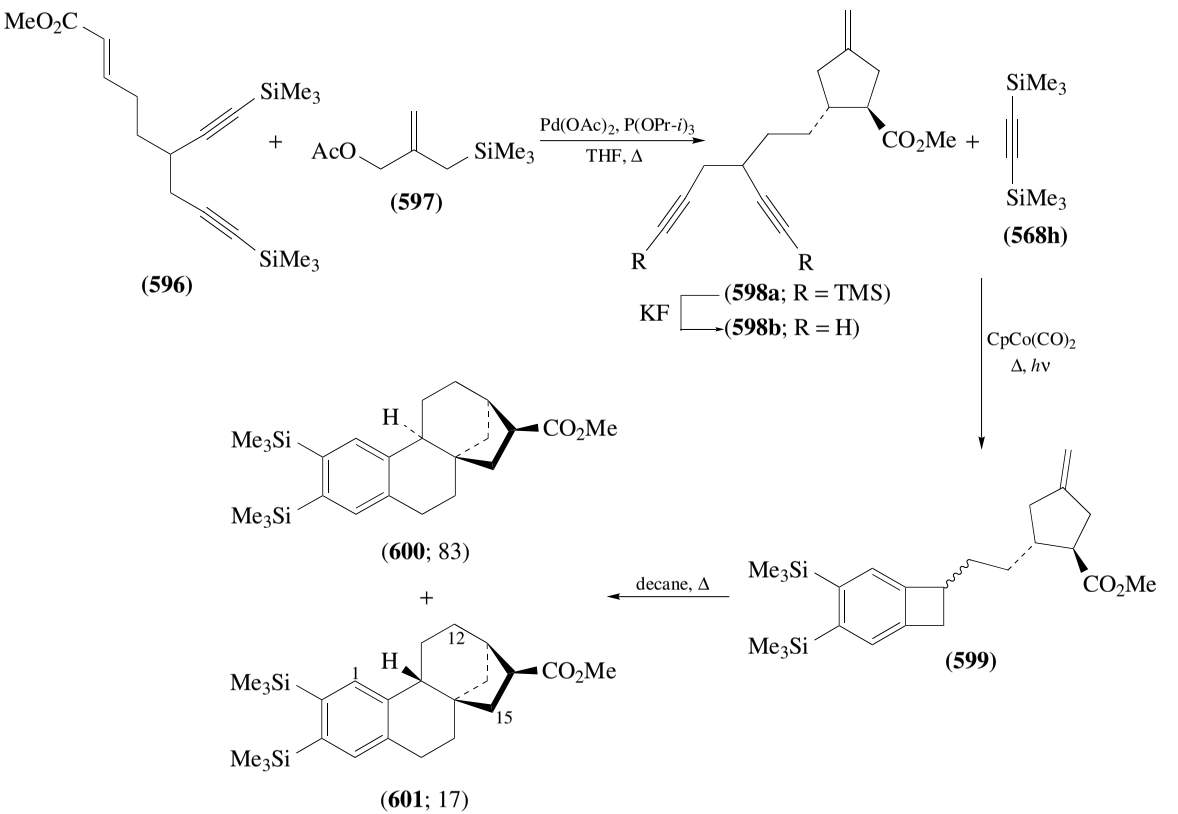


(**595a**; X = O)
(**595b**; X = S)

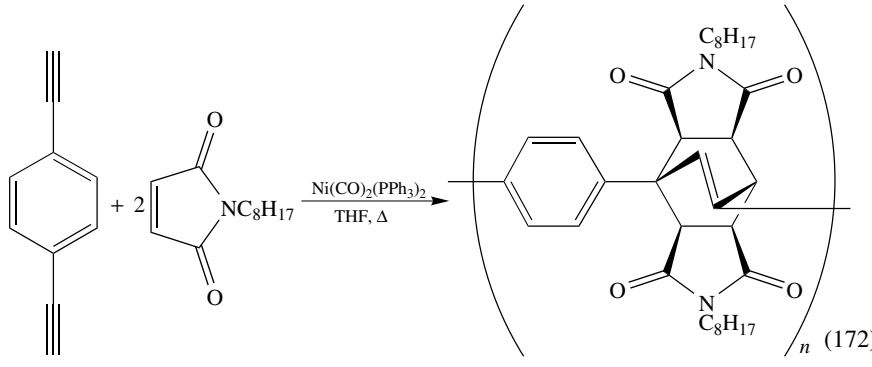
Rothwell and colleagues[352] studied the titanium mediated [2 + 2 + 2] cycloaddition of alkenes with monoynes and diynes. Among the reactions studied, the reaction between styrene **(29)** and diyne **609** in the presence of titanium catalyst **610** proved cleanest (equation 175). The reaction yielded **614** via a [2 + 2 + 2] cycloaddition followed by a titanium mediated suprafacial [1,5] H-shift involving **611**–**613**. The *cis* relationship between the trimethylsilyl group and the phenyl group indicated that the initially formed titananorbornene **611** had an *endo* stereochemistry.

The authors had evidence to believe that the addition of **29** to the titanacyclopentadiene complex proceeded in a Diels–Alder type of way, i.e. in a concerted manner instead of a stepwise manner via a titanacycloheptatriene intermediate.

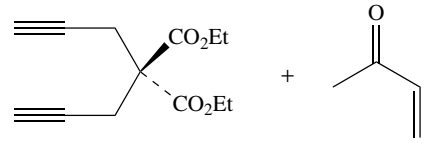
Kotha and Brahmachary[353] prepared some constrained α-amino acids using a rhodium mediated [2 + 2 + 2] cycloaddition reaction. The indane type of α-amino acids were synthesized by reacting diynes with monoynes using Wilkinson's catalyst[354]. Thus, the reaction of diyne **615** with **616** afforded α-amino acid derivative **617** (equation 176).


MeO2C
SiMe3
SiMe3
(596)
+
AcO
SiMe3
(597)
Pd(OAc)2, P(OPr-i)3
THF, Δ
CO2Me +
SiMe3
SiMe3
(568h)
R
R
(598a; R = TMS)
KF
(598b; R = H)
CpCo(CO)2
Δ, hν
Me3Si
Me3Si
CO2Me
(599)
decane, Δ
H
Me3Si
Me3Si
CO2Me
(600; 83)
+
12
H
1
15
Me3Si
Me3Si
CO2Me
(601; 17)

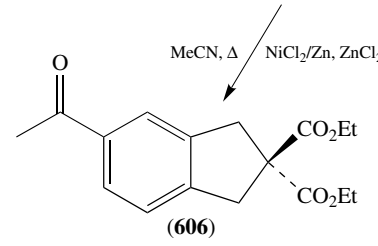
(171)



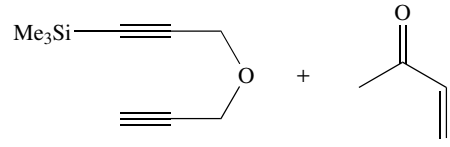
(602) **(603)** **(604)** (172)



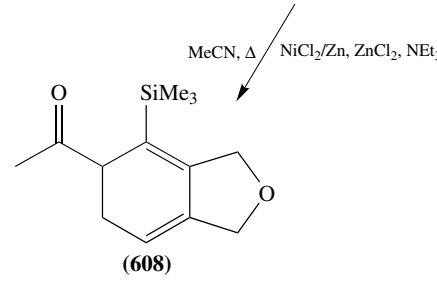
(605) **(100)**



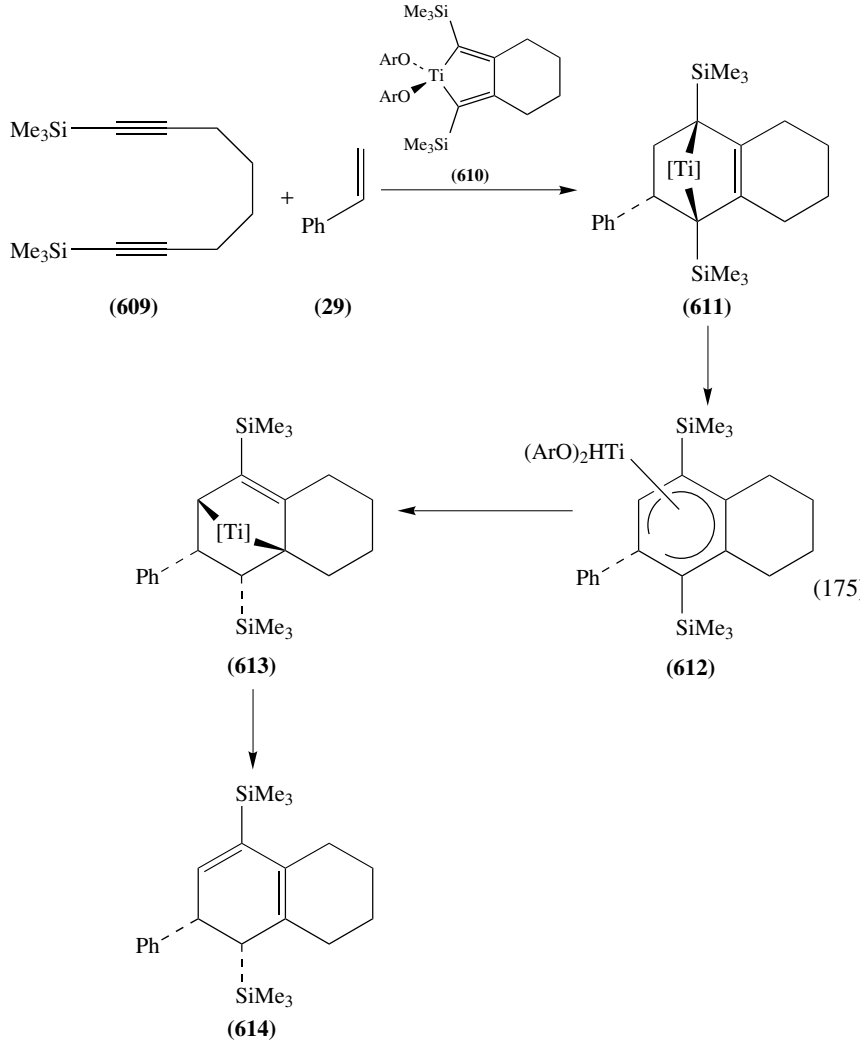
(606) (173)



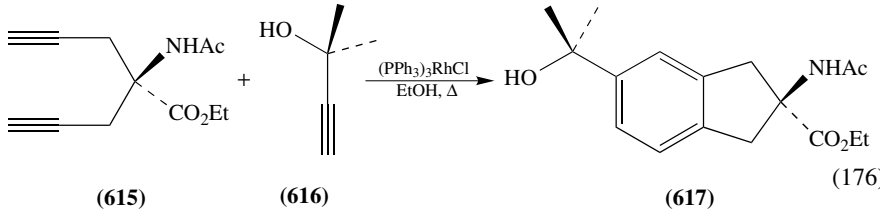
(607) **(100)**



(608) (174)



[Ti] = $Ti(OAr)_2$, ArO = 2,6-diphenylphenoxide



VII. REFERENCES

1. (a) W. T. Brady, in *The Chemistry of Ketenes, Allenes and Related Compounds* (Ed. S. Patai), Wiley, New York, 1980, p. 279–308.
   (b) D. Bellus and B. Ernst, *Angew. Chem., Int. Ed. Engl.*, **27**, 797 (1988).
   (c) E. Lee-Ruff, in *Houben-Weyl, Methoden der Organischen Chemie*, Vol. E17e (Ed. A. de Meijere), Chap. 1.3.5, Georg Thieme Verlag, Stuttgart, 1997, pp. 190–213.
2. V. K. Aggarwal, A. Ali and M. P. Coogan, *Tetrahedron*, **55**, 293 (1999).
3. F. Jin, Y. Xu and W. Huang, *J. Chem. Soc., Chem. Commun.*, 814 (1993).
4. H. Bienaymé and N. Guicher, *Tetrahedron Lett.*, **38**, 5511 (1997).
5. (a) H. E. Schuster and G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, 1984.
   (b) S. R. Landor, *The Chemistry of Allenes*, Vols. 1–3, Academic Press, New York, 1982.
   (c) W. T. Brady, in *The Chemistry of Ketenes, Allenes and Related Compounds* (Ed. S. Patai), Wiley, New York, 1980, pp. 279–413.
   (d) E. Lee-Ruff, in *Houben-Weyl, Methoden der Organischen Chemie*, Vol. E17e (Ed. A. de Meijere), Chap. 1.3.4, Georg Thieme Verlag, Stuttgart, 1997, pp. 169–178.
6. W. R. Dolbier, Jr., *Acc. Chem. Res.*, **24**, 63 (1991).
7. D. J. Pasto and K. D. Sugi, *J. Org. Chem.*, **56**, 3795 (1991).
8. D. J. Pasto and K. D. Sugi, *J. Org. Chem.*, **56**, 6216 (1991).
9. D. J. Pasto and K. D. Sugi, *J. Org. Chem.*, **57**, 12 (1992).
10. D. J. Pasto and J. Brophy, *J. Phys. Org. Chem.*, **6**, 95 (1993).
11. D. J. Pasto, K. D. Sugi and D. E. Alonso, *J. Org. Chem.*, **57**, 1146 (1992).
12. D. J. Pasto and J. E. Brophy, *J. Org. Chem.*, **56**, 4554 (1991).
13. Y. Hayashi, S. Niihata and K. Narasaka, *Chem. Lett.*, 2091 (1990).
14. K. Narasaka, Y. Hayashi, H. Shimadzu and S. Niihata, *J. Am. Chem. Soc.*, **114**, 8869 (1992).
15. M. Hojo, K. Tomita, Y. Hirohara and A. Hosomi, *Tetrahedron Lett.*, **34**, 8123 (1993).
16. M. Hojo, C. Murakama, S. Nakamura and A. Hosomi, *Chem. Lett.*, 331 (1998).
17. T. A. Engler, K. Agrios, J. P. Reddy and R. Iyengar, *Tetrahedron Lett.*, **37**, 327 (1996).
18. M. Christl, M. Braun and G. Müller, *Angew. Chem. Int. Ed. Engl.*, **104**, 473 (1992).
19. R. Janoschek, *Angew. Chem., Int. Ed. Engl.*, **104**, 476 (1992).
20. B. Jamart-Grégoire, S. Mercier-Girardot, S. Ianelli, M. Nardelli and P. Caubère, *Tetrahedron*, **51**, 1973 (1995).
21. R. L. Elliot, N. H. Nicholson, F. E. Peaker, A. K. Takle, C. M. Richardson, J. W. Tyler, J. White, M. J. Pearson, D. S. Eggleston and R. C. Haltiwanger, *J. Org. Chem.*, **62**, 4998 (1997).
22. M. Kimura, Y. Horino, Y. Wakamiya, T. Okajima and Y. Tamaru,, *J. Am. Chem. Soc.*, **119**, 10869 (1997).
23. Th. Zincke and H. Günther, *Justus Liebigs Ann. Chem.*, **272**, 243 (1893).
24. O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 98 (1928).
25. F. Fringuelli and A. Taticchi, *Dienes in the Diels–Alder Reaction*, Wiley, New York, 1990.
26. W. Oppolzer, in *Comprehensive Organic Transformations*, Vol. 5 (Eds. B. M. Trost, I. Fleming and L. A. Paquette), Chap. 4.1, Pergamon Press, Oxford, 1991, pp. 315–399.
27. W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, 1990.
28. (a) V. D. Kiselev and A. I. Konovalov, *Russ. Chem. Rev.*, **58**, 230 (1989).
   (b) C. Cativiela, J. I. García, J. A. Mayoral and L. Salvatella, *Chem. Soc. Rev.*, 209 (1996).
29. K. N. Houk, Y. Li and J. D. Evanseck, *Angew. Chem., Int. Ed. Engl.*, **31**, 682 (1992).
30. K. N. Houk, J. González and Y. Li, *Acc. Chem. Res.*, **28**, 81 (1995).
31. O. Wiest, D. C. Montiel and K. N. Houk, *J. Phys. Chem. A*, **101**, 8378 (1997).
32. J.-E. Bäckvall, R. Chinchilla, C. Nájera and M. Yus, *Chem. Rev.*, **98**, 2291 (1998).
33. O. C. Kappa, S. S. Murphree and A. Pawda, *Tetrahedron*, **53**, 14179 (1997).
34. (a) K. Krohn, *Angew. Chem., Int. Ed. Engl.*, **32**, 1582 (1993).
   (b) D. Enders and O. Meyer, *Justus Liebigs Ann. Chem.*, 1023 (1996).
35. K. Afarinkia, V. Vinader, T. D. Nelson and G. H. Posner, *Tetrahedron*, **48**, 9111 (1992).
36. (a) W. Sliwa, *Fullerene Sci. Technol.*, **5**, 1133 (1997).
   (b) A. Hirsch, *Synthesis*, 895 (1995).
   (c) J. Maynollo and B. Kraeutler, *Fullerene Sci. Technol.*, **4**, 213 (1996).
37. D. A. Singleton, *Adv. Cycloaddit.*, **4**, 121 (1997).
38. K. Neuschütz, J. Velker and R. Neier, *Synthesis*, 227 (1998).

39. (a) C. P. Dell, *Contemp. Org. Synth.*, **4**, 87 (1997).
(b) C. P. Dell, *J. Chem. Soc., Perkin Trans. 1*, 3873 (1998).
40. J. D. Winkler, *Chem. Rev.*, **96**, 167 (1996).
41. J. Jurczak, T. Bauer and C. Chapus, in *Houben-Weyl, Methoden der Organischen Chemie*, Vol. E21c (Eds. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann), Chap. 1.6.1.1.1, Georg Thieme Verlag, Stuttgart, 1995, pp. 2735–2871.
42. J. Barluenga, A. Suárez-Sobrino and L. A. López, *Aldrichimica Acta*, **32**, 4 (1999).
43. K. Narasaka, *Synthesis*, 1 (1991).
44. L. C. Dias, *J. Braz. Chem. Soc.*, **8**, 289 (1997).
45. J. Sauer and R. Sustmann, *Angew. Chem., Int. Ed. Eng.*, **19**, 779 (1980).
46. R. Sustmann, S. Tappanchai and H. Bandmann, *J. Am. Chem. Soc.*, **118**, 12555 (1996).
47. K. Lücking, M. Rese and R. Sustmann, *Justus Liebigs Ann. Chem.*, 1129 (1995).
48. E. Eibler, P. Höcht, B. Prantl, H. Roßmaier, H. M. Schuhbauer, H. Wiest and J. Sauer, *Justus Liebigs Ann./Recueil*, 2471 (1997).
49. K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971).
50. K. Fukui, *Theory of Orientation and Stereoselection*, Springer-Verlag, Berlin, 1975, p. 59.
51. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976, p. 86.
52. K. N. Houk, in *Pericyclic Reactions*, Vol. 2 (Eds. A. P. Marchand and R. E. Lehr), Chap. 4, Academic Press, New York, 1977, pp. 181–271
53. K. Fukui, *Angew. Chem., Int. Ed. Engl.*, **21**, 801 (1982).
54. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
55. B. S. Jursic and Z. Zdravkovski, *J. Mol. Struct., Theochem*, **115**, 249 (1994).
56. J. Motoyoshia, T. Kameda, M. Asari, M. Miyamoto, S. Narita, H. Aoyama and S. Hayashi, *J. Chem. Soc., Perkin Trans. 2*, 1845 (1997).
57. Y. Apeloig and E. Matzner, *J. Am. Chem. Soc.*, **117**, 5375 (1995).
58. A. A. Broekhuis, J. W. Scheeren and R. J. F. Nivard, *Recl. Trav. Chim. Pays-Bas*, **99**, 6 (1980).
59. F. K. Brown and K. N. Houk, *Tetrahedron Lett.*, **25**, 4609 (1984).
60. D. Suárez and J. A. Sordo, *Chem. Commun.*, 385 (1998).
61. P. V. Alston, M. D. Gordon, R. M. Ottenbrite and T. Cohen, *J. Org. Chem.*, **48**, 5051 (1983).
62. J. Alkonyi and Szabó, *Chem. Ber.*, **100**, 2773 (1967).
63. H.-D. Scharf, H. Plum, J. Fleischhauer and W. Schleker, *Chem. Ber.*, **112**, 862 (1979).
64. V. Branchadell, A. Oliva, R. M. Ortuño, S. Rafel and M. Ventura, *Tetrahedron*, **48**, 9001 (1992).
65. C. Spino, M. Pesant and Y. Dory, *Angew. Chem., Int. Ed. Engl.*, **37**, 3262 (1998).
66. C. Spino, J. Crawford, Y. Cui and M. Gugelchuk, *J. Chem. Soc., Perkin Trans. 2*, 1499 (1998).
67. G. D. Dunn and J. K. Donohue, *Tetrahedron Lett.*, 3485 (1968).
68. S. D. Kahn, C. F. Pau, L. E. Overman and W. J. Hehre, *J. Am. Chem. Soc.*, **108**, 7381 (1986).
69. (a) M. G. Banwell, P. Darmos, M. D. McLeod and D. C. R. Hockless, *Synlett*, 897 (1998).
(b) J. D. Dudones and P. Sampson, *J. Org. Chem.*, **62**, 7508 (1997).
(c) R. L. Funk and K. J. Yost, *J. Org. Chem.*, **61**, 2598 (1996).
(d) Y. Hirai, K. Ito and H. Nagaoka, *Heterocycles*, **48**, 235 (1998).
(e) J. Oh and J. K. Cha, *Synlett*, 967 (1994).
(f) Y. Queneau, W. J. Krol, W. G. Bornmann and S. J. Danishefsky, *J. Org. Chem.*, **57**, 4043 (1992).
(g) C. K. Sha, S. J. Lee and W. H. Tseng, *Tetrahedron Lett.*, **38**, 2725 (1997).
(h) M. W. Tjepkema, P. D. Wilson, T. Wong, M. A. Romero, H. Audrain and A. G. Fallis, *Tetrahedron Lett.*, **36**, 6039 (1995).
(i) J. D. Winkler, H. S. Kim, S. Kim, K. Ando and K. N. Houk, *J. Org. Chem.*, **62**, 2957 (1997).
(j) J. S. Yadav and P. K. Sasmal, *Tetrahedron Lett.*, **38**, 8769 (1997).
(k) M. A. Romero, R. P. Franco, R. Cruz-Almanza and F. Padilla, *Tetrahedron Lett.*, **35**, 3255 (1994).
(l) V. Theurillat-Moritz and P. Vogel, *Tetrahedron: Asymmetry*, **7**, 3163 (1996).
70. (a) K. C. Nicolaou, C.-K. Hwang, E. J. Sorensen and C. F. Clairborne, *J. Chem. Soc., Chem. Commun.*, 1117 (1992).

(b) K. C. Nicolaou, J. J. Liu, C.-K. Hwang, W.-M. Dai and R. K. Guy, *J. Chem. Soc., Chem. Commun.*, 1118 (1992).
71. K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Clairborne, J. Renaud, E. A. Couladouros, K. Paulvannan and E. J. Sorensen, *Nature*, **367**, 630 (1994).
72. (a) A. Guingant and M. M. Barreto, *Tetrahedron Lett.*, **28**, 3107 (1987).
(b) K. Katsuura and V. Snieckus, *Can. J. Chem.*, **65**, 124 (1987).
(c) K. Krohn and K. Khanbabaee, *Angew. Chem. Int. Ed. Engl.*, **33**, 99 (1994).
(d) K. Krohn, K. Khanbabaee and J. Micheel, *Justus Liebigs Ann. Chem.*, 1529 (1995).
(e) D. S. Larsen and M. D. O'Shea, *J. Chem. Soc., Perkin Trans. 1*, 1019 (1995).
(f) G. B. Caygill, D. S. Larsen and B. S. McFarlane, *Aust. J. Chem.*, **50**, 301 (1997).
73. G. A. Kraus and G. Zhao, *J. Org. Chem.*, **61**, 2770 (1996).
74. M. Adeva, E. Caballero, F. García, M. Medarde, H. Sahagún and F. Tomé, *Tetrahedron Lett.*, **38**, 6893 (1997).
75. A. R. Martínez and G. Y. M. Iglesias, *J. Chem. Res. (S)*, 169 (1998).
76. S. Kotha, E. Brahmachary and N. Sreenivasachary, *Tetrahedron Lett.*, **39**, 4095 (1998).
77. L. Minuti, A. Taticchi, E. Gacs-Baitz and A. Marrocchi, *Tetrahedron*, **54**, 10891 (1998).
78. Y. Ohfune, T. Kan and T. Nakajima, *Tetrahedron*, **54**, 5207 (1998).
79. Z. Pudukulathan, S. Manna, S.-W. Hwang, S. P. Khanapure, J. A. Lawson, G. A. FitzGerald and J. Rokach, *J. Am. Chem. Soc.*, **120**, 11953 (1998).
80. A. H. McNeill, S. V. Mortlock, R. M. Pratt and E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 709 (1998).
81. R. Beddoes, R. M. Pratt and E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 717 (1998).
82. J. E. Baldwin, D. R. Spring and R. C. Whitehead, *Tetrahedron Lett.*, **39**, 5417 (1998).
83. S. R. Magnuson, L. Sepp-Lorenzino, N. Rosen and S. J. Danishefsky, *J. Am. Chem. Soc.*, **120**, 1615 (1998).
84. G. Desimoni, G. Faita, M. Ricci and P. Righetti, *Tetrahedron*, **54**, 9581 (1998).
85. (a) C.-Y. Chen and D. J. Hart, *J. Org. Chem.*, **58**, 3840 (1993).
(b) D. J. Hart, W.-L. Wu and A. P. Kozikowski, *J. Am. Chem. Soc.*, **117**, 9369 (1995).
(c) D. J. Hart, J. Li, W.-L. Wu and A. P. Kozikowski, *J. Org. Chem.*, **62**, 5023 (1997).
86. C.-H. Byeon, C.-Y. Chen, D. A. Ellis, D. J. Hart and J. Li, *Synlett*, 596 (1998).
87. R. D. Hubbard and B. L. Miller, *J. Org. Chem.*, **63**, 4143 (1998).
88. S. Oi, K. Kashiwagi and Y. Inoue, *Tetrahedron Lett.*, **39**, 6253 (1998).
89. (a) K. Takahashi, *Chem. Rev.*, **98**, 2013 (1998).
(b) R. Breslow and S. D. Dong, *Chem. Rev.*, **98**, 1997 (1998).
90. U. Pindur, G. Lutz and C. Otto, *Chem. Rev.*, **93**, 741 (1993).
91. T. R. Kelly, P. Meghani and V. S. Ekkundi, *Tetrahedron Lett.*, **31**, 3381 (1990).
92. J. Kang, G. Hilmersson, J. Santamaría and J. Rebek, Jr., *J. Am. Chem. Soc.*, **120**, 3650 (1998).
93. J. Kang, J. Santamaría, G. Hilmersson and J. Rebek, Jr., *J. Am. Chem. Soc.*, **120**, 7389 (1998).
94. D. Philp and A. Robertson, *Chem. Commun.*, 879 (1998).
95. B. Wang and I. O. Sutherland, *Chem. Commun.*, 1495 (1997).
96. Z. Clyde-Watson, A. Vidal-Ferran, L. J. Twyman, C. J. Walter, D. W. J. McCallien, S. Fanni, N. Bampos, R. S. Wylie and J. K. M. Sanders, *New J. Chem.*, 493 (1998).
97. (a) C. J. Walter, H. L. Anderson and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 458 (1993).
(b) R. P. Bonar-Law, L. G. Mackay, C. J. Walter, V. Marvaud and J. K. M. Sanders, *Pure Appl. Chem.*, **66**, 803 (1994).
(c) C. J. Walter and J. K. M. Sanders, *Angew. Chem., Int. Ed. Engl.*, **34**, 217 (1995).
98. K. Endo, T. Koike, T. Sawaki, O. Hayashida, H. Masuda and Y. Aoyama, *J. Am. Chem. Soc.*, **119**, 4117 (1997).
99. S. P. Kolis, M. D. Chordia, R. Liu, M. E. Kopach and W. D. Harman, *J. Am. Chem. Soc.*, **120**, 2218 (1998).
100. Y. Kita, K. Iio, A. Okajima, Y. Takeda, K.-I. Kawaguchi, B. A. Whelan and S. Akai, *Synlett*, 292 (1998).
101. M. Sridhar, K. L. Krishna, K. Srinivas and J. M. Rao, *Tetrahedron Lett.*, **39**, 6529 (1998).
102. (a) S. G. Bott, A. P. Marchand and K. A. Kumar, *J. Chem. Crystallogr.*, **26**, 281 (1996).
(b) A. P. Marchand, B. Ganguly, W. H. Watson and S. G. Bodige, *Tetrahedron*, **54**, 10967 (1998).
103. D. F. Rothenfluh, D. C. Craig and M. N. Paddon-Row, *Tetrahedron Lett.*, **36**, 1129 (1995).

104. T. A. Kshirsagar and P. S. Portoghese, *J. Org. Chem.*, **63**, 1706 (1998).
105. (a) J. Ancerewicz and P. Vogel, *Heterocycles*, **36**, 537 (1993).
(b) A. Benítez, F. R. Herrera, M. Romero, F. X. Talamás and J. M. Muchowski, *J. Org. Chem.*, **61**, 1487 (1996).
(c) J. Laue and G. Seitz, *Justus Liebigs Ann. Chem.*, 773 (1996).
(d) D. N. Nicolaides, C. Bezergiannidou-Balouctsi, R. Wajih Awad, K. E. Litinas, E. Malamidou-Xenikaki, A. Terzis and C. P. Raptopoulou, *J. Org. Chem.*, **62**, 499 (1997).
106. L. S. Avalos, A. Benítez, J. M. Muchowski, M. Romero and F. X. Talamás, *Heterocycles*, **45**, 1795 (1997).
107. L. F. Tietze, *Chem. Rev.*, **96**, 115 (1996).
108. R. Brecht, F. Haenel, G. Seitz, G. Frenzen, A. Pilz and D. Guénard, *Eur. J. Org. Chem.*, 2451 (1998).
109. T. D. Golobish, J. K. Burke, A. H. Kim, S. W. Chong, E. L. Probst, P. J. Carroll and W. P. Dailey, *Tetrahedron*, **54**, 7013 (1998).
110. W.-D. Fessner, G. Sedelmeier, P. R. Spurr, G. Rihs and H. Prinzbach, *J. Am. Chem. Soc.*, **109**, 4626 (1987).
111. Y. Yamamoto, H. Kitahara, R. Hattori and K. Itoh, *Organometallics*, **17**, 1910 (1998).
112. (a) K. I. Guhr, M. D. Greaves and V. M. Rotello, *J. Am. Chem. Soc.*, **116**, 5997 (1994).
(b) B. Nie, K. Hasan, M. D. Greaves and V. M. Rotello, *Tetrahedron Lett.*, **36**, 3617 (1995).
113. B. R. Stranix and G. D. Darling, *J. Org. Chem.*, **62**, 9001 (1997).
114. A. Gügel, P. Belik, M. Walter, A. Kraus, E. Harth, M. Wagner, J. Spickermann and K. Müllen, *Tetrahedron*, **52**, 5007 (1996).
115. N. Kottner and E. Klemm, *Angew. Makromol. Chem.*, **254**, 39 (1998).
116. F. Morgenroth, A. J. Berresheim, M. Wagner and K. Müllen, *Chem. Commun.*, 1139 (1998).
117. A. Gandini and M. N. Belgacem, *Prog. Polym. Sci.*, **22**, 1203 (1997).
118. C. Goussé, A. Gandini and P. Hodge, *Macromolecules*, **31**, 314 (1998).
119. M. H. J. Cordes, S. de Gala and J. A. Berson, *J. Am. Chem. Soc.*, **116**, 11161 (1994).
120. S. M. Bachrach, *J. Org. Chem.*, **60**, 4395 (1995).
121. C. K. McClure and K. B. Hansen, *Tetrahedron Lett.*, **37**, 2149 (1996).
122. O. Arjona, F. Iradier, R. M. Mañas, J. Plumet, X. Grabuleda and C. Jaime, *Tetrahedron*, **54**, 9095 (1998).
123. A. Padwa, M. Dimitroff, A. G. Waterson and T. Wu, *J. Org. Chem.*, **62**, 4088 (1997).
124. C.-H. Chen, P. D. Rao and C.-C. Liao, *J. Am. Chem. Soc.*, **120**, 13254 (1998).
125. K. Afarinkia and F. Mahmood, *Tetrahedron Lett.*, **39**, 493 (1998).
126. N. Atanes, S. Escudero, D. Pérez, E. Guitián and L. Castedo, *Tetrahedron Lett.*, **39**, 3039 (1998).
127. R. P. Hsung, *J. Org. Chem.*, **62**, 7904 (1997).
128. R. P. Hsung, *Heterocycles*, **48**, 421 (1998).
129. J. L. Loebach, D. M. Bennett and R. L. Danheiser, *J. Org. Chem.*, **63**, 8380 (1998).
130. H. J. Reich, E. K. Eisenhart, W. L. Whipple and M. J. Kelly, *J. Am. Chem. Soc.*, **110**, 6432 (1988).
131. U. Koop, G. Handke and N. Krause, *Justus Liebigs Ann. Chem.*, 1487 (1996).
132. M. Murakami, M. Ubukata, K. Itami and Y. Ito, *Angew. Chem., Int. Ed. Engl.*, **37**, 2248 (1998).
133. M. Murakami, K. Itami and Y. Ito, *J. Am. Chem. Soc.*, **119**, 7163 (1997).
134. C. Spino, C. Thibault and S. Gingras, *J. Org. Chem.*, **63**, 5283 (1998).
135. M. Manoharan and P. Venuvanalingam, *J. Chem. Soc., Perkin Trans. 2*, 1423 (1996).
136. C. P. Raj, N. A. Dhas, M. Cherkinski, A. Gedanken and S. Braverman, *Tetrahedron Lett.*, **39**, 5413 (1998).
137. I. Ikeda, A. Gondo, M. Shiro and K. Kanematsu, *Heterocycles*, **36**, 2669 (1993).
138. I. Ikeda, K. Honda, E. Osawa, M. Shiro, M. Aso and K. Kanematsu, *J. Org. Chem.*, **61**, 2031 (1996).
139. (a) S. Eguchi, M. Ohno, S. Kojima, N. Koide, A. Yashiro, Y. Shirakawa and H. Ishida, *Fullerene Sci. Technol.*, **4**, 303 (1996).
(b) U. M. Fernández-Paniagua, B. M. Illescas, N. Martín and C. Seoane, *J. Chem. Soc., Perkin Trans. 1*, 1077 (1996).
(c) U. M. Fernández-Paniagua, B. M. Illescas, N. Martín, C. Seoane, P. de la Cruz, A. de la Hoz and F. Langa, *J. Org. Chem.*, **62**, 3705 (1997).

140. B. González, A. Herrera, B. Illescas, N. Martín, R. Martínez, F. Moreno, L. Sánchez and A. Sánchez, *J. Org. Chem.*, **63**, 6807 (1998).
141. K. Mikami, S. Matsumoto, T. Tonoi, Y. Okubo, T. Suenobu and S. Fukuzumi, *Tetrahedron Lett.*, **39**, 3733 (1998).
142. K.-F. Liou, T.-Y. Hsiao and C.-H. Cheng, *Fullerene Sci. Technol.*, **6**, 35, (1998).
143. (a) P. H. H. Hermkens, H. C. J. Ottenheim and D. C. Rees, *Tetrahedron*, **52**, 4527 (1996).
(b) P. H. H. Hermkens, H. C. J. Ottenheim and D. C. Rees, *Tetrahedron*, **53**, 5643 (1997).
(c) S. Booth, P. H. H. Hermkens, H. C. J. Ottenheim and D. C. Rees, *Tetrahedron*, **54**, 15385 (1998).
144. J. D. Winkler and Y.-S. Kwak, *J. Org. Chem.*, **63**, 8634 (1998).
145. M. Crawshaw, N. W. Hird, K. Irie and K. Nagai, *Tetrahedron Lett.*, **38**, 7115 (1997).
146. R. H. Schlessinger and C. P. Bergstrom, *Tetrahedron Lett.*, **37**, 2133 (1996).
147. B. M. Trost, D. O'Krongly and J. L. Belletire, *J. Am. Chem. Soc.*, **102**, 7595 (1980).
148. (a) D. A. Evans, H. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, **103**, 2127 (1981).
(b) D. A. Evans and E. B. Sjogren, *Tetrahedron Lett.*, **26**, 3788 (1985).
(c) D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, **108**, 6757 (1986).
149. (a) D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, **96**, 835 (1996).
(b) A. Studer, *Synthesis*, 793 (1996).
150. I. W. Davies, C. H. Senanayake, L. Castonguay, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, **36**, 7619 (1995).
151. H. Okamura, K. Morishige, T. Iwagawa and M. Nakatani, *Tetrahedron Lett.*, **39**, 1211 (1998).
152. T. Hintermann and D. Seebach, *Helv. Chim. Acta*, **81**, 2093 (1998).
153. A. Sudo and K. Saigo, *Chem. Lett.*, 97 (1997).
154. M. R. Banks, A. J. Blake, J. I. G. Cadogan, A. A. Doyle, I. Gosney, P. K. G. Hodgson and P. Thorburn, *Tetrahedron*, **52**, 4079 (1996).
155. T. Nakamura, N. Hashimoto, T. Ishizuka and T. Kunieda, *Tetrahedron Lett.*, **38**, 559 (1997).
156. H. Kunz and K. Rück, *Angew. Chem. Int. Ed. Engl.*, **32**, 336 (1993).
157. M. L. G. Ferreira, S. Pinheiro, C. C. Perrone, P. R. R. Costa and V. F. Ferreira, *Tetrahedron: Asymmetry*, **9**, 2671 (1998).
158. J. A. Serrano, L. E. Cáceres and E. Román, *J. Chem. Soc., Perkin Trans. 1*, 1863 (1998).
159. E. Román, M. Baños, F. J. Higes and J. A. Serrano, *Tetrahedron: Asymmetry*, **9**, 449 (1998).
160. M. R. Banks, J. I. G. Cadogan, I. Gosney, R. O. Gould, P. K. G. Hodgson and D. McDougall, *Tetrahedron*, **54**, 9765 (1998).
161. (a) D. S. Larsen and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1841 (1989).
(b) R. C. Gupta, C. M. Raynor, R. J. Stoodley, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1773 (1988).
(c) R. C. Gupta, D. S. Larsen, R. J. Stoodley, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 739 (1989).
(d) D. S. Larsen and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1339 (1990).
162. M. C. Aversa, A. Barattucci, P. Bonaccorsi and P. Giannetto, *Tetrahedron: Asymmetry*, **8**, 1339 (1997).
163. M. C. Carreño, *Chem. Rev.*, **95**, 1717 (1995).
164. (a) M. C. Carreño, A. Urbano and C. Di Vitta, *J. Org. Chem.*, **63**, 8320 (1998).
(b) M. C. Carreño, S. García-Cerrada, A. Urbano and C. Di Vitta, *Tetrahedron: Asymmetry*, **9**, 2965 (1998).
165. J. C. Carretero, J. L. García Ruano and L. M. Martín Cabrejas, *Tetrahedron: Asymmetry*, **8**, 2215 (1997).
166. (a) E. Arce, M. C. Carreño, M. B. Cid and J. L. García Ruano, *J. Org. Chem.*, **59**, 3421 (1994).
(b) M. C. Carreño, M. B. Cid, F. Colobert, J. L. García Ruano and G. Solladié, *Tetrahedron: Asymmetry*, **5**, 1439 (1994).
(c) M. C. Carreño, M. B. Cid, J. L. García Ruano and M. Santos, *Tetrahedron Lett.*, **39**, 1405 (1998).
167. R. Fernández de la Pradilla, C. Montero and A. Viso, *Chem. Commun.*, 409 (1998).
168. (a) M. C. Aversa, P. Bonaccorsi, P. Giannetto, S. M. A. Jafari and D. N. Jones, *Tetrahedron: Asymmetry*, **3**, 701 (1992).
(b) M. C. Aversa, P. Bonaccorsi, P. Giannetto and D. N. Jones, *Tetrahedron: Asymmetry*, **5**, 805 (1994).

(c) M. C. Aversa, A. Barattucci, P. Bonaccorsi, P. Giannetto and D. N. Jones, *J. Org. Chem.*, **62**, 4376 (1997).
(d) M. C. Aversa, A. Barattucci, P. Bonaccorsi, G. Bruno, P. Giannetto and M. Panzalorto, *Tetrahedron: Asymmetry*, **8**, 2989 (1997).
(e) M. C. Aversa, A. Barattucci, P. Bonaccorsi, P. Giannetto, M. Panzalorto and S. Rizzo, *Tetrahedron: Asymmetry*, **9**, 1577 (1998).
169. P. Gosselin, E. Bonfand and C. Maignan, *J. Org. Chem.*, **61**, 9049 (1996).
170. J. K. Whitesell, *Chem. Rev.*, **92**, 953 (1992).
171. J. Barluenga, M. Tomás, A. Suárez-Sobrino and L. A. López, *J. Chem. Soc., Chem Commun.*, 1785 (1995).
172. M. A. Brimble, L. J. Duncalf, D. C. W. Reid and T. R. Roberts, *Tetrahedron*, **54**, 5363 (1998).
173. M. Virgili, M. A. Pericàs, A. Moyano and A. Riera, *Tetrahedron*, **53**, 13427 (1997).
174. G. B. Jones, B. J. Chapman and J. E. Mathews, *J. Org. Chem.*, **63**, 2928 (1998).
175. (a) H. Ito, A. Saito and T. Taguchi, *Tetrahedron: Asymmetry*, **9**, 1979 (1998).
(b) H. Ito, A. Saito and T. Taguchi, *Tetrahedron: Asymmetry*, **9**, 1989 (1998).
176. M. A. Brimble, J. F. McEwan and P. Turner, *Tetrahedron: Asymmetry*, **9**, 1239 (1998).
177. M. M. Hansen, C. F. Bertsch, A. R. Harkness, B. E. Huff, D. R. Hutchison, V. V. Khau, M. E. LeTourneau, M. J. Martinelli, J. W. Misner, B. C. Peterson, J. A. Rieck, K. A. Sullivan and I. G. Wright, *J. Org. Chem.*, **63**, 775 (1998).
178. I. E. Marko, G. R. Evans, P. Seres, I. Chellé and Z. Tanousk *Pure Appl. Chem.*, **68**, 113 (1996).
179. (a) W. Oppolzer, *Tetrahedron*, **43**, 1969 (1987).
(b) W. Oppolzer, *Pure Appl. Chem.*, **60**, 39 (1988).
(c) W. Oppolzer, *Pure Appl. Chem.*, **62**, 1241 (1990).
180. W. Oppolzer, M. Wills, M. J. Kelly, M. Signer and J. Blagg, *Tetrahedron Lett.*, **31**, 5015 (1990).
181. W. H. Chan, A. W. M. Lee, L. S. Jiang and T. C. W. Mak, *Tetrahedron: Asymmetry*, **8**, 2501 (1997).
182. M. Flock, M. Nieger and E. Breitmaier, *Justus Liebigs Ann. Chem.*, 451 (1993).
183. (a) J. A. Tucker, K. M. Houk and B. M. Trost, *J. Am. Chem. Soc.*, **112**, 5465 (1990).
(b) C. Siegel and E. R. Thornton, *Tetrahedron Lett.*, **29**, 5225 (1988).
184. H. de Bie, *Thesis*, Nijmegen (1996).
185. P. Vogel, *Curr. Org. Chem.*, **2**, 255 (1998).
186. R. Bloch and N. Chaptal-Gradoz, *J. Org. Chem.*, **59**, 4162 (1994).
187. G. T. Crisp and M. G. Gebauer, *J. Org. Chem.*, **61**, 8425 (1996).
188. G. H. P. Roos and S. Balasubramaniam, *Tetrahedron: Asymmetry*, **9**, 923 (1998).
189. O. Kitagawa, H. Izawa, K. Sato, A. Dobashi, T. Taguchi and M. Shiro, *J. Org. Chem.*, **63**, 2634 (1998).
190. K. Tanaka, N. Asakawa, M. Nuruzzaman and K. Fuji, *Tetrahedron: Asymmetry*, **8**, 3637 (1997).
191. A. K. Ghosh and P. Mathivanan, *Tetrahedron: Asymmetry*, **7**, 375 (1996).
192. D. Enders and M. Klatt, *Synthesis*, 1403 (1996).
193. D. Enders, O. Meyer and G. Raabe, *Synthesis*, 1242 (1992).
194. (a) J. Barluenga, F. Aznar, C. Valdés, A. Martín, S. García-Granda and E. Martín, *J. Am. Chem. Soc.*, **115**, 4403 (1993).
(b) J. Barluenga, F. Aznar, C. Ribas and C. Valdés, *J. Org. Chem.*, **62**, 6746 (1997).
195. J. Barluenga, F. Aznar, C. Ribas and C. Valdés, *J. Org. Chem.*, **63**, 10052 (1998).
196. S. A. Kozmin and V. H. Rawal, *J. Am. Chem. Soc.*, **119**, 7165 (1997).
197. Y. Arai, T. Masuda and Y. Masaki, *Chem. Lett.*, 145 (1997).
198. J. A. Nieman and B. A. Keay, *Tetrahedron: Asymmetry*, **7**, 3521 (1996).
199. T. X. H. Le, J. C. Bussolari and W. V. Murray, *Tetrahedron Lett.*, **38**, 3849 (1997).
200. S. Shambayati, W. E. Crowe and S. L. Schreiber, *Angew. Chem., Int. Ed. Engl.*, **29**, 256 (1990).
201. (a) M. T. Reetz, M. Hüllman, W. Massa, S. Berger, P. Rademacher and P. Heymanns, *J. Am. Chem. Soc.*, **108**, 2405 (1986).
(b) J. M. Goodman, *Tetrahedron Lett.*, **33**, 7219 (1992).
(c) B. W. Gung and M. A. Wolf, *J. Org. Chem.*, **57**, 1370 (1992).

202. M. C. Amendola, K. E. Stockman, D. A. Hoice, W. M. Davis and G. C. Fu, *Angew. Chem., Int. Ed. Engl.*, **36**, 267 (1997).
203. I. W. Bassi, M. Calcaterra and R. Intrito, *J. Organomet. Chem.*, **127**, 305 (1977).
204. M. F. Ruiz-López, X. Assfeld, J. I. García, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, **115**, 8780 (1993).
205. (a) E. J. Corey, J. J. Rohde, A. Fisher and M. D. Azimiora, *Tetrahedron Lett.*, **38**, 33 (1997).
(b) E. J. Corey and J. J. Rohde, *Tetrahedron Lett.*, **38**, 37 (1997).
(c) E. J. Corey, D. Barnes-Seeman and T. W. Lee, *Tetrahedron Lett.*, **38**, 1699 (1997).
206. S. Hashimoto, N. Komeshima and K. Koga, *J. Chem. Soc., Chem. Commun.*, 437 (1979).
207. H. Takemura, N. Komeshima, I. Takahashi, S. Hashimoto, N. Ikota, K. Tomioka and K. Koga, *Tetrahedron Lett.*, **28**, 5687 (1987).
208. F. Rebiere, O. Riant and H. B. Kagan, *Tetrahedron: Asymmetry*, **1**, 199 (1990).
209. J. Bao, W. D. Wullf and A. L. Rheingold, *J. Am. Chem. Soc.*, **115**, 3814 (1993).
210. (a) J. M. Fraile, J. I. García, J. A. Mayoral and A. J. Royo, *Tetrahedron: Asymmetry*, **7**, 2263 (1996).
(b) J. M. Fraile, J. A. Mayoral, A. J. Royo, R. V. Salvador, B. Altava, S. V. Luis and M. I. Burguete, *Tetrahedron*, **52**, 9853 (1996).
211. L. Salvatella, A. Mokrane, A. Cartier and M. F. Ruiz-López, *J. Org. Chem.*, **63**, 4664 (1998).
212. A. Ketter, G. Glahsl and R. J. Herrmann, *J. Chem. Res. (S)*, 278 (1990).
213. K. Maruoka, A. B. Concepcion and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **65**, 3501 (1992).
214. D. P. Heller, D. R. Goldberg and W. D. Wulff, *J. Am. Chem. Soc.*, **119**, 10551 (1997).
215. E. J. Corey, R. Imwinkelried, S. Pikul and Y. B. Xiang, *J. Am. Chem. Soc.*, **111**, 5493 (1989).
216. E. J. Corey and S. Sarshar, *J. Am. Chem. Soc.*, **114**, 7938 (1992).
217. E. J. Corey, N. Imai and S. Pikul, *Tetrahedron Lett.*, **32**, 7517 (1991).
218. E. J. Corey, S. Sarshar and D. H. Lee, *J. Am. Chem. Soc.*, **116**, 12089 (1994).
219. E. J. Corey and M. A. Letavic, *J. Am. Chem. Soc.*, **117**, 9616 (1995).
220. R. A. Aitken and S. N. Kilényi, *Asymmetric Synthesis*, Blackie Academic & Professional, London, 1992.
221. T. R. Kelly, A. Whiting and N. S. Chandrakumar, *J. Am. Chem. Soc.*, **108**, 3510 (1986).
222. K. Maruoka, M. Sakurai, J. Fujiwara and H. Yamamoto, *Tetrahedron Lett.*, **27**, 4895 (1986).
223. G. Bir and D. Kaufmann, *Tetrahedron Lett.*, **28**, 777 (1987).
224. D. Kaufmann and R. Boese, *Angew. Chem., Int. Ed. Engl.*, **29**, 545 (1990).
225. J. M. Hawkins and S. Loren, *J. Am. Chem. Soc.*, **113**, 7794 (1991).
226. J. M. Hawkins, S. Loren and M. Nambu, *J. Am. Chem. Soc.*, **116**, 1657 (1994).
227. S. Kobayashi, M. Murakami, T. Harada and T. Mukaiyama, *Chem. Lett.*, 1341 (1991).
228. M. Takasu and H. Yamamoto, *Synlett*, 194 (1990).
229. D. Sartor, J. Saffrich and G. Helmchen, *Synlett*, 197 (1990).
230. D. Sartor, J. Saffrich, G. Helmchen, C. J. Richards and H. Lambert, *Tetrahedron: Asymmetry*, **2**, 639 (1991).
231. E. J. Corey, T.-P. Loh, T. D. Roper, M. D. Azimioara and M. C. Noe, *J. Am. Chem. Soc.*, **114**, 8290 (1992).
232. J.-P. Seerden and H. W. Scheeren, *Tetrahedron Lett.*, **34**, 2669 (1993).
233. E. J. Corey and T.-P. Loh, *J. Am. Chem. Soc.*, **113**, 8966 (1991).
234. J. A. Marshall and S. Xie, *J. Org. Chem.*, **57**, 2987 (1992).
235. E. J. Corey and T.-P. Loh, *Tetrahedron Lett.*, **34**, 3979 (1993).
236. P. Vogel, D. Fattori, F. Gasparini and C. Le Drian, *Synlett*, 173 (1990).
237. E. J. Corey, A. Guzman-Perez and T.-P. Loh, *J. Am. Chem. Soc.*, **116**, 3611 (1994).
238. (a) S. Itsuno, K. Kamahori, K. Watanabe, T. Koizumi and K. Ito, *Tetrahedron: Asymmetry*, **5**, 523 (1994).
(b) S. Itsuno, K. Watanabe and K. Ito, *React. Polym.*, **24**, 219 (1995).
(c) K. Kamahori, K. Ito and S. Itsuno, *J. Org. Chem.*, **61**, 8321 (1996).
(d) K. Kamahori, S. Tada, K. Ito and S. Itsuno, *Tetrahedron: Asymmetry*, **6**, 2547 (1995).
239. K. Furuta, Y. Miwa, K. Iwanaga and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 6254 (1988).
240. (a) K. Furuta, S. Shimizu, Y. Miwa and H. Yamamoto, *J. Org. Chem.*, **54**, 1481 (1989).
(b) K. Furuta, Q. Gao and H. Yamamoto, *Org. Synth. Theory Appl.*, **72**, 86 (1995).
241. K. Ishihara, Q. Gao and H. Yamamoto, *J. Org. Chem.*, **58**, 6917 (1993).
242. K. Ishihara, Q. Gao and H. Yamamoto, *J. Am. Chem. Soc.*, **115**, 10412 (1993).
243. T.-P. Loh, R.-B. Wang and K.-Y. Sim, *Tetrahedron Lett.*, **37**, 2989 (1996).

244. K. Ishihara and H. Yamamoto, *J. Am. Chem. Soc.*, **116**, 1561 (1994).
245. K. Ishihara and H. Yamamoto, *J. Am. Chem. Soc.*, **118**, 3049 (1996).
246. M. Reilly and T. Oh, *Tetrahedron Lett.*, **35**, 7209 (1994).
247. (a) M. Reilly and T. Oh, *Tetrahedron Lett.*, **36**, 217 (1995).
(b) M. Reilly and T. Oh, *Tetrahedron Lett.*, **36**, 221 (1995).
248. Y. Hayashi, J. J. Rohde and E. J. Corey, *J. Am. Chem. Soc.*, **118**, 5502 (1996).
249. K. Ishihara, S. Kondo, H. Kurihara and H. Yamamoto, *J. Org. Chem.*, **62**, 3026 (1997).
250. E. J. Corey and T. W. Lee, *Tetrahedron Lett.*, **38**, 5755 (1997).
251. K. Narasaka, M. Saitou and N. Iwasawa, *Tetrahedron: Asymmetry*, **2**, 1305 (1991).
252. K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989).
253. K. Narasaka, H. Tanaka and F. Kanai, *Bull. Chem. Soc. Jpn.*, **64**, 387 (1991).
254. (a) K. Narasaka and I. Yamamoto, *Tetrahedron*, **48**, 5743 (1992).
(b) K. Narasaka and I. Yamamoto, *Bull. Chem. Soc. Jpn.*, **67**, 3327 (1994).
255. E. J. Corey and Y. Matsumura, *Tetrahedron Lett.*, **32**, 6289 (1991).
256. T. A. Engler, M. A. Letavic, K. O. Lynch, Jr. and F. Takusagawa, *J. Org. Chem.*, **59**, 1179 (1994).
257. K. Mikami, M. Terada, Y. Motoyama and T. Nakai, *Tetrahedron: Asymmetry*, **2**, 643 (1991).
258. K. Mikami, Y. Motoyama and M. Terada, *J. Am. Chem. Soc.*, **116**, 2812 (1994).
259. E. J. Corey, T. D. Roper, K. Ishihara and G. Sarakinos, *Tetrahedron Lett.*, **34**, 8399 (1993).
260. K. Maruoka, N. Murase and H. Yamamoto, *J. Org. Chem.*, **58**, 2938 (1993).
261. J. B. Jaquith, J. Guan, S. Wang and S. Collins, *Organometallics*, **14**, 1079 (1995).
262. D. A. Evans, S. J. Miller and T. Lectka, *J. Am. Chem. Soc.*, **115**, 6460 (1993).
263. D. A. Evans, T. Lectka and S. J. Miller, *Tetrahedron Lett.*, **34**, 7027 (1993).
264. D. A. Evans, J. A. Murry, P. von Matt, R. D. Norcross and S. J. Miller, *Angew. Chem. Int. Ed. Engl.*, **34**, 798 (1995).
265. D. A. Evans, M. C. Kozlowski and J. S. Tedrow, *Tetrahedron Lett.*, **37**, 7481 (1996).
266. (a) I. W. Davies, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, **37**, 813 (1996).
(b) I. W. Davies, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, **37**, 1725 (1996).
267. I. W. Davies, L. Gerena, L. Gastonguay, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Chem. Comm.*, 1753 (1996).
268. I. W. Davies, L. Gerena, D. Cay, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, **38**, 1145 (1997).
269. A. K. Ghosh, P. Mathivanan and J. Cappiello, *Tetrahedron Lett.*, **37**, 3815 (1996).
270. D. A. Evans and D. M. Barnes, *Tetrahedron Lett.*, **38**, 57 (1997).
271. D. A. Evans and J. S. Johnson, *J. Org. Chem.*, **62**, 786 (1997).
272. D. A. Evans, E. A. Shaughnessy and D. M. Barnes, *Tetrahedron Lett.*, **38**, 3193 (1997).
273. S. Otto, G. Boccaletti and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **120**, 4238 (1998).
274. E. J. Corey and K. Ishihara, *Tetrahedron Lett.*, **33**, 6807 (1992).
275. T. Fujisawa, T. Ychiyanagi and M. Shimizu, *Tetrahedron Lett.*, **36**, 5031 (1995).
276. (a) G. Desimoni, G. Faita and P. Righetti, *Tetrahedron Lett.*, **37**, 3027 (1996).
(b) G. Desimoni, G. Faita, P. Righetti and N. Sardone, *Tetrahedron*, **52**, 12019 (1996).
277. M. Ordoñez, V. Guerrero-de la Rosa, V. Labastida and J. M. Llera, *Tetrahedron: Asymmetry*, **7**, 2675 (1996).
278. P. Carbone, G. Desimoni, G. Faita, S. Filippone and P. Righetti, *Tetrahedron*, **54**, 6099 (1998).
279. J. M. Takacs, E. C. Lawson, M. J. Reno, M. A. Youngman and D. A. Quincy, *Tetrahedron: Asymmetry*, **8**, 3073 (1997).
280. J. M. Takacs, D. A. Quincy, W. Shay, B. E. Jones and C. R. Ross, *Tetrahedron: Asymmetry*, **8**, 3079 (1997).
281. S. Kanemasa, Y. Oderaotoshi, H. Yamamoto, J. Tanaka and E. Wada, *J. Org. Chem.*, **62**, 6454 (1997).
282. Y. Honda, T. Date, H. Hiramatsu and M. Yamauchi, *Chem. Commun.*, 1411 (1997).
283. E. P. Kündig, B. Bourdin and G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.*, **33**, 1856 (1994).
284. A. D. Davenport, D. L. Davies, J. F. Fawcett, S. A. Garratt, L. Lad and D. R. Russell, *Chem. Commun.*, 2347 (1997).
285. D. L. Davies, J. Fawcett, S. A. Garratt and D. R. Russell, *Chem. Commun.*, 1351 (1997).

286. D. Carmona, C. Cativiela, S. Elipe, F. J. Lahoz, M. Pilar Lamata, M. Pilar López-Ram de Víu, L. A. Oro, C. Vega and F. Viguri, *Chem. Commun.*, 2351 (1997).
287. S. Kobayashi, I. Hachiya, H. Ishitani and M. Araki, *Tetrahedron Lett.*, **34**, 4535 (1993).
288. S. Kobayashi, M. Araki and I. Hachiya, *J. Org. Chem.*, **59**, 3758 (1994).
289. S. Kobayashi, H. Ishitani, I. Hachia and M. Araki, *Tetrahedron*, **50**, 11623 (1994).
290. I. E. Markó and G. R. Evans, *Tetrahedron Lett.*, **35**, 2771 (1994).
291. J. H. Rigby, *Org. React.*, **49**, 331 (1997).
292. K. N. Houk and L. J. Luskus, *J. Org. Chem.*, **38**, 3836 (1973).
293. B.-C. Hong and S.-S. Sun, *Chem. Commun.*, 937 (1996).
294. U. Niggli and M. Neuenschwander, *Helv. Chim. Acta*, **73**, 2199 (1990).
295. C.-Y. Liu and S.-T. Ding, *J. Org. Chem.*, **57**, 4539 (1992).
296. C.-Y. Liu, S.-T. Din, S.-Y. Chen, C.-Y. You and H.-Y. Shie, *J. Org. Chem.*, **58**, 1628 (1993).
297. M. F. Mahon, K. Molloy, C. A. Pittol, R. J. Pryce, S. M. Roberts, G. Ryback, V. Sik, J. O. Williams and J. A. Winders, *J. Chem. Soc., Perkin Trans. 1*, 1255 (1991).
298. (a) M. Yasuda, K. Harano and K. Kanematsu, *Tetrahedron Lett.*, **21**, 627 (1980).
(b) K. Harano and T. Hisano, *J. Chem. Res. (S)*, 356 (1993).
299. (a) H. Takeshita, Y. Z. Yan, N. Kato, A. Mori and T. Nozoe, *Tetrahedron Lett.*, **36**, 5195 (1995).
(b) H. Takeshita, Y. Z. Yan, N. Kato, A. Mori, H. Wakabayashi and T. Nozoe, *Tetrahedron Lett.*, **36**, 5199 (1995).
300. L. T. Scott and C. M. Adams, *J. Am. Chem. Soc.*, **106**, 4857 (1984).
301. A. Gamba, R. Gandolfi, R. Oberti and N. Sardone, *Tetrahedron*, **49**, 6331 (1993).
302. S. Özkar, H. Kurz, D. Neugebauer and C. G. Kreiter, *J. Organomet. Chem.*, **160**, 115 (1978).
303. T. van Houwelingen, D. J. Stufkens and A. Oskam, *Organometallics*, **11**, 1146 (1992).
304. C. G. Kreiter, R. Eckert, W. Frank and G. J. Reiß, *Inorg. Chim. Acta*, **251**, 95 (1996).
305. J. H. Rigby, H. S. Ateeq, N. R. Charles, S. V. Cuisiat, M. D. Ferguson, J. A. Henshilwood, A. C. Krueger, C. O. Ogbu, K. M. Short and M. J. Heeg, *J. Am. Chem. Soc.*, **115**, 1382 (1993).
306. J. H. Rigby and K. R. Fales, *Tetrahedron Lett.*, **39**, 5717 (1998).
307. J. H. Rigby and H. S. Ateeq, *J. Am. Chem. Soc.*, **112**, 6442 (1990).
308. J. H. Rigby, K. M. Short, H. S. Ateeq and J. A. Henshilwood, *J. Org. Chem.*, **57**, 5290 (1992).
309. J. H. Rigby, H. S. Ateeq and A. C. Krueger, *Tetrahedron Lett.*, **33**, 5873 (1992).
310. J. H. Rigby and K. R. Fales, *Tetrahedron Lett.*, **39**, 1525 (1998).
311. (a) V. Nair, G. Anilkumar, M. V. Nandakumar, B. Mathew and N. P. Rath, *Tetrahedron Lett.*, **38**, 6441 (1997).
(b) V. Nair, G. Anilkumar, K. V. Radhakrishnan, M. V. Nandakumar and S. Kumar, *Tetrahedron*, **53**, 15903 (1997).
312. (a) S. Kuroda, S. Hirooka, H. Iwaki, M. Ikeda, T. Nakao, M. Ogisu, M. Yasunami and K. Takase, *Chem. Lett.*, 2039 (1986).
(b) M. Yasunami, T. Hioki, Y. Kitamori, I. Kikuchi and K. Takase, *Bull. Chem. Soc. Jpn.*, **66**, 2273 (1993).
(c) S. Kuroda, M. Mouri, K. Hayashi, M. Oda, M. Yamada, I. Shimao, H. Osaki and M. Yasunami, *Chem. Lett.*, 85 (1994).
313. T. Nozoe, P.-W. Yang, C.-P. Wu, T.-S. Huang, T.-H. Lee, H. Okai, H. Wakabayashi and S. Ishikawa, *Heterocycles*, **29**, 1225 (1989).
314. T. Nozoe, H. Wakabayashi, S. Ishikawa, C.-P. Wu and P.-W. Yang, *Heterocycles*, **31**, 17 (1990).
315. T. Nozoe, H. Wakabayashi, K. Shindo, S. Ishikawa, C.-P. Wu and P.-W. Yang, *Heterocycles*, **32**, 213 (1991).
316. J. Daub, G. Hirmer, L. Jakob, G. Maas, W. Pickl, E. Pirzer and K. M. Rapp, *Chem. Ber.*, **118**, 1836 (1985).
317. A. Bäumler, J. Daub, W. Pickl and W. Rieger, *Chem. Ber.*, **118**, 1857 (1985).
318. J. Bindl, T. Burgemeister and J. Daub, *Justus Liebigs Ann. Chem.*, 1346 (1985).
319. E. Beer, M. Feuerer, A. Knorr, A. Mirlach and J. Daub, *Angew. Chem., Int. Ed. Engl.*, **33**, 1087 (1994).
320. T. Gareis, O. Köthe, E. Beer and J. Daub, *Proc. Electrochem. Soc.*, **96–10**, 1244 (1996).
321. V. Batroff and W. Flitsch, *Justus Liebigs. Ann. Chem.*, 617 (1987).
322. Y. Tominaga, Y. Shiroshita, Y. Matsuda and A. Hosomi, *Heterocycles*, **26**, 2073 (1987).

323. V. V. Simonyan, A. I. Zinin, E. V. Babaev and K. Jug, *J. Phys. Org. Chem.*, **11**, 201 (1998).
324. (a) N. E. Schore, *Chem. Rev.*, **88**, 1081 (1988).
(b) N. E. Schore, in *Comprehensive Organic Synthesis*, Vol. 5 (Eds. B. M. Trost, I. Fleming and L. A. Paquette), Chap. 9.4, Pergamon Press, Oxford, 1991, pp. 1129–1162.
(c) D. B. Grotjahn, in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds. E. W. Abel, F. G. A. Stone, G. Wilkinson and L. S. Hegedus), Chap. 7.3, Pergamon Press, Oxford, 1995, pp. 741–770.
325. M. Berthelot, *C. R. Acad. Sci.*, **62**, 905 (1866).
326. E. F. Ullman, *Chem. Ind. (London)*, 1173 (1958).
327. M. Lautens, W. Tam, J. C. Lautens, L. G. Edwards, C. M. Crudden and A. C. Smith, *J. Am. Chem. Soc.*, **117**, 6863 (1995).
328. M. Lautens, L. G. Edwards, W. Tam and A. J. Lough, *J. Am. Chem. Soc.*, **117**, 10276 (1995).
329. (a) R. Noyori, I. Umeda, H. Kawauchi and H. Takaya, *J. Am. Chem. Soc.*, **97**, 812 (1975).
(b) R. Noyori, H. Takaya and M. Yamakawa, *Bull. Chem. Soc. Jpn.*, **55**, 852 (1982).
330. (a) J. Furukawa, Y. Kobuke, T. Sugimoto and T. Fueno, *J. Am. Chem. Soc.*, **94**, 3633 (1972).
(b) G. Jenner, *Tetrahedron Lett.*, **28**, 3927 (1987).
(c) O. D. Lucchi, G. Licini, L. Pasquato and M. Senta, *Tetrahedron Lett.*, **29**, 831 (1988).
331. G. N. Fickes and T. E. Metz, *J. Org. Chem.*, **43**, 4057 (1978).
332. (a) J. E. Lyons, H. K. Myers and A. Schneider, *J. Chem. Soc., Chem. Commun.*, 636 (1978).
(b) J. E. Lyons, H. K. Myers and A. Schneider, *J. Chem. Soc., Chem. Commun.*, 638 (1978).
333. H. Brunner, M. Muschiol and F. Prester, *Angew. Chem. Int. Ed. Engl.*, **29**, 652 (1990).
334. H. Brunner and F. Prester, *J. Organomet. Chem.*, **414**, 401 (1991).
335. (a) G. Buono and O. Pardigon, *Tetrahedron: Asymmetry*, **4**, 1977 (1993).
(b) O. Pardigon, A. Tenaglia and G. Buono, *J. Org. Chem.*, **60**, 1868 (1995).
336. M. Lautens, J. C. Lautens and A. C. Smith, *J. Am. Chem. Soc.*, **112**, 5627 (1990).
337. K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.*, **23**, 539 (1984).
338. (a) D. B. Grotjahn and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **108**, 2091 (1986).
(b) R. Boese, A. P. Van Sickle and K. P. C. Vollhardt, *Synthesis*, 1374 (1994).
339. G. Sheppard and K. P. C. Vollhardt, *J. Org. Chem.*, **51**, 5496 (1986).
340. R. Boese, H.-J. Knölker and K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.*, **26**, 1035 (1987).
341. R. Boese, J. Rodriguez and K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.*, **30**, 993 (1991).
342. The terms *anti* and *syn* refer to the relative orientation of the cobalt atom with respect to the tertiary hydrogen atoms of the cyclohexadiene fragment.
343. K. P. C. Vollhardt, *Lect. Heterocycl. Chem.*, **9**, 59 (1987).
344. D. B. Grotjahn and K. P. C. Vollhardt, *Synthesis*, 579 (1993).
345. R. Boese, D. F. Harvey, M. J. Malaska and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **116**, 11153 (1994).
346. (a) J.-P. Gotteland and M. Malacria, *Tetrahedron Lett.*, **30**, 2541 (1989).
(b) J.-P. Gotteland and M. Malacria, *Synlett*, 667 (1990).
(c) C. Aubert, J.-P. Gotteland and M. Malacria, *J. Org. Chem.*, **58**, 4298 (1993).
347. P. Cruciani, C. Aubert and M. Malacria, *Synlett*, 105 (1996).
348. R. Stammler, K. Halvorsen, J.-P. Gotteland and M. Malacria, *Tetrahedron Lett.*, **35**, 417 (1994).
349. S. Brown, S. Clarkson, R. Grigg and V. Sridharan, *Tetrahedron Lett.*, **34**, 157 (1993).
350. (a) T. Tsuda, A. Tobisawa, H. Mizuno and A. Takeda, *Chem. Commun.*, 201 (1997).
(b) T. Tsuda, H. Mizuno, A. Takeda and A. Tobisawa, *Organometallics*, **16**, 932 (1997).
(c) T. Tsuda, M. Shimada and H. Mizuno, *J. Chem. Soc., Chem. Commun.*, 2371 (1996).
351. S. Ikeda, H. Watanabe and Y. Sato, *J. Org. Chem.*, **63**, 7026 (1998).
352. (a) G. J. Balaich and I. P. Rothwell, *J. Am. Chem. Soc.*, **115**, 1581 (1993).
(b) E. S. Johnson, G. J. Balaich and I. P. Rothwell, *J. Am. Chem. Soc.*, **119**, 7685 (1997).
353. S. Kotha and E. Brahmachary, *Tetrahedron Lett.*, **38**, 3561 (1997).
354. (a) R. Grigg, R. Scott and P. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1357 (1988).
(b) S. J. Neeson and P. J. Stevenson, *Tetrahedron*, **45**, 6239 (1989).

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CHAPTER **6**

Cycloaddition to give heterocycles

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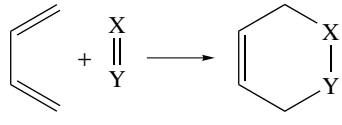
I. INTRODUCTION

The formation of heterocycles by cycloaddition reactions of conjugated dienes is the subject of this chapter. Almost the entire account is devoted to the Diels–Alder reaction of dienes with heterodienophiles to yield six-membered ring compounds (equation 1). Many such reactions have been reported and there is a plethora of reviews. Some[1a–p] are general; others are cited at appropriate places in the text. This account is highly selective, concentrating on recent work with particular regard to the stereochemistry of these processes.

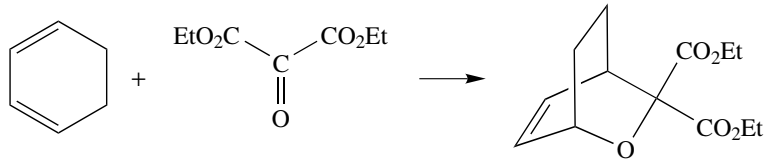


(1)

Some addition reactions leading to five-membered ring compounds are described at the end.

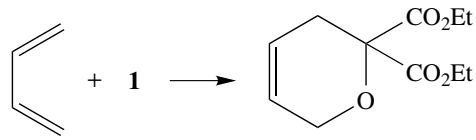
II. ADDITION TO CARBONYL COMPOUNDS

Dienes do not react with carbonyl compounds unless the latter are activated by electron-withdrawing substituents such as carboxyl groups. Cyclohexa-1,3-diene, for example, adds diethyl mesoxalate **(1)** at 120 °C to form **2** (equation 2)[2]. Other cycloadditions of this ester with various dienes, which were carried out in a sealed tube at 130–135 °C, are shown in equations 3 and 4[3]. It is noteworthy that no product was isolated from the action of diethyl mesoxalate on cyclopentadiene; it was suggested[3] that the cycloadduct reverted to its components at the high temperature required for the reaction.



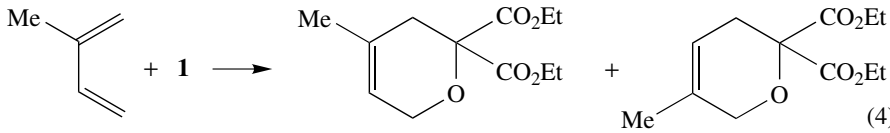
(2)

(1) **(2)**



(3)

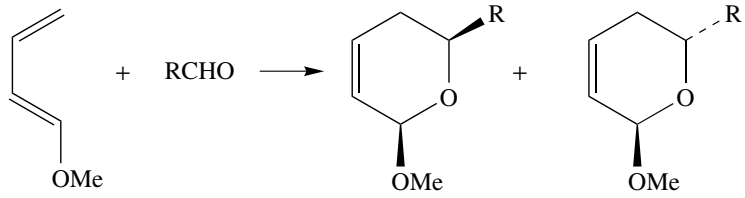
78%



(4)

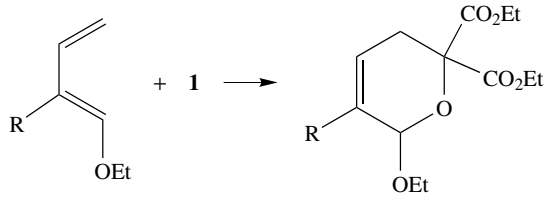
80% 7%

The presence of electron-donating substituents in the diene enables it to react with simple aldehydes: thus both acetaldehyde and benzaldehyde add to 1-methoxy-1,3-butadiene at 50–65 °C under high pressure (20 Kbar) to give dihydropyrans as 70 : 30 mixtures of *cis*- and *trans*-isomers (equation 5)[4]. The combination of electron-rich diene/electron-poor dienophile makes it possible to perform the reaction under milder conditions. 2-Alkyl-1-ethoxy-1,3-butadienes and diethyl mesoxalate afford dihydropyrans almost quantitatively (equation 6)[5].



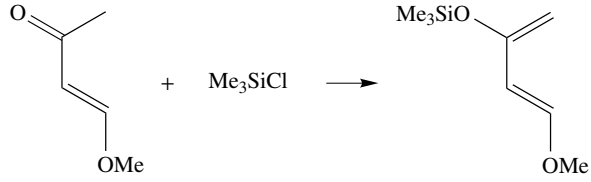
(5)

R = Me or Ph



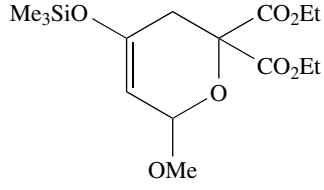
(6)

An outstandingly reactive diene is 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene ('Danishefsky's diene') **4**, prepared by the action of trimethylsilyl chloride on the ketone **3** in the presence of zinc chloride/triethylamine (equation 7)[6]. The reaction of diethyl mesoxalate with Danishefsky's diene gives the dihydropyran **5**; with the (trimethylsilyloxy)dienes **6** and **7**, mixtures of dihydropyrans are obtained, in which the 'meta-isomers' predominate (equations 8 and 9)[7].



(7)

(3) **(4)**



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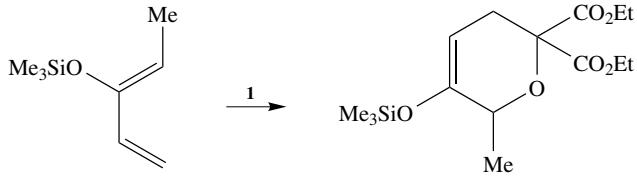
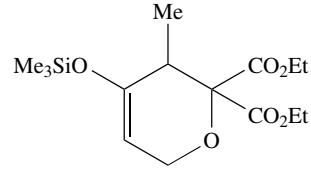


(6)

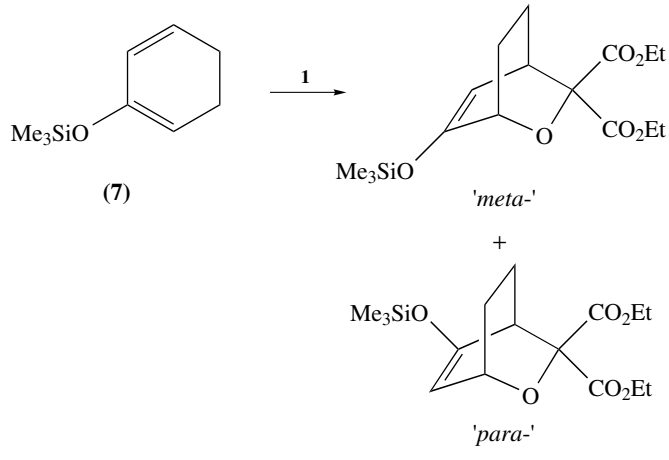
'meta-'

+



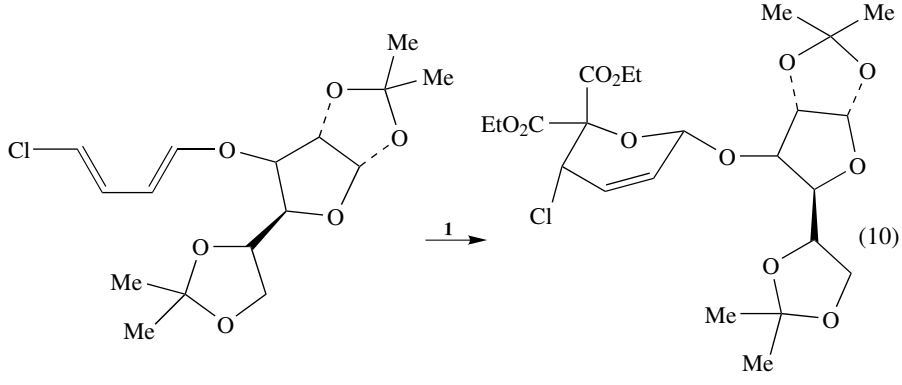
'para-'

(8)



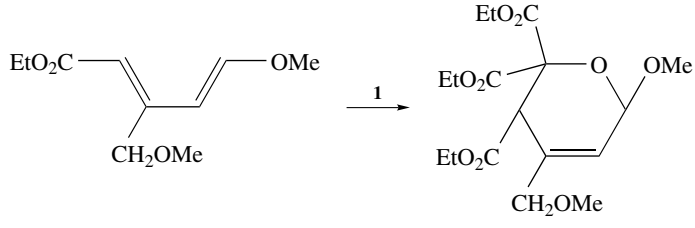
(9)

Equation 10 shows an example of the synthesis of a chiral functionalized hexapyranoside from diethyl mesoxalate and the butadienyl ether of a protected sugar[8a,b].

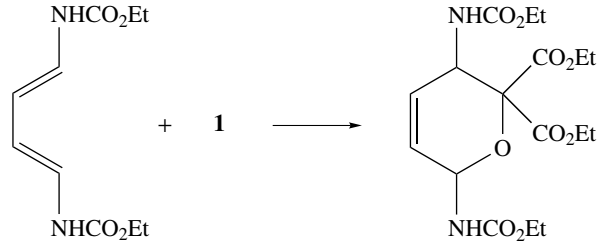


(10)

Other carbohydrate syntheses include the formation of dihydropyrans from diethyl mesoxalate and 1-methoxybutadienes (e.g. equation 11)[9]. The butadiene **8**, which is activated by the presence of two alkoxycarbonylamino groups, adds to diethyl mesoxalate in DMF during 44 h at 180 °C in an autoclave to give the cycloadduct **9** in 34% yield (equation 12)[10].

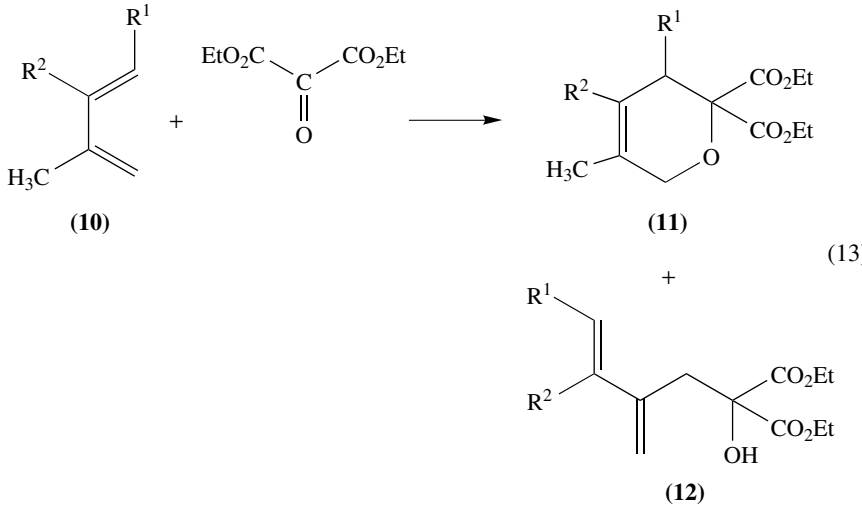


(11)

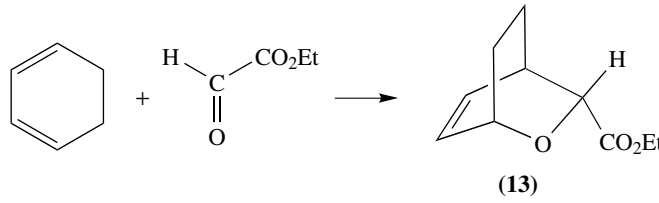


(8) (9) (12)

In recent years, much work has been done on catalyzed and asymmetric cycloaddition reactions. In the presence of 5 mol% bismuth trichloride, the simple dienes **10** ($R^1 = R^2 = H$; $R^1 = H$, $R^2 = Me$; or $R^1 = Me$, $R^2 = H$) react with diethyl mesoxalate to afford mixtures of the cycloadducts **11** and the products **12** of an ene-reaction (equation 13)[11,12]. 1,3-Cyclohexadiene and ethyl glyoxylate give solely the *endo* adduct **13** in 50% yield (equation 14)[12].



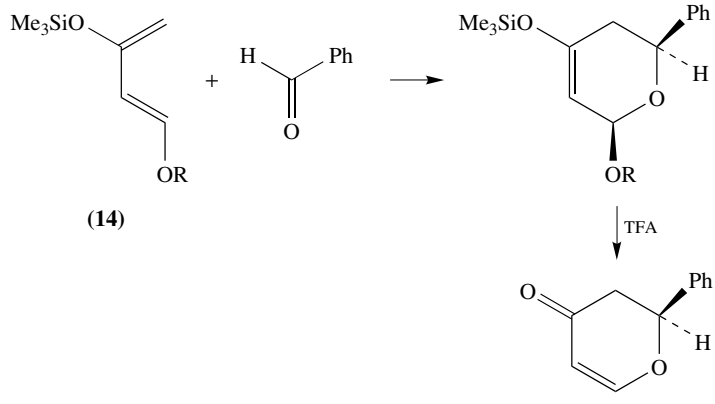
(10) (11) (13) (12)



(14) (13)

The first report of a cycloaddition reaction in the presence of an optically active catalyst[13] appeared in 1983[14a]. The dienes **14** add to benzaldehyde in the presence of 1 mol% of the chiral lanthanide NMR shift reagent Eu $(hfc)_3$, i.e. tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III), to give, after treatment with trifluoroacetic acid, the dihydro-γ-pyrone **15** enriched in the (*R*)-enantiomer, the degree of

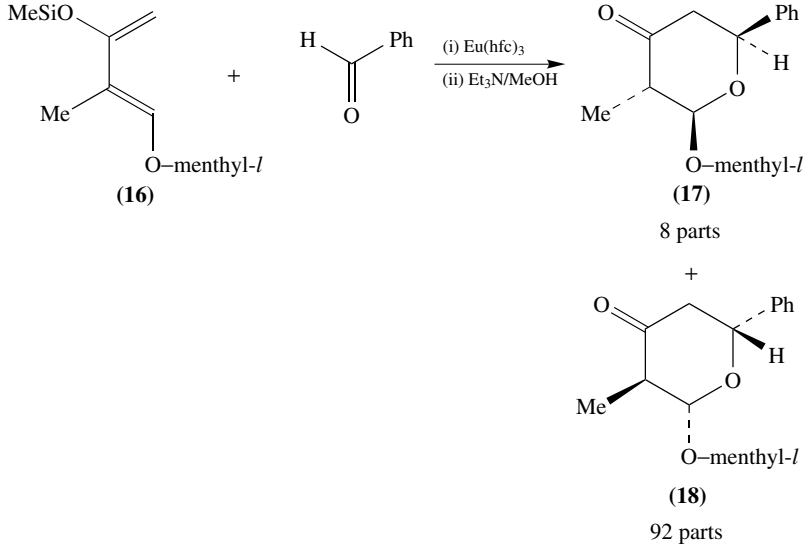
asymmetric induction depending on the nature of the group R (equation 15)[14].



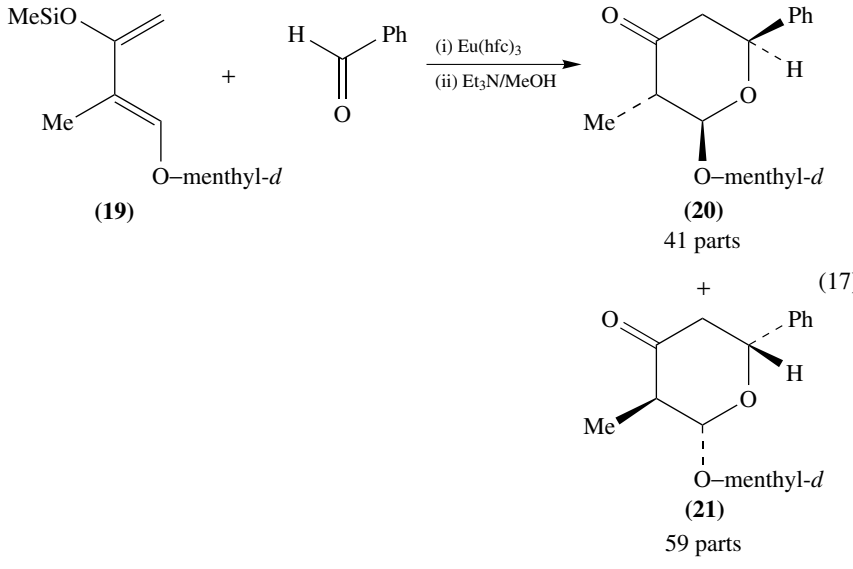
(15)

For R = Me : 18% ee
For R = *i*-Pr : 28% ee
For R = *t*-Bu : 38% ee

The 1,3-butadiene **16**, which contains the chiral auxiliary *l*-menthyl group, reacts with benzaldehyde in the presence of $Eu(hfc)_3$ to yield a mixture of the diastereomeric products **17** and **18** (equation 16); the butadiene **19** similarly affords a mixture of **20** and **21** (equation 17). It is seen that for the combination *l*-menthyl auxiliary/chiral catalyst the facial selectivity is much higher than for the combination *d*-menthyl auxiliary/chiral catalyst, which points to an 'interactivity' between the chiral auxiliary and the chiral catalyst[14].

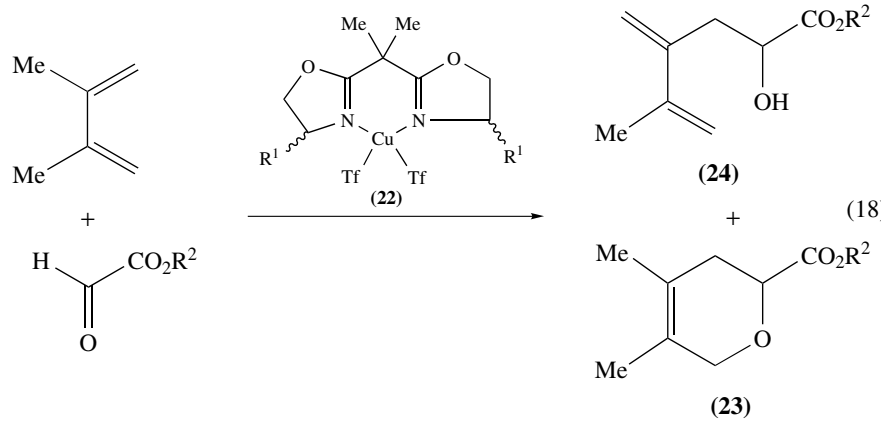


(16)

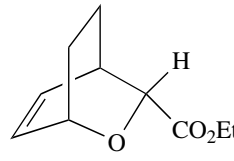


(17)

The chiral copper(II) bisoxazoline compounds **22** (R^1 = *t*-Bu or Ph, Tf = trifluoromethanesulfonyl) catalyze the enantioselective reactions of 2,3-dimethylbuta-1,3-diene with glyoxylic esters HCO_2R^2 (R^2 = Me, Et or *i*-Pr) to yield mixtures of Diels–Alder and ene products, **23** and **24**, the proportions of which depend on the structure of the chiral ligand, the nature of R^2 and the temperature of the reaction (equation 18). Thus, ethyl glyoxylate and the diene in the presence of (*R*)-**22** (R^1 = Ph) at −30 °C gave the (*S*)-dihydropyran **23** (R^2 = Et) (13%) in 85% enantiomeric excess (ee), together with 7% of the ene-product **24** (R^2 = Et)[15]. Treating 1,3-cyclohexadiene with ethyl glyoxylate in the presence of 5 mol% (*S*)-**22** (R^1 = *t*-Bu) in nitromethane led to the smooth formation of the cycloadduct **25** in 66% yield and 97% ee[16].

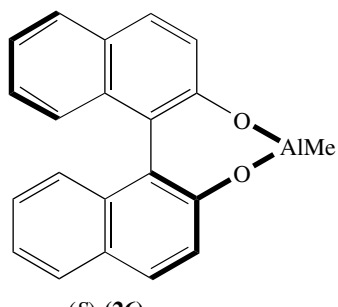


(18)

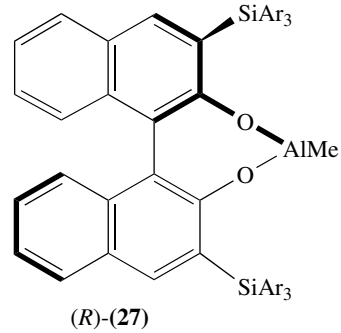


(25)

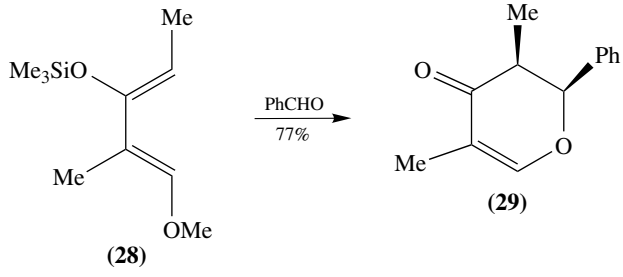
Under the influence of 20 mol% of the chiral aluminum complex (*S*)-**26**, 2,3-dimethyl-1,3-butadiene adds to ethyl glyoxylate in dichloromethane at −78 °C to room temperature during 20 h to produce a mixture of the cycloadduct **23** (R^2 = Et) (73% yield, 97% ee) and the ene product **24** (R^2 = Et) (9% yield, 88% ee)[17]. The analogous aluminum complexes (*R*)-**27** and (*S*)-**27** (Ar = Ph or 3,5-xylyl) (10 mol% in toluene) catalyze the Diels–Alder reaction of benzaldehyde with the diene **28** to give, after the addition of trifluoroacetic acid, the dihydropyrone **29** in 95% ee, accompanied by a small amount of the corresponding *trans*-isomer (equation 19)[18].



(*S*)-**(26)**

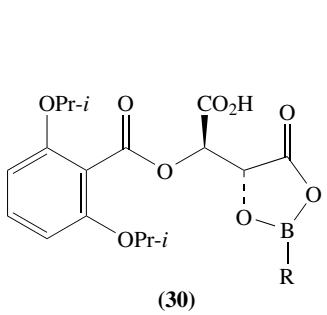


(*R*)-**(27)** (19)



(28) **(29)**

Benzaldehyde reacts with the diene **28** in the presence of 20 mol% of the chiral boric acids **30** (R = *n*-Bu, Ph or 2-$MeOC_6H_4$), obtained from alkylboric acids and the appropriate derivatives of tartaric acid, at −78 °C for 4–9 h to afford the *cis*-products **29** in 56–95% yields and 87–97% ee[19,20]. Benzaldehyde, cinnamaldehyde and various aliphatic aldehydes (*n*-hexanal, *n*-heptanal etc) add directly to Danishefsky's diene **4** in ether at −30 °C in the presence of the (*R*,*R*)-salen chromium complexes **31** (X = Cl, N_3, F or BF_4) and 4 Å molecular sieves to afford the cycloadducts **32** (e.g. R = Ph, PhCH=CH) in 70–93% ee[21].



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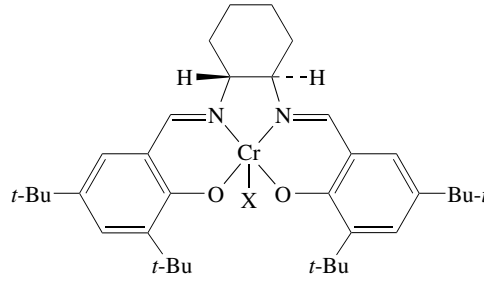

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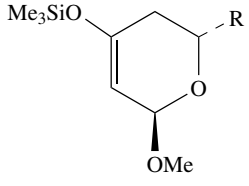

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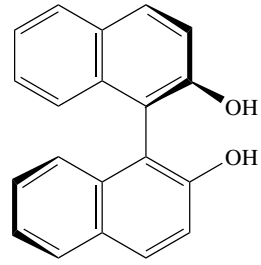
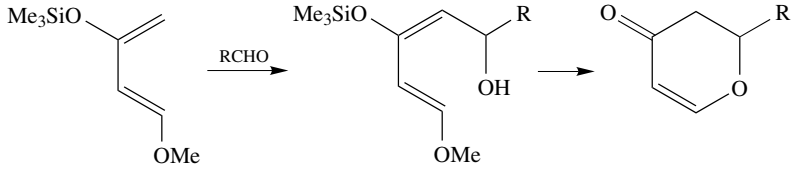


(33)

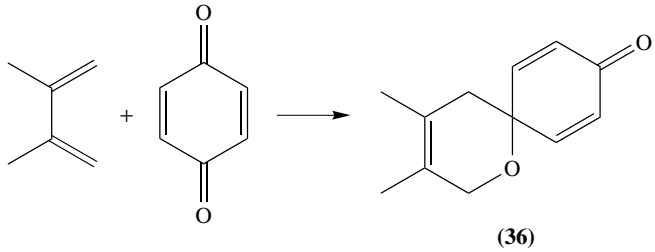
It has been shown[22] that the reaction of the diene **4** with aldehydes RCHO in the presence of a catalyst prepared from (*R*)-BINOL **(33)** and Ti(OPr-*i*)$_3$, which affords the dihydro-γ-pyrones **35** in good yields and high ee, proceeds by a two-step sequence via the open-chain adducts **34**, which cyclize to the products on treatment with trifluoroacetic acid (equation 20).



(20)

(4) **(34)** **(35)**

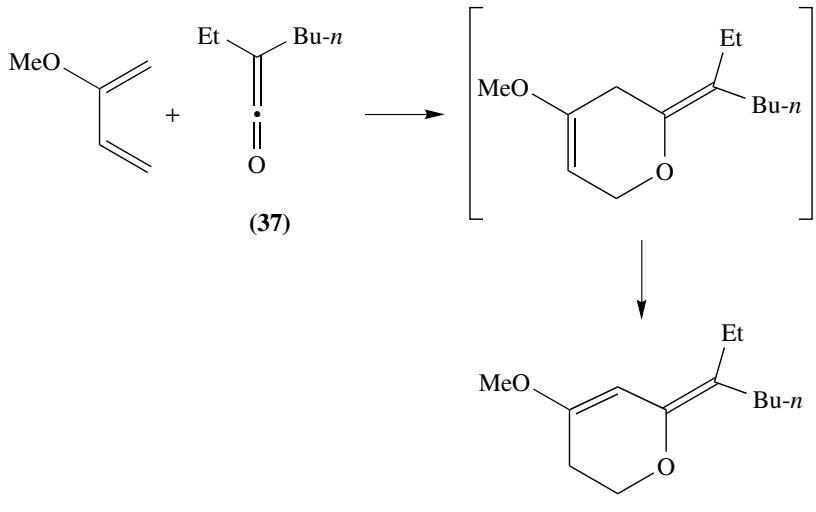
The carbonyl group of *p*-benzoquinone is capable of adding to dienes on irradiation to yield the spiro-compounds **36** (equation 21)[23].



(21)

(36)

The ketene **37** reacts with 2-methoxybutadiene to afford a 63% yield of the rearranged methylenedihydropyran **38** (equation 22)[24]. In contrast, dimethylketene and 1-methoxybutadiene form a 'normal cycloadduct', the cyclobutanone **39** (equation 23)[24].



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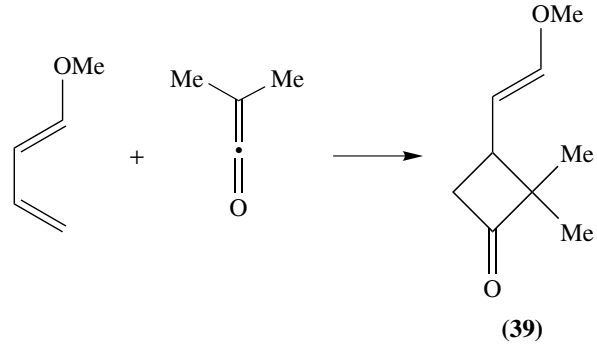
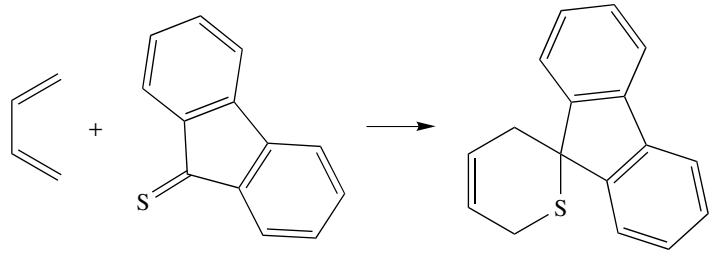


(23)

III. ADDITION TO C=S COMPOUNDS

Thiocarbonyl compounds are more reactive dienophiles than their carbonyl counterparts.

Thioketones, such as thiofluorenone, hexafluorothioacetone and perfluorocyclobutanone, add to a variety of 1,3-dienes to give dihydrothiapyrans (e.g. equation 24)[25]. Styrene yields a 1 : 2 adduct with hexafluorothioacetone (equation 25)[25]. The reactions of thioacetophenone and thiobenzophenone with isoprene and 2-chlorobutadiene yield mixtures of regioisomers in quantitative yields (e.g. equation 26)[26].



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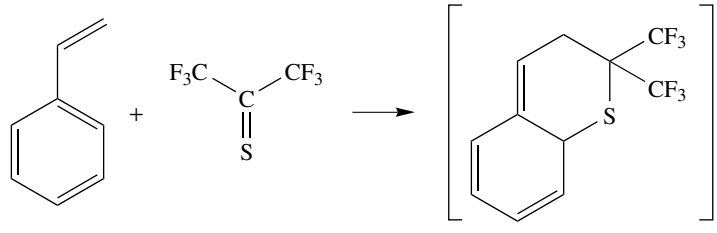
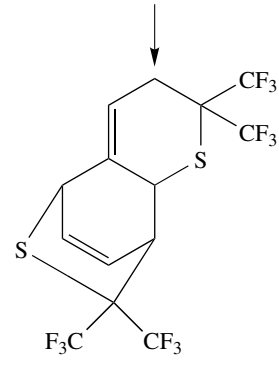
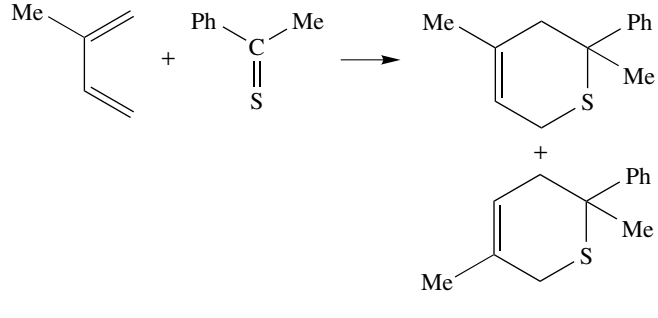




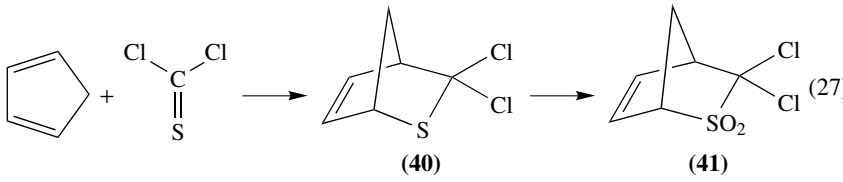
(25)



(26)

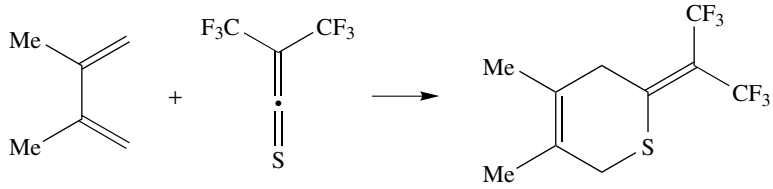
Thiophosgene forms the unstable cycloadduct **40** with cyclopentadiene, which was characterized by oxidation to the sulfone **41** with *m*-chloroperbenzoic acid (equation 27)[27].

Bis(trifluoromethyl)thioketene **(42)** is sufficiently stable to handle. It readily adds to 2,3-dimethyl-1,3-butadiene to yield **43** (equation 28)[28], 1,2,4,7-(tetrakis)methylenecyclooctane gives **44** (equation 29)[29] and cyclooctatetraene affords **46** via the valence isomer **45** (equation 30)[30].



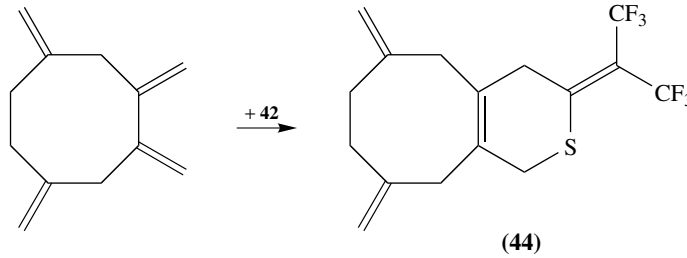
(27)

(40) **(41)**



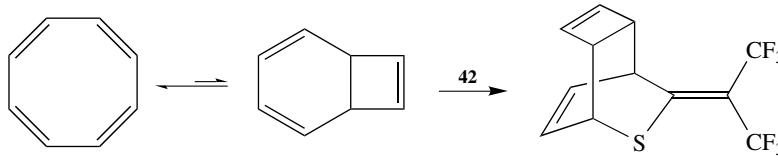
(28)

(42) **(43)**



(29)

(44)



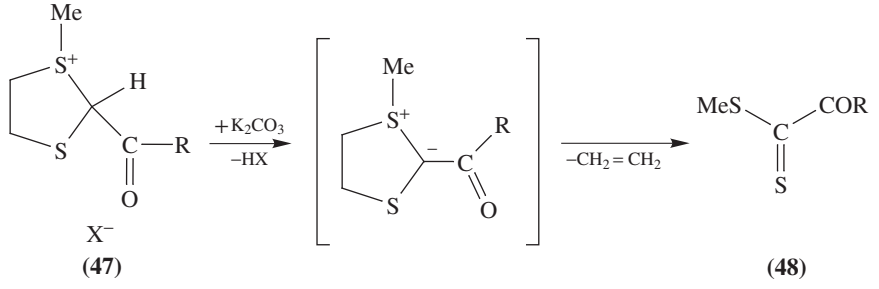
(30)

(45) **(46)**

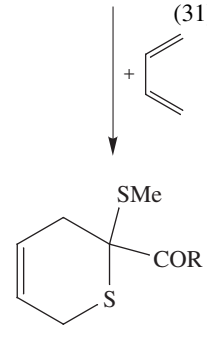
The dithio esters **48** (R = Me, Ph or OEt) are generated by treatment of the salts **47** with bases; they are trapped as Diels–Alder adducts in the presence of dienes (equation 31)[31]. Penta-1,3-diene gave mainly the regioisomers **49** in this reaction (equation 32)[31].

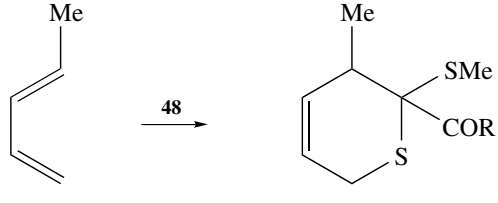
The cycloaddition of chlorosulfines to dienes may give mixtures of geometrically isomeric products (equation 33)[32]. A mixture of *exo*- and *endo*-cycloadducts is obtained from thiofluorenone *S*-oxide and cyclopentadiene (equation 34)[32].

Dichlorosulfine **(50)**, prepared by oxidation of thiophosgene with *m*-chloroperbenzoic acid, is a powerful dienophile. It reacts with cyclopentadiene in pentane at $-40\,^{\circ}C$ to give the cycloadduct **51** (equation 35)[32].



(47) **(48)**

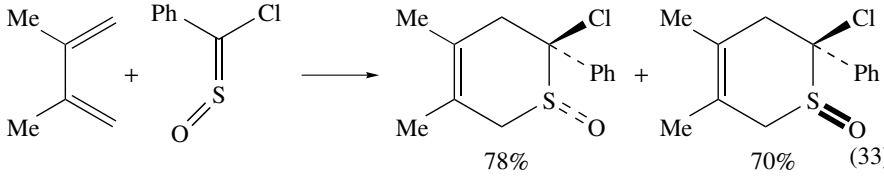




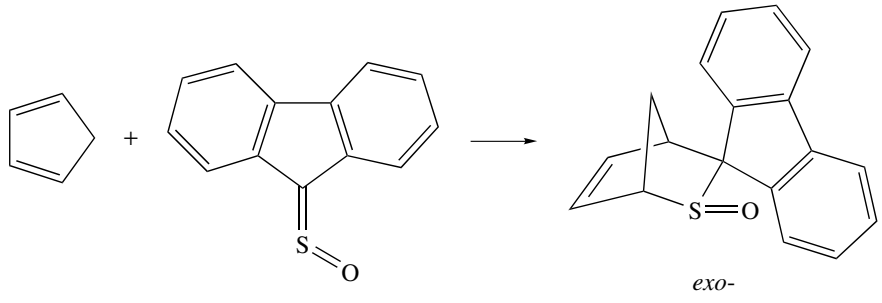
(32)

(49)

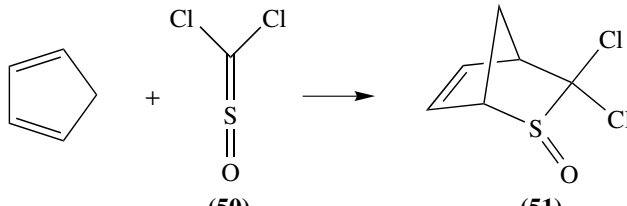
R = Me, Ph, OEt



(33)



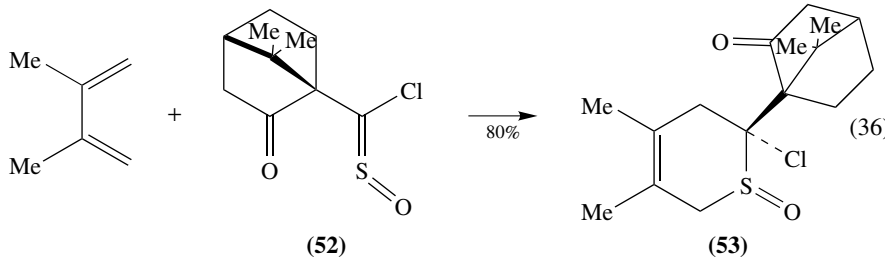
(34)



(50) (51)

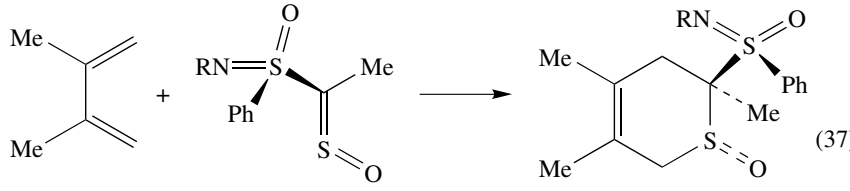
(35)

10-Chloro-10-sulfinylcamphor **(52)** reacts with 2,3-dimethyl-1,3-butadiene during one week at 70 °C to yield solely the diastereomer **53** (equation 36)[33]. Addition of the optically active sulfoximinosulfines **54a** and **54b** to the above diene during 16 h at room temperature gave in each case a single diastereomer **55a**, **55b** in 40 and 66% yields, respectively (equation 37); hence, complete asymmetric induction was observed[33].



(52) (53)

(36)

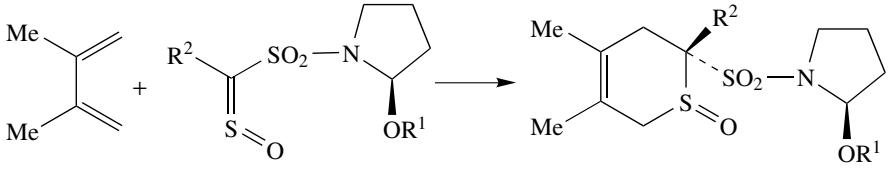


(37)

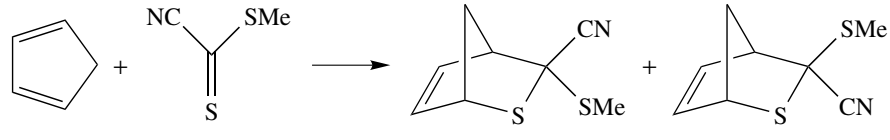
(54a) R = Me **(55a)** R = Me

(54b) R = Ts **(55b)** R = Ts

Reactions of the sulfonylsulfines **56** (e.g. $R^1 = R^2 =$ Bn; $R^1 =$ Me, $R^2 =$ Ph; $R^1 = CPh_3$, $R^2 =$ Ph etc.) derived from (*S*)-proline with 2,3-dimethyl-1,3-butadiene afford dihydrothiopyran *S*-oxides **57** with asymmetric induction of up to 40% (equation 38)[34]. Methyl cyanodithioformate **58** is a very reactive dienophile; with cyclopentadiene it forms a mixture of 40 parts of the *endo*-adduct **59** and 60 parts of the *exo*-isomer **60** (equation 39)[35].

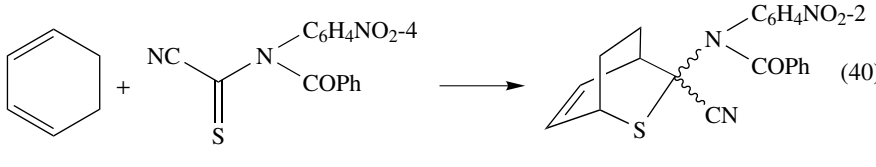


(56) **(57)** (38)

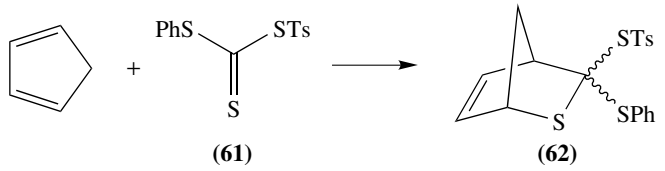


(58) **(59)** **(60)** (39)

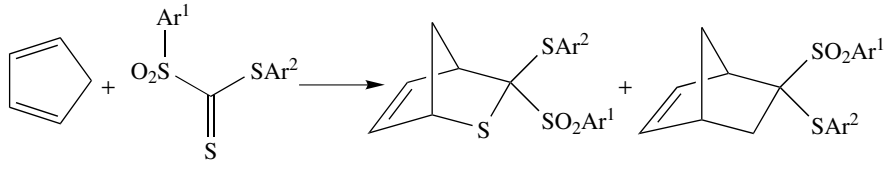
Cyanothioformamides NC−CS−NR^1−COR^2 (R^1 = Ph or 4-$O_2NC_6H_4$; $R^2 = CF_3$ or Ph) comprise another class of reactive dienophiles (e.g. equation 40)[36]. The trithiocarbonate **61** adds to cyclopentadiene to yield **62** (equation 41)[37]. Trithiocarbonate *S*,*S*-dioxides **63** (Ar^1 = 4-MeC_6H_4 or 4-ClC_6H_4; Ar^2 = Ph or 4-ClC_6H_4) react instantly with cyclopentadiene to afford mixtures of *endo*- and *exo*-cycloadducts **64** and **65**, respectively, in which the former predominate (equation 42)[38]. The adducts produced from acyclic dienes are unstable; they readily eliminate arylsulfinic acids to yield thiopyrans (equation 43)[38].



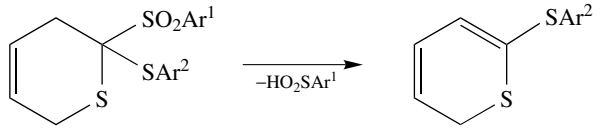
(40)



(61) (62) (41)

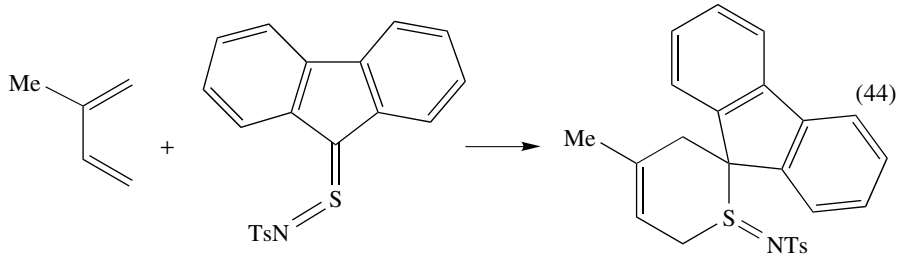


(63) (64) (65) (42)

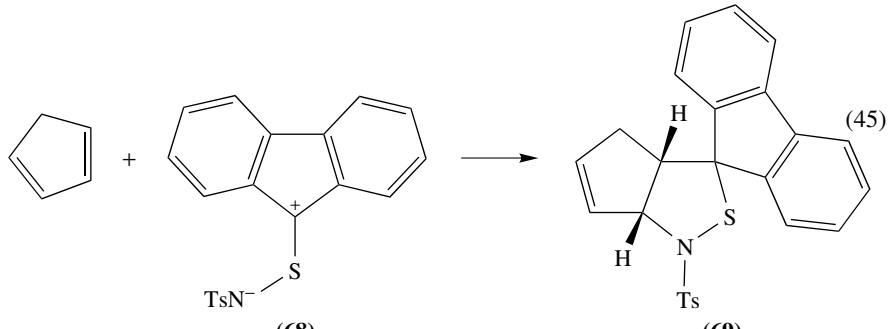


(43)

The thione *S*-imide **66** adds to isoprene to afford solely the regioisomer **67** (equation 44); in contrast, the imide functions as a 1,3-dipole **68** in the reaction with cyclopentadiene to yield **69** (equation 45)[39].



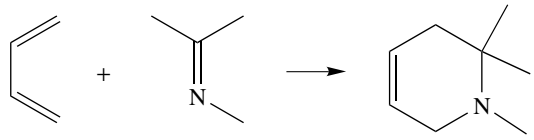
(66) (67) (44)



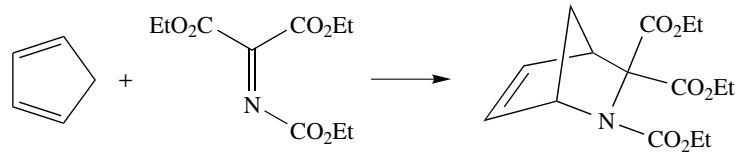
(68) (69) (45)

IV. ADDITION TO IMINES AND CYANIDES

The cycloaddition of dienes to imines to form tetrahydropyridines (equation 46) has been investigated extensively[40]. Ordinary imines are not sufficiently reactive to add to dienes; they have to be activated by the presence of electron-withdrawing substituents. Thus the triester **70** adds to cyclopentadiene under atmospheric pressure to form **71** (equation 47). The reactions with other dienes (cyclohexadiene, isoprene or 2,3-dimethylbuta-1,3-diene) require high pressures[41].



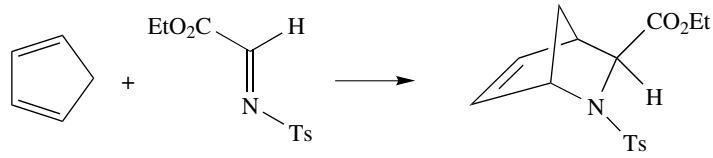
(46)



(47)

(70) **(71)**

The sulfonylimine **72** reacts with cyclopentadiene in benzene at 0 °C to afford solely the *exo*-adduct **73** in 84% yield (equation 48)[42]. The unstable imine **75**, formed from the phosphorus compound **74** and ethyl glyoxylate by an aza-Witig reaction, adds to dienes *in situ* (equation 49)[43].

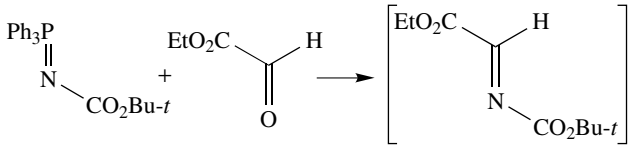


(48)

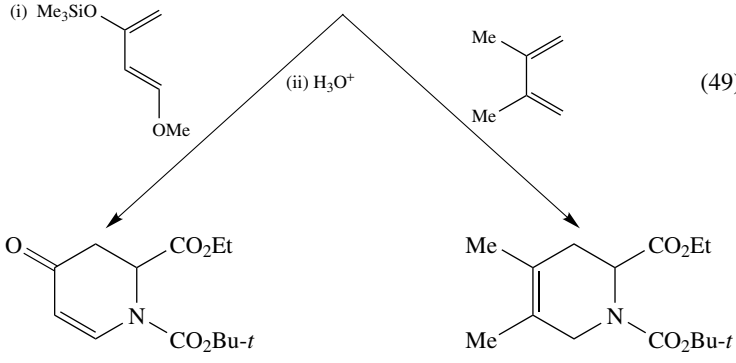
(72) **(73)**

Simple imines undergo Diels–Alder reactions in the presence of suitable catalysts. Lanthanide triflates, which are stable in water, are especially effective. Thus in the presence of 10 mol% of ytterbium or scandium triflate, Danishefsky's diene **4** reacts with benzylideneaniline in acetonitrile at 0 °C to give the dihydropyridone **76** quantitatively (equation 50)[44]; analogous products are obtained from **4** and furylideneaniline, benzylidenebenzylamine and pentylidenebenzylamine[45]. In a one-pot version of the reaction, a mixture of an aldehyde, an amine and the diene **4** in acetonitrile containing magnesium sulfate is treated with 10 mol% ytterbium triflate to afford the dihydropyridone in *ca* 80% yield[45]. Even phenylglyoxal monohydrate can be employed[44].

In the reaction of benzylideneaniline with cyclopentadiene, the imine functions as an azadiene to yield the rearranged Diels–Alder adduct **77** (equation 51)[44,45a]. In a study of the effect of various Lewis acids ($ZnCl_2$, $TiCl_4$, Et_2AlCl and $SnCl_4$) on diastereoselective cycloadditions of Danishefsky's diene to the imines **79**, obtained from the chiral aldehydes **78** (R = MeO or Cl), it was found that $SnCl_4$ was the most effective, giving the optically active products in high yields and excellent ee values (equation 52)[46].



(**74**) (**75**)



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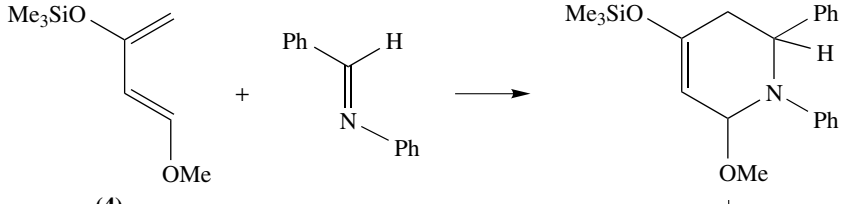
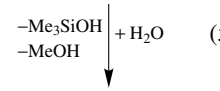
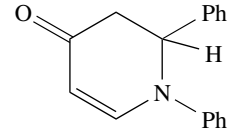


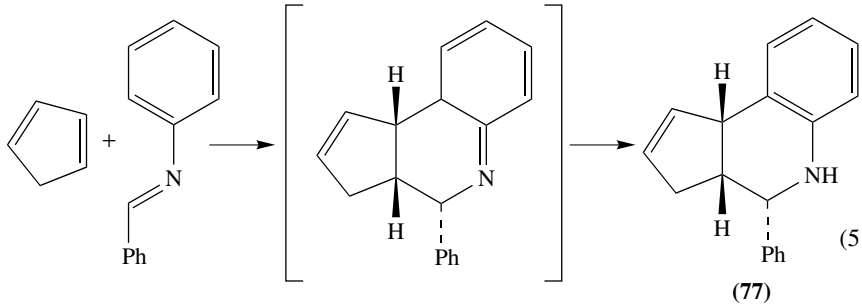
(**4**)



(50)

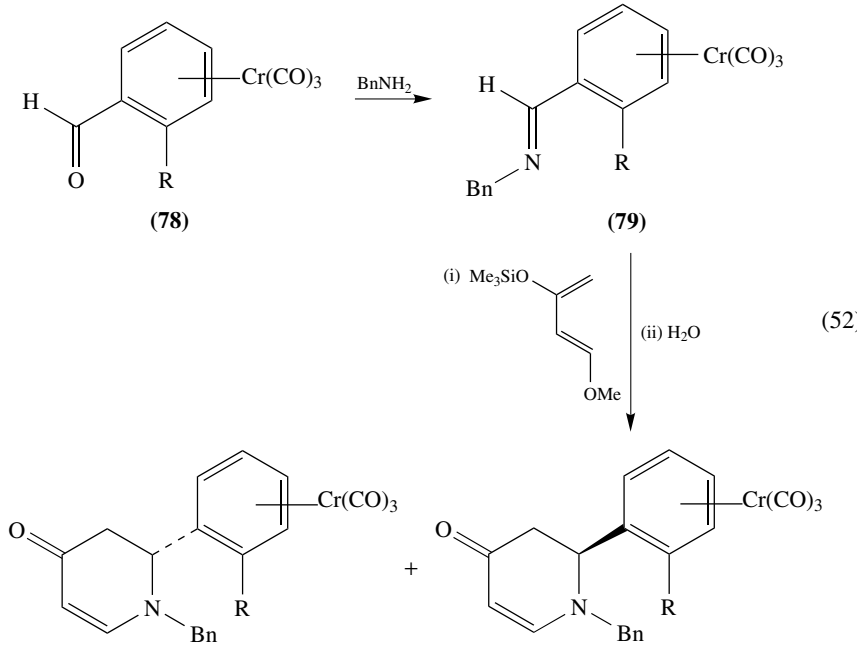


(**76**)



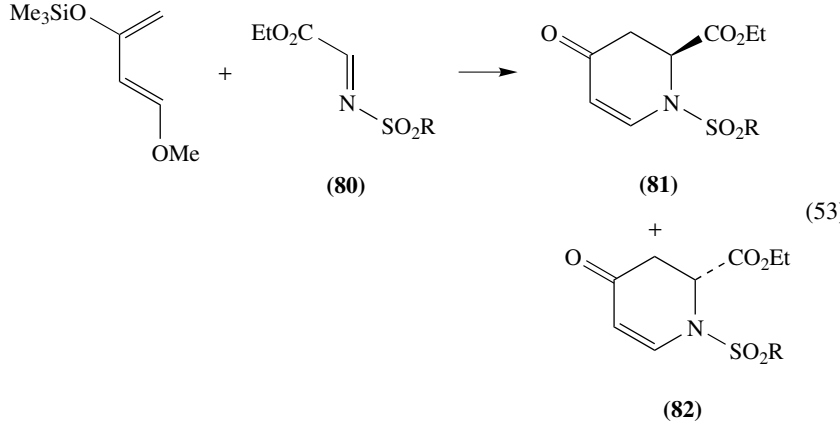
(51)

(**77**)



(52)

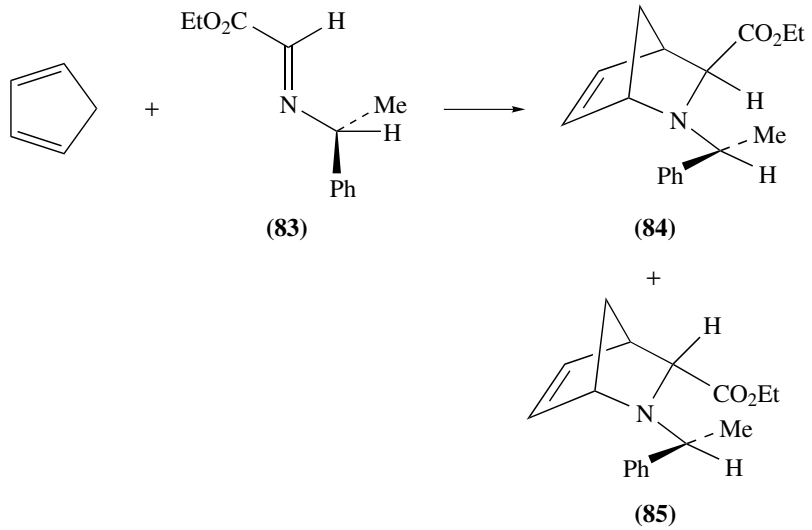
A moderate degree of diastereoselectivity was observed for the reaction of the *N*-[(1*R*)-(−)-camphor-10-ylsulfonyl]imine **80** [R = (1*R*)-(−)-camphor-10-yl] with Danishefsky's diene to yield, after treatment with concentrated hydrochloric acid, a 1 : 1.86 mixture of the dihydropyridones **81** and **82** (equation 53). In the presence of Ti(OPr-*i*)$_4$, the ratio was 1 : 2.33; with Et_2AlCl it was reversed to 1.44 : 1[47].



(53)

The imine **83** derived from (*R*)-phenylethylamine adds to cyclopentadiene in the presence of trifluoroacetic acid and a catalytic amount of water to afford a 97 : 3 mixture

of *exo*- and *endo*-isomers **84** and **85**, respectively, each of which was produced in high diastereomeric excess (equation 54). The reaction of **83** with cyclohexa-1,3-diene proceeded analogously, giving a 92 : 8 mixture of *exo*- and *endo*-cycloadducts[48].



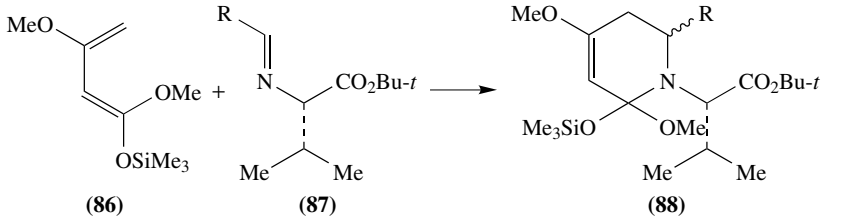
(83) **(84)** **(85)** (54)

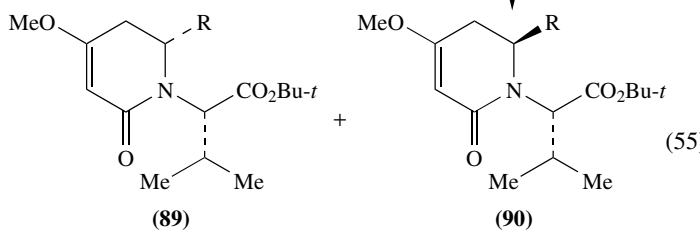
The action of the valine derivatives **87** on the diene **86** under $EtAlCl_2$ catalysis resulted in a mixture of cycloadducts **88**, which on hydrolysis with aqueous methanolic sodium carbonate furnished a mixture of the dihydro-2-pyridones **89** and **90** and the esters **91** and **92**. In the case of imines derived from aliphatic aldehydes, e.g. **87** (R = Pr), all four types of product were isolated, whereas imines from aromatic aldehydes, **87** (R = Ph, 3-ClC_6H_4 etc.), gave only the esters **91** and **92** (equation 55). All products were formed in yields of 64–84% and in high de[49].

The optically active catalyst **93**, formed from triphenyl borate and (*R*)-binaphthol, catalyzes the asymmetric reaction of the dienes **94** (R^1 = H or Me) with the imines **95** (R^2 = Ph, 3-pyridyl or cyclohexyl). The products **96** are formed in greater than 80% ee (equation 56). Treatment of the diene **94** (R^1 = H) (Danishefsky's diene) with the chiral imine **97** leads to the diastereomers **98** and **99** in the ratio 99 : 1 (equation 57)[50].

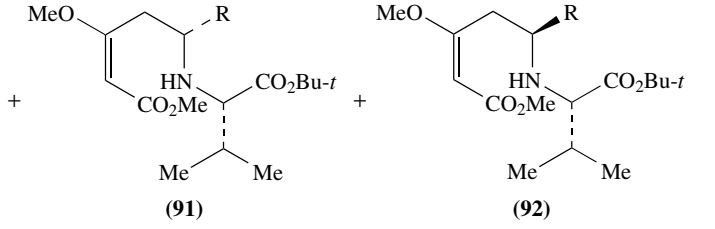
Under the influence of zinc chloride, Danishefsky's diene **4** reacts with simple imines to give dihydro-γ-pyridones **100** (e.g. R^1 = *n*-Bu, Ph, Bn; R^2 = Pr, *i*-Pr, Ph) in 62–76% yields (equation 58)[51]. In contrast, the Et_2AlCl-catalyzed reaction of the diene **86** with benzylidenemethylamine **(101)** results in the formation of the dihydro-α-pyridone **102** (equation 59)[52].

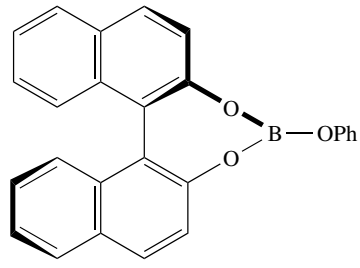
The first step in the total synthesis of the alkaloid (±)-ipalbidine **104** was the reaction of the diene **103** with Δ^1-pyrroline (equation 60)[53]. The proportions of *threo*- and *erythro*-dihydro-α-pyridones, **106** and **107**, respectively, produced in the diethylaluminium chloride-catalyzed reactions of the α-benzyloxyimines **105** (R = *n*-C_5H_{11}, *i*-Pr or *t*-Bu) with the diene **86** (equation 61), depend on the nature of R and the amount of imine used[54].

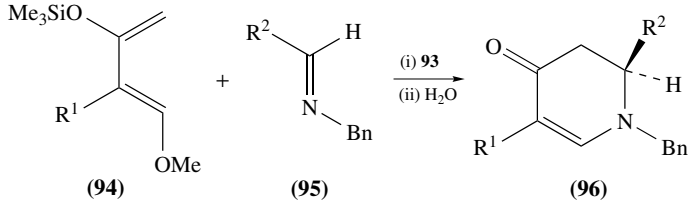

MeO
OMe
OSiMe3
R
N
CO2Bu-t
Me
Me
Me3SiO
OMe
(86)
(87)
(88)


MeO
R
N
CO2Bu-t
O
Me
Me
(89)
(90)

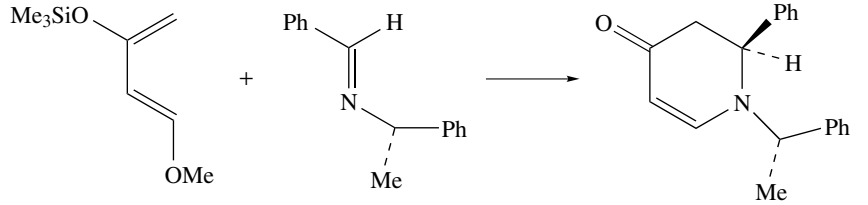
(55)


MeO
R
HN
CO2Me
CO2Bu-t
Me
Me
(91)
(92)


O
B
OPh
O
(93)

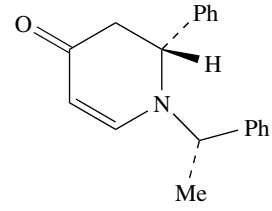

Me3SiO
R1
OMe
R2
H
N
Bn
(i) 93
(ii) H2O
O
R2
H
N
Bn
R1
(94)
(95)
(96)

(56)

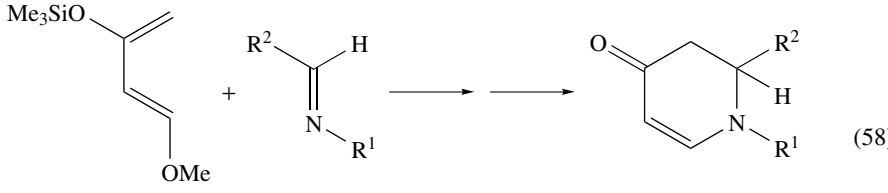


(94) $R^1 = H$ **(97)** **(98)**

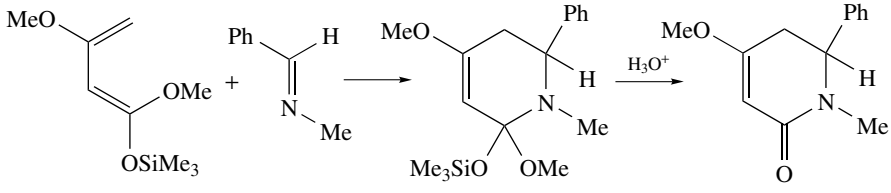
\+ (57)



(99)



(4) **(100)** (58)

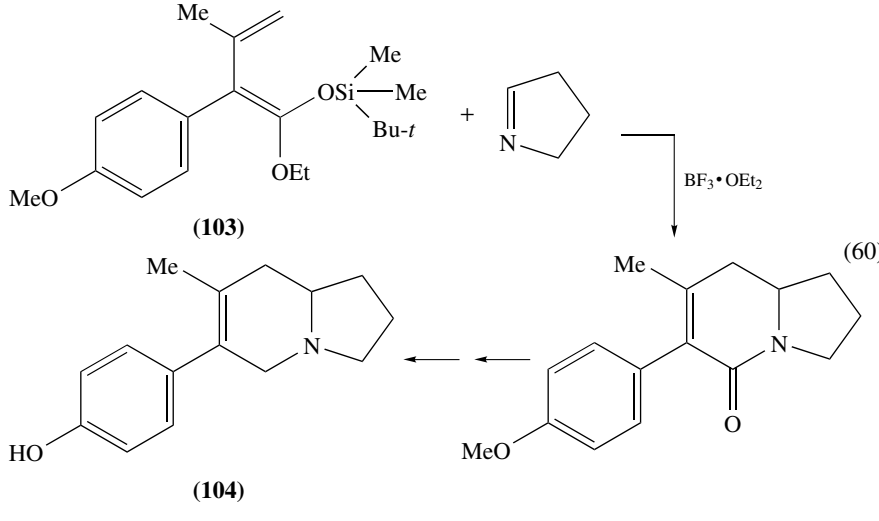


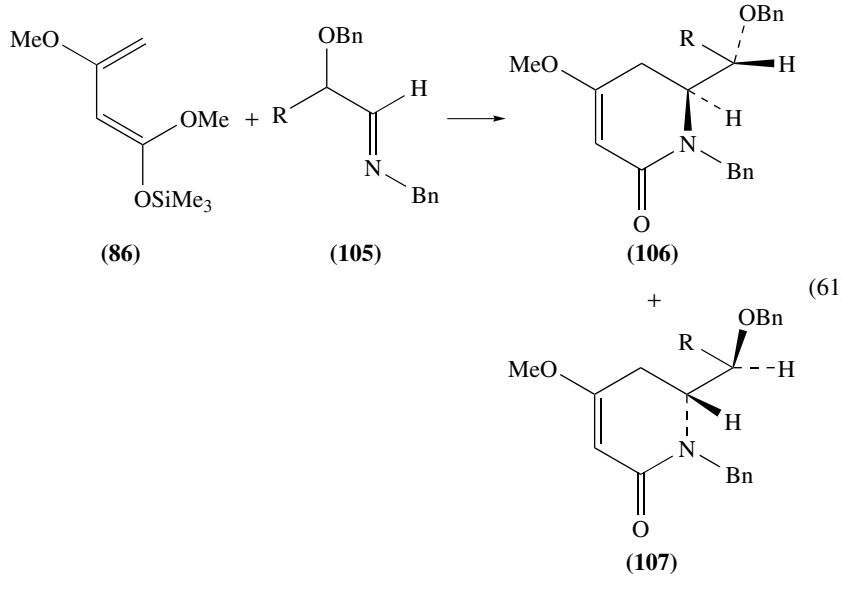
(86) **(101)** **(102)** (59)

Diastereoselectivities of up to 90% were observed for the cycloadditions of *N*-galactosylimines **108** (Piv = pivalyl; R = 2-furyl, 2-thienyl-, 4-FC_6H_4, 4-ClC_6H_4 or 3-pyridyl) to isoprene in the presence of zinc chloride to form the tetrahydropyridines **109** and **110** (equation 62)[55].

The enantioselective (76–90% ee) formation of the dihydro-γ-pyridones **113** from various imines **112** (R = Ph, 3,5-xylyl or 3-pyridyl) and Danishefsky's diene **4** in the presence of 4 Å molecular sieves and one equivalent of a catalyst prepared from triphenyl

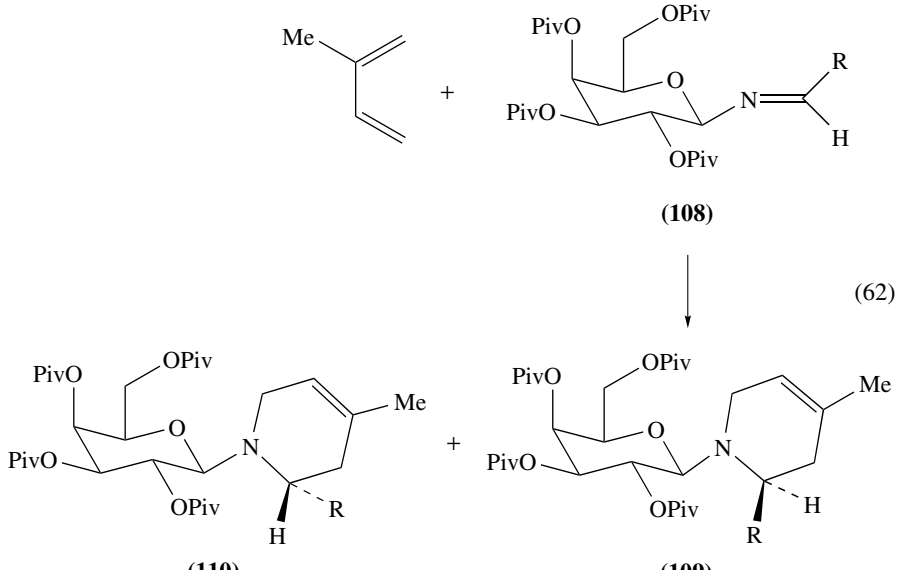
borate or a trialkyl borate and (*R*)-Binaphthol **111** in dichloromethane has been reported (equation 63)[56]. Similarly, the chiral zirconium complex **114** (L = 1-methylimidazole) catalyzes the reaction of the diene **4** with the Schiff's base **115** in toluene at −45 °C to yield, after hydrolysis, 88% of the optically active dihydropyridone **116** in 90% ee (equation 64)[57].



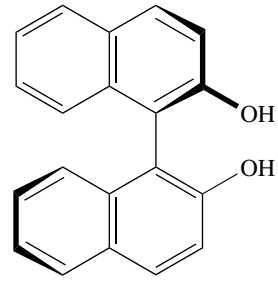


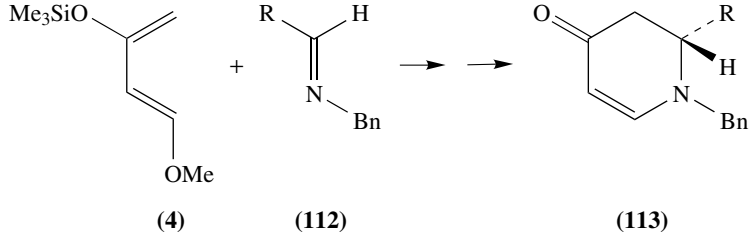
In a study of the Lewis-acid catalyzed formation of optically active dihydro-γ-pyridones **118** from the imines **117** (R = Ts, Ph, Bn or CO_2Et) and the diene **4** in the presence of chiral Lewis acids, it was found that only the tosyl compound reacted diastereoselectively,

giving the product in 68% yield and 80% de (equation 65)[58]. In the presence of 0.1 equivalent of diethylaluminum chloride, cyclopentadiene adds the chiral imine **119** to give a mixture of the diastereomers **120** and **121** in the ratio 12 : 88 (equation 66)[59].

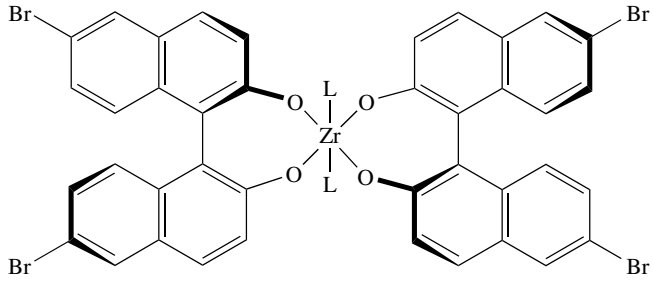


(62)

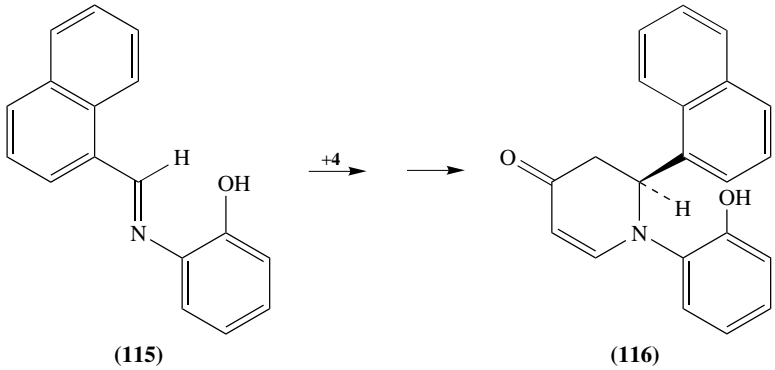




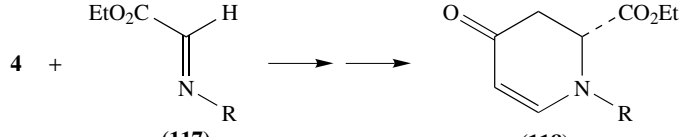
(63)



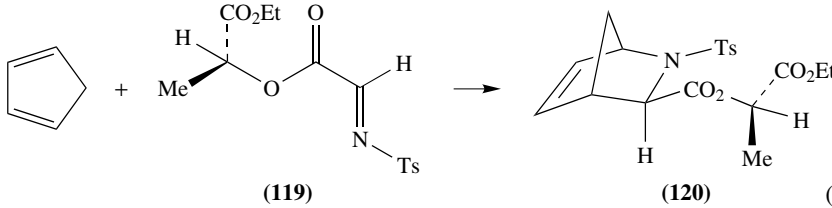
(114)



(115) **(116)** (64)

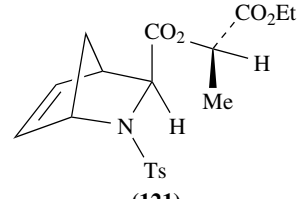


(117) **(118)** (65)



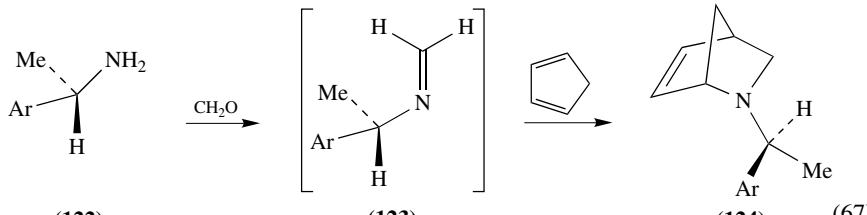
(119) **(120)** (66)

+



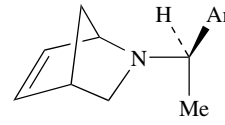
(121)

Imines **123**, generated from α-arylethylamines **122** (Ar = Ph, 4-BrC_6H_4 or 4-$O_2NC_6H_4$) and aqueous formaldehyde, react with cyclopentadiene *in situ* at room temperature to afford mixtures of the bridged dihydropyridines **124** and **125** (equation 67), whose relative configurations were deduced by ^1H NMR experiments and their absolute configurations assigned by reference to the X-ray structure of the aziridinium derivative **126** (equation 68)[60].

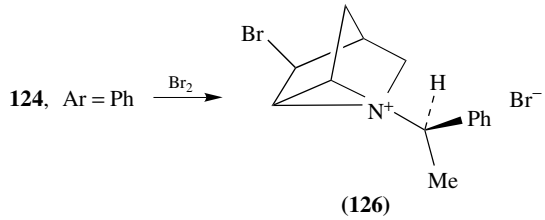


(122) **(123)** **(124)** (67)

+



(125)



(126) (68)

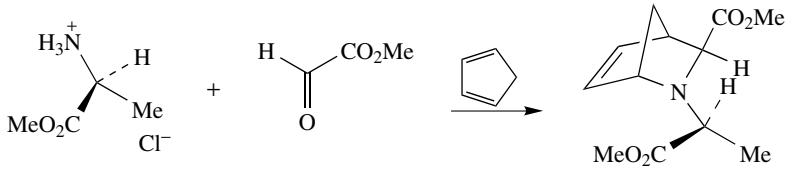
Protonated imines are effective dienophiles. Thus in the reaction of methyl glyoxylate with the hydrochloride **127** of alanine methyl ester in the presence of cyclopentadiene, a mixture of hydrochlorides of the *exo*- and *endo*-adducts **128**–**131** was formed (equation 69). The diastereomeric ratio of the *exo*-compounds was 83 : 17[61].

The iminium salt **132**, generated from benzylamine hydrochloride and aqueous formaldehyde, reacts with cyclopentadiene during 3 h at room temperature to give, after basification, the cycloadduct **133** in nearly quantitative yield (equation 70). Other examples of this reaction are shown in equations 71–75. The separable diastereomers **134** and **135** are formed in the ratio 4 : 1 from cyclopentadiene, (−)-α-methylbenzylamine hydrochloride and aqueous formaldehyde in a combined yield of 86% (equation 75)[62]. Hydrochlorides **136** of methyl esters of natural amino acids [(*S*)-valine, (*S*)-isoleucine] react with cyclopentadiene and formaldehyde in aqueous THF to produce mixtures of the diastereomers **137** and **138**, in which the former predominate (equation 76)[63].

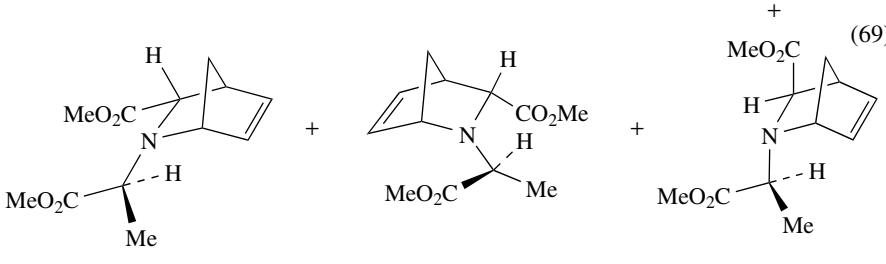
1-Azirines are reactive dienophiles[64]. The cycloadducts to cyclopentadienones spontaneously extrude carbon monoxide and undergo opening of the three-membered ring, followed by a 1,5-shift of hydrogen, to yield 3*H*-azepines (equation 77)[65,66].

Treatment of the azetidinone **139** with zinc chloride generates the highly unstable azetinone **140**, which is trapped as the carbacephem **142** in the presence of the diene

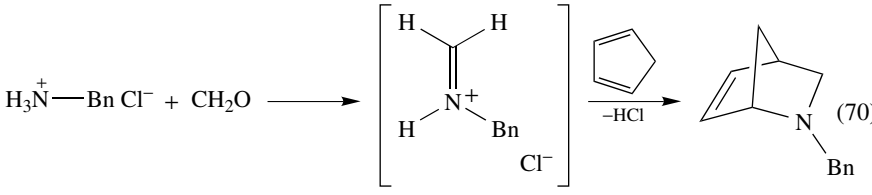
141[67]. The carbacephem was converted into the carbapenam-2-one system (±)-**143** by a multistep sequence (equation 78)[68].



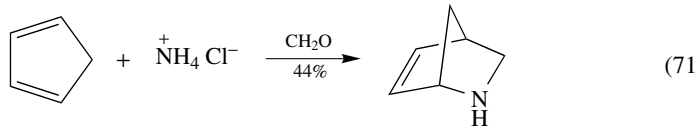
(127) **(128)**

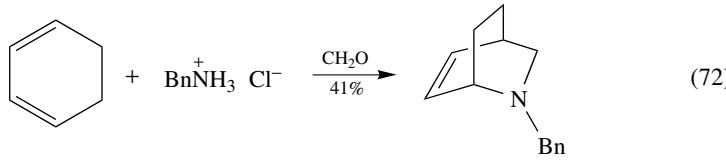


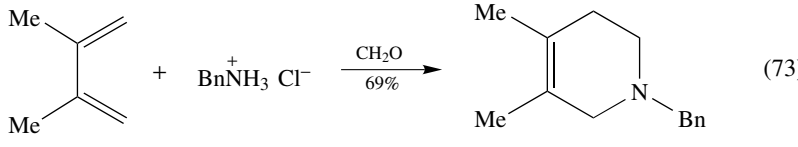
(131) **(130)** **(129)**

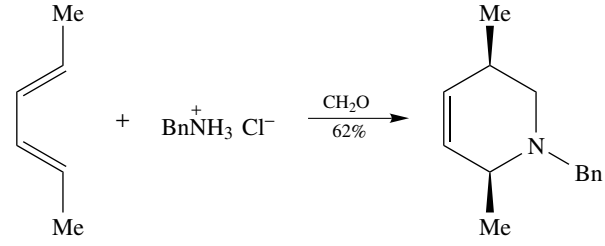


(132) **(133)**

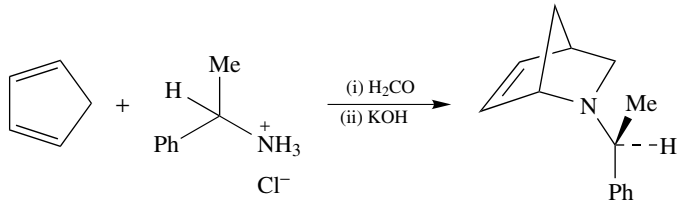






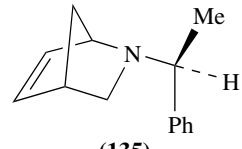


(74)

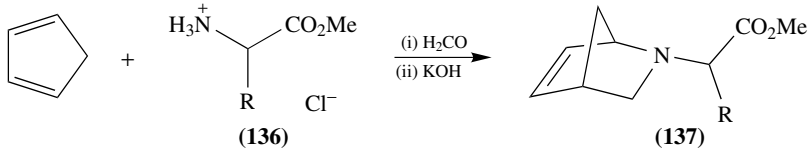


(134)

(75)

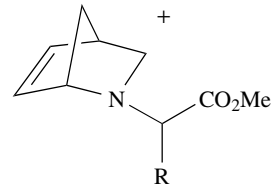


(135)



(136) **(137)**

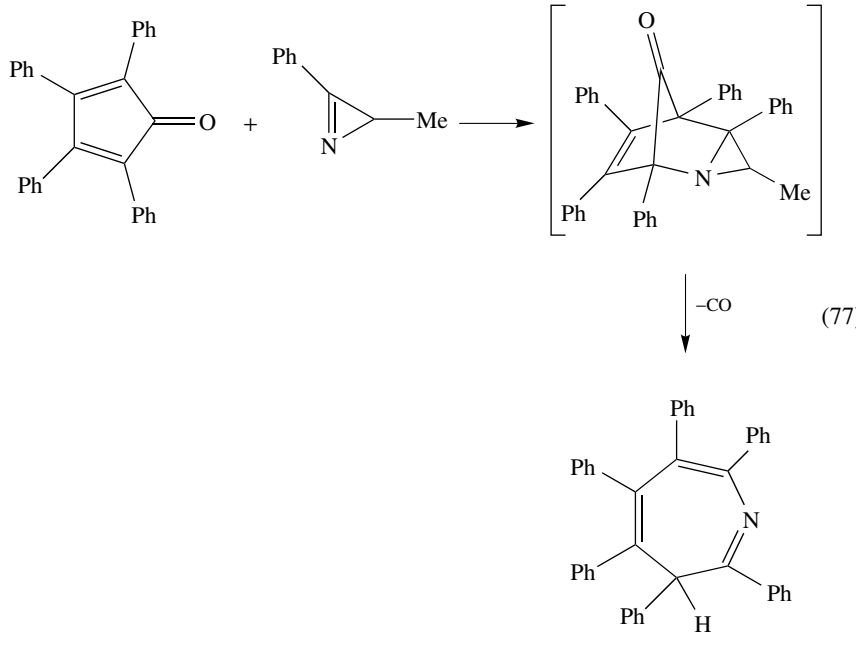
(76)

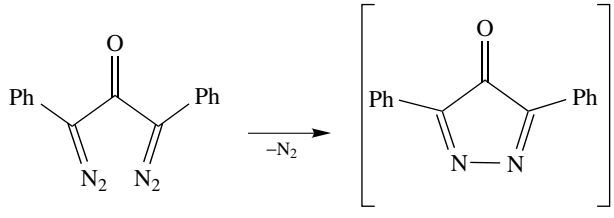


(138)

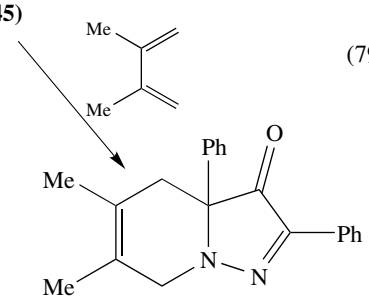
Heating the bis-diazoketone **144** generates the pyrazol-4-one **145**, which was trapped as the bicyclic adduct **146** in the presence of 2,3-dimethylbuta-1,3-diene (equation 79)[69].

Cycloadditions to a cyano group are comparatively rare. The high-temperature reactions of 1,3-dienes, e.g. butadiene, isoprene and 2-chloro-1,3-butadiene, with dicyanogen, propionitrile or benzonitrile result in formation of pyridines (equation 80)[70]. Sulfonyl cyanides **147**, obtained by the action of cyanogen chloride on sodium salts of sulfinic acids, add to dienes to give dihydropyridines **148**, which are transformed into pyridines **149** by oxidation (equation 81)[71].

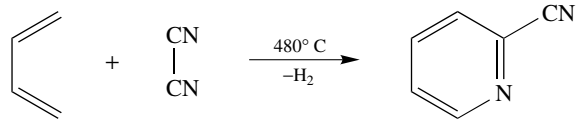

Ph
Ph
Ph
Ph
O
+
Ph
N
Me
O
Ph
Ph
Ph
N
Me
Ph
Ph
–CO
(77)
Ph
Ph
Ph
N
Ph
Ph
Ph
H
OSiMe2Bu-t
AcO
Me
HN
O
(139)
OSiMe2Bu-t
Me
N
O
(140)
t-BuMe2SiO
(141)
(78)
OSiMe2Bu-t
Me
O
N
MeO2C
(143)
t-BuMe2SiO
OSiMe2Bu-t
Me
N
O
(142)



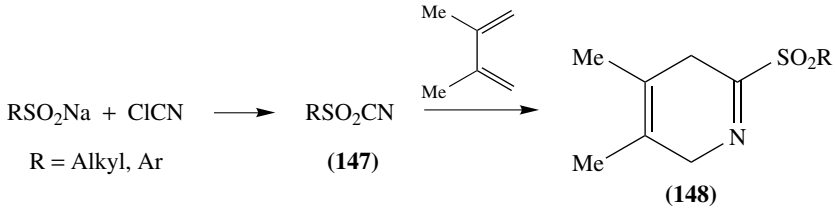
(144) **(145)**



(146) (79)

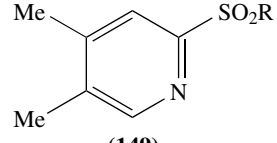


(80)

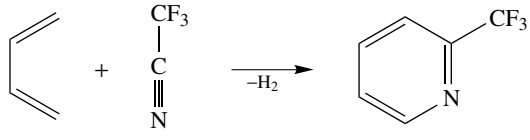


(147) **(148)**

(81)

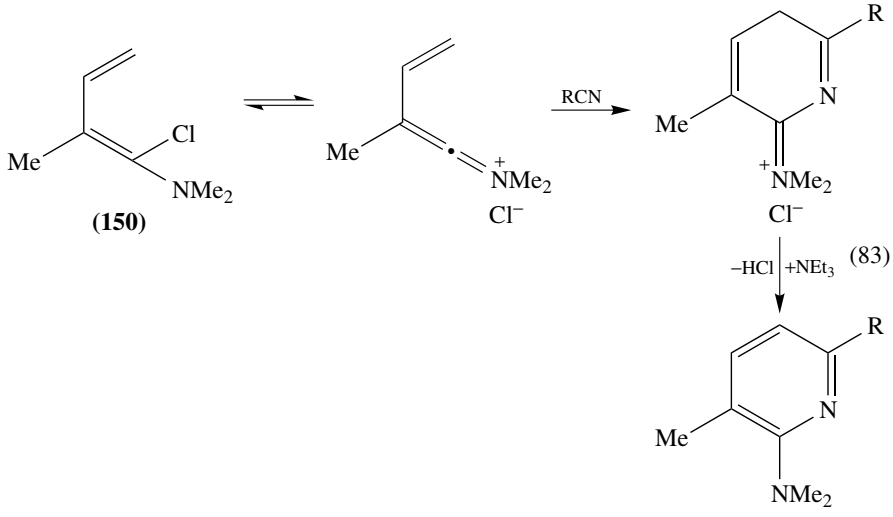


(149)



(82)

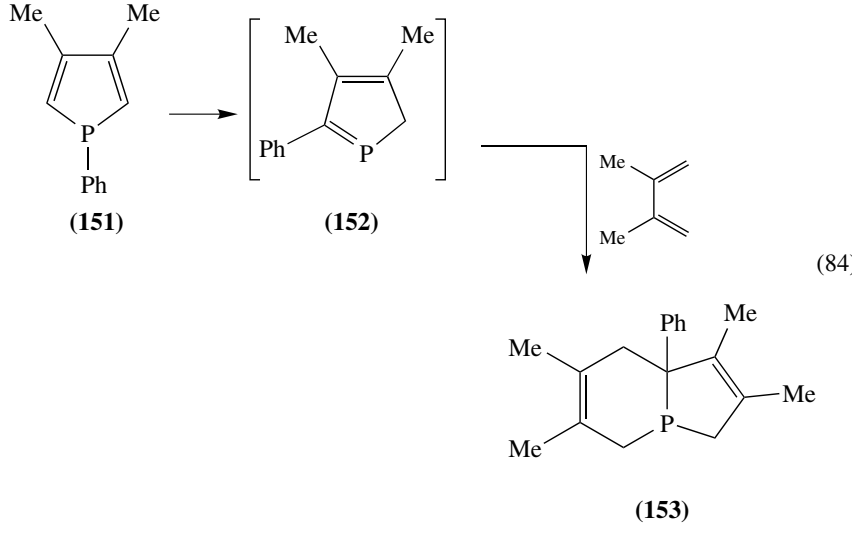
Fluorinated alkyl cyanides, such as trifluoroacetonitrile, pentafluoropropionitrile, perfluorobutyronitrile and chlorodifluoroacetonitrile, react with butadiene in the gas phase at 350–400 °C to afford pyridines in high yields (equation 82)[72]. The 'push–pull' diene **150** and electron-rich cyanides (acetonitrile or acrylonitrile) furnish pyridines (equation 83)[73].



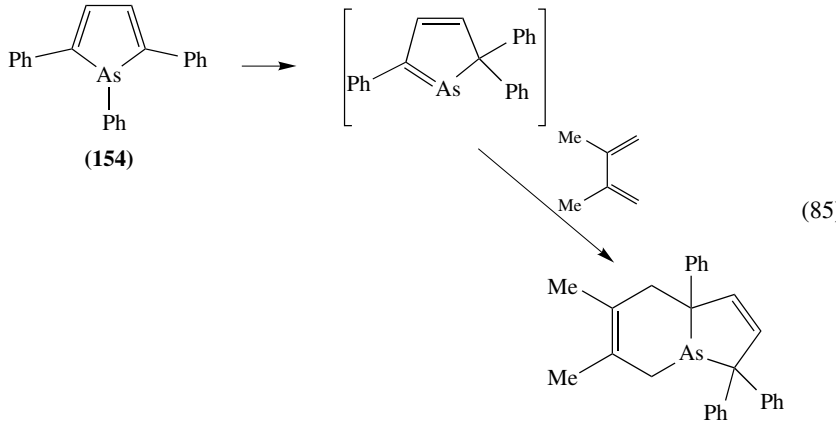
(83)

V. ADDITION TO C=P AND C=As COMPOUNDS

Heating the phosphole **151** with 2,3-dimethyl-1,3-butadiene at 170 °C gave the bicyclic phosphorus heterocycle **153**, presumably by way of the rearranged 2*H*-phosphole **152** (equation 84)[74]. The arsole **154** behaved analogously (equation 85)[75].



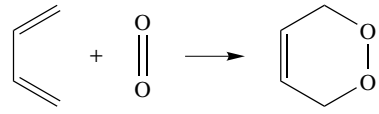
(84)



(85)

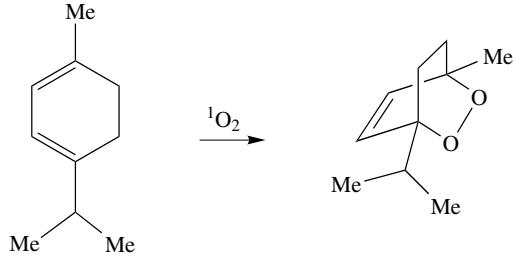
VI. ADDITION TO OXYGEN

The most powerful dienophile is singlet oxygen, produced by the dye-sensitized irradiation of oxygen. Its cycloaddition to dienes to give '*endo*-peroxides' (equation 86) has long been known[76].



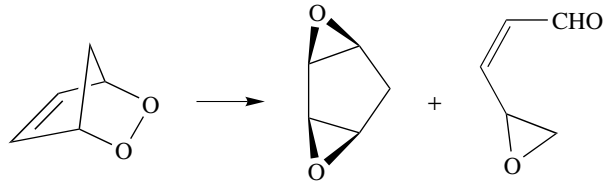
(86)

Photooxygenation of α-terpinene **155** in the presence of eosin (equation 87) produces ascaridole **156**, a constituent of the essential oil *Chenopodium ambrosioides L.*[77]. The *endo*-peroxide **157** derived from cyclopentadiene is a crystalline solid, stable at $-100\,^{\circ}C$[78]; above this temperature it rearranges to a mixture of the bis-epoxide **158** and the epoxy-aldehyde **159** (equation 88)[79,80].

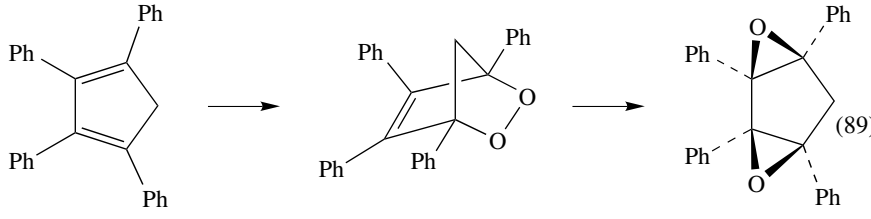


(87)

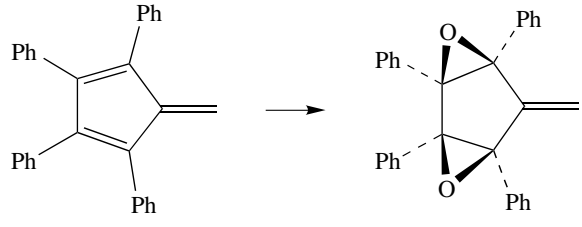
The tetraphenylcyclopentadiene **160** affords the peroxide **161**, which rearranges on heating to the bis-epoxide **162** (equation 89)[81]. In the case of the photooxygenation of the fulvene **163**, only the rearrangement product **164** could be isolated (equation 90)[81].



(157) (158) (159) (88)

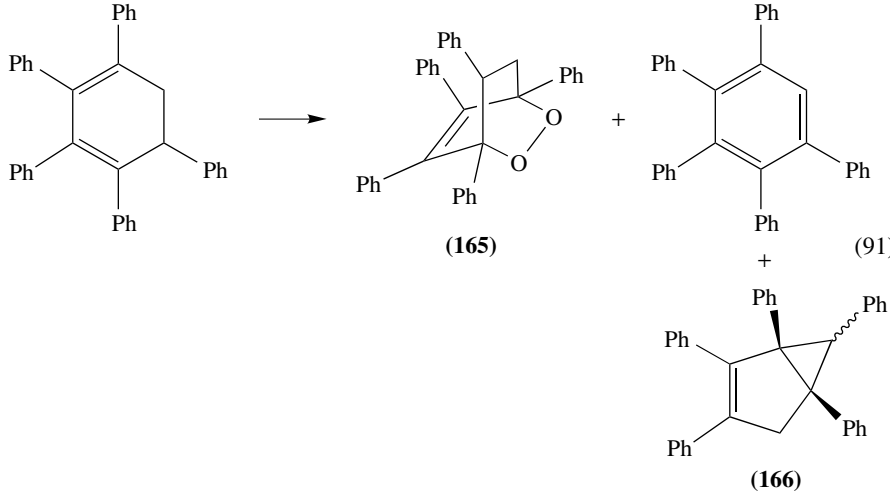


(160) (161) (162) (89)



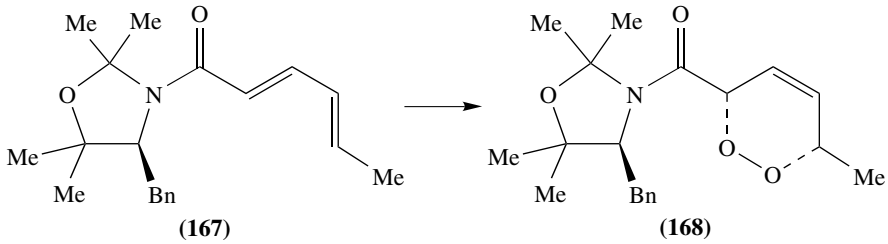
(163) (164) (90)

1,2,3,4,5-Pentaphenyl-1,3-cyclohexadiene gives a mixture of the cycloadduct **165**, pentaphenylbenzene and the bicyclic compound **166** (equation 91)[82]. Photooxygenation of



(165) (166) (91)

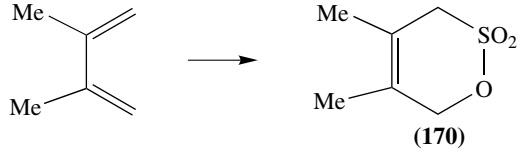
the chiral amide **167** derived from sorbic acid results in the quantitative formation of the diastereomeric cycloadducts **168** and **169** in a ratio of greater than 95 : 5 (equation 92)[83].



(92)

VII. ADDITION TO A S=O COMPOUND

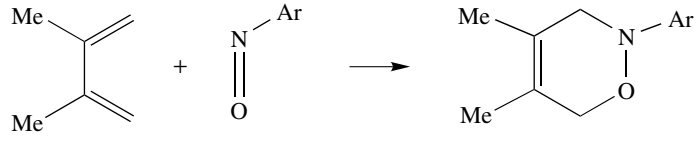
The dioxane–sulfur trioxide complex reacts with 2,3-dimethylbutadiene to give the sultone **170** in low yield (equation 93)[84].



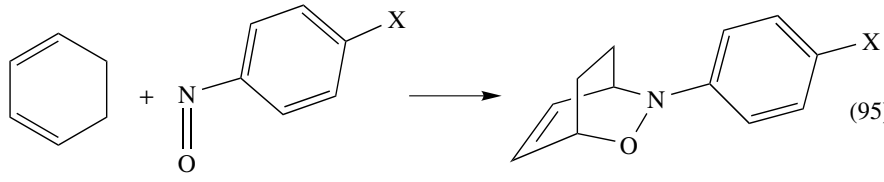
(93)

VIII. ADDITION TO NITROSO COMPOUNDS

The first examples of this reaction (which was reviewed several times[85]), i.e. the addition of nitrosoarenes to 2,3-dimethylbutadiene to give 2-aryl-3,6-dihydro-2*H*-1,2-oxazines (equation 94), were reported in 1947[86]. In general, the addition of nitroso compounds to 1,3-dienes to form dihydro-1,2-oxazines is only observed if the nitroso compound is activated by an electron-withdrawing group[87]. Kinetic studies of the reaction of cyclohexa-1,3-diene with *para*-substituted nitrosobenzenes (equation 95) show the accelerating effect of such groups (Hammett constant $\rho = +2.57$)[88].



(94)

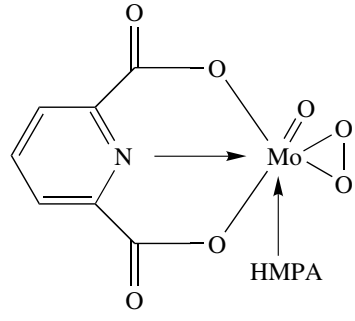


(95)

Rate constants in EtOH at 10 °C are as follows:

X	OMe	Me	H	Cl	NO_2
10^3 k	0.151	1.30	4.19	12.0	532

However, it was recently reported[89] that all nitrosoarenes (except the 4-nitro compound), when produced by the oxidation of arylamines p-$H_2NC_6H_4R$ (R = MeO, Me, Cl, COMe, $CONH_2$, CF_3) with 2.2 mol hydrogen peroxide in the presence of a catalytic amount of oxoperoxo(2,6-pyridinedicarboxylato-*O*,*N*,*O*′) (hexamethylphosphortriamide)-molybdenum(VII) **171**, react with cycohexa-1,3-diene *in situ* to give the bridged dihydrooxazines of equation 95 in 66–81% yields.

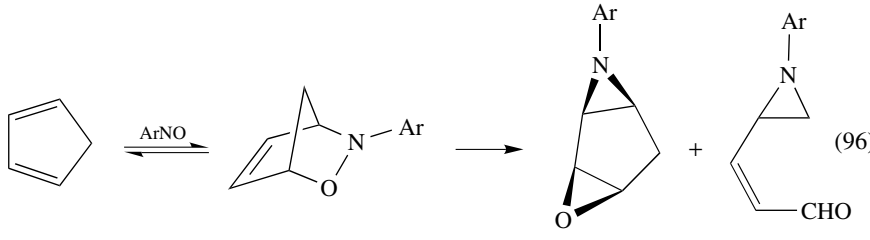


(171)

The regiochemistry of the addition of nitrosoarenes to unsymmetrical dienes has been discussed[90].

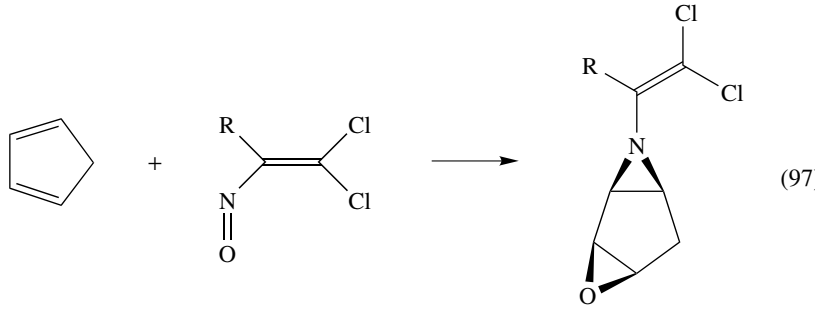
The reversible reaction of nitrosoarenes ArNO (Ar = 2, 6-$Cl_2C_6H_3$, 2,4,6-$Cl_3C_6H_2$ or Cl_5C_6) with cyclopentadiene results in unstable adducts **172**, which rearrange at room temperature to mixtures of 'epoxyepimines' **173** and 'epimines' **174** (equation 96)[91]. Similarly, treatment of cyclopentadiene with the vinylnitroso compounds **175** (R = H, Me or Cl) gives the rearranged adducts **176** (equation 97)[92]. In general, the adducts of trichloronitrosoethylene to cyclic dienes with five-, six- or seven-membered rings undergo this epoxyepimine rearrangement, whereas adducts to acyclic dienes do not[93].

Treatment of a mixture of a chloro oxime **177** (R = H, Ph, 4-BrC_6H_4 or 2-furyl) and a diene (cyclopentadiene or 2,3-dimethylbuta-1,3-diene) with solid sodium carbonate results in the formation of a dihydrooxazine, the intermediate nitrosoalkene **178** having reacted as a heterodiene (equation 98)[94]. In contrast, 1,1-dichloro-2-nitrosoethene and cyclopentadiene yield the epoxyepimine **179** (equation 99)[94].



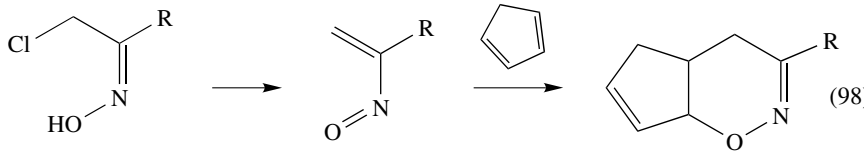
(96)

(172) **(173)** **(174)**



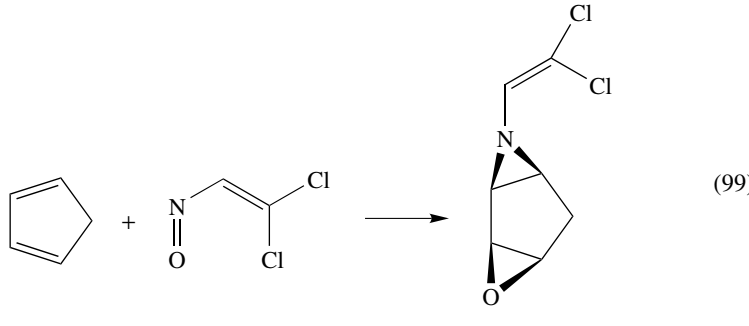
(97)

(175) **(176)**



(98)

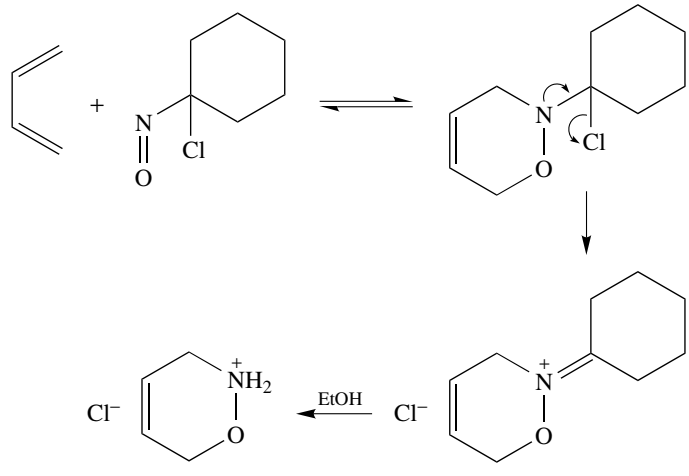
(177) **(178)**



(99)

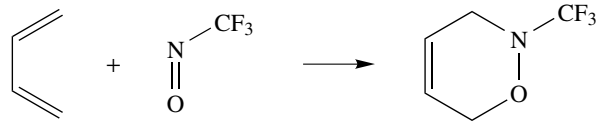
(179)

Unlike most tertiary nitrosoalkanes, 1-chloronitrosocyclohexane forms adducts with various 1,3-dienes. Although the reaction is sluggish and reversible, good yields of dihydrooxazines can be obtained if ethanol is present (equation 100)[95].



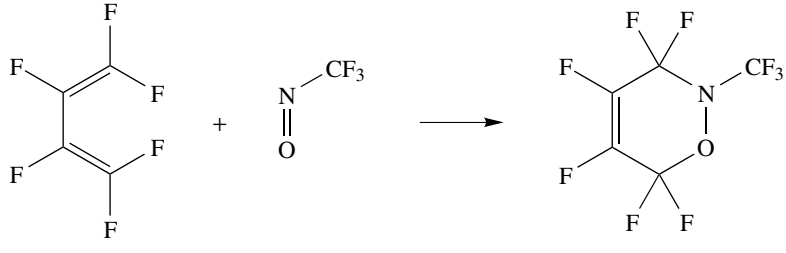
(100)

Trifluoronitrosomethane reacts with butadiene at −78 °C to give **180** (equation 101). Even perfluorobutadiene, which is unreactive toward conventional dienophiles, reacts with trifluoronitrosomethane to give **181** (equation 102)[96].



(101)

(180)



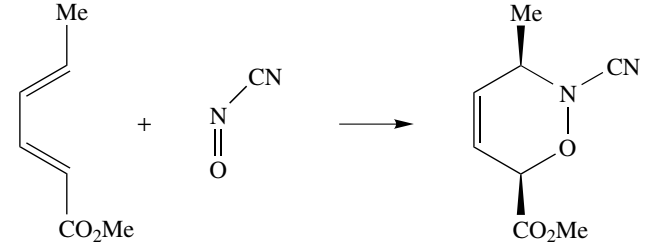
(102)

(181)

Nitrosyl cyanide, generated from nitrosyl chloride and silver cyanide in chloroform at −20 °C, affords unstable products with various dienes, e.g. butadiene and 2,3-dimethyl-1,3-butadiene. With methyl sorbate, compound **182** is produced (equation 103), thebaine **(183)** gives **184** (equation 104)[97] and 9,10-dimethylanthracene yields the stable cycloadduct **185**, which decomposes into its components on heating and consequently can serve as a source of nitrosyl cyanide. Thus heating **185** with 1,4-diphenylbuta-1,3-diene gives the dihydrooxazine **186** and dimethylanthracene (equation 105)[98].

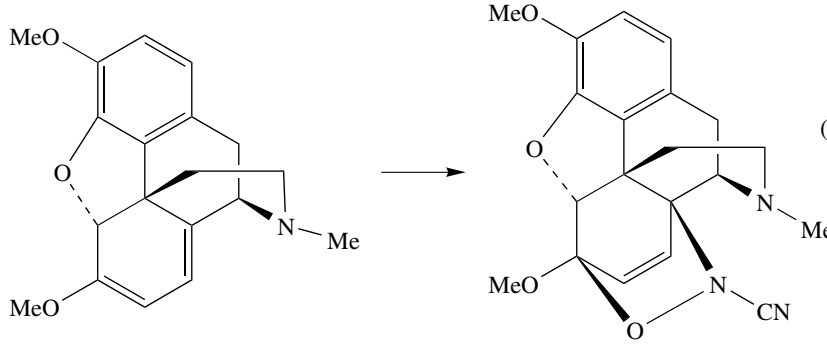
C-Nitrosocarbonyl compounds RCONO (R = Me or Ph), generated from hydroxamic acids and tetraethylammonium periodate, readily react with dienes such as butadiene and

cyclopentadiene. The adducts to 9,10-dimethylanthracene transfer RCONO to thebaine in refluxing benzene (equation 106)[99].



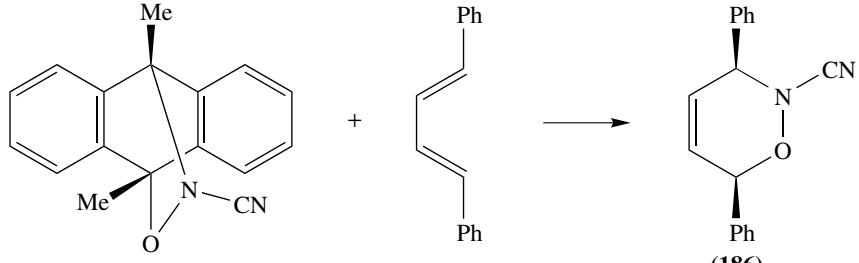
(103)

(182)



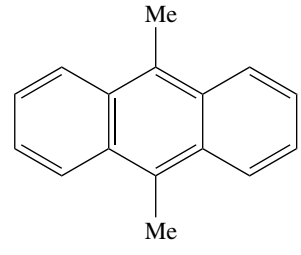
(104)

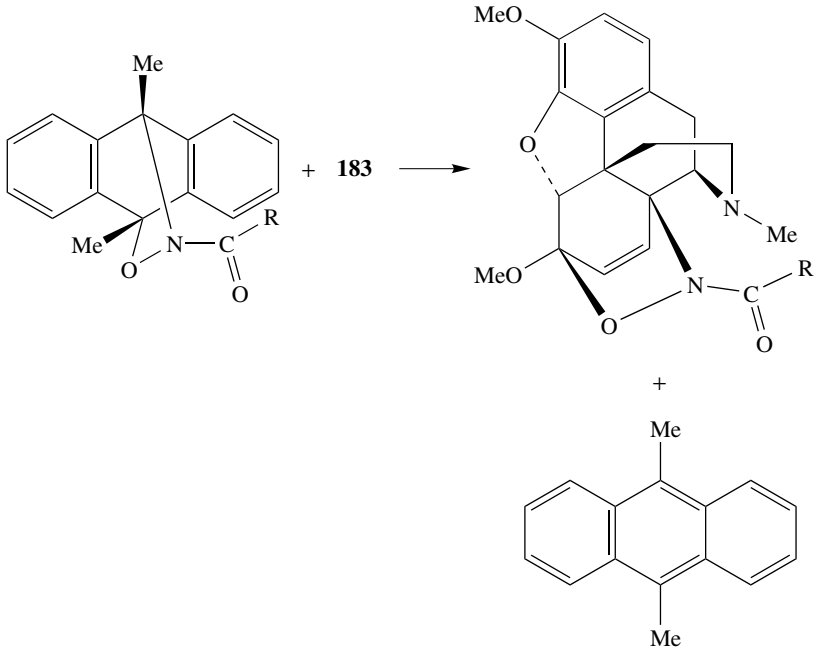
(183) **(184)**



(185) **(186)**

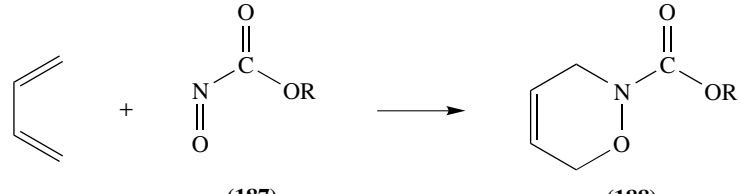
(105)





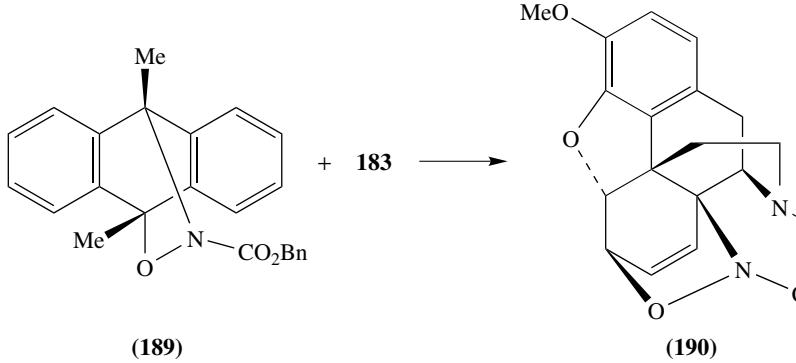
(106)

O-Nitrosocarbonyl compounds (nitrosoformates) **187** (R = *t*-Bu or Bn) are obtained from the hydroxylamines ROCONHOH. They can be trapped by reaction with butadiene to give the cycloadducts **188** (equation 107). With 9,10-dimethylanthracene the benzyl



(107)

(187) **(188)**

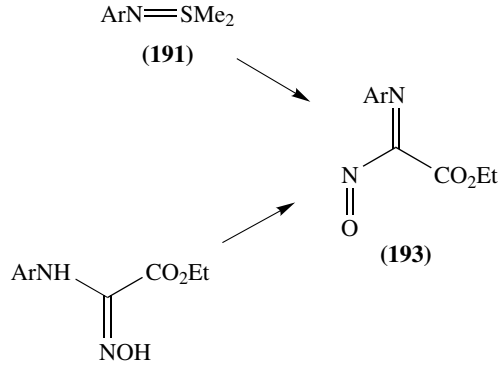


(108)

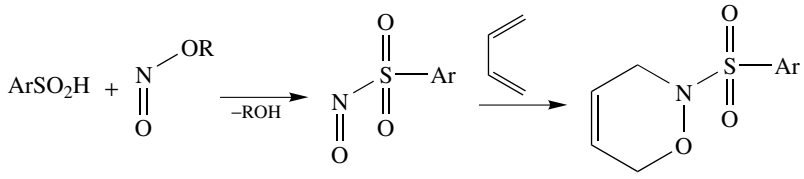
(189) **(190)**

compound forms **189**, which, when treated with thebaine, transfers benzyl nitrosoformate to the latter to give **190** (equation 108)[100]. The *C*-nitrosoformamide PhNHCONO is generated by periodate oxidation of PhNHCONHOH; in the presence of thebaine an analogue of **190** is obtained[100].

The transient *C*-nitrosoimine **193** (Ar = 4-ClC_6H_4) is formed by the action of ethyl cyanoformate on the sulfimide **191** and also by the oxidation of the amidoxime **192** with lead tetraacetate. In the presence of thebaine, both reactions yield an identical dihydrooxazine[101].



Treatment of alkyl nitrites with arylsulfinic acids **194** generates the unstable nitroso compounds **195**, which, in the presence of dienes, are trapped as cycloadducts **196** (equation 109)[102].

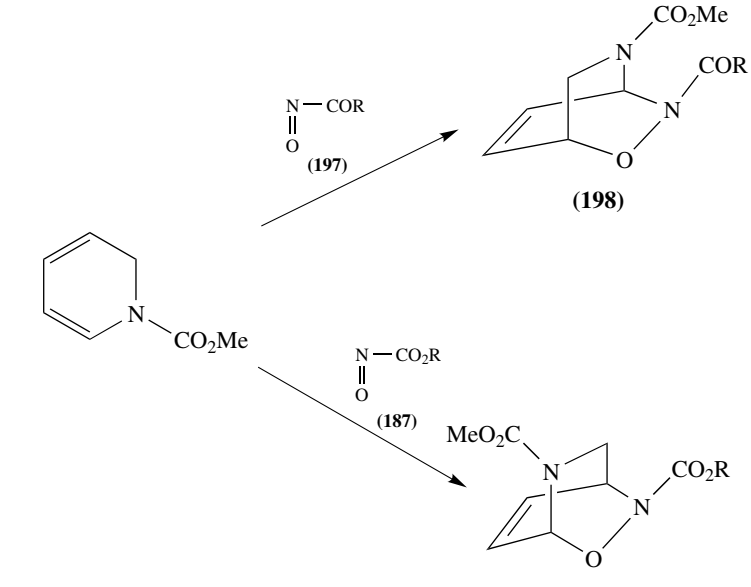


(109)

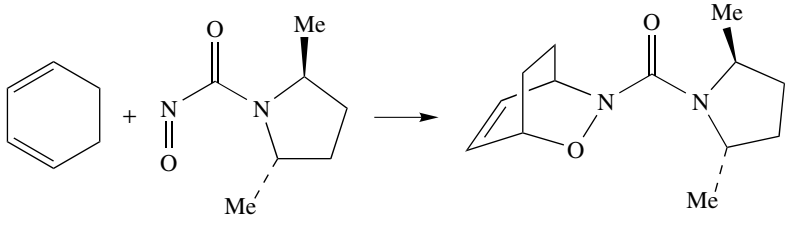
Acylnitroso compounds **197** (R = Me, Ph or Bn) react *in situ* with 1-methoxycarbonyl-1,2-dihydropyridine to yield solely the bridged adducts **198** quantitatively. On the other hand, 1 : 1 mixtures of the regioisomers **199** and **200** were formed from the nitrosoformates **187** (R = Me or Bn) (equation 110)[103]. The chiral acylnitroso compounds **201** and **202**, which are of opposite helicity, add to cyclohexadiene to give optically active dihydrooxazines in greater than 98% diastereomeric excess (equations 111 and 112)[104]. Similarly, periodate oxidation of the optically active hydroxamic acid **203** in the presence of cyclopentadiene, cyclohexa-1,3-diene and cyclohepta-1,3-diene affords chiral products **204** (n = 1, 2 and 3, respectively) in 70–88% yields and 87–98% de (equation 113)[105].

The unstable cycloadducts **207**, obtained from the dihydropyridines **205** (R = Me or Bn) and the benzoyl nitroso compound **206**, undergo a hetero-Cope rearrangement in the presence of silicic acid to yield fused dioxazines **208** (equation 114)[106]. Adding the racemic hydroxamic acid **209** (R = *t*-Bu, cyclohexyl or Ph) to a two-phase mixture of

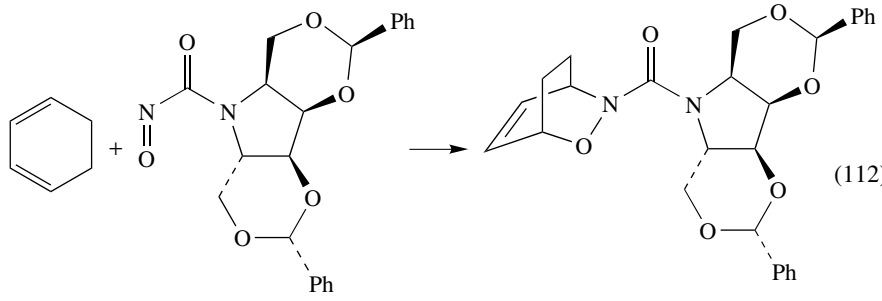
cyclopentadiene or cyclohexadiene and sodium periodate in ethyl acetate/water at 0 °C produced mixtures of diastereomers **210** and **211** in the ratios 3.4–5.1 : 1 and 2.5–4.6 : 1, respectively, indicating a moderate degree of asymmetric induction[107].



(110)

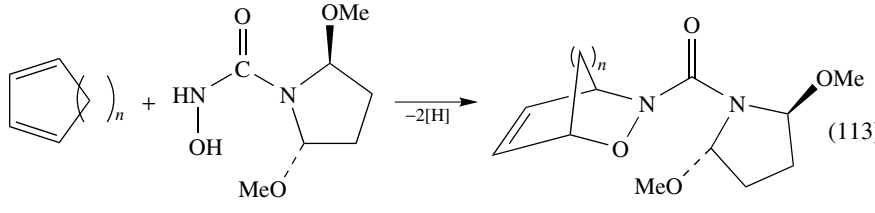


(111)



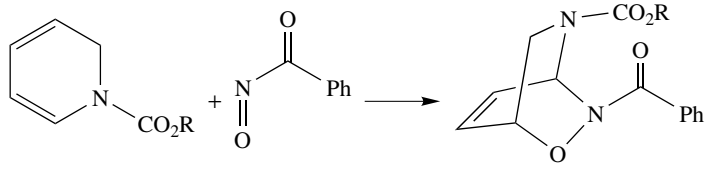
(112)

(202)

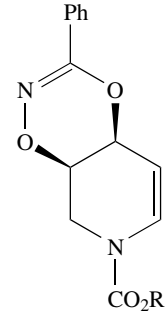


(113)

(203) **(204)**

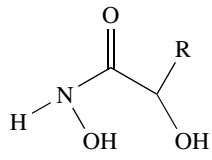


(205) **(206)** **(207)**



(114)

(208)



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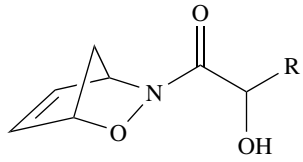
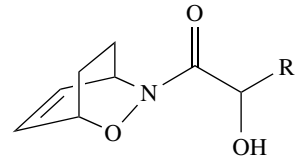
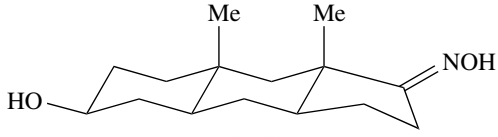


(210)

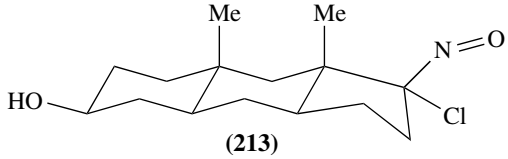


(211)

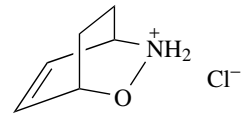
17-Chloro-17-nitroso-3β-hydroxy-5α-androstane **213**, generated from the oxime **212** of epiandrosterone and *t*-butyl hypochlorite, reacts with cyclohexadiene in chloroform/methanol at $-20\,^{\circ}C$ to yield, after two weeks, epiandrosterone and the bridged dihydrooxazine **214** in an enantiomeric excess of better than 95%[108].



(212)



(213)



(214)

Tetra-*n*-propylammonium periodate oxidation of the hydroxamic acids **215** (R = CH_2OH, CH_2OMe, CH_2NHPh or CO_2Me), derived from L-proline, generates nitroso compounds **216**, which, in the presence of cyclohexadiene, give mixtures of diastereomeric cycloadducts **217** in 79–89% yields and 26–68% de values (equation 115)[109].

The chiral nitroso compound **218** derived from camphor (equation 116) adds to various types of dienes to afford adducts **219**–**222** in high yields and excellent de values (equations 117–120)[110].

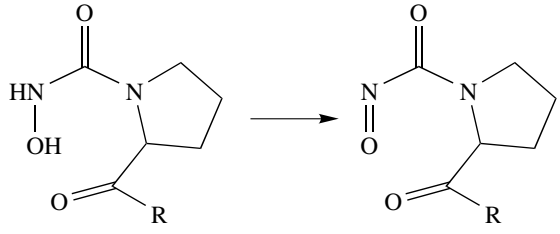
Chiral dienes or chiral dienophiles or chiral Lewis acid catalysts may be involved in cycloaddition reactions. When any two of these are combined 'double asymmetric induction' operates[111]. Thus the chiral diene **223** and the optically active dienophile **224** (from D-mandelic acid) gave **225** in high de values, whereas the same diene and the enantiomeric dienophile **226** (from L-mandelic acid) — a mismatched pair — formed the diastereomeric cycloadduct **227** in only 4% de (equation 121)[112].

Optically active dihydrooxazines **230** are produced by the reaction of the chiral α-chloronitroso compound **228** derived from D-mannofuranose with a variety of 1,3-dienes in the presence of ethanol at low temperatures via the primary adducts **229** (equation 122). Penta-1,3-diene, for instance, yields a mixture of the regioisomers **231** and **232**[113].

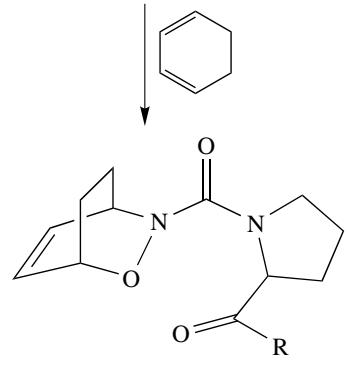
Nitrosocarbonyl-D-bornane-10,2-sultam **233** adds to cyclopentadiene to yield **234** with complete facial selectivity (equation 123)[114].

cis-5,6-Diacetoxy-1,3-cyclohexadiene **235** reacts with the chiral chloronitroso compound **228** in chloroform/ethanol to give 89% of the optically active product **236** in 94% ee, four asymmetric centers having been created (equation 124). The latter was

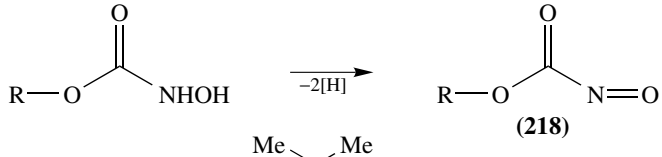
transformed into tetraacetylconduramine A1 **237** by reduction with zinc/hydrochloric acid, followed by acetylation[115].



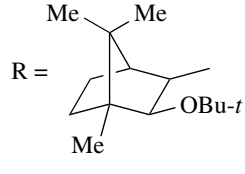
(215) **(216)**



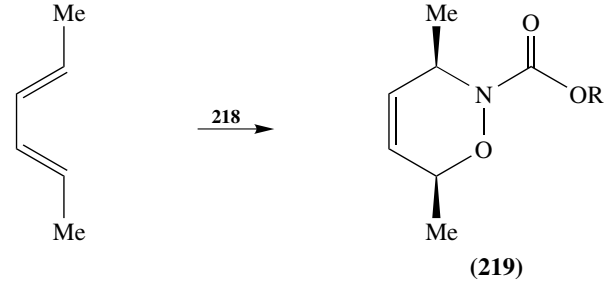
(217) (115)



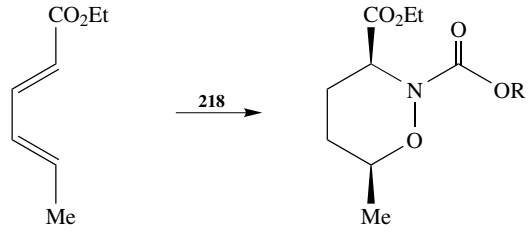
(218)



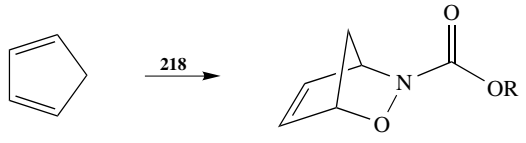
(116)



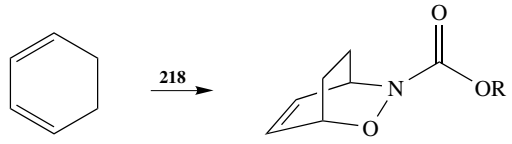
(219) (117)



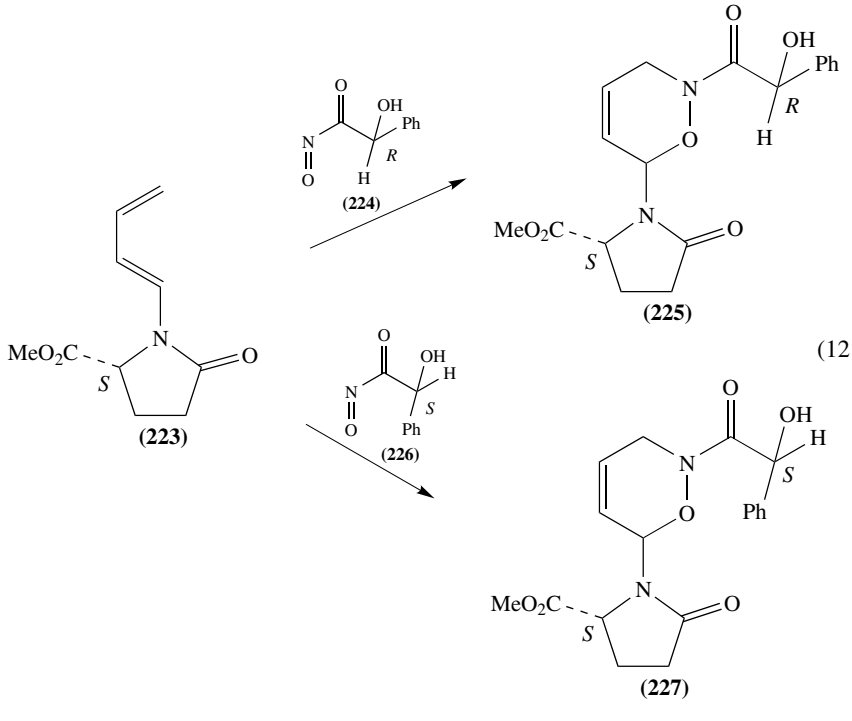
(220) (118)



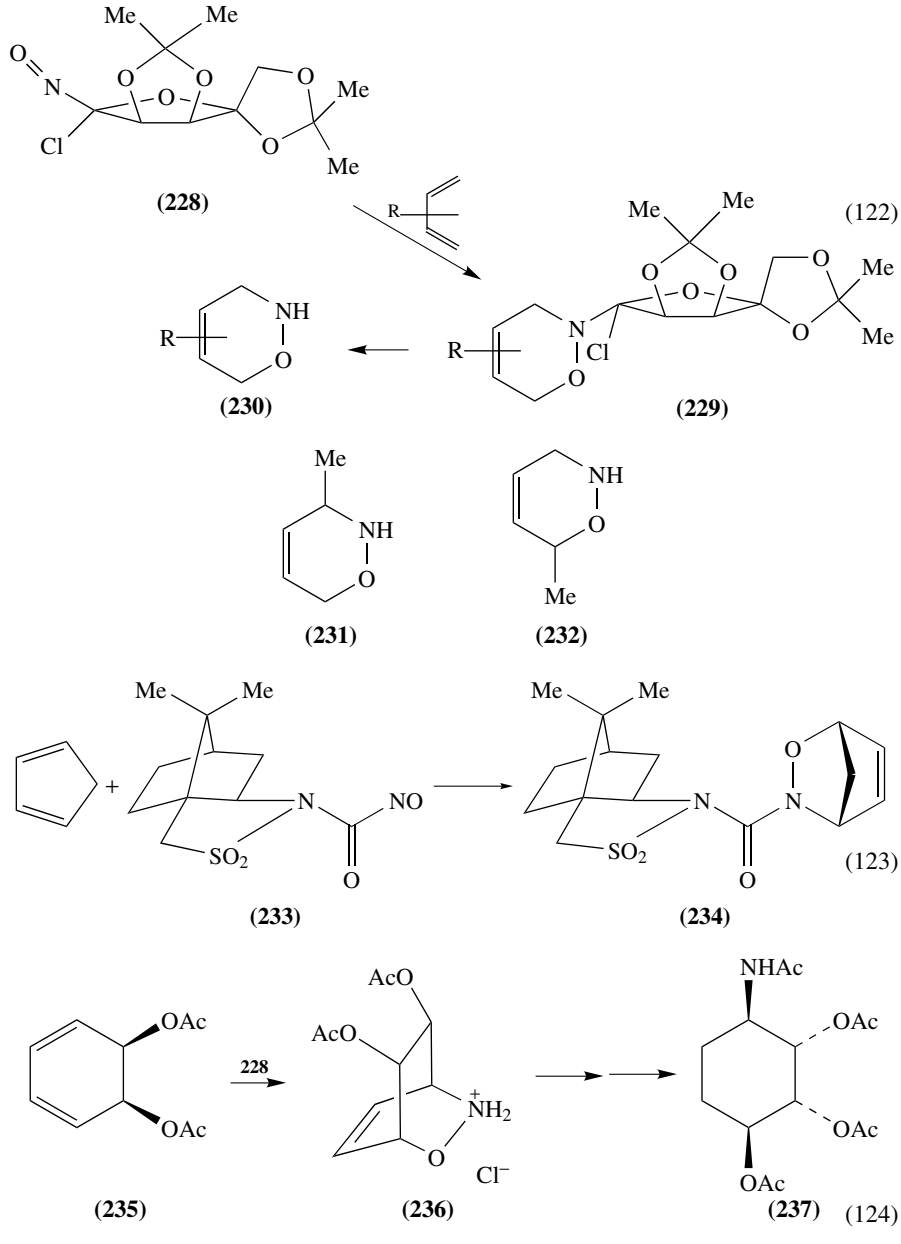
(221) (119)



(222) (120)



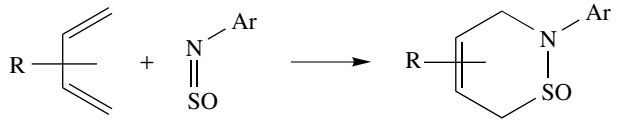
(121)



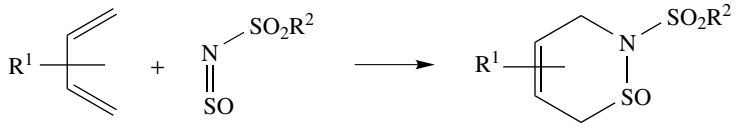
IX. ADDITION TO S=N COMPOUNDS

N-Sulfinylarylamines react sluggishly with dienes (equation 125)[116,117]. *N*-Sulfinylsulfonamides (from sulfonamides and thionyl chloride) are much more reactive dienophiles

(equation 126)[118]. In some cases, the Diels–Alder reactions of *N*-sulfinylsulfonamides are reversible; thus the adduct **238** to cyclopentadiene decomposes into its components at room temperature (equation 127)[119] and the products **240** obtained with 1-substituted dienes **239** (R = Me, *t*-Bu, Ar or CO_2Me) at 5 °C rearrange to the isomers **241** at higher temperatures (equation 128). In contrast, 2-substituted dienes **242** (R = Me, Ph or Cl) yield adducts **243** which are thermally stable (equation 129)[120].

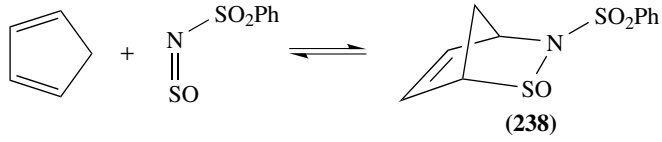


(125)



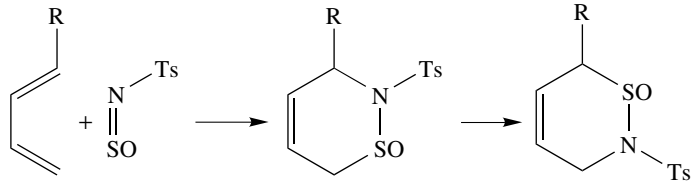
(126)

R^1 = H, Alkyl; R^2 = Alkyl, Ar



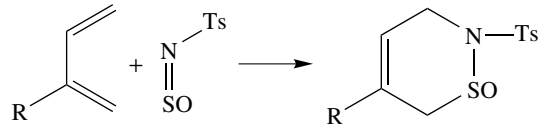
(127)

(238)



(128)

(239) **(240)** **(241)**

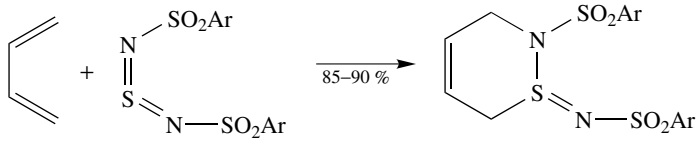


(129)

(242) **(243)**

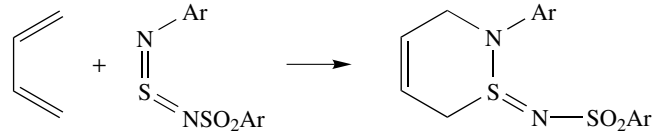
N,*N*′-Disulfonylsulfodiimides **244** react exothermically with butadiene to give 1-sulfonylimino-2-sulfonyl-3,6-dihydro-1,2-thiazines **245** (equation 130)[121,122]. *N*-Aryl-*N*′-sulfonylsulfodiimides **246** are much less reactive as dienophiles. The addition to butadiene to yield **247** takes place in boiling benzene (equation 131)[123]. No cycloaddition reactions of dialkyl- or diarylsulfodiimides are known.

The chiral *N*-sulfinylcarbamate **248** derived from 8-phenylmenthol formed a mixture of two epimeric cycloadducts **249** and **250** with cyclohexa-1,3-diene (equation 132)[124], whereas the reaction with (*E*,*E*)-hexa-2,4-diene in the presence of tin(IV) chloride gave solely the epimer **251** (equation 133)[125].



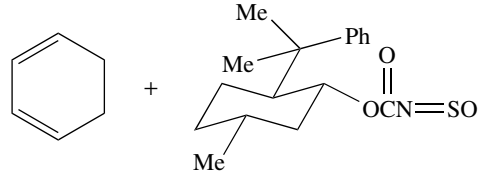
(130)

(244) **(245)**

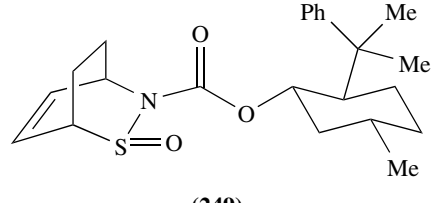


(131)

(246) **(247)**



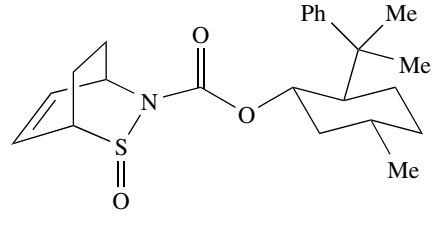
(248)



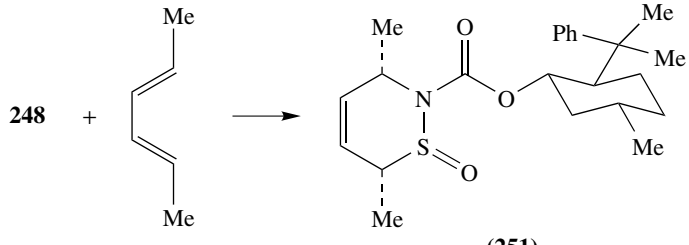
(132)

(249)

+



(250)

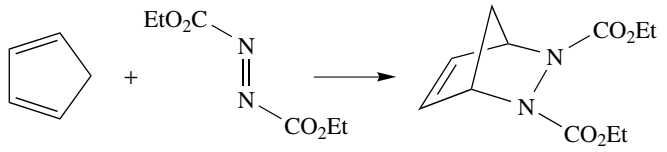


(133)

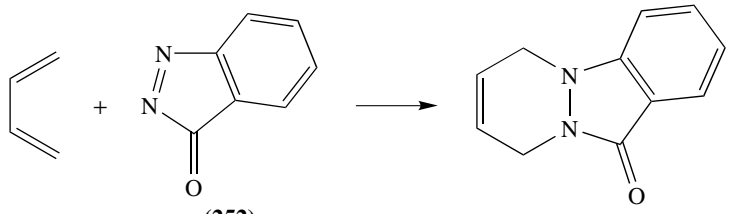
(251)

X. ADDITION TO AZO COMPOUNDS[126,127]

Azo compounds are reactive dienophiles. Indeed, one of the very first Diels-Alder reactions was the addition of diethyl azodicarboxylate to cyclopentadiene (equation 134)[128,129]. Other early examples of the reaction are the formation of tetrahydropyridazines from indazolone **252** and phthalazinedione **253** (equations 135 and 136)[130].

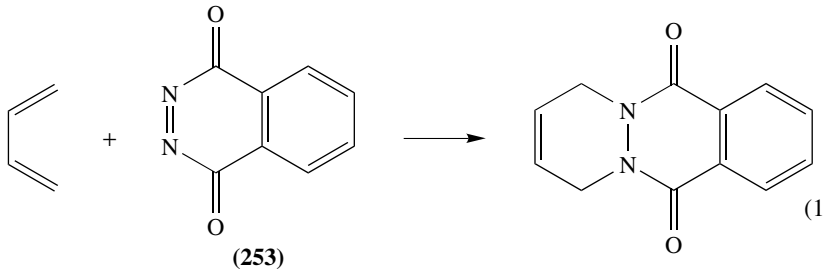


(134)



(135)

(252)

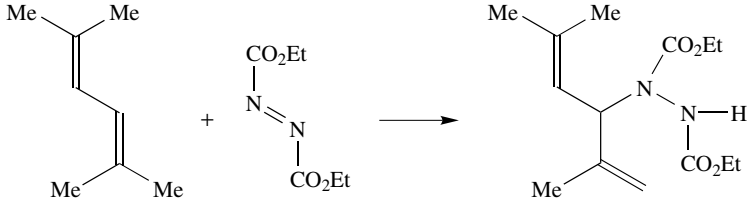


(136)

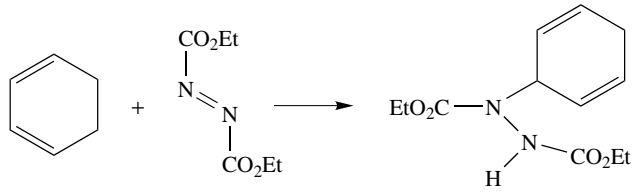
(253)

Diethyl azodicarboxylate forms normal adducts with 2,3-dimethylbutadiene and with ethyl sorbate; however, it is not a very good dienophile, presumably because it exists in the *trans*-configuration. The sterically hindered diene **254** adds the ester to give mainly the ene product **255** (equation 137) and even cyclohexa-1,3-diene undergoes an analogous

reaction, yielding **256** (equation 138)[131].



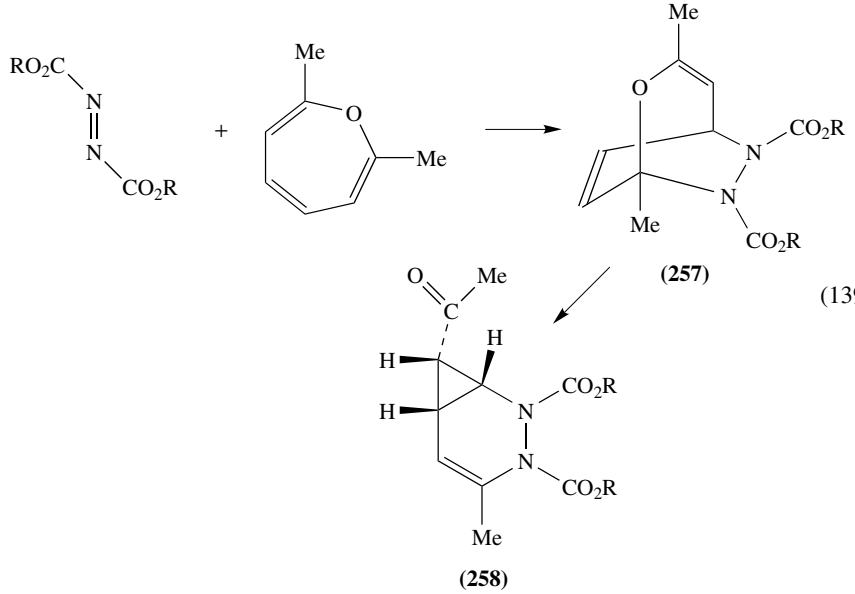
(254) (255) (137)



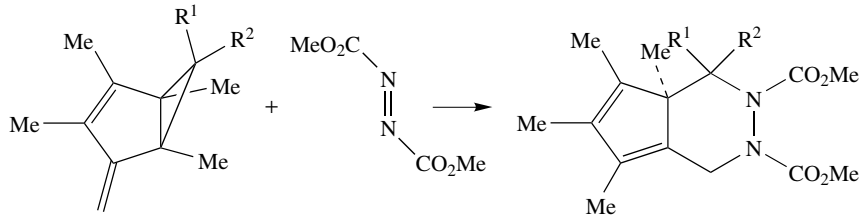
(256) (138)

The cycloadducts **257** of esters of azodicarboxylic acid to 2,7-dimethyloxepin undergo a spontaneous Claisen rearrangement to form the dihydrocyclopropapyridazines **258** (equation 139)[132]. Homofulvenes **259** (R^1, R^2 = H or Me) react to form rearranged adducts **260** (equation 140)[133].

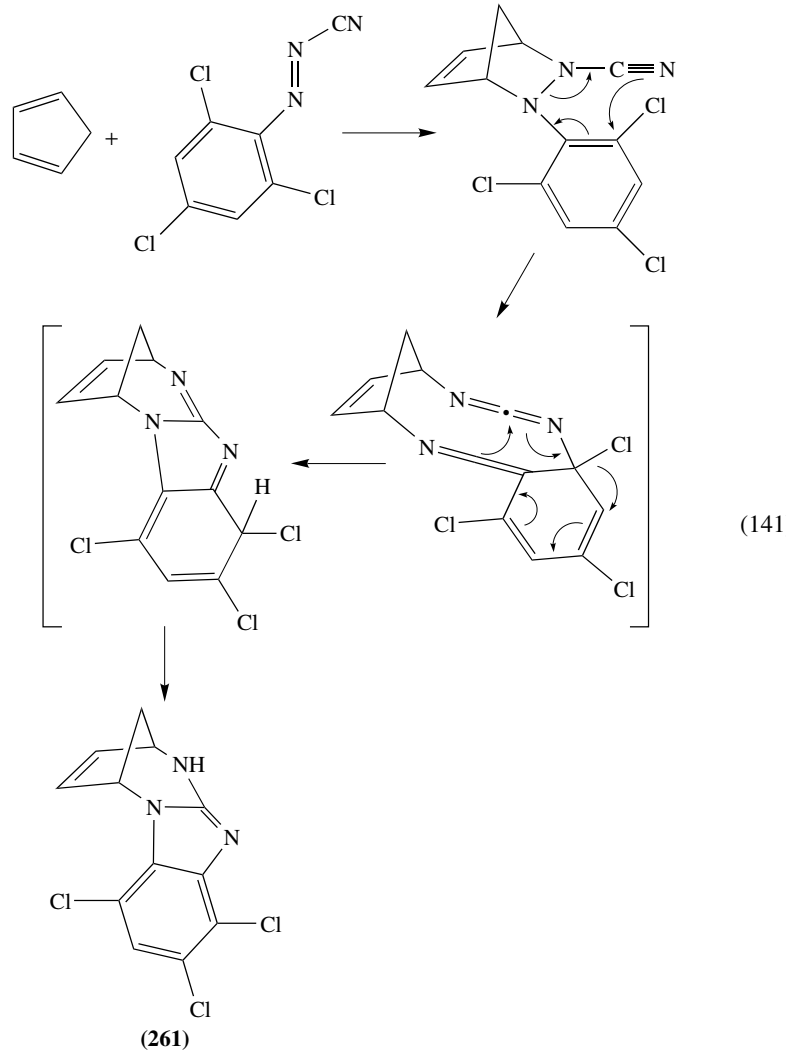
The action of 2,4,6-trichlorobenzenediazocyanide on cyclopentadiene results in an unstable cycloadduct, which over several days undergoes a 'trisaza-Cope' rearrangement to the fused benzimidazole **261** (equation 141). By contrast, the analogous adduct to cyclohexadiene is stable[134].



(257) (258) (139)



(259) **(260)** (140)

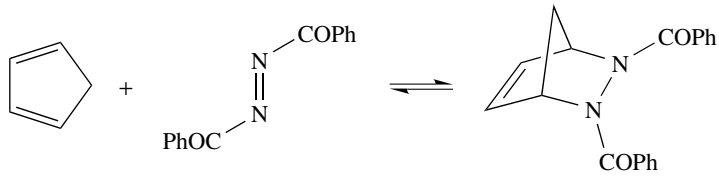


(141)

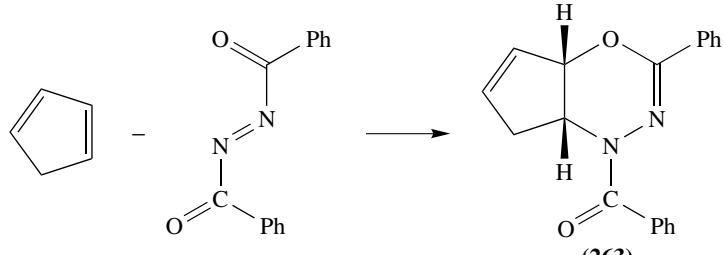
(261)

The labile cycloadduct **262** of azodibenzoyl to cyclopentadiene rearranges to the fused oxadiazine **263** on heating. The process involves dissociation of **262** into its components, followed by a Diels–Alder reaction in which the azo compound functions as a hetero diene (equation 142)[135].

The most powerful azo dienophile is the *cisoid* 4-phenyl-1,2,4-triazoline-3,5-dione **264**, which is surpassed in reactivity only by singlet oxygen. The dione adds rapidly to all types of dienes and the process can be followed visually since the bright-red color of the reagent is discharged when the reaction is complete[136].

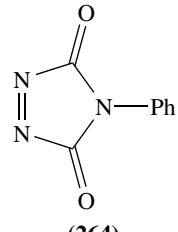


(262)

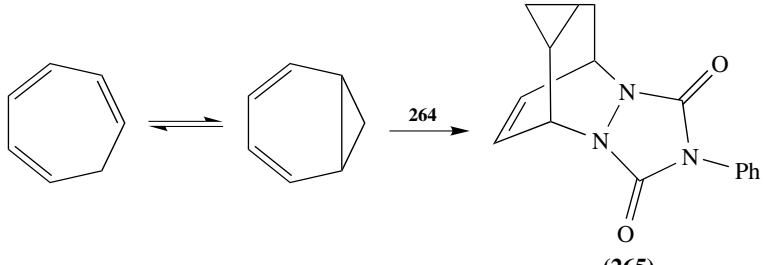


(263) (142)

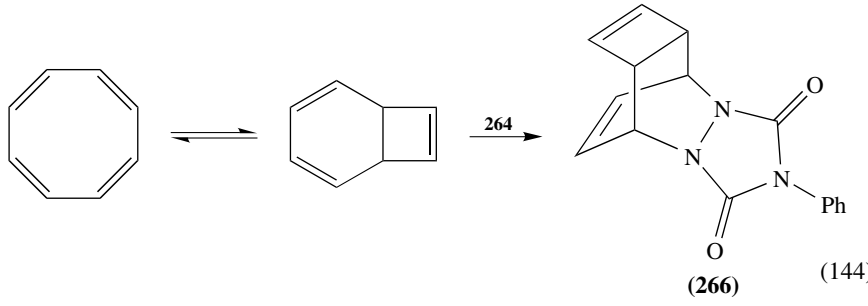
The triazolinedione adds to cycloheptatriene and cyclooctatetraene to yield the valence-isomeric adducts **265** and **266**, respectively (equations 143 and 144)[136].



(264)

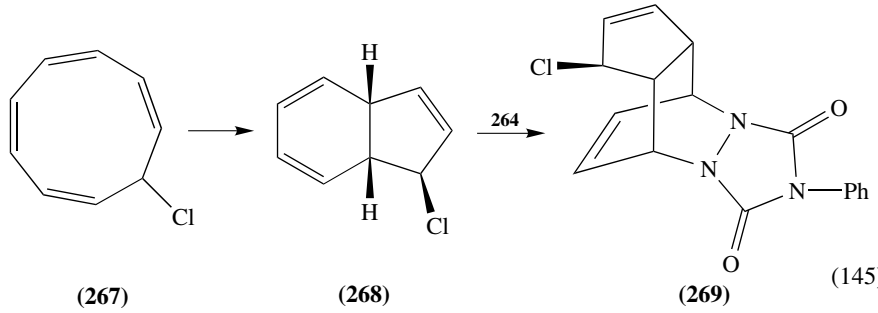


(265) (143)

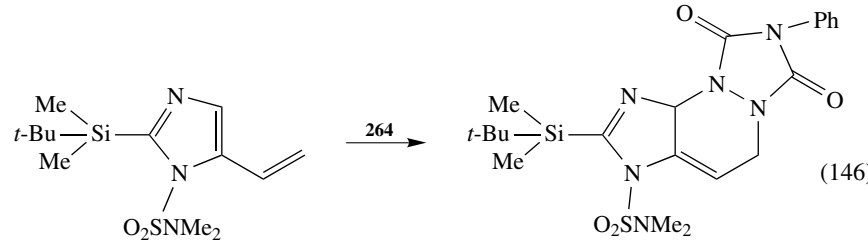


(266) (144)

9-Chlorocyclononatetraene **267** rapidly rearranges in liquid sulfur dioxide to 1-chloro-8,9-dihydroindene **268**, which forms the cycloadduct **269** with the triazolinedione **264** (equation 145)[137]. The vinylimidazole **270** affords the purine analogue **271** (equation 146)[138].



(267) **(268)** **(269)** (145)

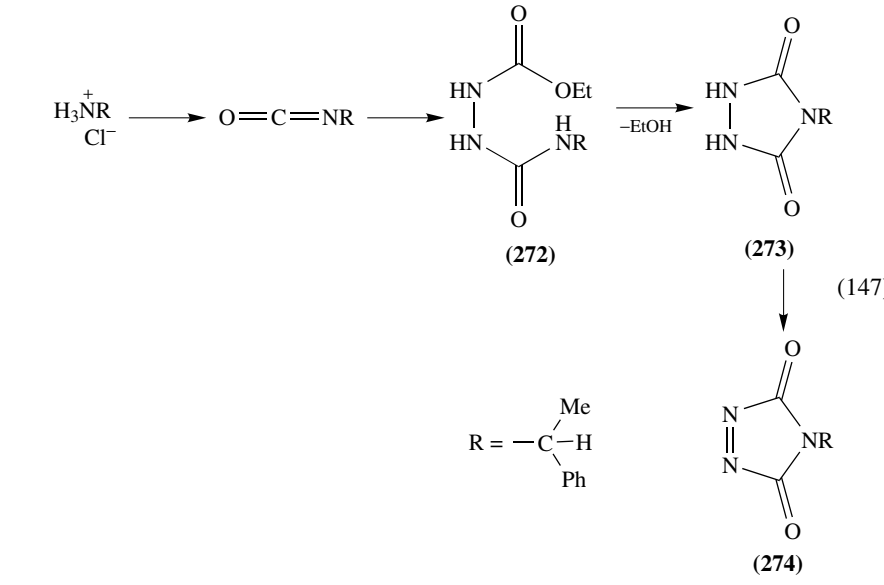


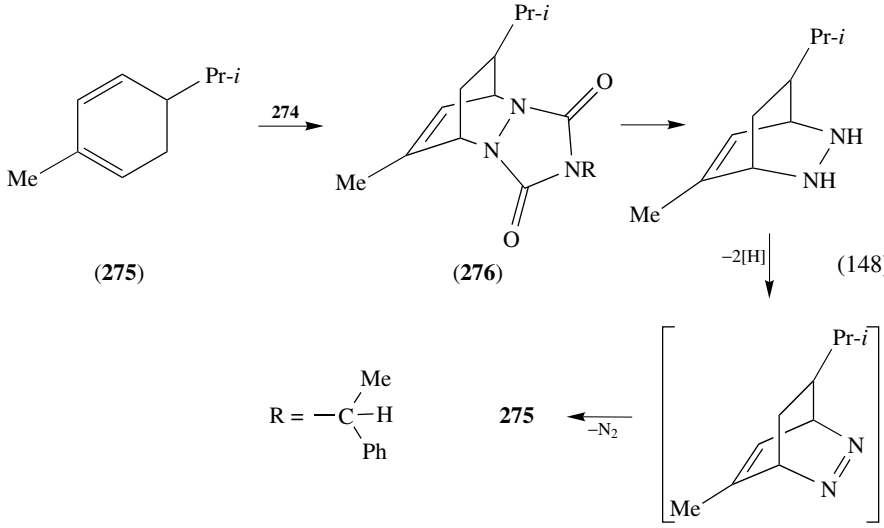
(270) **(271)** (146)

A selection of the many applications of cycloaddition with the triazolinedione **264** follows.

The preparation of an optically active triazolinedione, compound **274**, is shown in equation 147. Commercially available (−)-α-methylbenzylamine hydrochloride is converted into the hydrazine derivative **272** by treatment with phosgene, followed by H_2NNHCO_2Et. Thermal cyclization gives the urazole **273**, which is dehydrogenated to the product by means of dinitrogen tetroxide. The reagent has been used for the optical resolution of various 1,3-dienes. α-Phellandrene **275**, for instance, forms the cycloadduct **276**, which is separated into its diastereomeric components chromatographically. The chiral diene is then regenerated by alkaline hydrolysis, followed by treatment with manganese

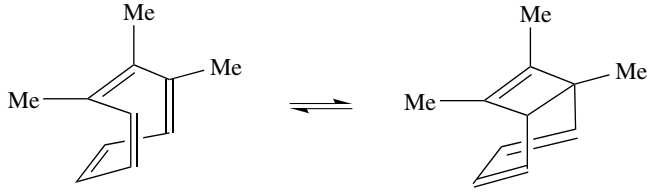
dioxide (equation 148)[139]. *Endo*-Bornylamine has similarly been converted into a chiral derivative of triazolinedione[139].



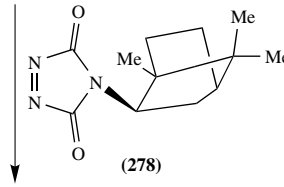


The optical resolution of the rigid racemic 1,2,3-trimethylcyclooctatetraene **277a**, which exists in equilibrium with a small amount of the valence isomer **277b**, was accomplished by means of (−)-*endo*-bornyl-1,2,4-triazoline-3,5-dione **278**. The diastereomeric mixture

of the adducts **279** was separated by fractional crystallization and the chiral cyclooctatetraenes were regenerated as described above (equation 149).[140] 1,2,3,4-Tetramethylcyclooctatetraene **280** was similarly resolved by way of the (−)-*endo*-bornyltriazolinedione adduct **281** (equation 150)[140], as was the conformationally rigid cyclooctatetraene derivative **282a** ⇌ **282b** via **283** (equation 151)[141].

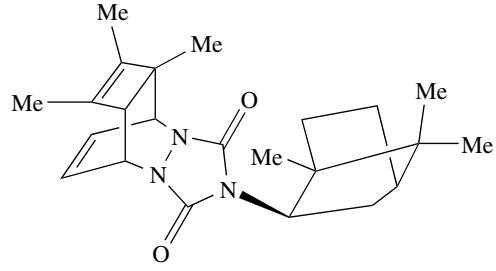


(277a) **(277b)**

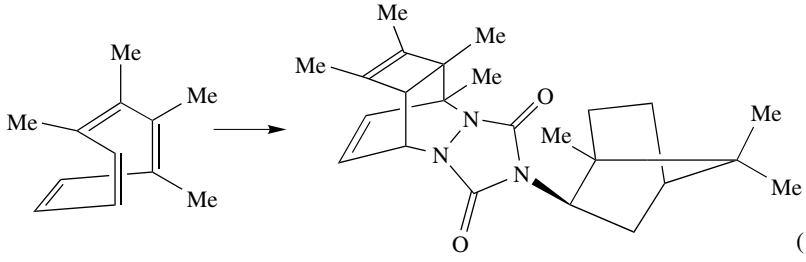


(278)

(149)

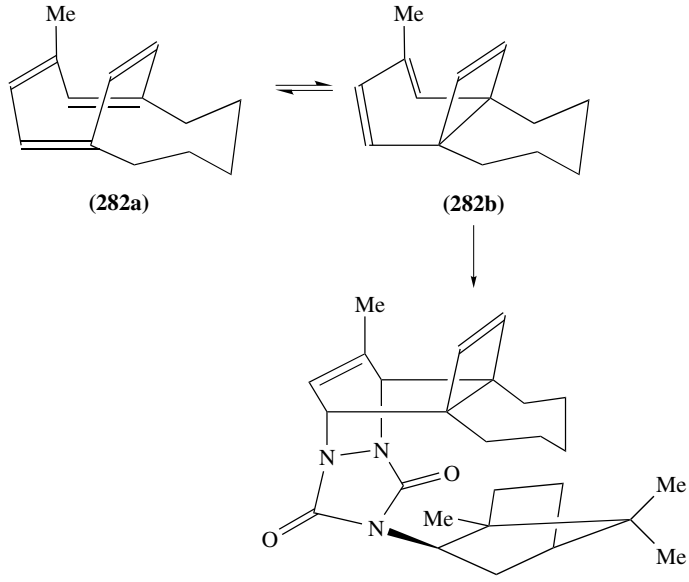


(279)



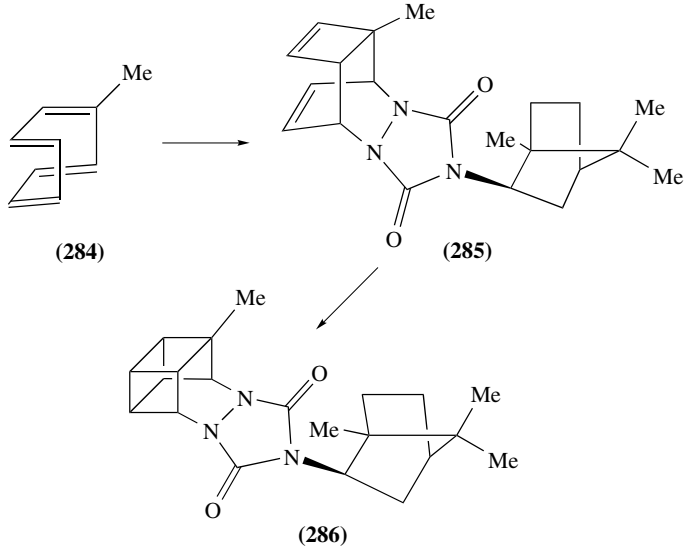
(150)

(280) **(281)**

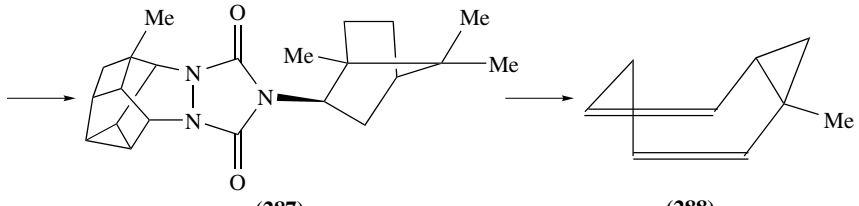


(283) (151)

Chiral 2(4)-methylsemibullvalene **288** was prepared from methylcyclooctatetraene **284** as follows. Sensitized irradiation of the (−)-*endo*-bornyltriazolinedione adduct **285** gave **286**, which, in the presence of silver nitrate/silver chloride/potassium nitrate, rearranged to **287**. The latter was resolved by column chromatography and the product **288** was obtained by successive treatment with sodium hydroxide and manganese dioxide (equation 152)[142].



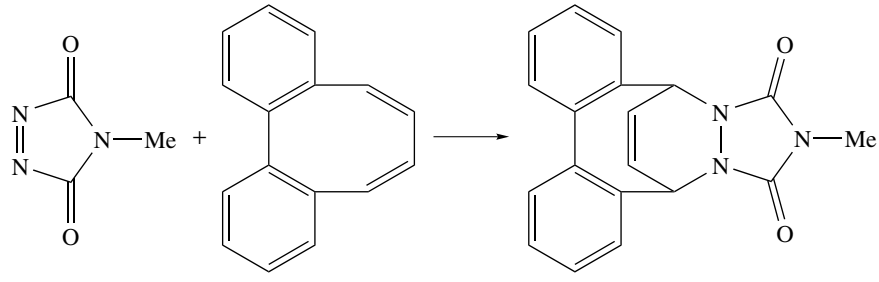
(152)



(287) **(288)**

(eq. 152 *continued*)

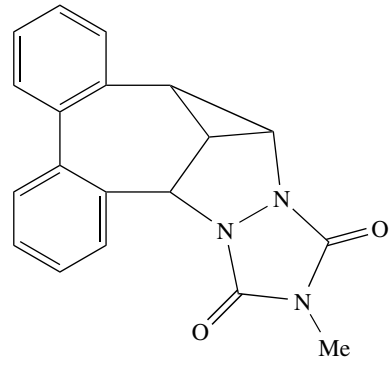
The photochemical cycloaddition of 4-methyl-1,2,4-triazoline-3,5-dione to the dibenzocyclooctatetraene **289** yields 3.5% of the cycloadduct **290**, together with 36% of **291**, the product of a di-π-methane rearrangement (equation 153)[143]. Anthrasteroids **293** (R = H, Ac or COPh) are produced in an oxidative rearrangement when the phenyltriazolinedione adduct of **292** is treated with boron trifluoride etherate[144]. The 5,7-diene system of ergosteryl acetate **294** can be protected by cycloadduct formation, allowing selective hydrogenation of the 22,23-double bond[145].



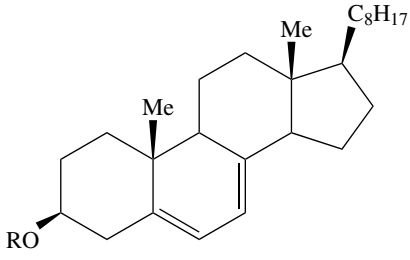
(289) **(290)**

\+

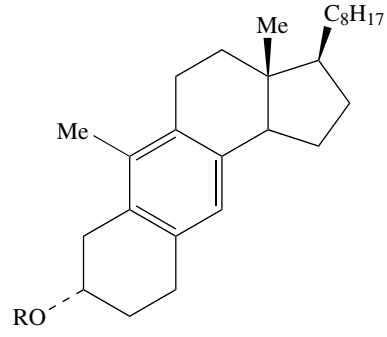
(153)



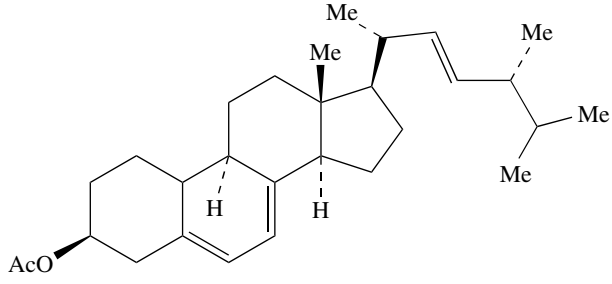
(291)



(292)



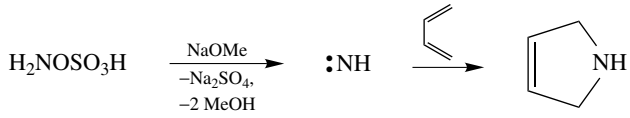
(293)



(294)

XI. FORMATION OF FIVE-MEMBERED RINGS

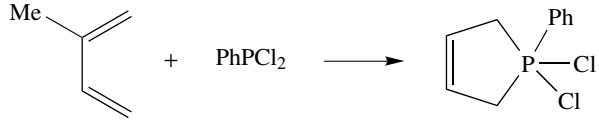
The action of methanolic sodium methoxide on hydroxylamine *O*-sulfonic acid generates nitrene NH, which adds to butadiene *in situ* to give a low yield of 1*H*-pyrroline **295** (equation 154)[146].



(154)

(295)

The formation of 1-chlorophospholene chlorides, e.g. **296**, by the action of dichlorophosphines on 1,3-dienes (equation 155) was first reported by McCormack in 1953[147].

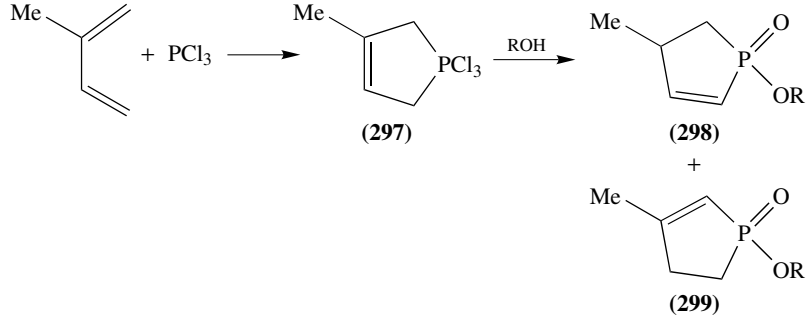


(155)

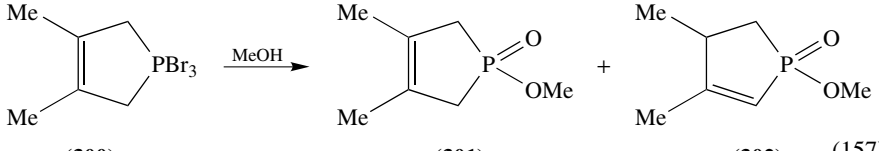
(296)

Butadiene, isoprene, chloroprene and 2,3-dimethyl-1,3-butadiene add phosphorus trihalides to form 3-phospholene 1,1,1-dihalides, e.g. **297** from isoprene and phosphorus

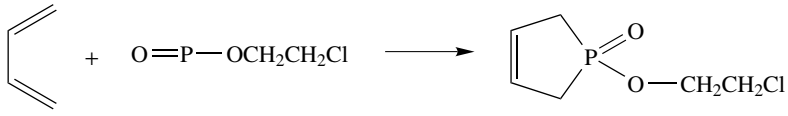
trichloride. The products react with methanol or ethanol to afford 1-alkoxy-2-phospholene 1-oxides. For instance, a mixture of **298** and **299** is obtained from **297** (equation 156)[148]. In contrast, the action of methanol on the adduct **300** of phosphorus tribromide to 2,3-dimethylbutadiene results in a mixture of 65% of 1-methoxy-3,4-dimethyl-3-phospholene 1-oxide **301** and 35% of 1-methoxy-3,4-dimethyl-2-phospholene 1-oxide **302** (equation 157)[148]. Halophosphites also react with dienes, e.g. equation 158[149].



(156)

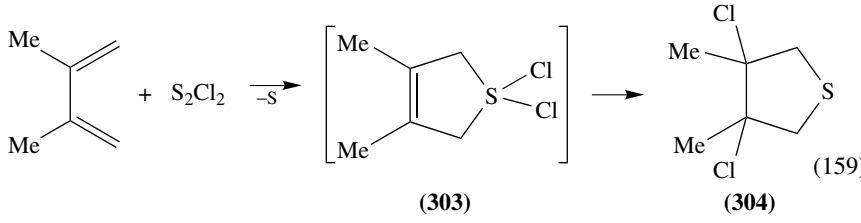


(157)

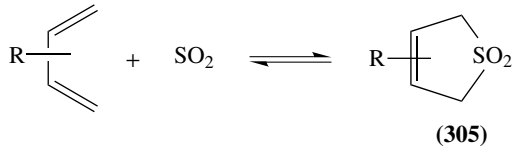


(158)

The product **303** from disulfur dichloride and 2,3-dimethylbuta-1,3-diene rearranges spontaneously to the tetrahydrothiophene **304** (equation 159)[150]. The reaction of liquid sulfur dioxide with conjugated dienes **305** (e.g. butadiene, isoprene) results in cyclic sulfones which dissociate into their components on heating (equation 160)[151,152].

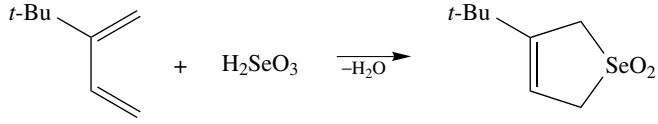


(159)



(160)

Isoprene, 2,3-dimethylbuta-1,3-diene and other dienes (but not butadiene itself) readily furnish analogous 2,5-dihydroselenophene 1,1-dioxides, e.g. **306**, on treatment with selenious acid in chloroform at room temperature (equation 161)[153].



(161)

(306)

XII. REFERENCES

1. Reviews: (a) J. Hamer (Ed.), *1,4-Cycloaddition Reactions. The Diels–Alder Reaction in Heterocyclic Syntheses*, Academic Press, New York, 1967.
   (b) J. Sauer and R. Sustmann, *Angew. Chem., Int. Ed. Engl.*, **19**, 779 (1980).
   (c) M. Petrzilka and J. I. Grayson, *Synthesis*, 753 (1981).
   (d) S. M. Weinreb and R. R. Staib, *Tetrahedron*, **38**, 3087 (1982).
   (e) P. Wetzel, *Nachr. Chem. Tech. Lab.*, **31**, 979 (1983).
   (f) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **23**, 876 (1984).
   (g) D. L. Boger, *Chem. Rev.*, **86**, 781 (1986).
   (h) R. R. Schmidt, *Acc. Chem. Res.*, **19**, 250 (1986).
   (i) D. L. Boger and S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, San Diego, 1987.
   (j) K. Krohn, *Nachr. Chem. Tech. Lab.*, **35**, 836 (1987).
   (k) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, 1990.
   (l) S. M. Weinreb, in *Comprehensive Organic Synthesis*, Vol. 5 (Ed. L. A. Paquette), Pergamon, Oxford, 1991, p. 401.
   (m) D. L. Boger, in *Comprehensive Organic Synthesis*, Vol. 5 (Ed. L. A. Paquette), Pergamon, Oxford, 1991, p. 451.
   (n) H. Waldmann, *Synthesis*, 535 (1994).
   (o) F. Fringuelli, O. Piermatti and F. Pizzo, *Targets Heterocycl. Syst.*, **1**, 57 (1997).
   (p) D. T. Parker, *Org. Synth. Water*, 47 (1998).
2. O. Achmatowicz, Jr., J. Jurczak and J. S. Pyrek, *Tetrahedron*, **32**, 2113 (1976).
3. R. Bonjouklian and R. A. Ruden, *J. Org. Chem.*, **42**, 4095 (1977).
4. J. Jurczak, M. Chmielewski and S. Filipek, *Synthesis*, 41 (1979).
5. B. Potthoff and E. Breitmaier, *Chem. Ber.*, **119**, 2059 (1986).
6. S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).
7. J. Bélanger, N. L. Landry, J. R. J. Paré and K. Jankowski, *J. Org. Chem.*, **47**, 3649 (1982).
8. (a) S. David and J. Eustache, *J. Chem. Soc., Perkin Trans. 1*, 2230 (1979).
   (b) S. David and J. Eustache, *J. Chem. Soc., Perkin Trans. 1*, 2521 (1979).
9. W. Abele and R. R. Schmidt, *Tetrahedron Lett.*, **22**, 4807 (1981).
10. R. R. Schmidt and A. Wagner, *Synthesis*, 273 (1981).
11. Reviews: (a) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).
    (b) G. V. Boyd, in *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2 (Ed. S. Patai), Wiley, Chichester, 1989, p. 477.
12. H. Robert, B. Garrigues and J. Dubac, *Tetrahedron Lett.*, **39**, 1161 (1998).
13. Review: K. Narasaka, *Synthesis*, 1 (1991).
14. (a) M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, **105**, 6968 (1983).
    (b) M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, **108**, 7060 (1986).
15. M. Johannsen and K. A. Jørgensen, *J. Org. Chem.*, **60**, 5757 (1995).
16. M. Johannsen and K. A. Jørgensen, *Tetrahedron*, **52**, 7321 (1996).
17. A. Graven, M. Johannsen and K. A. Jørgensen, *J. Chem. Soc., Chem. Commun.*, 2373 (1996).
18. K. Maruoka, T. Itoh, T. Shirasaka and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 310 (1988).
19. Q. Gao, T. Maruyama, M. Mouri and H. Yamamoto, *J. Org. Chem.*, **57**, 1951 (1992).
20. Q. Gao, K. Ishihara, T. Maruyama, M. Mouri and H. Yamamoto, *Tetrahedron*, **50**, 979 (1994).

21. S. E. Schaus, J. Brånalt and E. N. Jacobsen, *J. Org. Chem.*, **63**, 403 (1998).
22. G. E. Keck, X.-Y. Li and D. Krishnamurthy, *J. Org. Chem.*, **60**, 5998 (1995).
23. J. A. Barltrop and B. Hesp, *J. Chem. Soc.*, 5182 (1965).
24. J. C. Martin, P. G. Gott, W. W. Goodlett and R. H. Hasek, *J. Org. Chem.*, **30**, 4175 (1965).
25. W. J. Middleton, *J. Org. Chem.*, **30**, 1390 (1965).
26. A. Ohno, Y. Ohnishi and G. Tsuchihashi, *Tetrahedron*, **25**, 871 (1969).
27. C. R. Johnson, J. E. Keiser and J. C. Sharp, *J. Org. Chem.*, **34**, 860 (1969).
28. M. S. Raasch, *J. Org. Chem.*, **35**, 3470 (1970).
29. M. S. Raasch, *J. Org. Chem.*, **40**, 161 (1975).
30. M. S. Raasch, *J. Org. Chem.*, **43**, 2500 (1978).
31. E. Vedejs, M. J. Arnost and J. M. Dolphin, *J. Org. Chem.*, **45**, 2601 (1980).
32. (a) B. Zwanenburg, L. Thijs and J. Strating, *Tetrahedron Lett.*, 4461 (1969).
    (b) B. Zwanenburg, L. Thijs, J. B. Broens and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **91**, 443 (1972).
33. P. A. T. W. Porskamp, R. C. Haltiwanger and B. Zwanenburg, *Tetrahedron Lett.*, **24**, 2035 (1983).
34. L. A. G. M. van den Broek, P. A. T. W. Porskamp, R. C. Haltiwanger and B. Zwanenburg, *J. Org. Chem.*, **49**, 1691 (1984).
35. (a) D. M. Vyas and G. W. Hay, *Can. J. Chem.*, **49**, 3755 (1971).
    (b) D. M. Vyas and G. W. Hay, *J. Chem. Soc., Perkin Trans. 1*, 180 (1975).
36. (a) K. Friedrich and M. Zamkanei, *Tetrahedron Lett.*, 2139 (1977).
    (b) K. Friedrich and M. Zamkanei, *Chem. Ber.*, **112**, 1867 (1979).
37. H. C. Hansen and A. Senning, *J. Chem. Soc., Chem. Commun.*, 1135 (1979).
38. J. A. Boerma, N. H. Nilsson and A. Senning, *Tetrahedron*, **30**, 2735 (1974).
39. T. Saito and S. Motoki, *J. Org. Chem.*, **44**, 2493 (1979).
40. Review: S. M. Weinreb and J. I. Levin, *Heterocycles*, **12**, 949 (1979).
41. D. vor der Brück, R. Bühler and H. Plieninger, *Tetrahedron*, **28**, 791 (1972).
42. M. Maggini, M. Prato and G. Scorrano, *Tetrahedron Lett.*, **31**, 6243 (1990).
43. M. E. Jung, K. Shishido, L. Light and L. Davis, *Tetrahedron Lett.*, **22**, 4607 (1981).
44. S. Kobayashi, H. Ishitani and S. Nagayama, *Synthesis*, 1195 (1995).
45. (a) S. Kobayashi, M. Akari, H. Ishitani, S. Nagayama and I. Hachiya, *Synlett*, 233 (1995).
    (b) S. Kobayashi, H. Ishitani and S. Nagayama, *Chem. Lett.*, 423 (1995).
46. E. P. Kündig, L. H. Xu, P. Romanens and G. Bernadinelli, *Synlett*, 270 (1996).
47. A. K. McFarlane, G. Thomas and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 2803 (1995).
48. P. D. Bailey, G. R. Brown, F. Korber, A. Reed and R. D. Wilson, *Tetrahedron: Asymmetry*, **2**, 1263 (1991).
49. (a) H. Waldmann, M. Braun and M. Dräger, *Angew. Chem., Int. Ed. Engl.*, **29**, 1468 (1990).
    (b) H. Waldmann, M. Braun and M. Dräger, *Tetrahedron: Asymmetry*, **2**, 1231 (1991).
50. K. Hattori and H. Yamamoto, *Tetrahedron*, **49**, 1749 (1993).
51. J. F. Kerwin, Jr. and S. Danishefsky, *Tetrahedron Lett.*, **23**, 3739 (1982).
52. M. M. Midland and J. I. McLoughlin, *Tetrahedron Lett.*, **29**, 4653 (1988).
53. S. Danishefsky and C. Vogel, *J. Org. Chem.*, **51**, 3915 (1986).
54. M. M. Midland and R. W. Koops, *J. Org. Chem.*, **57**, 1158 (1992).
55. W. Pfrengle and H. Kunz, *J. Org. Chem.*, **54**, 4261 (1989).
56. (a) K. Hattori and H. Yamamoto, *J. Org. Chem.*, **57**, 3264 (1992).
    (b) K. Ishihara, M. Miyata, K. Hattori, T. Tada and H. Yamamoto, *J. Am. Chem. Soc.*, **116**, 10520 (1994).
57. S. Kobayashi, S. Komiyama and H. Ishitani, *Angew. Chem., Int. Ed. Engl.*, **37**, 979 (1998).
58. S. Yao, M. Johannsen, R. G. Hazell and K. A. Jørgensen, *Angew. Chem., Int. Ed. Engl.*, **37**, 3121 (1998).
59. P. Hamley, G. Helmchen, A. B. Holmes, D. R. Marshall, J. W. M. MacKinnon, D. F. Smith and J. W. Ziller, *J. Chem. Soc., Chem. Commun.*, 786 (1992).
60. E. Pombo-Villar, J. Boelsterli, M. M. Cid, J. France, B. Fuchs, M. Walkinshaw and H.-P. Weber, *Helv. Chim. Acta*, **76**, 1203 (1993).
61. H. Waldmann and M. Braun, *Justus Liebigs Ann. Chem.*, 1045 (1991).
62. S. D. Larsen and P. A. Grieco, *J. Am. Chem. Soc.*, **107**, 1768 (1985).
63. (a) H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, **27**, 274 (1988).
    (b) H. Waldmann, *Justus Liebigs Ann. Chem.*, 231 (1989).

64. Review: A. Hassner, *Synthesis*, 483 (1975).
65. (a) D. J. Anderson and A. Hassner, *J. Am. Chem. Soc.*, **93**, 4339 (1971).
(b) A. Hassner and D. J. Anderson, *J. Am. Chem. Soc.*, **94**, 8255 (1972).
(c) D. J. Anderson and A. Hassner, *J. Org. Chem.*, **39**, 3070 (1974).
66. V. Nair, *J. Org. Chem.*, **37**, 802 (1972).
67. Y. Ueda and S. C. Maynard, *Tetrahedron Lett.*, **26**, 6309 (1985).
68. A. I. Meyers, T. J. Sowin, S. Scholz and Y. Ueda, *Tetrahedron Lett.*, **28**, 5103 (1987).
69. B. M. Trost and P. J. Whitman, *J. Am. Chem. Soc.*, **96**, 7421 (1974).
70. (a) G. J. Janz, R. G. Ascah and A. G. Keenan, *Can. J. Res.*, **B25**, 272 (1947).
(b) G. J. Janz and A. G. Keenan, *Can. J. Res.*, **B25**, 282 (1947).
71. (a) A. M. van Leusen and J. C. Jagt, *Tetrahedron Lett.*, 9711 (1970).
(b) J. C. Jagt and A. M. van Leusen, *Recl. Trav. Chim. Pays-Bas*, **92**, 1343 (1973).
(c) J. C. Jagt and A. M. van Leusen, *J. Org. Chem.*, **39**, 564 (1974).
72. G. J. Janz and A. R. Monohan, *J. Org. Chem.*, **29**, 569 (1964).
73. M. Gillard, C. T'Kint, E. Sonveaux and L. Ghosez, *J. Am. Chem. Soc.*, **101**, 5837 (1979).
74. F. Mathey, F. Mercier, C. Charrier, J. Fischer and A. Mitschler, *J. Am. Chem. Soc.*, **103**, 4595 (1981).
75. F. Sennyey and F. Mathey, *Tetrahedron Lett.*, **22**, 4713 (1981).
76. Review: M. Balci, *Chem. Rev.*, **81**, 91 (1981).
77. G. O. Schenck, K. G. Kinkel and H.-J. Mertens, *Ann. Chem.*, **584**, 125 (1953).
78. G. O. Schenck and E. D. Dunlap, *Angew. Chem.*, **68**, 248 (1956).
79. K. H. Schulte-Elte, B. Willhalm and G. Ohloff, *Angew. Chem., Int. Ed. Engl.*, **8**, 985 (1969).
80. W. R. Adams and D. J. Trecker, *Tetrahedron*, **27**, 2631 (1971).
81. C. Dufraisse, G. Rio and J. J. Basselier, *Compt. rend.*, **246**, 1640 (1958)
82. G. R. Evanega, W. Bergmann and J. English, Jr., *J. Org. Chem.*, **27**, 13 (1962).
83. W. Adam, M. Güthlein, E.-M. Peters, K. Peters and T. Wirth, *J. Am. Chem. Soc.*, **120**, 4091 (1998).
84. H. J. Backer and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **54**, 52 (1935).
85. (a) G. W. Kirby, *Chem. Soc. Rev.*, **6**, 1 (1977).
(b) J. Streith and A. Defoin, *Synthesis*, 1107 (1994).
(c) C. Kibayashi and S. Aoyagi, *Synlett*, 873 (1995).
(d) P. Aped and H. Senderowitz, in Supplement F2: *The Chemistry of Amino, Nitroso and Related Groups* (Ed. S. Patai), Wiley, Chichester, 1996, p. 1.
86. O. Wichterle, *Collect. Czech. Chem. Commun.*, **12**, 292 (1947).
87. J. Hamer, A. Ahmad and R. E. Holliday, *J. Org. Chem.*, **28**, 3034 (1963).
88. G. Kresze, J. Firl, H. Zimmer and U. Wollnik, *Tetrahedron*, **20**, 1605 (1964).
89. (a) E. R. Møller and K. A. Jørgensen, *J. Am. Chem. Soc.*, **115**, 11814 (1993).
(b) E. R. Møller and K. A. Jørgensen, *J. Org. Chem.*, **61**, 5770 (1996).
90. G. Kresze and J. Firl, *Tetrahedron Lett.*, 1163 (1965).
91. D. Rousselle, E. Francotte, J. Feneau-Dupont, B. Tinant, J. P. Declerq and H. G. Viehe, *Tetrahedron*, **47**, 8323 (1991).
92. H. G. Viehe, R. Merényi, E. Francotte, M. Van Meerssche, G. Germain, J. P. Declerq and J. Bodart-Gilmont, *J. Am. Chem. Soc.*, **99**, 2340 (1977).
93. (a) E. Francotte, R. Merényi, B. Vandenbulcke-Coyette and H. G. Viehe, *Helv. Chim. Acta.*, **64**, 1208 (1981).
(b) J.-L. Vaerman and H. G. Viehe, *Tetrahedron*, **45**, 3183 (1989).
(c) M. Sana, G. Leroy, J.-L. Vaerman and H. G. Viehe, *Can. J. Chem.*, **68**, 1625 (1990).
94. R. Faragher and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 249 (1979).
95. O. Wichterle and J. Novak, *Collect. Czech. Chem. Commun.*, **15**, 309 (1950).
96. (a) R. E. Banks, M. G. Barlow and R. N. Haszeldine, *J. Chem. Soc.*, 4714 (1965).
(b) R. E. Banks, M. G. Barlow and R. N. Haszeldine, *J. Chem. Soc.*, 6949 (1965).
97. P. Horsewood and G. W. Kirby, *J. Chem. Soc., Chem. Commun.*, 1139 (1971)
98. G. W. Kirby and J. G. Sweeny, *J. Chem. Soc., Chem. Commun.*, 704 (1973).
99. G. W. Kirby and J. G. Sweeny, *J. Chem. Soc., Perkin Trans. 1*, 3250 (1981).
100. G. W. Kirby, J. W. M. MacKinnon and R. P. Sharma, *Tetrahedron Lett.*, 215 (1977).

101. T. L. Gilchrist, M. E. Peck and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 913 (1975).
102. G. Kresze and W. Kort, *Chem. Ber.*, **94**, 2624 (1961).
103. (a) J. Streith, G. Augelmann, H. Fritz and H. Strub, *Tetrahedron Lett.*, **23**, 1909 (1982).
(b) G. Augelmann, J. Streith and H. Fritz, *Helv. Chim. Acta*, **68**, 95 (1985).
(c) A. Defoin, H. Fritz, C. Schmidlin and J. Streith, *Helv. Chim. Acta*, **70**, 554 (1987).
104. A. Defoin, A. Brouillard-Poichet and J. Streith, *Helv. Chim. Acta*, **74**, 103 (1991).
105. V. Gouverneur and L. Ghosez, *Tetrahedron: Asymmetry*, **1**, 363 (1990).
106. F. Backenstrass, J. Streith and T. Tschamber, *Tetrahedron Lett.*, **31**, 2139 (1990).
107. G. W. Kirby and M. Nazeer, *Tetrahedron Lett.*, **29**, 6173 (1988).
108. M. Sabuni, G. Kresze and H. Braun, *Tetrahedron Lett.*, **25**, 5377 (1984).
109. A. Brouillard-Poichet, A. Defoin and J. Streith, *Tetrahedron Lett.*, **30**, 7061 (1989).
110. S. F. Martin, M. Hartmann and J. A. Josey, *Tetrahedron Lett.*, **33**, 3583 (1992).
111. Review: S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, **24**, 1 (1985).
112. A. Defoin, J. Pires, I. Tissot, T. Tschamber, D. Burb, M. Zehnder and J. Streith, *Tetrahedron: Asymmetry*, **2**, 1209 (1991).
113. (a) H. Felber, G. Kresze, H. Braun and A. Vasella, *Tetrahedron Lett.*, **25**, 5381 (1984).
(b) H. Felber, G. Kresze, R. Prewo and A. Vasella, *Helv. Chim. Acta*, **69**, 1137 (1986).
(c) H. Braun, H. Felber, G. Kresze, F. P. Schmidtchen, R. Prewo and A. Vasella, *Justus Liebigs Ann. Chem.*, 261 (1993).
114. V. Gouverneur, G. Dive and L. Ghosez, *Tetrahedron: Asymmetry*, **2**, 1173 (1991).
115. O. Werbitzky, K. Klier and H. Felber, *Justus Liebigs Ann. Chem.,* 267 (1990).
116. O. Wichterle and J. Roček, *Collect. Czech. Chem. Commun.*, **19**, 282 (1954).
117. G. Kresze and W. Wucherpfennig, *Angew. Chem., Int. Ed. Engl.*, **6**, 149 (1967).
118. (a) E. S. Levchenko, Ya. G. Balon and A. V. Kirsanov, *Zh. Obshch. Khim.*, **33**, 1579 (1963); *Chem. Abstr.*, **59**, 12801 (1963).
(b) E. S. Levchenko, Ya. G. Balon and A. A. Kisilenko, *Zh. Org. Khim.*, **1**, 155 (1965); *Chem. Abstr.*, **62**, 14664 (1965).
119. J. Hamer and A. Macaluso, *J. Org. Chem.*, **31**, 3049 (1966).
120. G. Kresze and U. Wagner, *Chem. Ann.*, **762**, 93 (1972).
121. E. S. Levchenko and Ya. G. Balon, *Zh. Org. Khim.*, **1**, 150 (1965); *Chem. Abstr.*, **62**, 14663 (1965).
122. W. Wucherpfennig and G. Kresze, *Tetrahedron Lett.*, 1671 (1966).
123. E. S. Levchenko and Ya. G. Balon, *Zh. Org. Khim.*, **1**, 305 (1965); *Chem. Abstr.*, **62**, 16235 (1965).
124. S. W. Ramiszewski, J. Yang and S. M. Weinreb, *Tetrahedron Lett.*, **27**, 1853 (1986).
125. J. K. Whitesell, D. James and J. F. Carpenter, *J. Chem. Soc., Chem. Commun.*, 1449 (1985).
126. Review: H. Zollinger, *Azo- and Diazo-Chemistry*, Wiley (Interscience), New York, 1961, p. 286.
127. Review: S. B. Needleman and M. C. Chang Kuo, *Chem. Rev.*, **62**, 405 (1962).
128. O. Diels, J. H. Blom and W. Koll, *Ann. Chem.*, **443**, 242 (1925).
129. O. Diels and K. Alder, *Ann. Chem.*, **460**, 98 (1928).
130. T. J. Kealy, *J. Am. Chem. Soc.*, **84**, 966 (1962).
131. B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **27**, 1947 (1962).
132. W. H. Rastetter and T. J. Richard, *Tetrahedron Lett.*, 2999 (1978).
133. R. Askani and J. P. Chesick, *Chem. Ber.*, **106**, 8 (1973).
134. (a) D. Rousselle, C. Musick, H. G. Viehe, B. Tinant and J. P. Declerq, *Tetrahedron Lett.*, **32**, 907 (1991).
(b) D. Rousselle, T. Ryckmans and H. G. Viehe, *Tetrahedron*, **48**, 5249 (1992).
135. D. Mackay, J. A. Campbell and C. P. R. Jennison, *Can. J. Chem.*, **48**, 81 (1970).
136. (a) R. C. Cookson, S. S. H. Gilani and I. D. R. Stevens, *Tetrahedron Lett.*, 615 (1962).
(b) R. C. Cookson, S. S. H. Gilani and I. D. R. Stevens, *J. Chem. Soc. (C)*, 1905 (1967).
(c) H. Isaksen and J. P. Snyder, *Tetrahedron Lett.*, 889 (1977).
137. A. G. Anastassiou and E. Yakali, *J. Chem. Soc., Chem. Commun.*, 92 (1972).
138. P. Y. F. Deghati, M. J. Wanner and G.-J. Koomen, *Tetrahedron Lett.*, **39**, 4561 (1998).

139. L. A. Paquette and R. F. Doehner, Jr., *J. Org. Chem.*, **45**, 5105 (1980).
140. (a) J. M. Gardlik and L. A. Paquette, *Tetrahedron Lett.*, 3597 (1979).
(b) L. A. Paquette and J. M. Gardlik, *J. Am. Chem. Soc.*, **102**, 5016 (1980).
(c) L. A. Paquette, J. M. Gardlik, L. K. Johnson and K. J. McCullough, *J. Am. Chem. Soc.*, **102**, 5026 (1980).
141. L. A. Paquette and M. P. Trova, *Tetrahedron Lett.*, **27**, 1895 (1986).
142. L. A. Paquette, R. F. Doehner, Jr. and J. A. Jerkins, *J. Am. Chem. Soc.*, **102**, 1188 (1980).
143. U. Burger, Y. G. Mentha, P. Millasson, P. A. Lottaz and J. Maseda, *Helv. Chim. Acta*, **72**, 1722 (1989).
144. N. Bosworth, A. Emke, J. M. Midgley, C. J. Moore, W. B. Whalley, G. Ferguson and W. C. Marsh, *J. Chem. Soc., Perkin Trans. 1*, 805 (1977).
145. (a) D. H. R. Barton, T. Shioiri and D. A. Widdowson, *J. Chem. Soc. (C)*, 1968 (1971).
(b) D. H. R. Barton, A. A. L. Gunatilaka, T. Nakanishi, H. Patin, D. A. Widdowson and B. R. Worth, *J. Chem. Soc., Perkin Trans. 1*, 821 (1976).
146. R. Appel and O. Büchner, *Angew. Chem.*, **74**, 430 (1962).
147. W. B. McCormack, U.S. Patent 2663736 (1953); *Chem. Abstr.*, **49**, 7602 (1955).
148. (a) V. Hasserodt, K. Hunger and F. Korte, *Tetrahedron*, **19**, 1563 (1963).
(b) K. Hunger, V. Hasserodt and F. Korte, *Tetrahedron*, **20**, 1593 (1964).
149. N. A. Razumova and A. A. Petrov, *Zh. Obshch. Khim.*, **33**, 783 (1963); *Chem. Abstr.*, **59**, 8783 (1963).
150. H. J. Backer and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **54**, 52 (1935).
151. G. de Bruin, *Verslag Akad. Wetenschappen*, **23**, 445 (1914); *Chem. Abstr.*, **9**, 623 (1915).
152. (a) H. J. Backer and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **53**, 525 (1934).
(b) H. J. Backer and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **54**, 170 (1935).
153. H. J. Backer and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **53**, 1113 (1934).

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CHAPTER **7**

Electrophilic additions to dienes and polyenes

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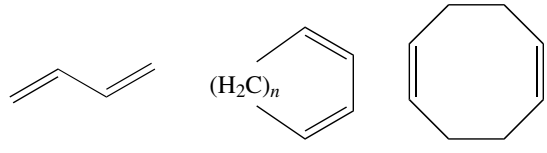
I. INTRODUCTION

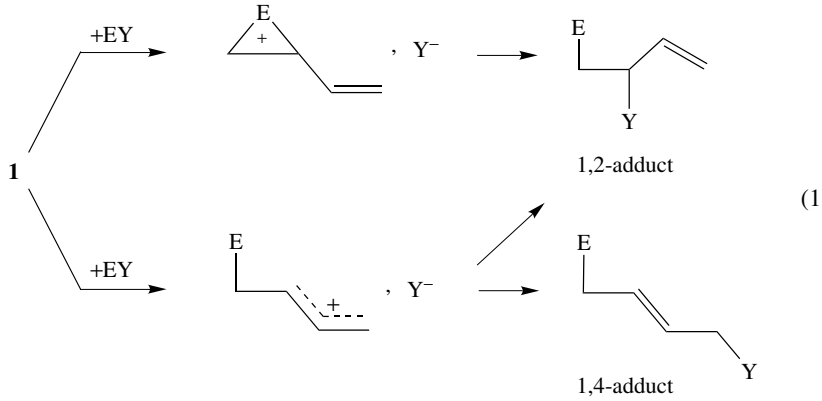
Electrophilic additions to carbon–carbon double bonds, a very large chapter in any organic textbook[1], have been for a long time[2] and recently[3] the object of intensive research because of their interest in fundamental mechanistic approaches, synthetic methodology and industrial procedures. In this context, the electrophilic reactions of dienes and polyenes have been reviewed frequently in specific paragraphs of extensive reports[2] on the reactivity of carbon–carbon bonds and, sometimes, more specifically[4] as a particular class of unsaturated compounds exhibiting properties markedly different from that of monoethylenic compounds. When there is no interaction between the several double bonds included in a polyenic molecule, the reactivity of each of these bonds toward usual electrophiles is not altered by the presence of other double bonds. No particular attention will be paid in this review to this category of polyenes since many previous reports on electrophilic reactivity covered the field[2]. In contrast, when two or more ethylenic bonds interact, a particular reactivity of the system is expected. The present review on studies carried out over the last 25 years is focused on this second category which involves mainly acyclic and cyclic conjugated 1,3-dienes, derived from **1** and **2**, respectively, and non-conjugated cyclic dienes, *cis*,*cis*-1,5-cyclooctadiene **(3)** being the most popular representative in this series.



(1) **(2)** **(3)**

The few kinetic results and the extensive product data on the electrophilic reactions of these dienes have been mainly interpreted in terms of the simplistic mechanism described in equation 1 and postulated by analogy to that established a long time ago[5] for the reactions of monoethylenic compounds. According to this naive picture, an ionic intermediate with two possible limiting structures would be formed by electrophilic addition

of the molecule EY to one of the two double bonds, viewing the dienic system as a monoethylenic compound substituted by a conjugated vinyl group. This approach was actually justified very early by the pioneering work of Tidwell and coworkers[6] in their extensive kinetic investigation of the acid-catalyzed hydration of ethylenic compounds, including a number of substituted 1,3-dienes. The rates of addition to the conjugated dienes fitted fairly well the general structure–reactivity relationship for monoenes when the appropriate substituent constant for the vinyl group was used. Unfortunately, no further studies have been undertaken to support the reliability of this conclusion for other electrophiles. It is also surprising that the numerous recent details and improvements of the general mechanism for electrophilic additions to monoenes[2d,3,7] (including the role of charge transfer complexes, the reversibility of the intermediate-forming step, the solvent-independent bridging and nucleophilic solvent assistance, etc.) have not been extended to reactions of dienes.



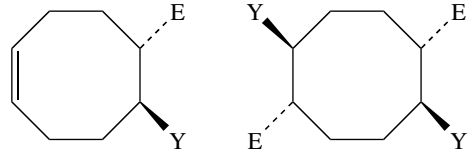
(1)

Actually, the main specific feature of the reaction of conjugated dienes has been the competition between 1,2- and 1,4-additions, which has to be associated with the Markovnikov/anti-Markovnikov regiochemistry and the *anti* vs *syn* stereochemistry usually exhibited in the monoene reactions[2,3,8]. The product mixtures obtained from conjugated polyenes are highly complex. Therefore, most of the interest in these reactions was focused on the reaction products and interpretation of their formation in terms of allylic and/or bridged structures of the ionic intermediates. A basic experiment on the deuterium incorporation in 1,3-pentadiene in its reaction with DCl raised this problem very early[9]. Not only 1,2- but also 1,4-adducts were observed as a result of the fast interconversion of the two isomeric ion pairs (*vide infra*). From this result and many others emerged the idea of two limiting structures for these intermediates, an allylic carbenium ion with extensive charge delocalization into the second double bond and a bridged cation whose charge is stabilized by the entering electrophile. Therefore, 1,2-adducts would result from nucleophilic trapping of strongly bridged intermediates whereas 1,4-additions would arise from an unbridged allylic carbocation. In agreement with this assumption, significant amounts of 1,4-adducts were obtained with electrophilic fluorine[10], a poorly bridging atom, while electrophilic sulfur additions which involve an efficient bridging afforded mainly 1,2-products[11]. Moreover, the bridged vinyl-substituted intermediate is expected to lead to a mixture of Markovnikov and anti-Markovnikov addition products. *Syn* adducts with a predominant Markovnikov regioselectivity should also be obtained from an allylic intermediate. Indeed, the addition of sulfenyl halides to butadienes[12] afforded *anti* 1,2-adducts with either a Markovnikov or anti-Markovnikov regiochemistry,

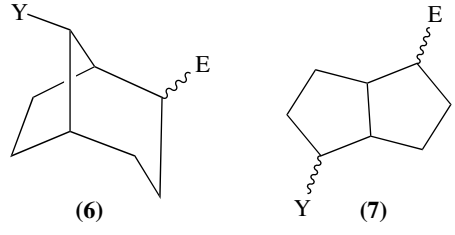
consistent with a vinyl-substituted thiiranium ion intermediate. Analogously, 1,2-bromine adducts were found to be mainly *anti*[13] whereas the 1,4-products were formed non-stereoselectively.

Nevertheless, the product data have been exceptionally interpreted only in these terms. (i) An allylic carbocation can afford significant amounts of 1,2-products. For instance, in the above-mentioned DCl addition, 1,2-adducts were the major products whatever the solvent. (ii) In addition to the electrophile and substituent dependence of the charge distribution in the intermediate, solvent and steric effects probably play an important role in the product-forming step of these reactions, as they do in the reactions of monoenes[7d,8]. (iii) 1,2-Adducts isomerize frequently to the more stable 1,4-adducts. Therefore, the kinetic or thermodynamic control of the product distribution[12,14] should be questioned. As a consequence, a number of early results were later revised when this problem was recognized. (iv) Finally, it has also been suggested[15] that 1,4-addition products do not necessarily arise from allylic intermediates but could also result from bridged intermediates via an S_N2' process implying a *syn* stereochemistry.

The electrophilic additions of reagents EY to non-conjugated cyclic dienes with two interactive double bonds such as in **3** have been also widely investigated because of their potential interest in organic synthesis[16–18] and also since they are useful models for hydrocarbon skeleton rearrangements of cyclic carbocations[19]. Mono- and bis-1,2-addition products, **4** and **5**, have been sometimes observed when the electrophilic atom was strongly bridging and under poorly ionizing and dissociating conditions, as for example in the reaction[20] of methanesulfenyl chloride with **3**. However, in most cases and in particular when strong interactions between the positive charge of the intermediate and the second double bond promoted transannular reactions, i.e. parallel and/or cross π-cyclizations, rearranged products such as **6** or **7** were usually obtained[21–23].



(4) **(5)**



(6) **(7)**

The industrial use of 1,3-dienes and of their electrophilic reactions has strongly stimulated the field in recent years. Because of the low cost of butadiene, abundantly available from the naphtha cracking process, very large scale applications in the synthesis of polymers, solvents and fine chemicals have been developed, leading to many basic raw materials of the modern chemical industry. For example, the primary steps in the syntheses of acrylonitrile and adiponitrile have been the electrophilic addition of hydrocyanic acid to butadiene[24]. Chlorination of butadiene was the basis of chloroprene synthesis[25].

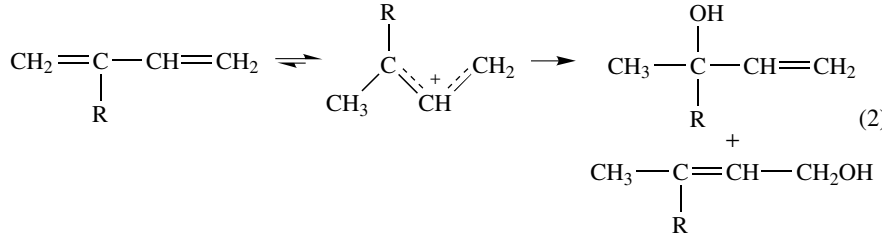
Its hydration opened the route[26] to a large scale production of solvents such as *n*-butanol and 2-ethylhexanol (>2 million tons in 1990). Most of these processes have involved the use of metal catalysts for activation of the π-system. The first catalysts used were mainly expensive noble or environmentally non-friendly metals, such as Rh, Pd or Ni. In this context, a number of works from academic laboratories reported in this review have been devoted to the catalytic activity of various other metals[27]. Their results on the selectivities of these catalyzed reactions were sometimes surprising and have not yet received consistent mechanistic interpretations.

In more general terms, the present review reports much experimental data, essentially on the distribution of addition products of a large variety of dienes. It is not the intention to provide a comprehensive approach to these highly versatile reactions. Many of the mechanistic interpretations suggested by the authors are still controversial or need to be confirmed. This is not surprising since the regio- and stereochemical outcome of the monoethylenic compounds reactions which a priori are simpler than those of dienes, is not yet fully understood despite recent significant progress[3,7,8]. Nevertheless, most of the presently available results on electrophilic additions to dienes are of great interest in many fields of organic chemistry.

II. ELECTROPHILIC HYDROGEN

A. Addition of Water and Carboxylic Acids

At the time when the $A_{SE}2$ mechanism of the acid-catalyzed hydration of alkenes was firmly established[2a,c], the reaction of conjugated dienes was also investigated. It was shown that the same mechanism also applied to dienes (equation 2). The first step is generally reversible but, under well-chosen reaction conditions, the formation of an allylic carbocation by proton addition to one of the two double bonds is rate-limiting. The fast trapping of the carbocation by water in the second step affords the two allylic alcohols corresponding either to a 1,2-addition or to a 1,4-addition. Several pieces of evidence supported this mechanism.



(2)

(i) The rates of acid-catalyzed hydration of 2-substituted-1,3-butadienes[6], $CH_2{=}C(R)CH{=}CH_2$, R = EtO, *c*-Pr, Me, H and Cl, fit the general structure–reactivity relationship[28] (equation 3) established for the hydration of 1,1-disubstituted alkenes, $R^1R^2C{=}CH_2$, under similar reaction conditions, with $\sigma_p^+ = -0.16$ for the vinyl substituent.

$$\log k = -12.3\sigma_p^+ - 10.1 \tag{3}$$

(ii) A linear dependence of $\log k$ for the hydration of a variety of dienes on H_0, the appropriate acidity function of aqueous solutions of sulfuric and perchloric acids (equation 4), was observed[6,29,30], as found also for alkenes. The slopes γ of these relationships were all close to unity, e.g. $\gamma = -1.00$, -1.16, -1.22, -1.2 and -1.3 for

chloroprene[6], isoprene[6], 1,3-butadiene[6], 1-Ph-1,3-butadiene[29] and 1,3-cyclohexadiene[30], respectively.

$$\log k_{obs} = \gamma H_0 + \varepsilon \quad (4)$$

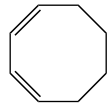
The acidity dependence of the activation enthalpies and entropies, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, of the hydration of 1,3-cyclohexa- and 1,3-cyclooctadienes was ascribed[30] to a dielectric solvation effect in dilute acids, which is overcome by increasing solvent structure as the availability of water decreased in concentrated acids. This suggestion was one of the early premises of a more recent interpretation[31] of acidity effects in terms of water activity and solvation of cationic species.

(iii) The kinetic isotope effects, $k_{H_3O^+}/k_{D_3O^+}$, for the hydration of 1,3-cyclohexadiene[29] and 2-substituted 1,3-butadienes[6] were in the range of 1.1 to 1.8, very similar to those observed for the reaction of alkenes.

(iv) The effects of ring size on hydration rates and equilibria for 1,3-cycloalkadienes (C_5, C_6, C_7 and C_8 dienes) in aqueous sulfuric acid have been interpreted in terms of changes in free energy of conjugative stabilization of the allylic carbocation[32]. An approximately linear inverse relationship between strain energy and $\log k_{hydr}$ was obtained (Table 1). The comparison of these data with those obtained for the hydration of cyclic monoalkenes suggested earlier transition states for the diene hydration than those for the alkene reaction.

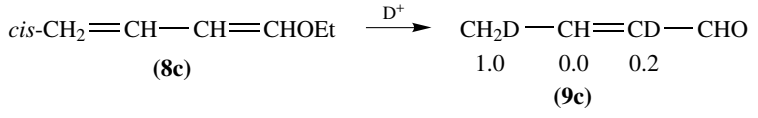
The regiochemistry of the acid-catalyzed water addition to *cis*- **(8c)** and *trans*- **(8t)** 1-ethoxy-1,3-butadienes leading to **9c** and **9t**, respectively[33], has been investigated in deuterium incorporation experiments (equations 5 and 6). The *cis*-isomer incorporated deuterium at the 2-position as well as the 4-position whereas deuterium was added to the *trans*-isomer exclusively at the 4-position. This result has been interpreted in terms of equations 7 and 8: γ-protonation in the *trans*-isomer was assumed to be controlled mainly by thermodynamic factors whereas α-protonation was assumed to arise from charge control

TABLE 1. Effect of ring size on hydration of 1,3-cycloalkadienes[a]

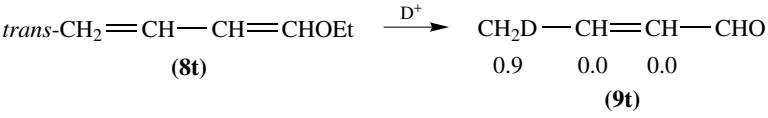
1,3-Cycloalkadiene	k_{rel}[b]	Strain energy[c]
	200	0.8
	2000	−1.2
	4	1.4
	1	3.8

[a]Data of Reference 32.
[b]Relative rates of hydration in 1.05 M H_2SO_4 at 80 °C.
[c]In kcal mol^{-1}.

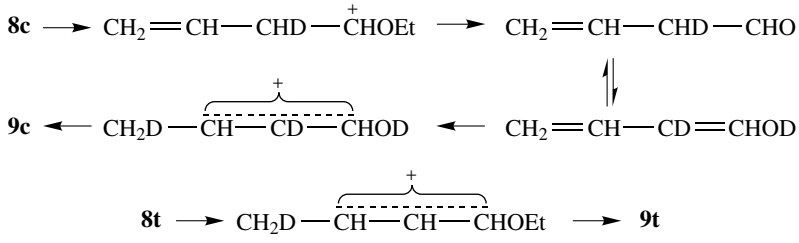
because the transition state for the *trans*-isomer is earlier than that for the *cis*-isomer. This interpretation was supported by the fact that **8t** reacted 14 times faster than **8c**.



(8c) **(9c)** (5)



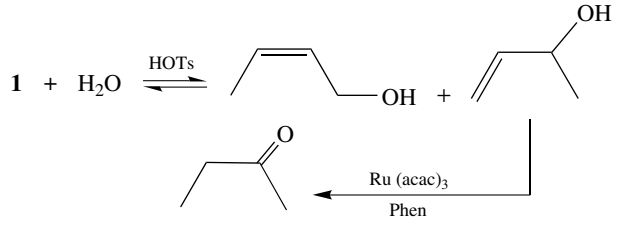
(8t) **(9t)** (6)



(7)

(8)

1,3-butadiene was converted[34] into methyl ethyl ketone with a yield of 90% in a one-pot synthesis at 155 °C with a conversion rate of 100 mol mol^{-1} h^{-1} (100 mol of butadiene per 1 mol of catalyst per hour) in water or in water–diglyme mixtures in the presence of a catalytic system involving a 1 : 2 : 14 (molar) ratio of ruthenium(acac)$_3$, 1,10-phenanthroline (Phen) and *p*-toluenesulfonic acid. Other transition metals (Pd, Rh or Ir) associated to various ligands (e.g. pyridines) with other Brönsted acids (H_2SO_4, H_3PO_4, CF_3CO_2H, HCl, CF_3SO_3H) also promoted the reaction, but with lower yields and selectivities. The reaction was suggested to occur in two consecutive steps: (i) 1,2- and 1,4-addition of water to 1,3-butadiene and (ii) rearrangement of the formed allylic alcohol, 3-buten-2-ol, into methyl ethyl ketone (equation 9). Formally, the primary allylic alcohol, 2-buten-1-ol, could rearrange into *n*-butanol. However, this has not been observed and instead, this alcohol which is involved in hydration–dehydration equilibrium with butadiene was also converted indirectly into methyl ethyl ketone.



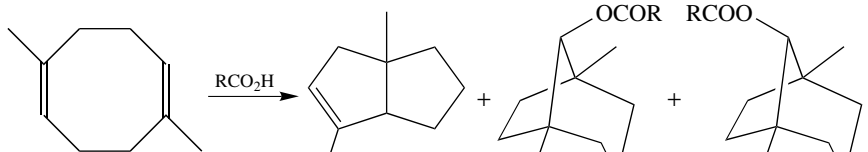
(9)

The first hydration step was promoted by Brönsted acids containing weakly or non-coordinating anions. In the second step, an intramolecular hydrogen transfer in the secondary alcohol was catalyzed by ruthenium(III) salts with chelating bipyridyl-type ligands. The possible complexation of the latter with the diene did not inhibit its catalytic activity in the allylic rearrangements, under acid-catalyzed hydration conditions.

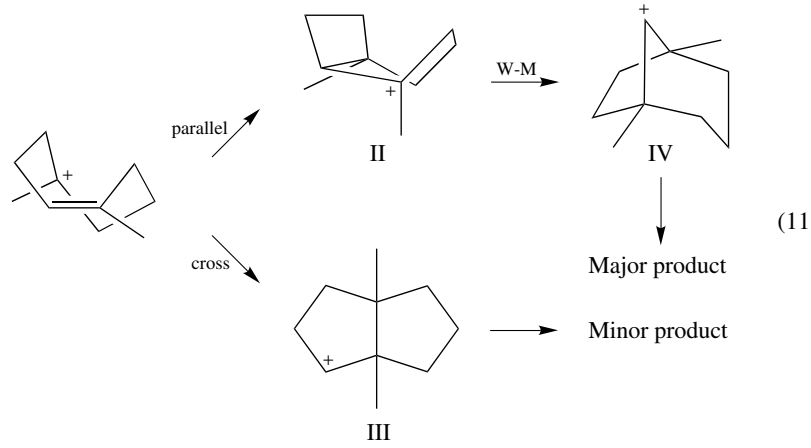
The procedure worked also with 1,3-octadiene and with isoprene which produced methyl isopropyl ketone in 80–85% yield.

These transformations have been potentially useful at an industrial level[35], considering the large-scale availability and application of butadiene and methyl ethyl ketone.

The electrophilic additions of formic and acetic acids to 1,5-dimethyl-1,5-cyclooctadiene yielded mainly[23] *syn*-8-substituted-1,5-dimethylbicyclo[3.2.1]octanes (equation 10) via parallel π-cyclization and subsequent Wagner–Meerwein (W-M) type rearrangement. Cross π-cyclization leading to bicyclo[3.3.0]octane derivatives, which were the major adducts in other electrophilic additions to unsubstituted 1,5-cyclooctadiene[21,22] comprised only a minor route. This different behavior has been interpreted (equation 11) in terms of a significantly larger stability of the tertiary carbocation II than that of the secondary ion III, both ions being the two potential intermediates derived from I by a parallel and a cross π-cyclization, respectively.



(10)

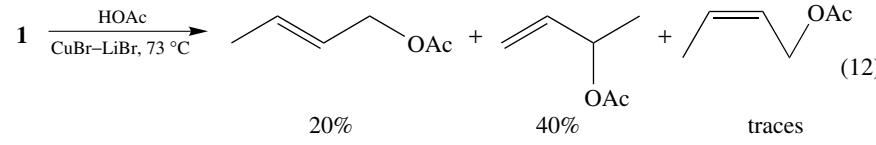


(11)

The predominantly *syn* stereochemistry of the products arising from the bicyclo[3.2.1] octyl cation IV would results from the large ring strain in II, the chair conformation of which, (but not boat) facilitate the Wagner–Meerwein type rearrangement.

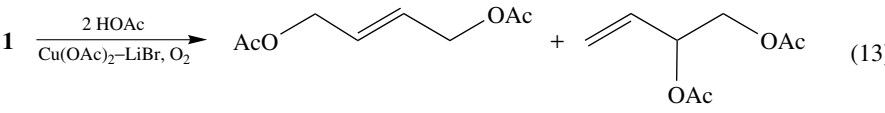
In a context of industrial interest, the copper-catalyzed addition of acetic acid[36] to **1** (hydroacetoxylation) in the absence of oxygen was shown to be non-regioselective, a 1 : 0.5 mixture of 1,2- and 1,4-addition products being obtained in a yield of 60% based on butadiene. The effect of various additives on the regiochemistry and the yield has been carefully studied. The butadiene conversion was mainly efficient with the CuBr–LiBr catalytic system (equation 12). The role of the catalyst in the reaction mechanism has been discussed but not fully understood. It has been shown that the dominant formation

of the 1,2-isomer during the acetic acid addition was kinetically controlled, the equilibrium mixture of the 1,2- and 1,4-isomers in the presence of the catalyst being 1 : 1. The results were compared with those obtained by the same authors for the hydrocyanation (*vide infra*) which was markedly more regioselective than hydroacetoxylation.



(12)

When this reaction was carried out under oxygen pressure (generally 10 bars) using $Cu(OAc)_2$ in association with LiBr as a catalyst in an acetic acid–acetic anhydride (2 : 1) solvent mixture, diacetoxylation[37] leading to 1,2- and 1,4-diacetoxyethylenic adducts took place (equation 13). The regioselectivity, which did not depend significantly on the reaction conditions, was poor in all cases, the 1,4- to 1,2-isomer ratio being close to unity. The formation of the 1,2-isomer seemed to be kinetically controlled, as was found for the hydroacetoxylation. A variety of reaction intermediates, such as an epoxybutene, and in particular hydroxyacetates, has been suggested but the mechanism is far from being elucidated. The absence of regioselectivity is in contrast to that found for the same reaction promoted by much more expensive palladium catalysts[38].



(13)

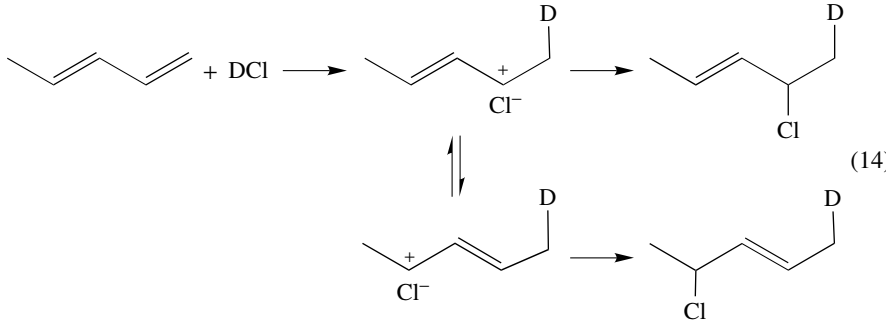
B. Addition of Hydrochloric Acid, Hydrocyanic Acid and Hydrogen Sulfide

The regiochemistry of the addition of DCl to *trans*-1,3-pentadiene was investigated very early in various solvents in order to understand the competition between 1,2- and 1,4 additions to conjugated dienes[9]. The results (Table 2) indicated a marked predominance of 1,2-addition. This has been interpreted in terms of ion pairing as described in equation 14, assuming that the addition of undissociated DCl gave the carbenium–chloride ion pair with the anion associated at C(2). Interconversion with the isomeric ion pair having the chloride associated with C(4) at a rate not much faster than that of the ion pair collapse would produce the 1,2-adduct in excess of the 1,4-adduct. These results were in contrast with those observed for other electrophilic additions in more dissociating solvents (*vide infra*).

TABLE 2. Regiochemistry of DCl addition to *trans*-1,3-pentadiene[a]

Solvent	T (°C)	% 1,2-Addition	% 1,4-Addition
None	−78	75.5	24.5
	25	61.5	38.5
Pentene	−78	77.7	22.3
	25	63.8	36.2
CH_3CO_2D	25	65.0	35.0
CH_3NO_2	25	67.7	32.3

[a]The two adducts result from at least 96% *anti* addition.



(14)

The orientation of the addition of HCl to a variety of halogen-substituted 1,3-butadienes has been extensively studied under preparative conditions[39–43]. The results are given in Table 3. No significant polymerization was observed and the products were in all cases those resulting from a 1 : 1 addition process. The regiochemistry control by the position of the chlorine atom was quite versatile. A Cl at C(1) favored formation of the 4,3-adduct whereas with Cl on C(2) the 1,4-adduct predominated. The competition between substitution by chlorine and methyl attenuated but did not markedly modify this orientation. However, all these reactions were quite slow and took from 5 to 10 h, even in the presence of a catalyst (mostly cuprous chloride). Therefore, product

TABLE 3. Product distribution in hydrogen chloride addition to halogeno-substituted 1,3-butadienes, $R^1CH{=}CR^2{-}CR^3{=}CH_2$

R^1	R^2	R^3	% 1,2-Addition[a]	% 1,4-Addition[b]	% 4,3-Addition[c]	% 4,1-Addition[d]	% Yield[e]	Conditions[f]	References
Cl	H	H	0	5	78	7	86	A	40
Cl	H	H	0	1	94	5	75	B	40
H	Cl	H	3	97	0	0	—	C	42
H	Br	H	2	85	0	0	—	D	42
H	Br	H	1	73	0	0	—	E	42
H	Cl	Cl	0	90[h,i]	0	0	63	F[j]	41
Cl	H	CH_3	3	9	75	13	90	E	43
H	CH_3	Cl	15	49	3	33	71	D	40
H	CH_3	Cl	3	57	1	39	—	E	40
H	CH_3	Cl	40	21	8	31	25	G	40

[a] $R^1CH_2{-}C(R^2)Cl{-}CR^3{=}CH_2$.
[b] $R^1CH_2{-}CR^2{=}CR^3{-}CH_2Cl$.
[c] $R^1CH{=}CR^2{-}C(R^3)Cl{-}CH_3$.
[d] $R^1CHCl{-}CR^2{=}CR^3{-}CH_3$.
[e] Overall yield.
[f] Reaction conditions (in every case, excess of HCl, vigorous stirring): A, 20% HCl + 25% CuCl + 7% NH_4Cl, 40–45 °C. B, A without catalyst. C, concentrated hydrochoric acid at constant [HCl], maintained by addition of gaseous HCl, in the presence of catalytic CuCl, at 40 °C. D, C without catalyst, at room temperature. E, C at room temperature. F, in CCl_4 in the presence of $FeCl_3$, at −10 °C. G, in ether at −15 °C.
[g] Substantial amounts (24% and 12%, with and without catalyst, respectively) of 1,3-dichloro-2-butene arising from bromine–chlorine exchange were formed.
[h] *cis* + *trans*.
[i] 5–15% of 1,2,3,6,7-pentachloro-2,6-octadiene were formed.
[j] In water, no addition products were formed.

isomerization either during the addition or the work-up (GC or fractional distillation) cannot be ruled out.

The addition of HCl to 1,3-butadiene in the gas phase at total pressures lower than 1 atmosphere and at temperatures in the range of 294–334 K yielded mixtures of 3-chloro-1-butene and (*E*)- and (*Z*)-1-chloro-2-butenes, in a ratio close to unity[44,45]. Surface catalysis has been shown to be involved in the product formation (Figure 1). The reaction has been found to occur at the walls of the reaction vessel with a high order in HCl and an order less than unity in diene. The wall-catalyzed process has been described by a multilayer adsorption of HCl, followed by addition of butadiene in this HCl layer. This highly structured process is likely to involve near simultaneous proton and chloride transfers.

Strong evidence for a π-allylnickel complex as an intermediate in the nickel catalyzed addition of hydrogen cyanide to conjugated dienes[46] has been obtained in a brief but clear-cut investigation of deuterium cyanide addition to 1,3-cyclohexadiene. This result has been of wide interest in relation to the mechanism of the industrial process for formation of adiponitrile in which two molecules of hydrogen cyanide added to butadiene via a three-step reaction catalyzed by nickel or palladium complexes (equation 15). The HCN addition to 1,3-cyclohexadiene in acetonitrile at 60 °C in the presence of $Ni[P(OPh)_3]_4$ with $P(OPh)_3$ produced 2-cyclohexenecarbonitrile with high selectivity. The same reaction using DCN afforded the two monodeuteriated nitriles **10** and **11** resulting from 1,2- and 1,4-additions, in approximately equal amounts. The postulated mechanism (Figure 2), which is analogous to that previously established for the hydrocyanation of monoenes, involves the following steps. The active catalytic species, $DNiL_3CN$

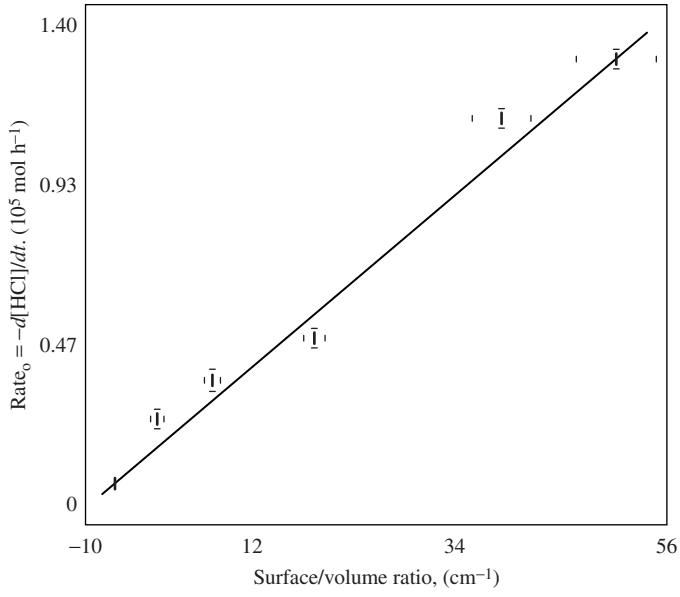


FIGURE 1. The variation in the initial rate of disappearance of hydrogen chloride (g) in the reaction of HCl with 1,3-butadiene as a function of the surface-to-volume ratio at 295 K. The initial concentrations of hydrogen chloride and 1,3-butadiene are 3.4×10^{-4} M and 1.6×10^{-4} M, respectively. (Reprinted from Reference 44, copyright 1991, with permission Elsevier Science)

[L = $P(OPh)_3$] formed by oxidative addition of DCN to NiL_4, coordinates one of the two double bonds of the diene. The coordination is followed by a *cis*-migration of the coordinated deuterium, producing a π-allyl nickel complex in which a further *cis*-migration of the cyanide gave the two products **10** and **11**.

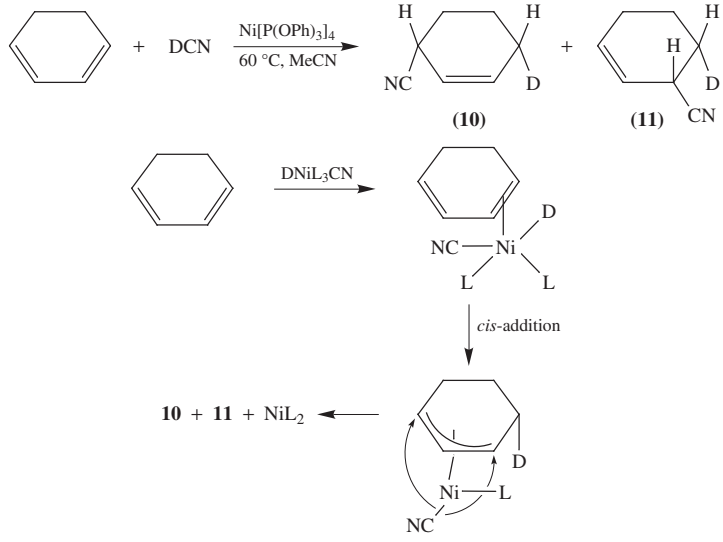
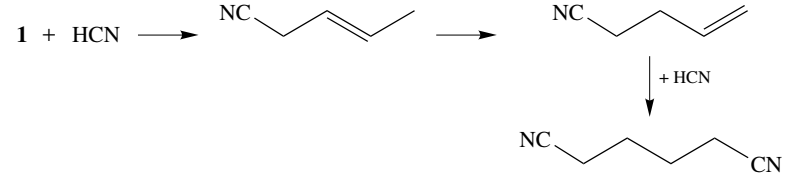


FIGURE 2. The mechanism of the nickel-catalyzed addition of hydrogen cyanide to 1,3-cyclohexadiene. Reproduced by permission of the Royal Society of Chemistry from Reference 46

In an extension of an early work on the nickel-catalyzed addition of hydrogen cyanide to unsaturated compounds, a basic reaction in various large-scale processes in the polymer industry, the hydrocyanation of butadiene (equation 15) and the efficiency of catalysis of this reaction by low-cost copper salts has been studied extensively by Belgium researchers[47,48].



(15)

Copper-catalyzed monoaddition of hydrogen cyanide to conjugated alkenes proceeded very conveniently with 1,3-butadiene, but not with its methyl-substituted derivatives. The most efficient catalytic system consisted of cupric bromide associated to trichloroacetic acid, in acetonitrile at 79 °C. Under these conditions, 1,3-butadiene was converted mainly to (*E*)-1-cyano-2-butene, in 68% yield. A few percents of (*Z*)-1-cyano-2-butene and 3-cyano-1-butene (3% and 4%, respectively) were also observed. Polymerization of the olefinic products was almost absent. The very high regioselectivity in favor of 1,4-addition of hydrogen cyanide contrasted markedly with the very low regioselectivity of acetic acid addition (*vide supra*). Methyl substituents on 1,3-butadiene decreased significantly the efficiency of the reaction. With isoprene and piperylene, the mononitrile yields were reduced

to 39% and 12%, respectively, and the percent of polymerization increased. With two methyl substituents, polymerization was the exclusive reaction. Kinetic studies have established a key activating role of a variety of organic and inorganic bromides, crotyl bromide being the most efficient. Several mechanisms involving π- or σ-allylcopper complexes, analogous to the well-established π-allylnickel intermediates, have been proposed.

Oxycyanation[27] affording 1,4-dicyano-2-butene occurred exclusively when the HCN addition was carried out under oxygen atmosphere ($P_{O_2} = 40-50$ psig). In addition to the catalytic CuBr–LiBr system which works conveniently in the monohydrocyanation, the presence of cupric iodide has been found necessary in order to avoid the oxidation of HCN into cyanogen. With 1,3-butadiene, the yield reached 60%. Much lower yields have been found with 1,3-pentadiene (17%) and isoprene (3%) in acetonitrile solvent. In pyridine or DMSO, 2-cyanopyridine probably resulting from the addition of cyanide radicals has been formed from 1,3-butadiene in poor yield (15%). This observation has suggested a solvent-dependent competition between the ionic pathway leading to the dinitriles and a radical pathway responsible for the cyclization to the pyridine ring.

The similarities and differences between copper-catalyzed oxycyanation and diacetoxylation (*vide supra*), which are summarized in Figure 3, have been discussed. The main difference in the regiochemistry of the two reactions, i.e. an almost exclusive 1,4-addition in the cyanation and a non-regioselective acetoxylation, has been emphasized but was not interpreted in mechanistic terms.

The electrophilic addition of hydrogen sulfide and 1-butanethiol to 1,3-conjugated dienes[49] in chloroform at $-10\,^{\circ}C$ has been reported in a quite old paper of a Russian team. The yields were generally low, in the range of 20%, even when the reaction was catalyzed by a mixture of two Lewis acids, $EtAlBr_2/EtAlCl_2$; however, polymerization of the diene was not significant.

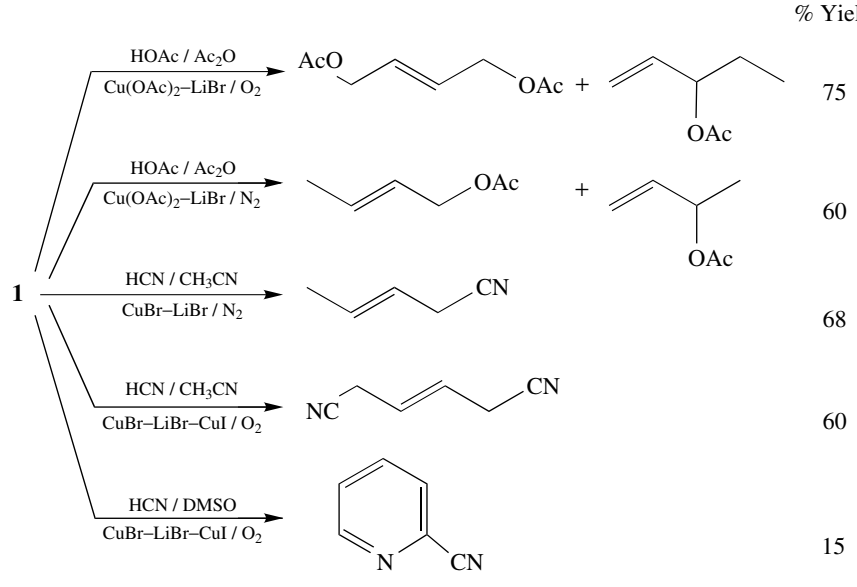
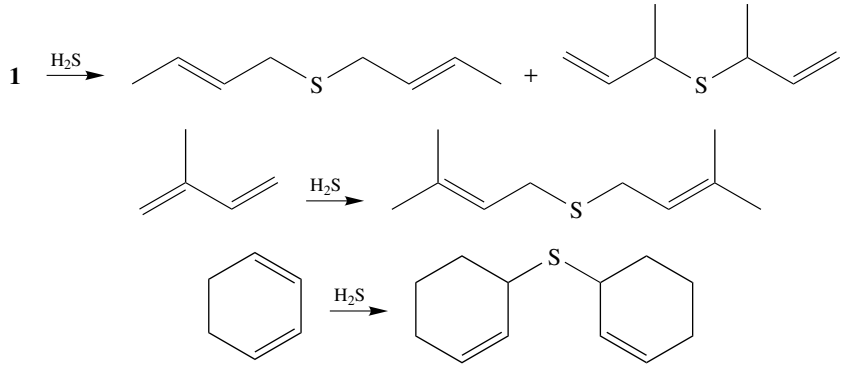


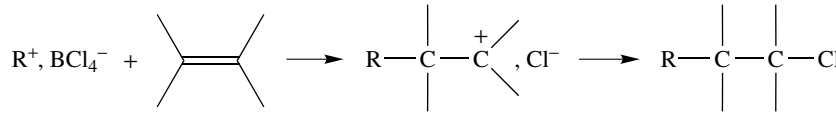
FIGURE 3. Copper-catalyzed additions of acetic and hydrocyanic acids to butadiene. Reproduced by permission of Academic Press from Reference 27

Depending on the linear, branched or cyclic structure of the unsaturated compound, a variety of dialkyl sulfides has been obtained in the reaction with H_2S (equations 16–18). The regiochemistry depended markedly on the structure of the diene. For a mechanistic purpose, some experiments have been carried out using deuterium sulfide, D_2S. The results have been interpreted in terms similar to those of Nordlander and coworkers[9] (*vide infra*). The thiylation of 1,3-dienes was assumed to start with a regiospecific addition of a proton or a deuteron to one of the two double bonds to form two isomeric ion pairs as in equation 14 which, in the poorly dissociating solvent, collapse into products with equal probability.



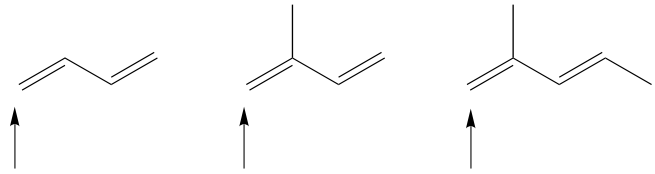
III. ELECTROPHILIC CARBENIUM IONS

In a review on the addition of carbenium ions to alkenes (equation 19) as a general procedure for carbon–carbon bond formation[50], Mayr reported on investigations which also include the reactions of a variety of 1,3-dienes toward electrophilic carbon species generated by Lewis acid-promoted heterolysis of alkyl chlorides.



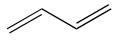
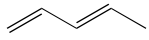
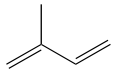
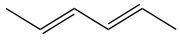
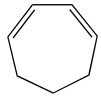
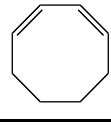
As a general rule, alkyl-substituted 1,3-dienes reacted so that the corresponding allyl cation with the highest possible number of alkyl substituents at the cationic center was formed, leading to the regioselectivity[51] indicated below. The subsequent nucleophilic addition to these cations afforded mainly mixtures of diastereoisomeric 1,4-addition products (>90%). An example is the reaction of *p*-methoxydiphenylcarbenium tetrachloroborate with 2-methyl- and 2,3-dimethyl-1,3-butadiene and 1,3-cycloalkadienes[52,53]. Nevertheless, some 1,2-addition products were also observed for 1,3-butadiene and 1-methyl-1,3-butadiene. This regiochemistry is in agreement with recent semiempirical AM1 calculations on the corresponding allyl cations[54].

The kinetic behavior of 1,3-dienes has also been investigated in as much detail as that of alkenes[52]. Some data are collected in Table 4. The effect of a vinyl group on the reactivity of carbon–carbon double bonds toward *p*-methoxydiphenylcarbenium ion has been compared with that of methyl and phenyl substituents (Table 5). Whereas butadiene reacted 21 times faster than propene, the reactivity of isoprene was significantly lower



Sites of attack by carbenium ions

TABLE 4. Rate constants and activation parameters[a] for the reaction[b] of *p*-methoxydiphenylcarbenium tetrachloroborate with various dienes

Compound	k ($M^{-1}\,s^{-1}$)	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal $mol^{-1}\,K^{-1}$)	$k_{H_3O^+}$[a] ($M^{-1}\,s^{-1}$)
	9.39×10^{-4}	7.8	−33.3	2.38×10^{-9}
	2.33×10^{1}	5.0	−26.8	3.71×10^{-4}
	1.09×10^{1}	4.6	−30.4	2.40×10^{-7}
	1.93×10^{-2}			3.96×10^{-3}
	4.62×10^{1}	5.4	−23.7	
	1.56×10^{1}	5.5	−25.4	3.19×10^{-5}
	1.82×10^{2}	3.6	−29.7	
	1.74×10^{3}			7×10^{-7}
	2.75×10^{1}	4.4	−29.4	7×10^{-6}
	3.04	5.3	−29.4	1.4×10^{-8}
	3.26×10^{-1}			3.5×10^{-9}

[a] Data from Reference 52
[b] At −70 °C in dichloromethane.
[c] At 25 °C; data from Reference 55

TABLE 5. Comparison of substituent effects on the relative rates of carbenium ion addition to carbon–carbon double bonds

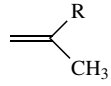
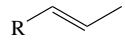
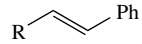
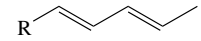
Alkene/R	Me	$CH{=}CH_2$	Ph
	1.00	21	1.2×10^4
	1.00	0.67	62

TABLE 6. Effect of the methyl group at the electrophilically attacked vinylic carbon by *p*-methoxydiphenylmethyl carbenium ion

			
k_{CH_3}/k_H	1.3	0.36	3.9
$\delta\Delta H^{\neq}$ (kcal mol^{-1})	−0.6	−0.9	−7.3
$\delta\Delta S^{\neq}$ (cal mol^{-1}K^{-1})	−2.6	−6.0	−27

than that of isobutene. It is also noticeable that the effect of a phenyl group is much larger than that of the vinyl group. The effect of a methyl group at the initially attacked vinylic carbon atom depended also on the nature of the unsaturated system as shown in Table 6.

The similar order of magnitude of the reactivities of methyl-substituted 1,3-dienes (Table 4) which depended on the number but not on the position of the substituent was strong evidence that allyl cations[55] serve as reaction intermediates in these reactions. The rate decrease with increase in the ring size of the cycloalkadienes was attributed to the increased deviation of the π-system from planarity. The reactivities of 1,3-dienes deviated markedly from the roughly linear relationship between the rates of proton and carbenium ion additions to alkenes. These deviations were ascribed to abnormally low reactivity[32] of the conjugated π-systems, although this interpretation was inconsistent with the similar behavior of alkenes and dienes in the structure–reactivity relationship for hydration[6].

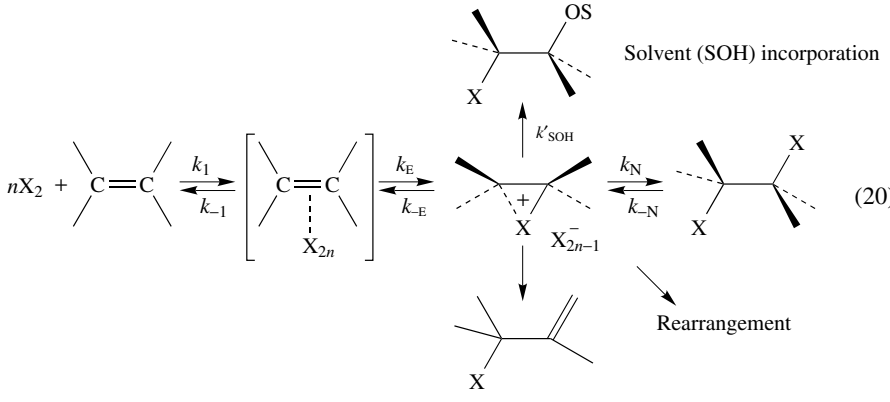
IV. ELECTROPHILIC HALOGENS AND POSITIVE HALOGEN DONORS

A. General Aspects

The electrophilic addition of halogens, interhalogens and pseudohalogens to carbon–carbon double bonds, although extensively studied and repeatedly reviewed[2], is still the object of kinetic and product investigations. The more recent studies, often concerning bromine additions[3,7c], have revealed the complexities that underlie the simple representation generally given in organic chemistry textbooks[1]. The structure of the intermediate, the kinetics of the reaction, and both its stereochemistry and regiochemistry are all complex functions of the nature and concentration of the halogenating agent, of the solvent, of the added nucleophiles and of the structure of the alkene.

The first step is usually the formation of a halogen–olefin charge transfer complex[3c,7c], which rapidly evolves to an ionic intermediate. Protic solvents can electrophilically assist

the ionization process through hydrogen bonding. This is not possible in non-polar solvents, but further halogen molecules may assist in removing X^- as polyhalides. The cationic moiety of the intermediate may be a bridged or weakly bridged halonium ion, or a β-halocarbenium ion, depending on the nature of the electrophile and on the olefin. Nucleophilic trapping of the intermediate by the counteranion, solvent or added nucleophiles yields the reaction products (equation 20).



(20)

The regio-, stereo- and chemoselectivities have been mainly interpreted in terms of bridging of the ionic intermediate and/or ion pair dissociation. Solvent-separated ion pairs and free ions have often been considered to explain the product selectivities of these reactions. Nevertheless, the stereochemical outcomes can also be determined by the relative rates of the ion pair dissociation and of the nucleophilic trapping of the intermediate, i.e. by the lifetime of the intermediate[7d].

The rate laws for the addition of halogens are generally complex. Second, third and fourth overall order terms have been identified (equation 21), depending on reagent and reaction conditions, solvent and added salts.

$$-d[X_2]/dt = [\text{Alkene}](k_2[X_2] + k_3[X_2]^2 + k_4[X_2]^3 + k_{X^-}[X_3^-]) \tag{21}$$

Furthermore, on the basis of the multistep mechanism reported in equation 20 and considering that the electrophilic and/or nucleophilic step may be rate determining depending on halogen and/or olefin, k_{obsd} is always a composite constant (equation 22), even under the simplified conditions where only one path contributes to the product formation and the reverse reaction (k_{-N}) does not occur.

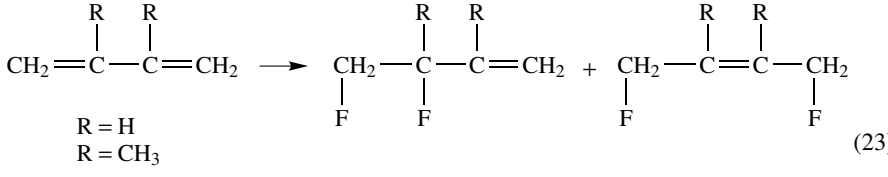
$$k_{obsd} = k_1 k_E k_N/(k_{-1}k_{-E} + k_{-1}k_N + k_E k_N) \tag{22}$$

Since the structural factors and the solvent can affect the individual rate constants in ways which may differ in magnitude and sign, comparison of the experimental rate constants for various systems cannot always be straightforward.

B. Fluorine

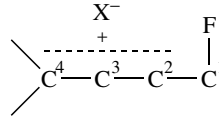
Fluorine is the most electrophilic halogen and only few examples of controlled addition of fluorine to carbon–carbon double bonds have been reported[56] Milder reagents, such as XeF_2, are generally used to form fluorine addition products.

The first data about fluorination of 1,3-dienes were reported[10] by Shellhamer and coworkers, who described the additions of xenon difluoride and (difluoroiodo)benzene to butadiene, 2,3-dimethyl-1,3-butadiene and *cis*- and *trans*-1,3-pentadienes, in chlorinated solvents. Both reagents give 1,2- and 1,4-difluoro adducts (equation 23). XeF_2 yields primarily 1,2-products while $C_6H_5IF_2$ gives significantly more 1,4-products.



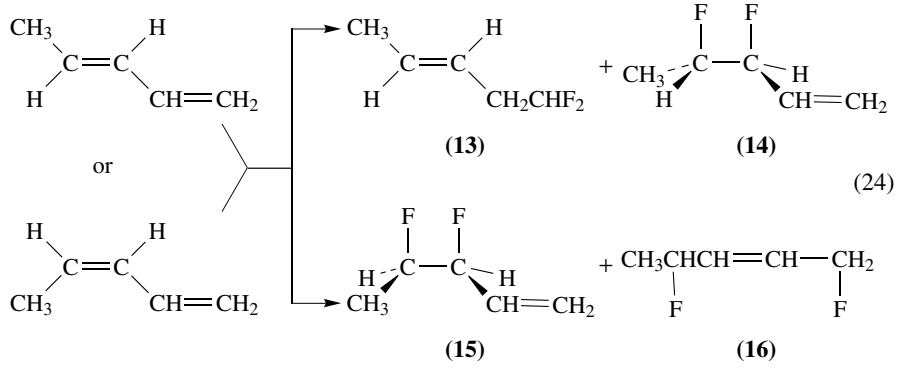
(23)

The difference in the product distributions has been attributed to the steric effect of the counterion, X^-. The steric interaction between the large anion $C_6H_5IF^-$ and the diene would favor the attack at the less-hindered C(4) atom of the intermediate **12**.



(12)

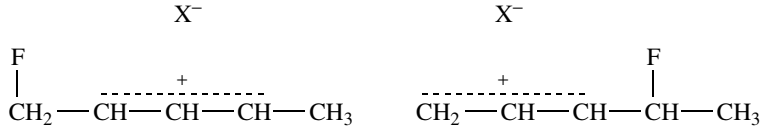
It is noteworthy that, at variance with bromination and chlorination which generally occur without isomerization of the disubstituted double bond, fluorine addition to the 1,2-bond of *cis*- and *trans*-1,3-pentadienes gives mainly the *trans*-adduct **13**, besides smaller amounts of compounds **14–16** (equation 24).



(24)

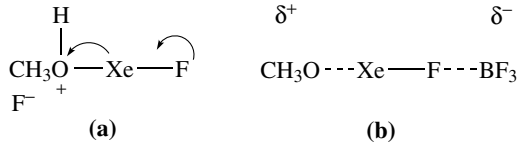
Thus, fluorination of 1,3-dienes proceeds through an allylic ion, while weakly bridged halonium ions are the intermediates in chlorination and bromination of dienes (*vide infra*). Furthermore, starting from the experimental evidence that **13** is produced under kinetic conditions and not from subsequent rearrangement of the 1,2- and 1,4-adducts, the authors suggested that **13** arose from rearrangement of the allyl cation intermediate, **17**. Consistent with an open ion pair intermediate is also the stereoselective formation of the *threo* isomer from both 1,3-pentadienes, as well as the preference for the addition to the 1,2-bond observed in the reaction of both isomeric pentadienes. This selectivity may indeed

be related to a significant charge delocalization into the adjacent double bond in the rate-determining transition state, which favors the formation of intermediate **17** over **18**.

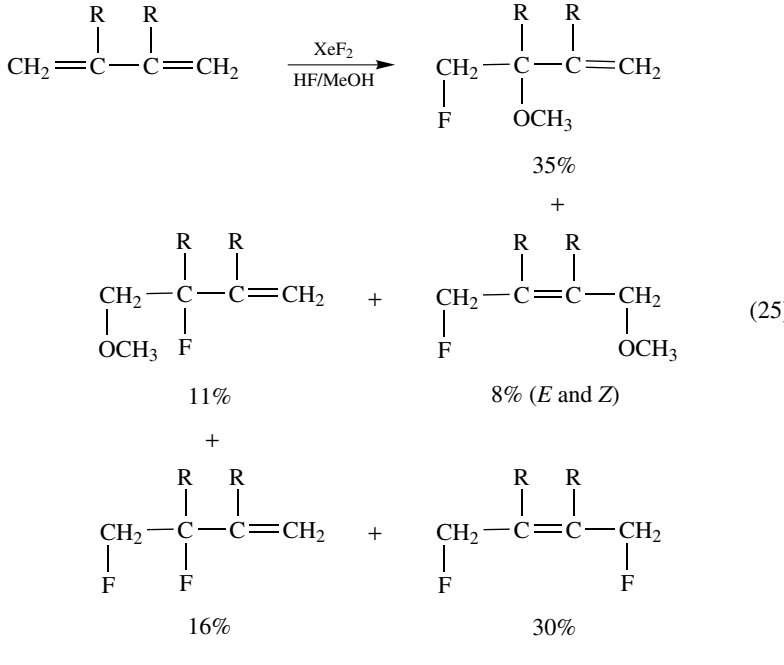


(17) **(18)**

A different stereochemical behavior has, however, been observed in methanol[57]. In this solvent XeF_2 reacts with the solvent to form an unstable reactive species (CH_3OXeF), which gives quantitatively formaldehyde by disproportionation in the absence of unsaturated hydrocarbons or with unreactive alkenes. Hydrogen fluoride generated *in situ* complexes the electrophilic CH_3OXeF species to form a protonated derivative **a** which reacts with activated dienes such as 2,3-dimethylbutadiene, as an apparent fluorine electrophile to give 1,4- and 1,2-fluoromethoxy products, together with 1,2- and 1,4-difluoro derivatives (equation 25).

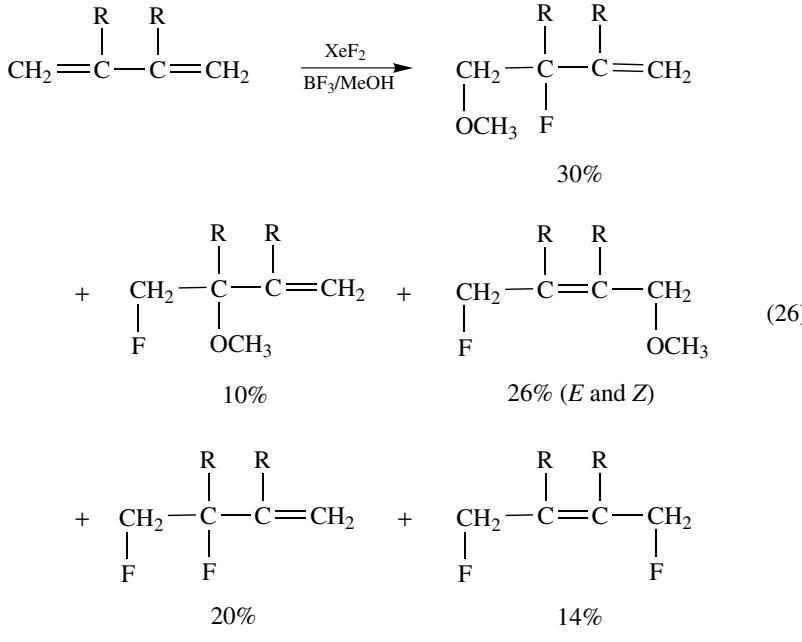


(a) **(b)**



(25)

Adducts of type **13**, arising from the rearrangement of the allylic intermediate, have never been observed. The product distribution in methanol depends, however, on the reaction conditions. When the addition of XeF_2 is carried out in the presence of boron trifluoride as a catalyst, the formation of the complex **b** has been suggested. This complex would react with 2,3-dimethylbutadiene as a positive oxygen electrophile to give, besides 1,2- and 1,4-difluoro derivatives, 1,4- and 1,2-fluoromethoxy products with a predominance of the anti-Markovnikov adduct (equation 26).



(26)

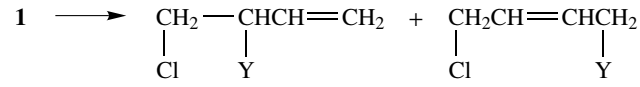
Furthermore, kinetic measurements have shown that the reaction is zero order in alkene when equimolar concentrations of XeF_2, alkene and BF_3 are used, whereas a dependence on olefin concentration is found when higher concentrations of alkene are utilized. On the basis of these kinetic data and taking into account that the regioselectivity of the reaction changes on increasing the olefin concentration, a mechanistic scheme has been proposed for this reaction in which two reaction pathways compete: in one the alkene is intercepted in a fast step, leading to both addition products and formaldehyde, and in a second one XeF_2 reacts directly with the olefinic bond.

C. Chlorine

1. Conjugated double bonds

The first studies of chlorine addition to the simplest diene, 1,3-butadiene, carried out in solvents of various polarity, showed[58] that the reaction always led to mixtures of 1,2- and 1,4-addition products, in ratios almost independent of the solvent polarity. Furthermore, the addition of Cl_2 in acetic acid gave, besides the 1,2- and 1,4-dichlorides, 3-acetoxy-4-chloro-1-butene and 1-acetoxy-4-chloro-2-butene arising from solvent incorporation (equation 27). By comparison of these data with those related to Br_2 addition

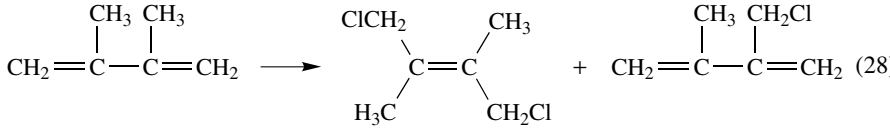
under identical conditions, it was suggested[58] that the intermediate involved in the ionic chlorine addition has a greater carbenium ion character with respect to that arising from bromine addition. However, the lack of any data on the product stereochemistry made it practically impossible to attribute a bridged or an open ion structure to the intermediate.



(27)

Y = Cl or OAc

The reaction of 2,3-dimethyl-1,3-butadiene with an equimolar amount of chlorine in carbon tetrachloride at $-20\,^{\circ}C$ has instead been reported[59a] to give mainly *trans*-1,4-dichloro-2,3-dimethyl-2-butene and 2-chloromethyl-3-methyl-1,3-butadiene, arising from the loss of one of the acidic hydrogen atoms in the ionic intermediate (equation 28).



(28)

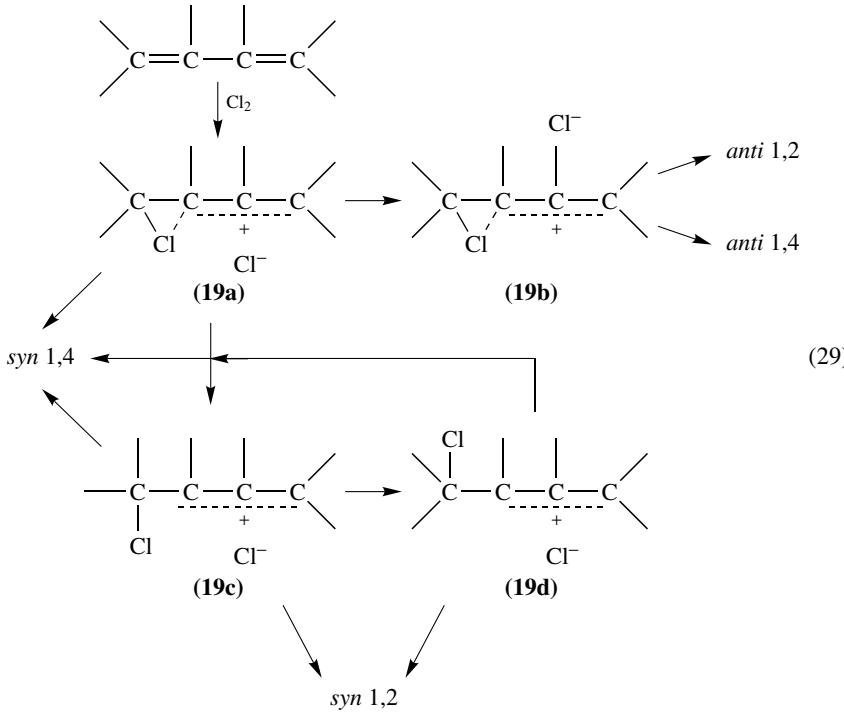
However, a later investigation of the chlorination of the same substrate has shown[59b] that the product distribution observed immediately after the end of the chlorine addition was markedly different. Small amounts (5%) of the kinetically favored 1,2-dichloride were detected. Furthermore, although the yields of 1,4-dichloro adducts from the two experiments were the same, the yield of the monochloride was much lower in the latter experiment in which detectable amounts of trichlorides were also found.

Later on, product distribution studies[15] of the ionic addition of chlorine to conjugated dienes, and in particular to cyclopentadiene, 1,3-cyclohexadiene, *cis*,*cis*-, *trans*,*trans*- and *cis*,*trans*-2,4-hexadienes, and *cis*- and *trans*-1,3-pentadienes have supplied the first stereochemical data, showing that the stereochemistry of 1,4-addition is predominantly *syn*, although to an extent smaller than that of bromine addition. Moreover, the 1,2-addition is generally non stereoselective, except for the addition to the 3,4-bond of *cis*- and *trans*-1,3-pentadienes where the attack is 89–95% *anti*. Finally, appreciable amounts of *cis*-1,2-dichlorides were obtained from the two cyclic dienes, whereas 2,4-hexadienes showed a preference for *anti* 1,2-addition, at least in the less polar solvents (carbon tetrachloride and pentane). On the basis of all these results the mechanism shown in equation 29 was proposed.

According to this mechanism, the first formed ion pair is **19a**. Owing to dispersal of charge in the allylic system, the bond between halogen and C(2) is weakened so that an open carbenium ion **(19c)** readily forms, allowing for the possibility of front-side attack by the anion with the resulting formation of *syn* 1,2-adducts. This intermediate explains the formation of the *cis*-1,2-adducts by chlorine addition to cyclic systems. However, *syn* 1,2-dichlorides can also result from linear dienes by rotation around the C(1)–C(2) bond in **19c** to produce **19d**, followed by back-side attack by the anion with respect to its position in **19d**. *Syn* 1,4-adducts should instead arise by attack of the anion on C(4) in either **19a**, **19c** or **19d**. Formation of *anti* dichlorides (1,2- or 1,4-) can only occur when there is appreciable translocation in the ion pair **19a** to give **19b**. Attack by the anion at C(2) in **19b** yields *anti* 1,2-dichloride and attack at C(4) yields *anti* 1,4-dichloride.

At variance with the earlier study[58] on butadiene, the data related to halogenation of these substituted dienes reveal also that solvents have striking effects on product ratios,

although the solvent-dependent product distribution cannot be interpreted in terms of the above mechanism, as evidenced by the authors.

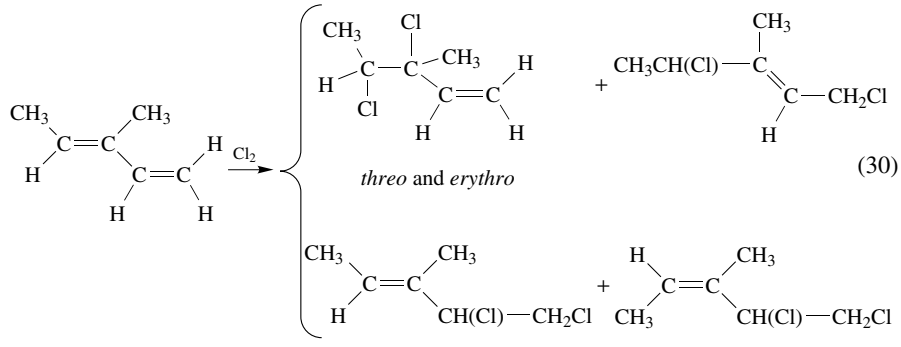


Independently of the latter observation, the stereochemical results of a subsequent study[60] on the chlorine addition to *cis*-3-methyl-1,3-pentadiene, which gives five products, different from those of 1,3-pentadiene, i.e. the 1,4-adduct, *threo*- and *erythro*-3,4-dichloro derivatives and *cis*- and *trans*-1,2-adducts (equation 30), have been interpreted once again on the basis of the mechanism reported above (equation 29). In this case, however, the presence of a methyl group at C(3) should reduce the bridging between the halogen and the carbon in the corresponding intermediate, decreasing the *anti* stereoselectivity of the reaction. Furthermore, the presence of the methyl group at C(3) has been assumed to promote the isomerization of the double bond observed in the formation of the 1,2-adducts starting from the *cis* but not from the *trans* isomer. The presence of two *cis* methyl groups in the ionic intermediate probably provides the driving force for the isomerization.

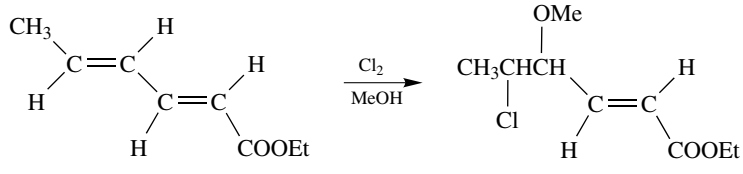
More recent data[61] on the chlorination of 1,3-pentadienes have confirmed that chlorine addition in 1,2-dichloroethane or carbon tetrachloride gives 4,5- and 1,4-dichloro-2-pentenes as main products, besides smaller amounts of 3,4-dichloropentenes, although chloropentenes have been detected as minor products. Furthermore, it has been shown that the yields of the latter products are reduced when the reaction is carried out in the presence of quaternary ammonium or phosphonium salts.

Finally, a high regioselectivity has been observed[62] in the chlorine addition to ethyl sorbate **(20)** in methanol (equation 31). Under ionic conditions the reaction gives mainly products arising from addition to the $\gamma-\delta$ bond and the solvent opens the corresponding ionic intermediate preferably at the allylic carbon to give product **21**. A bridged structure

has been proposed for the intermediate since nucleophilic attack at the δ carbon to yield *erythro*-**22** has been noted. Furthermore, taking into account the bridged nature of the intermediate, the minor formation of **23** has been rationalized as the result of an S_N2'-like reaction with the solvent when the halonium intermediate is formed at the $\gamma-\delta$ bond of **20**.

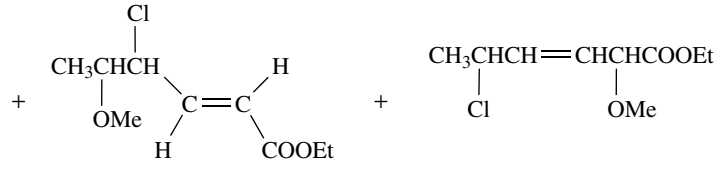


(30)



(20) **(21)** 83%

(31)

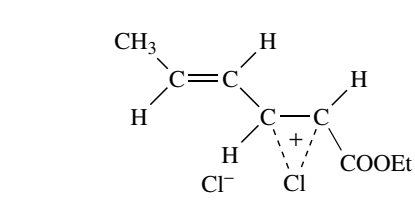


(22) 10% **(23)** 7%

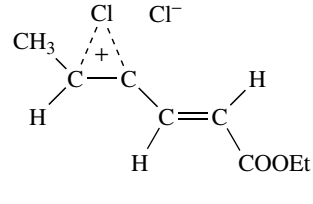
The different reactivity of the two double bonds of **20** has therefore been related to the relative energies of the transition states leading to the intermediates **24a** and **24b**. The preferential addition of an electrophile at the $\gamma-\delta$ bond has been attributed to its more nucleophilic character and to the fact that conjugation with the ester carbonyl is not disrupted. Furthermore, with the assumption that a later transition state should favor attack at the $\alpha-\beta$ bond, since a more stable (delocalized) intermediate can be formed, and taking into account that product distribution data show that the lower-energy transition state leading to addition to the $\gamma-\delta$ bond is favored with these electrophiles (chlorine and bromine), it has been concluded that the chlorine reaction has an earlier transition state than the bromine one in accordance with the relative product distribution data.

A complete regioselectivity has also been observed[63] in chlorine addition to *trans*,*trans*-1-phenyl-4-(2,6-dichlorophenyl)-1,3-butadiene **(25a)** leading to the addition product **(26)** on the more hindered double bond (equation 32). The *cis*,*trans*-isomer **25b** reacts similarly, although in this case the higher reactivity of the *cis* double bond might contribute

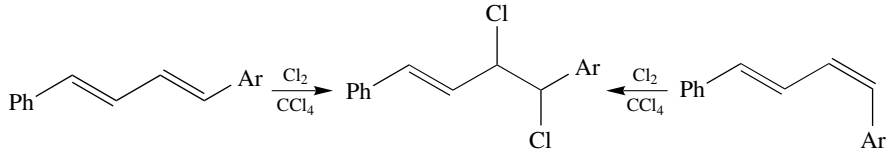
to the regioselectivity, which has been explained for **25b** in terms of a Cl–Cl interaction.



(24a)



(24b)



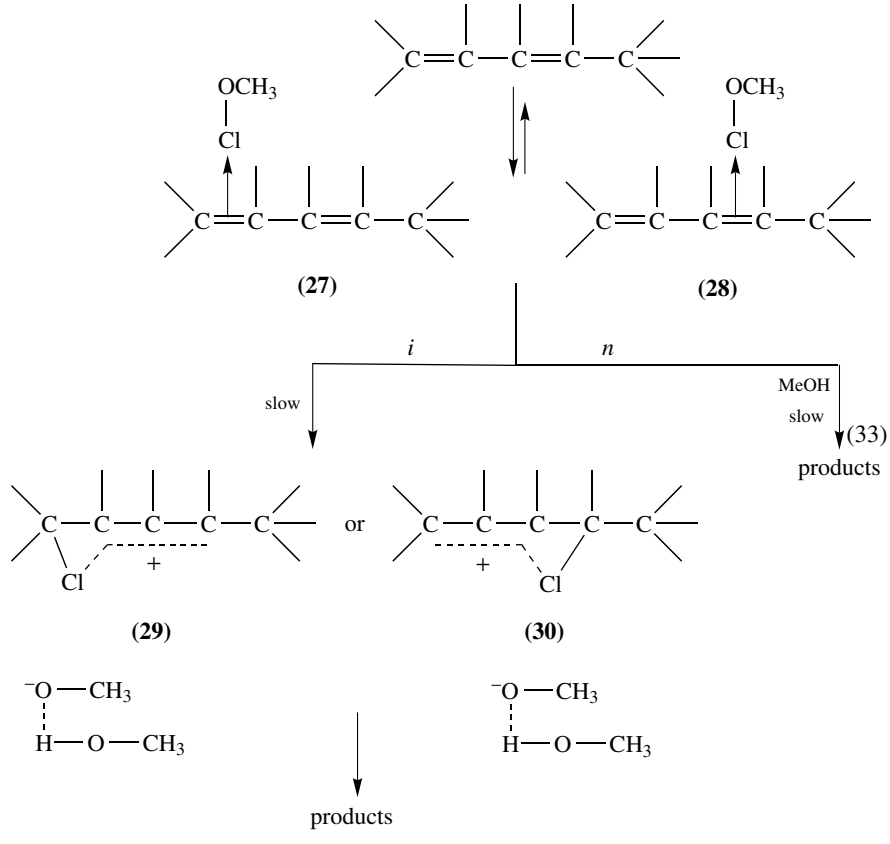
(25a) **(26)** **(25b)**

Ar = 2,6-dichlorophenyl (32)

Although bromination, iodochlorination and iodobromination of unsaturated compounds in aprotic solvents are generally described as following a third-order rate law, chlorination was always found to obey, in the presence of radical inhibitors, second-order kinetics[2b]. However, it has been recently shown[64], through kinetic studies on chlorine addition to 1,3-butadiene in carbon tetrachloride, that in the presence of *tert*-butylpyrocatechol as a radical chain inhibitor the reaction may follow a second-order (first order in halogen) or a third-order (second order in halogen) rate law, depending on the chlorine concentration. Furthermore, third-order kinetics were found in a selected concentration range for the formation of the 1,2-addition product only. The 1,4-adduct accumulated in agreement with a kinetic equation first order in chlorine. The third-order process was, moreover, characterized by a small and negative value of the effective activation energy (-3 kcal mol^{-1}) and a large and negative value of the activation entropy (-65 Kcal mol^{-1} deg^{-1}), which have been interpreted in terms of the molecular mechanism, previously proposed exclusively for bromination in non-protic solvents[2b]. Two chlorine molecules and one alkene molecule are assumed to form a 2 : 1 complex, which rearranges into a non-polar cyclic six-membered transition state without dissociation into ions or radicals. The exclusive formation of 3,4-dichloro-1-butene under third-order conditions has been considered as a further support of the molecular mechanism. Indeed, if a chloroalkenyl cation was formed in this reaction, delocalization of the electron density in the conjugated system would lead to the formation of 1,4-dichloro-2-butene in addition to 3,4-dichloro-1-butene.

Although alkyl hypochlorites have been extensively utilized in radical reactions, their electrophilic additions to dienes occurring through an ionic mechanism were observed only in polar solvents[65], or with boron trifluoride[66] as a promoter. The inertness of methyl hypochlorite toward alkenes in typical aprotic non-nucleophilic solvents, generally used for brominations and chlorinations, has been attributed to the inability of this reagent to form, with an alkene, the corresponding ion pair intermediate, because of the high basicity of the methoxy anion. Two possible mechanisms which could account for the role of methanol have therefore been suggested. As shown in equation 33, the diene

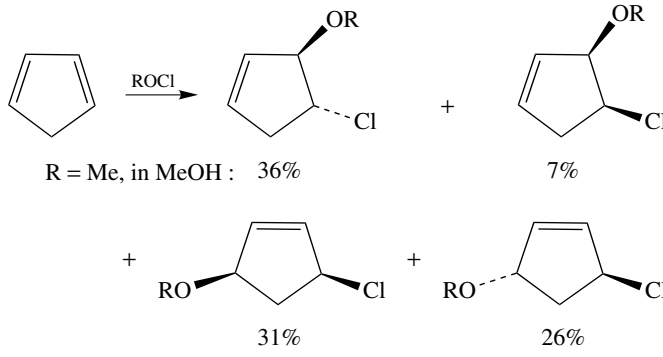
reacts with methyl hypochlorite in a fast reversible step to produce the complexes **27** and **28**. In mechanism *i* (ionization) the first formed π-complexes (or CTCs) undergo a rate-determining ionization, electrophilically assisted by the solvent acting as an acid, to give the ion pair intermediates **29** and **30**. Reaction of **29** or **30** with methanol or methoxide ion would take place in a fast step. In mechanism *n* (nucleophilic attack), the reaction occurs through a product- and rate-determining nucleophilic attack of the methanol on the first formed complexes.



Since chlorination of alkenes occurs rapidly in aprotic non-nucleophilic solvents by mechanism *i*, and since the products (chloroethers and dichlorides) obtained from the reaction of butadiene, isoprene and 1,3-pentadienes with chlorine and methyl hypochlorite in methanol are strikingly similar, it has been suggested that both reagents react essentially in the same way, via carbenium ion intermediates (path *i*). To support this hypothesis it has been remarked that, in agreement with an appreciable carbenium ion character of the rate-determining transition state, a higher reactivity of the 1,2-bond of 1,3-pentadienes has been observed with both reagents. The relative reactivities of the two double bonds should indeed be a reflection of the stabilities of the allylic ion pairs **29** and **30**. Furthermore, the fact that methyl hypochlorite gives an even larger percent of attack than that of chlorine at the 1,2-bond of 1,3-pentadienes, has been explained in terms of reactivity. The greater

reactivity of chlorine would imply an 'earlier' ionization transition state for the chlorine reaction than that for methyl hypochlorite.

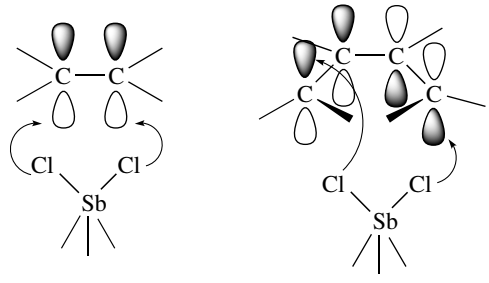
It is noteworthy that both methyl and *tert*-butyl hypochlorites react[67] in several solvents with cyclopentadiene to give 1,2- and 1,4-addition products arising from both *syn* and *anti* additions, although the amount of *syn* 1,2-products is the smallest in methanol (equation 34).



(34)

The formation of the *syn* adducts has been explained by considering that carboxylic acids or BF_3 catalyze the formation of the ionic intermediate by stabilizing the methoxy ion. This intermediate can then collapse directly to the *cis* product. Reactions in methanol give instead mainly the *trans*-1,2-adduct, the solvent collapse from the back-side being very rapid. Furthermore, the difference in *syn* selectivity, slightly larger for 1,4- than for 1,2-addition, has been attributed to a smaller steric hindrance for *syn* methoxy (methanol) attack at C(4) than at C(2).

Chlorination of olefins has also been achieved with $SbCl_5$ in chlorinated solvents, which gives with mono-olefins vicinal dichloroalkanes by a *syn* addition. A concerted mechanism was initially proposed[68] to rationalize this stereochemical behavior and the unexpectedly large amount of *cis*-1,4-dichloro-2-butene found in the reaction of butadiene. In this case, however, because of orbital symmetry control it has been suggested that the addition occurs in an antarafacial direction[69].

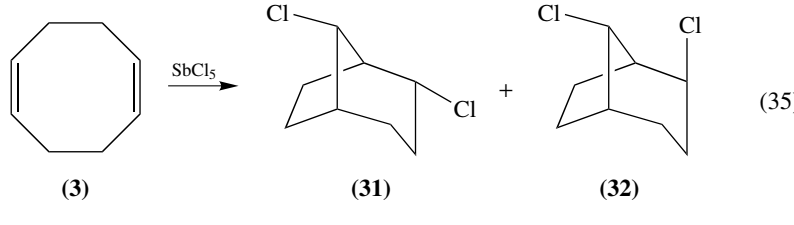


Subsequent studies on cyclopentadiene, in which the antarafacial concerted 1,4-addition is impossible because of interference between the antimony system and the methylene of cyclopentadiene, have however shown[70] that both butadiene and cyclopentadiene react with $SbCl_5$ through a stepwise mechanism involving a carbenium ion intermediate. In agreement with a non-concerted mechanism are also the data related to the 1,4-addition

to 2,4-hexadienes; nearly equimolar amounts of *syn* and *anti* 1,4-addition products were observed, although symmetry considerations indicated that a concerted mechanism should give only *anti* 1,4-addition. On the basis of experimental evidence arising from previous studies on $SbCl_5$ reactions with olefins and more recent data, essentially related to its reaction with dienes, it has been concluded that $SbCl_5$ can add to olefins and dienes either via a carbenium ion or by a concerted mechanism, depending on the stability of the ionic intermediate.

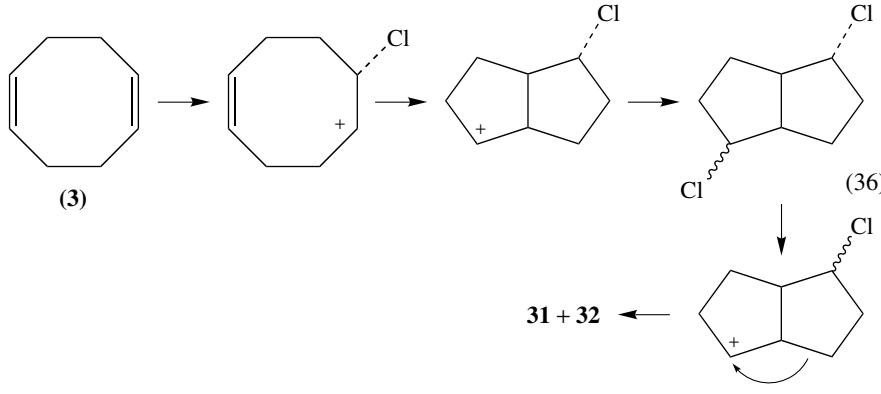
2. Non-conjugated double bonds

In agreement with a non-concerted mechanism, the chlorination of *cis*,*cis*-1,5-cyclooctadiene **3** with $SbCl_5$ in CCl_4 gives two products **31** and **32** both arising from a transannular interaction (equation 35)[71]. It is noteworthy that usually transannular cyclizations of **3** give bicyclo[3.3.0]octane derivatives. However, since $SbCl_5$ is a very efficient catalyst, at least for isomerizations of dichloronorbornanes, it has been suggested that, in agreement with a transannular cyclization, a mixture of *endo*,*endo*-2,6- and *endo*,*exo*-2,6-dichlorobicyclo[3.3.0]octanes is probably formed initially through the chlorocyclooctenyl cation and only a subsequent rapid isomerization yields the mixture of **31** and **32** (equation 36).



(35)

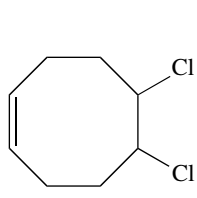
(3) **(31)** **(32)**



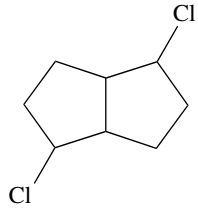
(36)

(3)

3 reacts also with chlorine at $-50\,^{\circ}C$ in CH_2Cl_2 to give a 93 : 7 mixture of 5,6-dichlorocyclooctene **(33)** and 2,6-dichlorobicyclo[3.3.0]octane **(34)** in 70% yield, whereas when the solvent is acetonitrile only the transannular 2,6-dichlorobicyclo[3.3.0]octane **(34)** was obtained as the sole product[22]. In agreement with a strongly solvent-dependent product distribution, the reaction in methanol gave, besides the 1,2-addition products **33** and **35**, also dichloro-9-oxabicyclo[3.3.1]nonane **(36)** arising from the electrophilic addition to the two double bonds.



(33)



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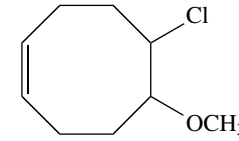

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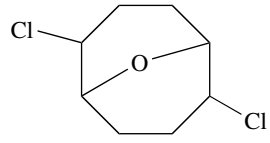
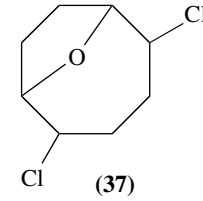


(36)



(37)

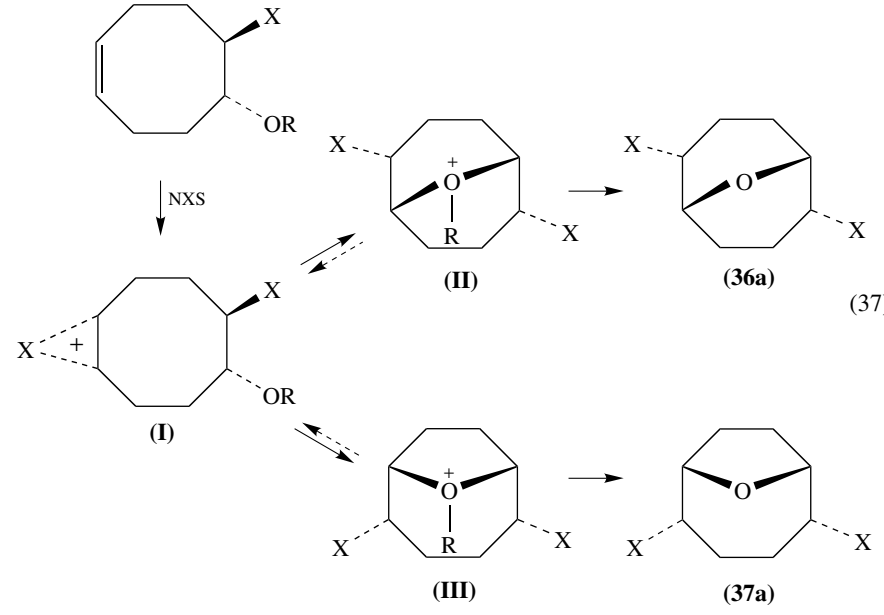
This latter compound, **36**, and the isomeric 9-oxabicyclo[4.2.1]nonane, **37**, were obtained as the sole products, in *ca* 13 : 87 ratio, by reaction of **3** with *N*-chlorosuccinimide (NCS) in protic solvents (methanol, dioxane–water mixtures)[72]. It is noteworthy that similar ratios of the two disubstituted bicyclononane derivatives were obtained, independently of the solvent, also by using *N*-bromosuccinimide (NBS) as electrophile, whereas a strongly solvent-dependent ratio was observed when *N*-iodosuccinimide (NIS) was used. Since these reactions should proceed through hydroxy- or alkoxyhalogenation of one of the double bonds, followed by transannular attack of the oxygen function on the cationic center which is formed on the other side of the ring by the reaction of another electrophile with the second double bond, the isomer ratio has been rationalized in terms of a different nature of the intermediates.

In the reaction of NCS, a weakly bridged chlorocarbenium ion is probably the intermediate. The positive charge is mainly on the carbons, and therefore the transannular cyclization of **I** is assumed to be irreversible independently of the leaving group R. As a consequence of the greater tendency to form a five-membered ring, the kinetically favored compound **37a** is formed preferentially. In the NBS reaction the intermediate should be more strongly bridged and the transannular step reversible so that the portion of the thermodynamically favored compound **36a** increases. In the case of the reaction with NIS, the charge is localized essentially on iodine and the transannular bridging step is considered reversible. Under these conditions, when R is not a good leaving group (Me, Et), intermediate **III** isomerizes to the thermodynamically more stable **II** from which **36a** is formed. When R is a better leaving group (R = *tert*-Bu), elimination is faster than isomerization and the kinetically favored **37a** is obtained (equation 37).

D. Bromine

1. Conjugated double bonds

Bromine addition to conjugated dienes gives 1,2- and 1,4-addition products (equation 38), with a stereochemical outcome which is strongly dependent on the diene structure and the reaction conditions.



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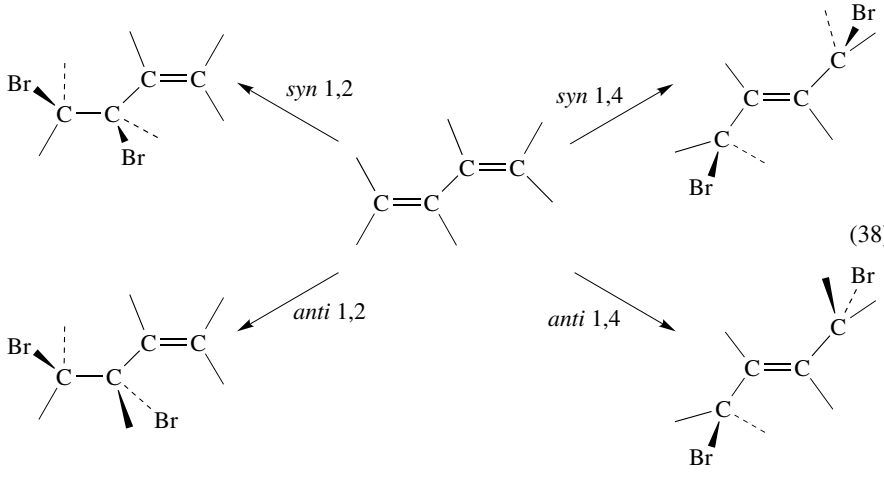


(38)

Generally, in bromine addition to carbon–carbon double bonds, bromine bridging, solvent dependent dissociation of the ionic intermediates, steric interactions between the counteranion and the first bonded halogen during the nucleophilic step, the possibility of carbon–carbon rotation in the carbenium ion intermediate, preassociation phenomena and nucleophilic assistance determine the stereochemical behavior of the reaction[3a,c,7d,8]. Several of these factors have been invoked to explain the stereochemistry of bromine addition to dienes, although others have been completely ignored or neglected. Bromine addition to cyclopentadiene, 1,3-cyclohexadiene, 2,4-hexadienes and 1,3-pentadienes has been examined repeatedly by Heasley and coworkers and the product distribution has been

compared to that of chlorine addition[13,15]. These studies have shown that, at variance with chlorine addition, cyclic dienes react with bromine, in solvents of different polarity, leading exclusively to *anti* 1,2-addition products. Although the different stereoselectivity of the two halogens could suggest the involvement of open ion intermediates in chlorine addition and bridged ions in that of bromine, considering that the 1,2-bromine addition to 2,4-hexadienes proceeds non-stereospecifically, it has been proposed[13,15] that in the reaction of bromine with cyclic dienes the ionic intermediates could, to a considerable extent, be open carbenium ions. Therefore, the absence of *syn* 1,2-addition products with these substrates has been attributed to the greater steric interaction of the counterion with the already bound halogen in bromine addition than in chlorine addition.

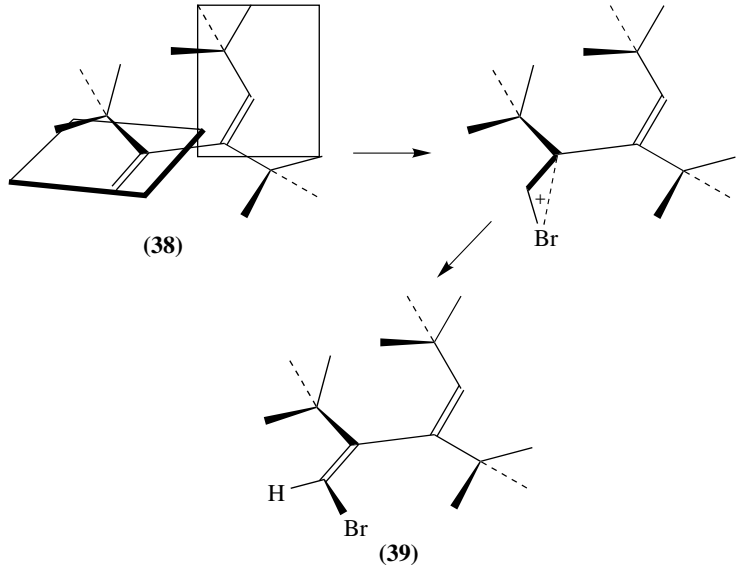
Furthermore, in the addition to the 3,4-bond of 1,3-pentadienes, the *anti* stereoselectivity observed with both bromine and chlorine has been attributed to a tightly bridged bromonium ion intermediate involving less charge dispersal in the vinyl group. In support of this hypothesis, it has been noted that bromine addition to the terminal double bond of the 1,3-pentadienes occurs without isomerization of the internal *cis* or *trans* double bond[15].

A mechanistic scheme involving weakly bridged intermediates, liable to undergo carbon–carbon bond rotation and counteranion translocation, analogous to that proposed for chlorination (see above), has been reported also for the bromination of dienes in order to rationalize the product stereochemistry.

The literature is more controversial concerning the relation between the bridging of the intermediate and the stereochemistry of the 1,4-addition. It has been suggested[15] that if 1,4-addition occurs via a bridged intermediate, an S_N2' process should be involved and the stereochemistry of the product should be completely *syn*. Alternatively, an increase in the amount of *anti* 1,4-addition would be expected when an open carbenium ion is involved[15]. Furthermore, the lack of any 1,4-product has been considered as evidence for an at least weakly bridged bromonium ion, and therefore the dependence of 1,4- vs 1,2-addition of bromine on the solvent polarity has been related to a solvent-dependent structure of the intermediate. However, it is noteworthy that although more bridging is expected in bromination than in chlorination intermediates, the amount of 1,4-addition, compared to 1,2-addition, is appreciably higher in brominations than in chlorinations. Furthermore, whereas chlorine addition occurs primarily via a *syn* addition process, the stereoselectivity of bromine addition is greatly variable, even if a strong preference for *syn* additions has been generally observed. Finally, both dependence and independence of this ratio on the solvent polarity have been claimed, although, with the exception of methanol and acetonitrile, a general trend toward greater 1,4-addition of bromine to 1,3-butadiene with increasing solvent polarity has been observed[60]. The latter results have been explained by assuming that Br_2 addition to butadiene in methanol occurs through an intermediate with little, if any, charge delocalization, whereas a delocalized carbenium ion should be involved in the bromine addition in chlorinated solvents. The weak solvating power of the medium should favor intramolecular charge stabilization. Once again, however, it must be stressed that in methanol, preassociation phenomena and nucleophilic solvent assistance, observed in the bromine addition to olefins, could affect the stereochemistry of the addition, which could therefore be determined by these factors but not by changes in the intermediate bridging[7d].

As observed with alkenes, bromine addition to sterically hindered dienes shows a peculiar behavior. Highly substituted dienes, existing predominantly in non-planar conformations, often present a chemical reactivity distinctly different from that of planar 1,3-dienes. (*Z*)-4-*tert*-Butyl-2,2,6,6-tetramethyl-5-methylene-3-heptene **(38)** reacts[73] with bromine in chloroform to give, instead of the expected 1,2- and 1,4-adducts, the monobromide **39**. The formation of this elimination product has been rationalized on the basis

of an initial bromine attack at the sterically less hindered side of the less hindered double bond of **38** to give an ionic intermediate. This intermediate, which cannot be captured by the usual back-side attack because of the extreme steric shielding, undergoes deprotonation to form **39** (equation 39). It has therefore been stressed that diene **38** behaves regeneratively, like a classical arene.



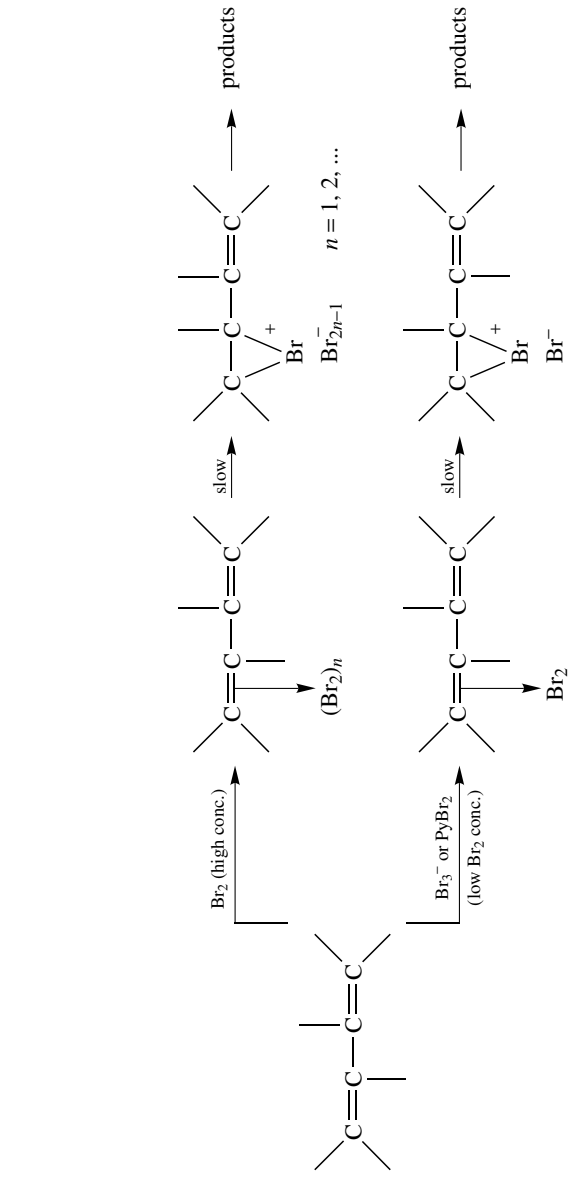
(38) **(39)** (39)

Bromination of dienes has been carried out also with pyridine–bromine complexes and tribromide ions as electrophilic reagents. Generally, they react with dienes to give much more 1,2 to 1,4 adducts and larger ratios of *anti* to *syn* adducts than those with molecular bromine. For instance, 2,4-hexadienes, which give non-stereospecific 1,2-additions with bromine, approach 100% *anti* addition when pyridine halogen complexes or tribromide are used as brominating agents[74]. Furthermore, the stereochemistry of 1,4-bromine addition with hexadienes and cyclopentadiene is mainly *anti* in the presence of an amine.

These results have been rationalized[74] by Heasley and coworkers by assuming that the primary function of the complexes is to limit the concentration of free halogen. In the reaction of free bromine where the reaction is second order in bromine, two or more molecules of halogen participate in the transition state while the halogen complexes with pyridine or amines impose a first-order mechanism by limiting the availability of free halogen (equation 40).

According to this hypothesis the structures of the counterions in the intermediates would therefore justify the differences between the mechanisms. Whereas in the presence of an excess of bromine the counterion is a tribromide or polybromide species, when the reaction is carried out with a tribromide salt or a pyridine bromine complex, the counterion would be a simple bromide ion. Because the latter should be unstable relative to Br_3^-, it has been suggested that the bromonium–bromide ion pair undergoes a fast collapse to the *anti* 1,2-adduct before the opening of the bromonium ion could occur. In contrast, the higher stability of polybromide anions would result in an ion pair of longer lifetime, thus permitting bromonium ion ring opening and the concurrent *syn* 1,2-addition.

However, attempts to test the hypothesis that the product distribution was affected significantly by the halogen concentration have not been encouraging. Only a very slightly


Br2 (high conc.)
slow
products
Br
Br2n−1
n = 1, 2, ...
(Br2)n
Br3− or PyBr2
(low Br2 conc.)
slow
products
Br
Br−
Br2

(40)

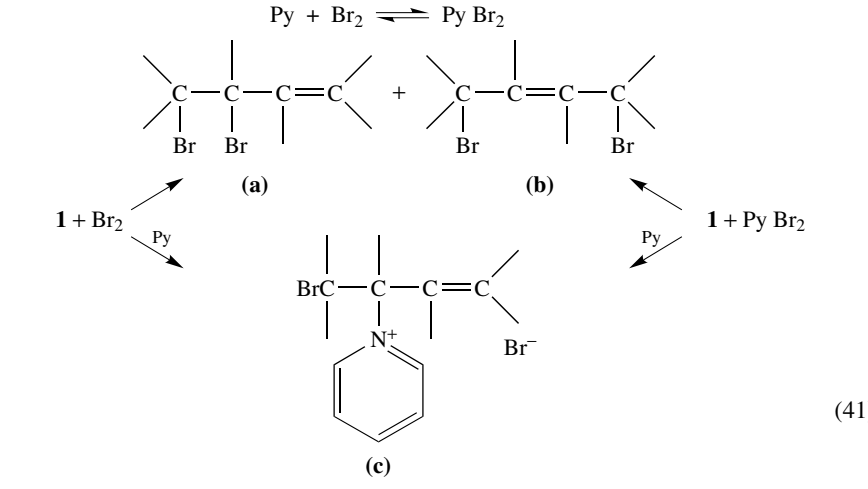
detectable effect of dilution was observed in methylene chloride or nitromethane. The alternative explanation of a change of mechanism from a stepwise Ad_EC_1 to a concerted Ad_EC_2 on going from free bromine to the $PyBr_2$ and Br_3^- reactions, which would account for some features of these reactions, was instead excluded[74] on the basis of the absence of a steric effect (reflected by a decrease in the relative amount of attack on the more substituted double bond) on the bromination of isoprene on going from BrCl to 2,6-lutidine-Br_2.

Subsequent kinetic and product distribution data on the reactions of 1,3-butadiene with molecular bromine, pyridine–bromine complex and tetra-*n*-butylammonium tribromide in chlorinated solvents have shown that pyridine-Br_2 and tribromide ion act as independent electrophiles, rather than as sources of molecular bromine[75].

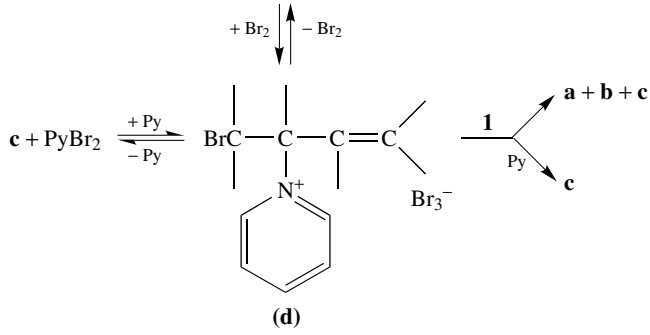
Whereas the reaction with Br_2 followed the usual third-order rate law (second order in halogen), those with the other two types of reagents were first order in the halogenating species. The solvent change from 1,2-dichloroethane to the slightly less polar dichloromethane produced a threefold decrease in the rate of the reaction with Br_2 and a fourfold increase in that with Br_3^-, showing that the reactions follow two different mechanisms. Indeed, if the only role of tribromide, as well as of $PyBr_2$, was to limit the concentration of free bromine, affecting the nature of the counterion of the ionic intermediate, a change from second to first order in the electrophile could occur, but the rates of the two processes involving the same cation as the intermediate should not exhibit an opposite trend to the solvent sensitivity[75]. Once again, significant differences in the ratios of 1,2- to 1,4-adducts on changing from molecular bromine to complexed bromine were found. Furthermore, in the reaction of $PyBr_2$ (and to a lesser extent in that with Br_3^- in the presence of pyridine) substantial amounts of *N*-(4-bromo-1-buten-3-yl)pyridinium bromide accompanied the expected dibromo adducts. This salt was converted into the corresponding tribromide as long as free Br_2 or $PyBr_2$ was present in the medium. The tribromide therefore remained the only brominating species during the later stages of the reaction. The reaction mechanism reported in equation 41 has been consequently proposed to rationalize the kinetic and product distribution data.

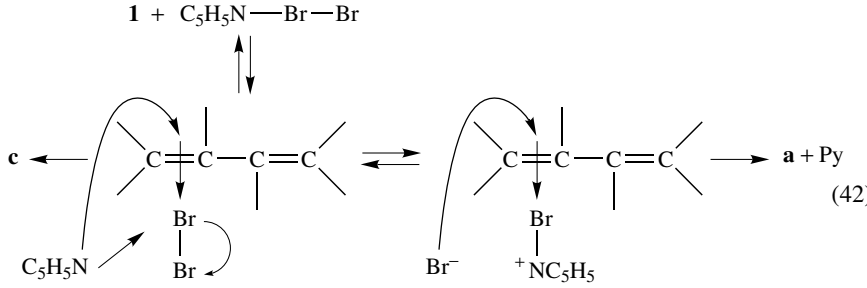
It is noteworthy that this mechanism implies an equilibrium between $PyBr_2$ and a diene-Br_2 charge transfer complex (CTC). Nucleophilic attack by pyridine at the carbon of the CTC with concerted Br−Br bond breaking gives the pyridine incorporation product (equation 42). On the other hand, the formation of a dibromo adduct requires a preliminary breaking of the Br−Br bond in the first formed CTC. Since under the reaction conditions there is no free bromine which is able to provide electrophilic assistance, it has been suggested that this breaking may be achieved through nucleophilic assistance by pyridine to give a new CTC and a bromide ion. The collapse of this latter compound would give the dibromo adduct. Finally, considering that the reaction of Br_3^- in the presence of pyridine proceeds also with a significant incoporation of pyridine, the mechanism reported in equation 43 has been proposed.

The diene-Br_2 complex is again in equilibrium with the reagents, and nucleophilic attack at carbon can be carried out either by the bromide of the ammonium bromide ion pair, formed at the moment of the electrophilic attack, or by the less nucleophilic pyridine added in excess in the reaction medium. It is noteworthy that this mechanism is characterized by a rate- and product-limiting nucleophilic step which should be quite insensitive to steric hindrance around the double bond. In agreement with a weak influence of the steric effects, pyridinium perbromide reacts[76] in chloroform and tetrahydrofuran with substituted conjugated and non-conjugated dienes to give selectively (>95%) bromine addition to the more alkylated double bond (equation 44).



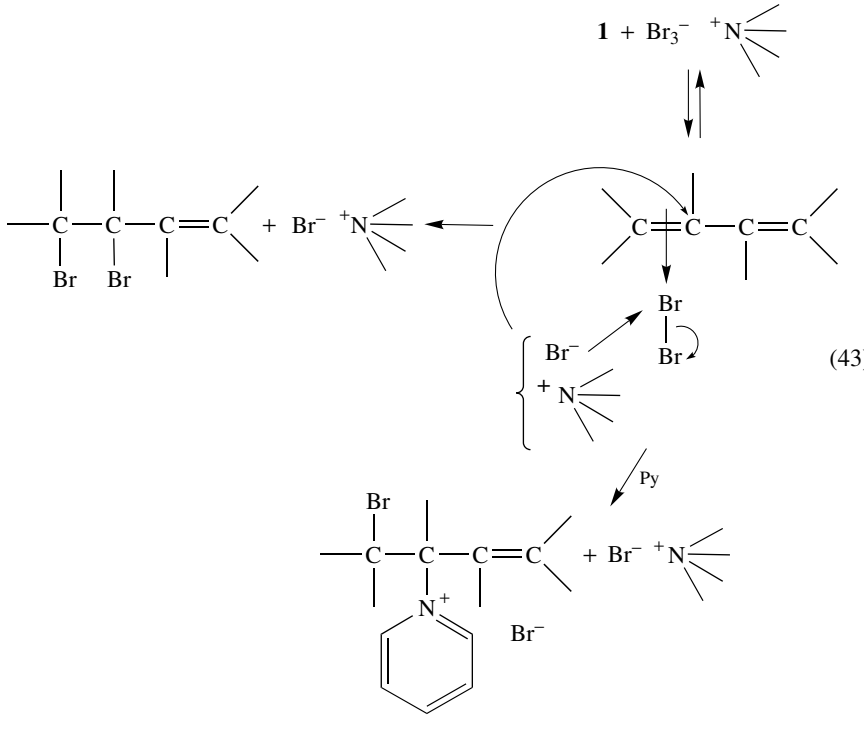
(41)



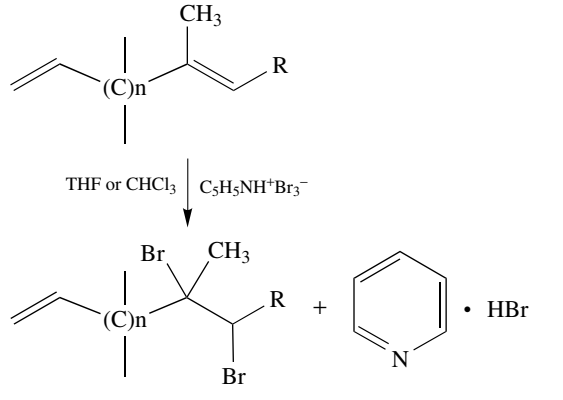


(42)

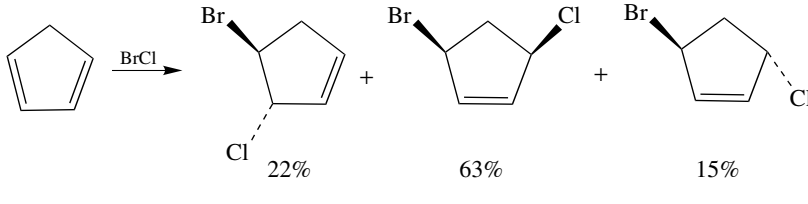
The addition of bromine chloride (BrCl) and amine–bromine chloride complexes to cyclopentadiene, isoprene and *cis*- and *trans*-1,3-pentadienes has been also investigated[74,77]. The amine–bromine chloride complexes react with these dienes to give mixtures of bromochlorides in ratios markedly different from those obtained with BrCl. In particular, in analogy with Br_2, BrCl gives significantly more 1,4-addition and the complexes give more *anti* 1,2-addition. Only Markovnikov 1,2-adducts have been reported for BrCl addition to these dienes. Furthermore, in the case of cyclopentadiene, 1,2-addition proceeds completely *anti* whereas 1,4-addition gives predominantly the *cis* adducts (equation 45).


1 + Br3−
Br
Br
Br−
Py
Br
Br−

(43)


CH3
(C)n
R
THF or CHCl3
C5H5NH+Br3−
Br
CH3
R
Br
HBr

(44)


BrCl
Br
Cl
Br
Cl
Br
Cl
22%
63%
15%

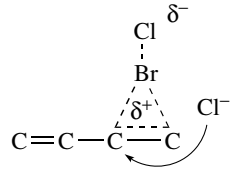
(45)

The stereochemical behavior observed in the addition of BrCl has been compared with that related to the Br_2 and Cl_2 additions to the same diene and discussed in terms of steric hindrance of the nucleophile approach (chloride ion with respect to bromide or tribromide ion) and different bridging in the bromonium or chloronium intermediates[77].

A completely different stereoselectivity, with respect to BrCl, has more recently been observed with tetrabutylammonium dichlorobromate as a bromochlorinating agent[78]. The reaction of this electrophile with 1,3-butadiene, isoprene, *cis*- and *trans*-1,3-pentadienes and cyclopentadiene gives selectively, in good yields, the corresponding 1,2-bromochloro adducts. Moreover, the addition to the 3,4-bond of pentadienes and to cyclopentadiene proceeds with a complete *anti* stereoselectivity. In the case of the unsubstituted butadiene the reaction gives a mixture of Markovnikov and anti-Markovnikov 1,2-adducts (equation 46).

$$H_2C{=}CH{-}CH{=}CH_2 \xrightarrow{BrCl_2^-} CH_2(Br)CH(Cl)CH{=}CH_2 + CH_2(Cl)CH(Br)CH{=}CH_2 \quad (46)$$

A mechanism involving a nucleophilic attack of chloride ions on a three-center π complex-type intermediate, with an unimportant delocalization of the positive charge across the system as shown below, has therefore been suggested to rationalize the stereochemical results.



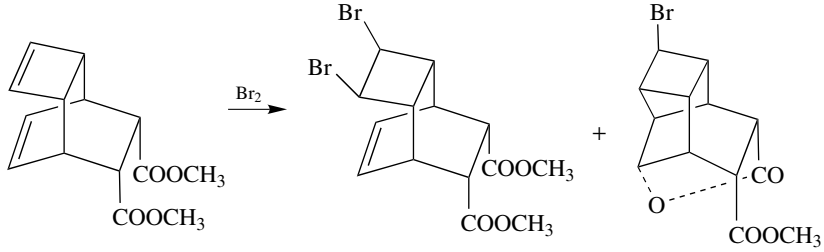
2. Non-conjugated double bonds

Dimethyl tricyclo[4.2.2.$0^{2,5}$]deca-3,7-diene-9,10-dicarboxylate adds bromine and iodine only to the less hindered double bond to give the *syn* 1,2-addition product of the cyclobutene moiety[79]. The product composition from this compound depends on the temperature and the solvent. At high temperatures, the 1,2-addition predominates over the transannular reaction, but this predominance is small in a solvent like chloroform and is lost in a protic solvent such as acetic acid (equation 47).

These results have been interpreted in terms of HOMO–LUMO interactions. As a result of the orbital perturbation, the interaction of the HOMO of the cyclohexene double bond with the LUMO of the developing cation may become effective. At the first stage of this interaction, an overlap of the LUMO of the cyclobutyl cation with the p lobe of the double bond located close to the cation center is probably important. However, when the reaction progresses, the interaction with the p lobe on the remote carbon atom has been assumed to increase significantly.

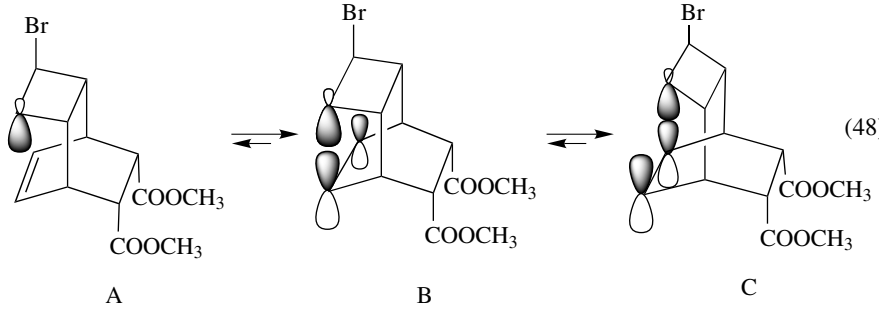
Therefore, when the reaction is carried out under conditions which facilitate the stabilization of the cationic intermediate, electrophilic attack on the cyclobutene double bond of A gives intermediate C, which on lactonization affords the cage compound. At higher temperature, cation B might be trapped by the counterion before the formation of C (equation 48). The attack of the bromide ion on this intermediate occurs from the

less-hindered and electronically favored side to give the *exo-cis*-adduct.



CCl_4	20 °C	14%	84%
CCl_4	77 °C	93%	–
$CHCl_3$	20 °C	–	quant.
$CHCl_3$	61 °C	68%	28%
AcOH	20 °C	–	quant.
AcOH	80 °C	37	63%

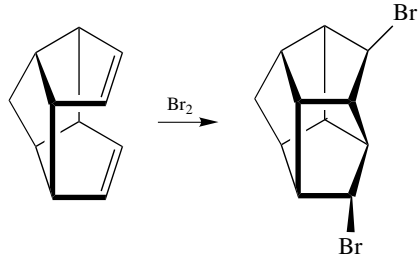
(47)



A B C

(48)

A transannular reaction involving a through-space interaction has been observed also when bromine was added to homohypostrophene **(40)**. The bromination proceeds straightforwardly by 1,4-addition to give exclusively the dibromo adduct **41** (equation 49)[80].

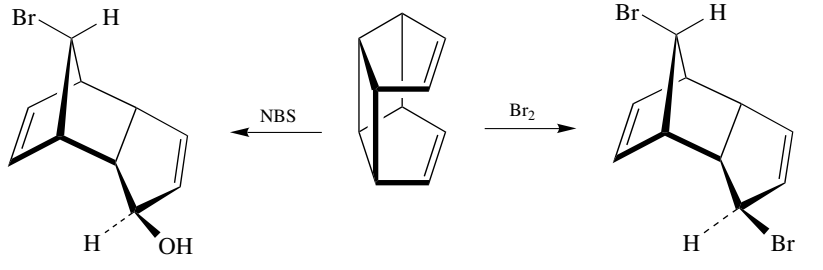


(40) **(41)**

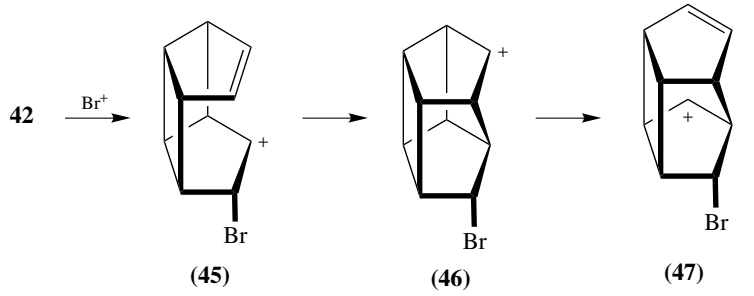
(49)

At variance with homohypostrophene, the related hypostrophene **(42)** reacts with bromine or with *N*-bromosuccinimide in wet dimethyl sulfoxide to give products arising from an extensive structural rearrangement, i.e. the *endo*-dicyclopentadiene derivatives

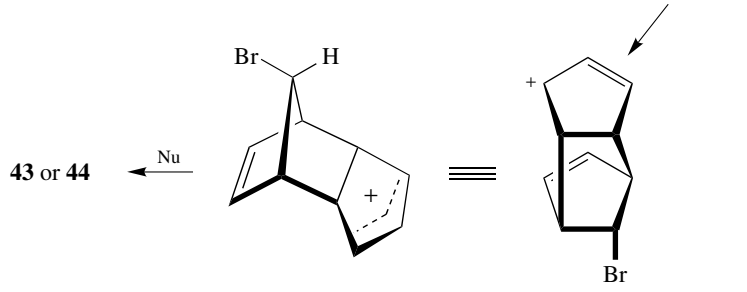
43 and **44**, respectively (equation 50)[80]. A striking feature of the conversion of hypostrophene into **43** and **44** is the involvement of *eight* of its ten carbon atoms in the skeletal rearrangement, which has been explained on the basis of an initial *exo* electrophilic attack to give the intermediate **45**, which should undergo transannular bonding with the normal kinetic preference for 5-ring closure to give **46** (equation 51). Two subsequent cyclobutane bond cleavages are suggested. The formation of **47** should be favored by the electron-rich nature of the lateral bond and controlled by strain release, while the further formation of **48** should be favored by the development of allylic resonance, and a further reduction of strain could also contribute. Nucleophilic attack at either allylic terminus would finally give compounds **43** or **44**. It is, however, possible that the conversion of **45** to **48** can occur through a concerted electronic reorganization since all attempts to intercept these intermediates, even with highly reactive electrophiles, have failed.



(43) (42) (44) (50)



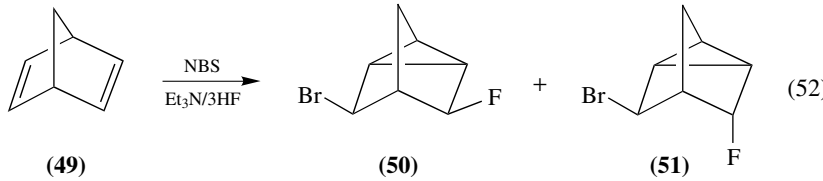
(45) (46) (47) (51)



(48)

Transannular cyclization has also been observed in the bromofluorination of norbornadiene **(49)** using NBS in the presence of Et_3N-3HF which led to a 3 : 2 mixture of

3-*exo*-bromo-5-*exo*-fluoronortricyclane **(50)** and 3-*exo*-bromo-5-*endo*-fluoronortricyclane **(51)**, arising from an exclusive *exo* attack of the Br^+ species on **49** (equation 52)[81].

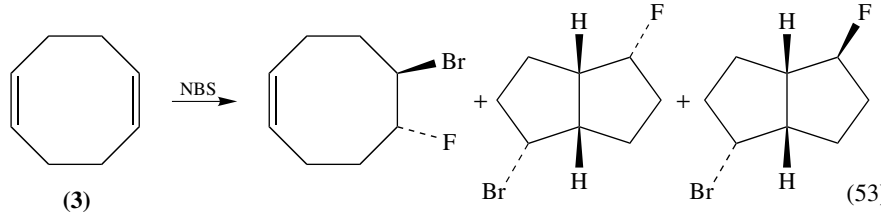


(52)

(49) **(50)** **(51)**

Although the possibility of an *endo* attack was considered[82] previously on the basis of the reported formation of 3-*endo*-bromo-5-*exo*-fluoronortricyclane as the major product in the bromofluorination of **49** with NBS and Olah's reagent (pyridine/10HF), it was subsequently shown[81] that this assumption arose from an incorrect assignment of the structure. With both reagents the minor compound is always the isomer **51**.

Nevertheless, a different selectivity has really been observed[83] in bromofluorination reactions of 1,5-cycloalkadienes with NBS/Et_3N–3HF or Olah's reagent. The reaction of 1,5-cyclooctadiene **(3)** with the former reagent yields mainly the 1,2-addition product **52**, but when the reaction is carried out with Olah's reagent only compounds **53** and **54**, arising from the usual transannular π-cyclization, are formed (equation 53).



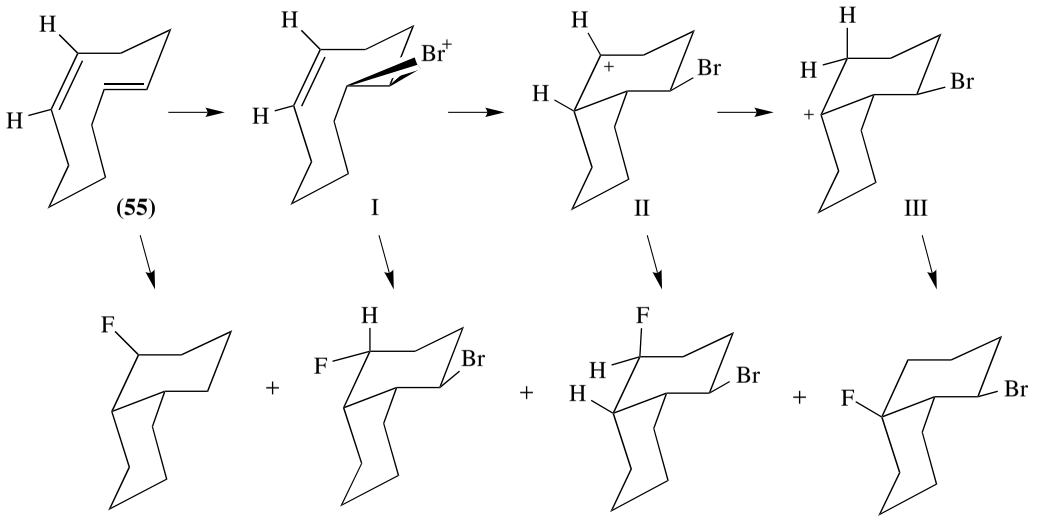
(53)

(3) **(52)** **(53)** **(54)**

Et_3N/3HF	92%	2%	6%
pyridine/10HF		26%	66%

Under similar conditions the reaction of (*E*,*Z*)-1,5-cyclodecadiene **(55)** with either reagent gives exclusively transannular cyclization products **56**–**59** (equation 54). In the reaction of diene **55** the initial formation of the cationic intermediate I, arising from the electrophilic addition to the *E*-double bond of the most stable chair–boat–chair conformation of **55**, has been suggested. A parallel transannular π-cyclization may lead either to the carbenium ion II, or preferentially to the main product **57** through concerted nucleophilic attack by the fluoride ion. With **55**, cyclization should be favored by the fact that one conformation of this diene resembles that of *cis*-decalin, so that carbons C(1) and C(6) are in close spatial proximity. On the other hand, the attack of fluorine on C(1) or C(2) is probably sterically hindered. The cation II is attacked by the nucleophile, producing the product **58** or, particularly under the stronger acidic conditions of the reaction with Olah's reagent, it undergoes a 1,2-shift to give the tertiary cation III from which **59** is obtained.

On the basis of these latter results, the bicyclic products derived from **3** have been explained by cross-transannular π-cyclization. The different behavior observed in the reaction of **55** with the two reagents has been attributed to the strong nucleophilicity of the fluoride ion, which competes with the internal double bond for the bromonium ion attack.

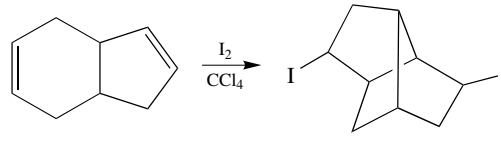


(54)

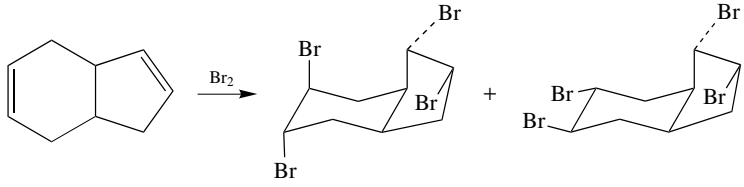
$Et_3N/3HF$	8%	78%	12%	1%
pyridine/10HF	17%	46%	19%	18%

It is noteworthy that Br_2 addition to **3** in aprotic and protic solvents gives exclusively the *anti* 1,2-addition product. For diene **55**, the intramolecular nucleophilic attack of the *Z*-double bond on the cationic center is exclusive, even in the presence of Et_3N-3HF. This has been ascribed to a large strain release in the formation of the *cis*-decalin system from the highly strained medium-sized system.

Although *cis*-bicyclo[4.3.0]nona-3,7-diene reacts with I_2 in CCl_4 or $CHCl_3$ through a regio- and stereoselective transannular cyclization to give *endo*-4-*exo*-8-diiodotricyclo[4.3.0.$0^{3,7}$]nonane (*endo*-4-*exo*-8-diiodobrexane)[84] (*vide infra*) (equation 55), the reaction of this diene with Br_2 at $-8\,^{\circ}C$ leads to a 2 : 1 mixture of the isomeric tetrabromides with the *trans*-diaxial and *trans*-diequatorial arrangements of the bromine atoms in the six-membered ring and with identical *trans* position for the bromine atoms in the five-membered ring (equation 56)[85]. Because of the conformational flexibility of the diene molecule and of the competition in the bromine addition to the cyclohexene and cyclopentene double bonds, the stereoselectivity has been explained in terms of steric factors, whereas no rationalization has been given for the halogen dependent product distribution.



(55)



(56)

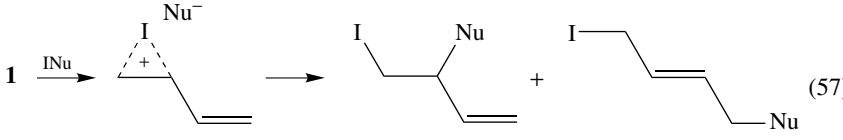
E. Iodine

1. Conjugated double bonds

The addition of iodine electrophiles, *tert*-butyl hypoiodite (*t*-BuOI) in the presence of BF_3, acetyl hypoiodite (AcOI), iodine monochloride (ICl) and iodine monobromide (IBr), to 1,3-butadiene gives always, under ionic conditions, mixtures of 1,2- and 1,4-Markovnikov adducts (equation 57). These mixtures are the kinetic products, since rearrangement to the thermodynamically stable products occurs under the appropriate conditions[86].

At variance with 1-hexene, no addition to the α-carbon (anti-Markovnikov, AM 1,2-addition) was observed when *t*-BuOI-BF_3 was used as the electrophile. Since steric factors in the iodonium ions from 1-hexene and 1,3-butadiene should be similar, the different regioselectivity of the nucleophilic attack has been attributed to the greater reactivity of the allylic β- (M 1,2-addition) and δ-carbons (1,4-addition) of the intermediate, although no extensive development of charge should be present on these carbon atoms. The positive charge is indeed mainly on iodine. An S_N2' attack has therefore been proposed to explain the formation of the 1,4-adducts. Furthermore, assuming that the charge distributions are the same in the iodonium ions, regardless of the anion, the differences in product distribution from *t*-BuOI to IBr have been attributed to differences in the stabilities of the ion pairs and in the rates of their collapse. The anions having lower nucleophilicity (Br^- and Cl^-) should have more time to migrate to the γ-carbon before collapse occurs. On

the other hand, the different product distributions observed in the reactions of the three *tert*-butyl hypohalites have been related to the relative bridging abilities of the halogens. The magnitude of bonding between the halogen and the β-carbon should decrease from iodine to chlorine with increasing charge dispersal into the allylic system, and apparently this shift of charge to the δ-carbon outweighs the influence of ion pair stability and leads to greater 1,4-addition.



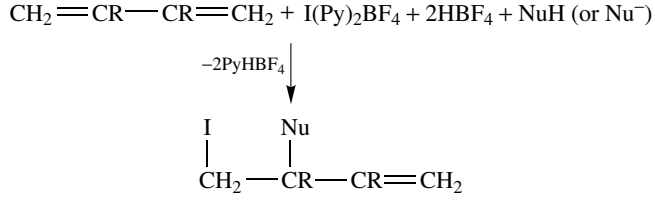
(57)

Nu = nucleophile M 1,2-adduct 1,4-adduct

Electrophile	M 1,2-	: 1,4-	Yield (%)
t-BuOI	92	8	82
AcOI	90	10	75
ICl	65	35	89
IBr	56	44	73
t-BuOBr	69	31	66
t-BuOCl	54	46	55

Bis(pyridinium)iodonium tetrafluoroborate [$I(Py)_2BF_4$] reacts readily with alkenes to afford 1,2-disubstituted products arising from addition of iodine and pyridine. Synthetically more important is, however, the reaction of unsaturated systems with $I(Py)_2BF_4$ in the presence of nucleophiles, which provides a general method for vicinal iodofunctionalization of alkenes. In this regard, the addition of a stoichiometric amount of tetrafluoroboric acid to the reaction medium is often required to avoid the competitive formation of products resulting from pyridine acting as a nucleophile.

Terminal dienes such as butadiene, isoprene and 2,3-dimethylbutadiene react regiospecifically with $I(Py)_2BF_4$, in the presence of a nucleophile, to give 1,2-iodofunctionalization (equation 58)[87]. In contrast, internal dienes such as (*Z*,*E*)-2,4-hexadiene and 1,3-cyclooctadiene yield the 1,4-addition products under similar conditions (equation 59).

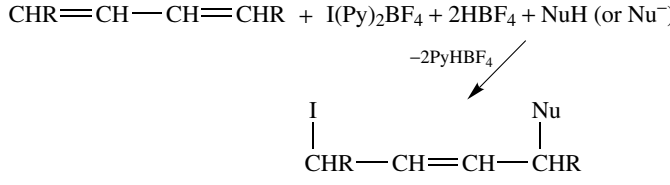


(58)

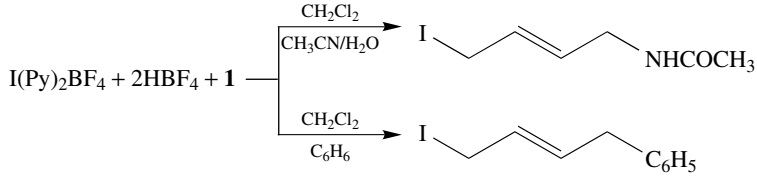
NuH = CH_3OH, HCl, DMF, CH_3CN, $HSiEt_3$; M $^+Nu^-$ = LiCl, $NaNO_2$

However, when the addition to butadiene is carried out in the presence of benzene or acetonitrile as nucleophiles, the iodofunctionalization leads to the *E*-1,4-regioisomers as the only product[14] (equation 60), unlike the previously reported 1,2-functionalization of

butadiene[87].



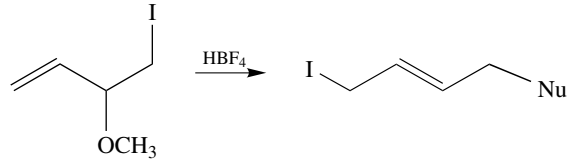
(59)



(60)

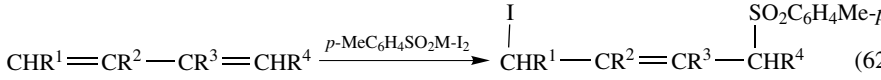
The latter results have been explained on the basis of the following reaction scheme. The 1,2-regioisomers derived from butadiene are obtained through a non-symmetrical iodonium ion intermediate. The subsequent nucleophilic attack on the allylic position gives, under kinetic control, 1,2-derivatives. Nevertheless, when poorer nucleophiles such as benzene or acetonitrile are employed, the conversion of the initially formed iodonium ion into the allylic cation has been suggested to give 1,4-products, under thermodynamic control. However, other alternatives like nucleophilic attack involving allylic participation have not been excluded for the formation of 1,4-derivatives.

To support the assumption of a kinetic or thermodynamic control, it has been underlined that treatment of a solution of 4-iodo-3-methoxy-1-butene with an etheral solution of HBF_4, in acetonitrile, benzene or methanol, affords the corresponding 1,4-iodofunctionalized substrates (Nu = $NHCOCH_3$, C_6H_5, or OCH_3) as the major product (equation 61).



(61)

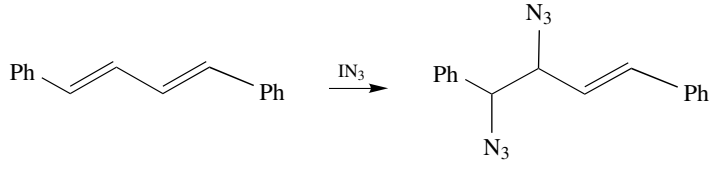
An exclusive 1,4-addition has also been observed[88] in iodosulfonylation of conjugated dienes with *in situ* generated tosyl iodide. With symmetrical acyclic dienes the corresponding δ-iodobut-2-enyl sulfones were obtained. In the case of asymmetrical acyclic dienes, with the exception of isoprene, mixtures of regioisomeric products were isolated (equation 62).



(62)

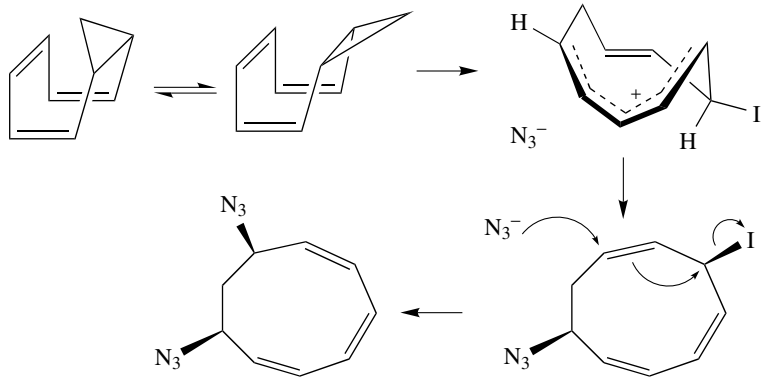
Finally, although only few data have been reported about the addition of halogen azides[14] to conjugated dienes, it has been shown that whereas BrN_3 addition affords 1,2- and/or 1,4-adducts, depending on temperature, the addition of IN_3 (generated *in situ* from NaN_3 and ICl) generally gives the corresponding diazide, arising from allylic displacement by azide ions on the initially formed adduct. This behavior has been observed in the

reaction of the acyclic 1,4-diphenyl-1,3-butadiene (equation 63)[89] as well as in additions to medium-size cyclic dienes and polyenes[90].



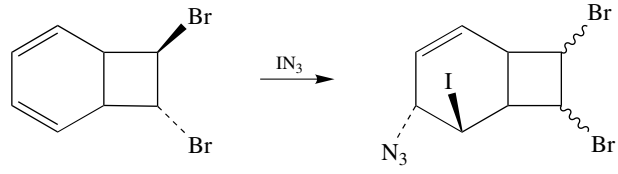
(63)

A diazide was obtained[91] as the sole product also by addition of IN_3 in acetonitrile to *cis*-bicyclo[6.1.0]nonatriene. In this case, however, at variance with the medium-size ring unsaturated compounds, the reaction did not afford a normal *vic*-diazide. A mechanism involving a bishomotropylium or cyclopentadienyl cation has been proposed (equation 64).

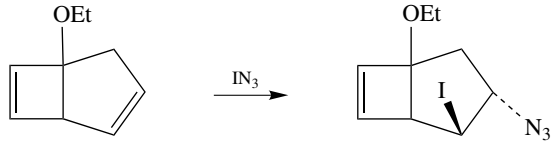


(64)

The reaction of IN_3 with *trans*-7,8-dibromobicyclo[4.2.0] (equation 65) and 5-ethoxybicyclo[3.2.0]hepta-2,6-dienes (equation 66) gives β-iodoazides as normal adducts[91].



(65)

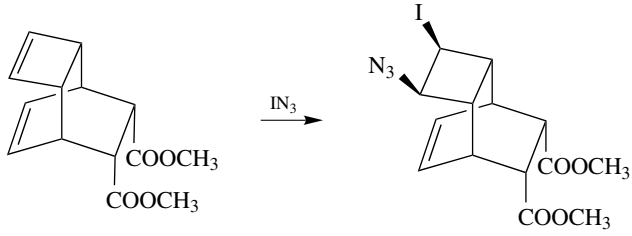


(66)

2. Non-conjugated double bonds

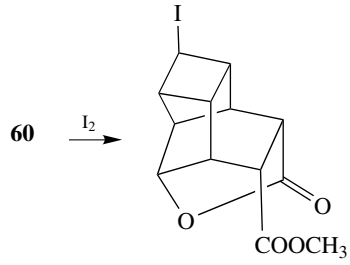
Electrophilic addition of IN_3 to the tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivative **60** has been reported[92,93] to give exclusively or predominantly the *syn* azido iodide **61**

(equation 67). The *syn* addition of IN_3 to the cyclobutene moiety has been explained by examination of the transition state in terms of the 'twist strain' theory. In contrast, it has been reported that I_2 addition to the same diene gives almost exclusively (94%), at least at room temperature, a transannular iodolactone (equation 68), whose formation has been rationalized, in analogy to the bromine addition, on the basis of HOMO–LUMO interactions[79].



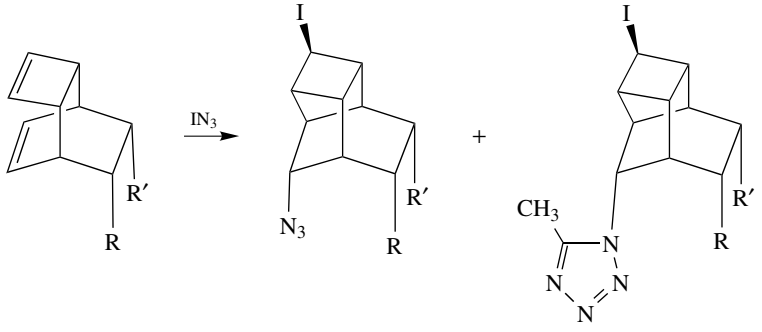
(67)

(60) **(61)**



(68)

A transannular solvent participation has instead been observed in the IN_3 addition in CH_3CN to tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives **62** and **63**, which give adducts **64** and **65** as well as tetrazoles **66** and **67** via Hassner–Ritter reaction (equation 69).



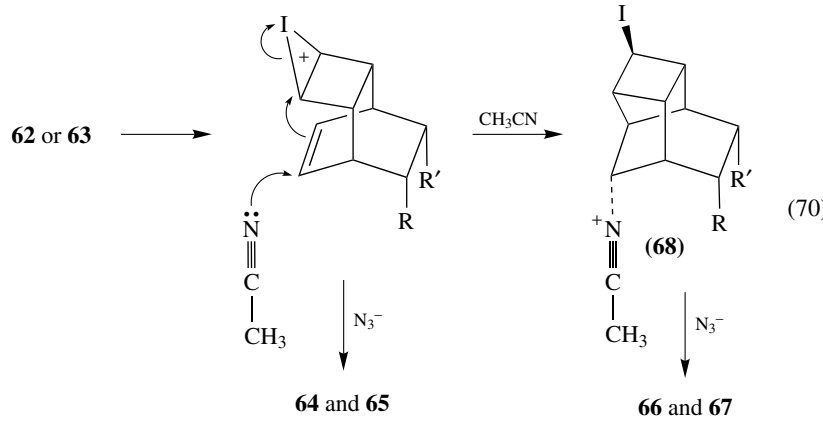
(69)

(62) R = R′ = CH_3 **(64)** R = R′ = CH_3 **(66)** R = R′ = CH_3

(63) RR′ = CH_2OCH_2 **(65)** RR′ = CH_2OCH_2 **(67)** RR′ = CH_2OCH_2

The formation of the tetrazoles **66** and **67** from **62** and **63**, respectively, has been rationalized on the basis of the solvent-assisted opening of the initially formed iodonium ion to give the Ritter reaction intermediate **68**, which undergoes cycloaddition with azide

ion to form the substituted tetrazoles. When the reaction is carried out in CH_2Cl_2, only the iodo azide (**64** or **65**) resulting from participation and nucleophilic capture by the azide ion is obtained (equation 70).

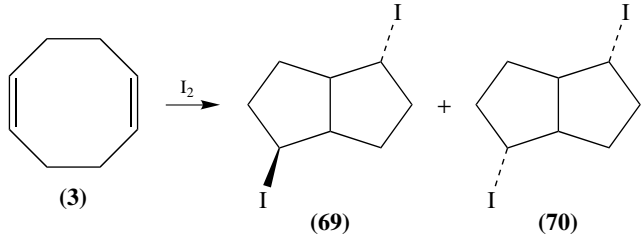


(70)

The difference in the stereochemical behavior of **62** and **63** as compared to that of **60** has been explained by assuming that the presence of the electron-withdrawing carbomethoxy substituents at C(9) and C(10) in the latter markedly decreases the availability of electrons from the participating C(7)−C(8) double bond, thus forcing the reaction to proceed mainly via the iodonium ion.

The electrophilic addition of iodine donors to 1,5-cyclooctadiene **(3)** gives, analogously to those of BrX, a product distribution which is strongly dependent on the nature of the nucleophile and reaction conditions.

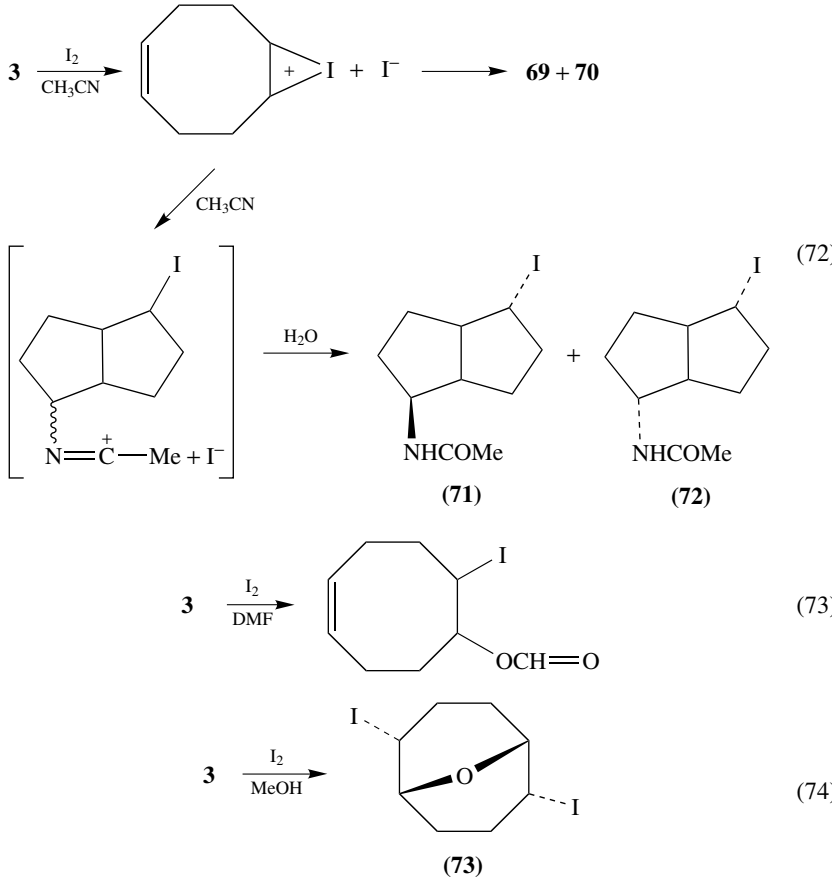
The I_2 addition to **3** in chlorinated solvents yields a mixture of isomeric 2,6-diiodobicyclo[3.3.0]octanes (*endo*,*exo*-**69** and *endo*,*endo*-**70**) (equation 71)[22]. When the reaction was carried out in aqueous acetonitrile under similar conditions, the formation of a mixture of acetamido derivatives **71** and **72**, arising from iodocyclization followed by the capture of the iodonium ion by the solvent to give a Ritter reaction intermediate, accompanied the formation of products **69** and **70** (equation 72)[22].



(71)

In *N*,*N*-dimethylformamide, the 1,2-addition product was obtained as the main product (60% yield) (equation 73) together with small amounts of **69** and **70**. Small amounts of 1,2-adducts were also obtained in acetic acid, the main products being again **69** and **70**[22].

In methanol, only the oxa bridged compound **73** was instead isolated in a yield of 28% (equation 74)[22].

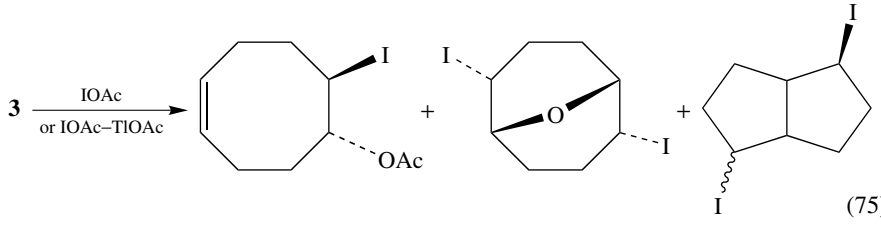


Higher yields of disubstituted 9-oxabicyclo[4.2.1]nonane and 9-oxabicyclo[3.3.1]nonane derivatives from **3** have been obtained using *N*-halosuccinimides as reagent[72] (*vide supra*). In this case, a solvent dependent isomer ratio has been observed only with *N*-iodosuccinimide and the different dependence on the solvent shown by the three *N*-halosuccinimides has been explained again in terms of the different nature of the intermediates (*vide supra*).

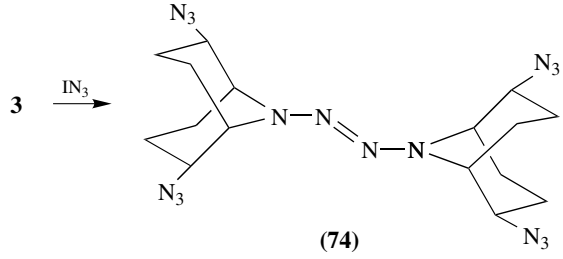
Significant amounts of the bicyclo[3.3.1]nonane adduct and of the octahydropentalenes were isolated also from the reaction of **3** with preformed iodine acetate and iodine acetate thallium (equation 75)[94] whereas only the monocyclic 1,2-adducts were obtained from treatment of **3** with iodine azide, iodine isocyanate or iodine nitrate[95]. The different propensity to give transannular products with these latter reagents has been related to the different positive charge density on carbons in the corresponding iodonium ion intermediates.

Finally, it is noteworthy that the addition of iodine azide to **3** leads mainly to the surprisingly stable tetrazido-substituted 2-tetrazene **74** (equation 76)[96]. The formation of **74** should start with the addition of IN_3 to the double bonds of **3**, giving four possible isomers. Under the applied conditions these compounds seem to be unstable.

Elimination of HI, which in the presence of an excess of IN_3 can form hydrazoic acid, followed by its addition to the vinyl azides can give an intermediate triazide **75**. The same compound could arise directly by substitution of one iodine atom by an azido group. The intermediate **75** has been considered to undergo a transannular reaction with homolytic cleavage of the weak C−I bond to form the radical **76**, which loses a nitrogen atom to a radical **77**. Combination of the two radicals leads to the 2-tetrazene **74** (equation 77).



(75)



(74)

(76)

Recent studies on iodination and iodochlorination of bicyclo[4.3.0]nona-3,7-diene **(78)** and its derivatives have shown that the reactions depend strongly on the presence and position of the methyl groups on the cyclohexene double bond and on reaction conditions. When I_2 reacted with *cis*-bicyclo[4.3.0]nona-3,7-diene the only product was *endo*-4-*exo*-8-diiodobrexane[84]. The addition of ICl or IBr to the same diene gives exclusively unrearranged products in an identical conformation, with the substituents in the six-membered ring in *trans*-diequatorial position (equation 78)[85].

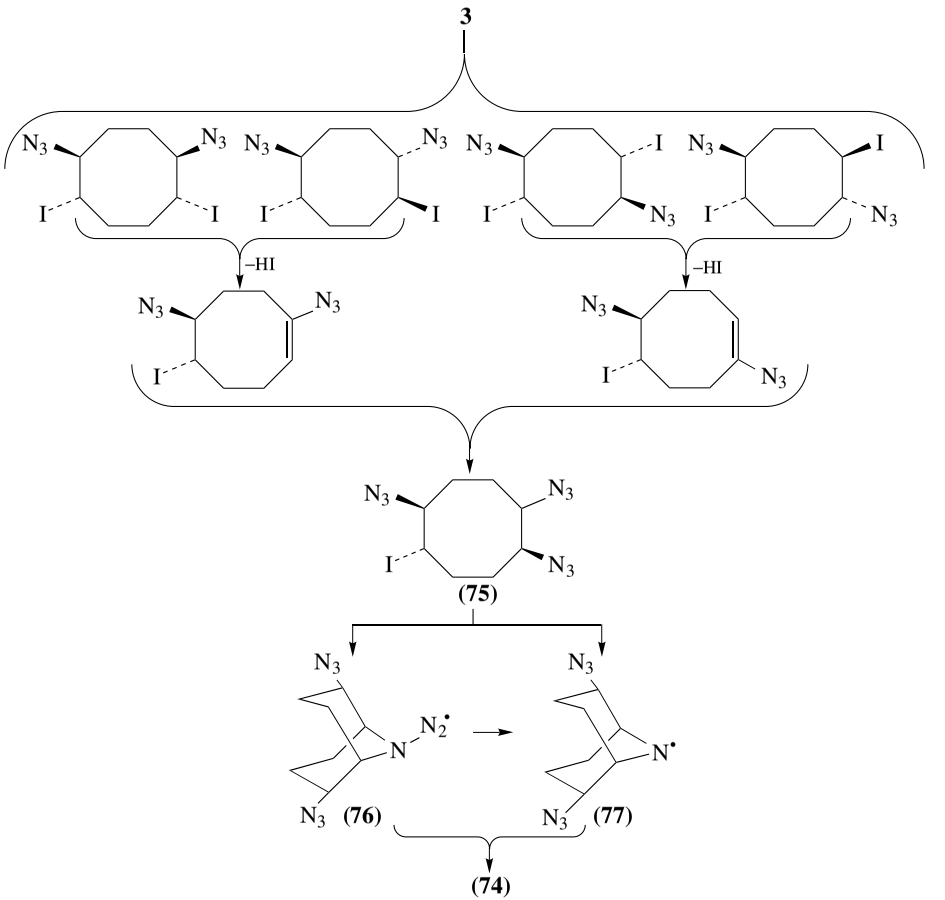
The presence of two methyl groups on C(3) and C(4) in **79** completely changes the product distribution. The addition of I_2 in CCl_4 leads to the tricyclic monoiodides *exo*-5-iodo-*exo*- and *exo*-5-iodo-*endo*-1,9-dimethylbrexanes (**80a** and **80b**)[97], differing in the configuration of the methyl group at C(9) (equation 79).

Since similar compounds are found in the reaction of the same diene with hydroiodic acid, it has been assumed that the monoiodides were formed by electrophilic addition of HI, which may be due to proton elimination from the first formed ion pair intermediate (equation 80).

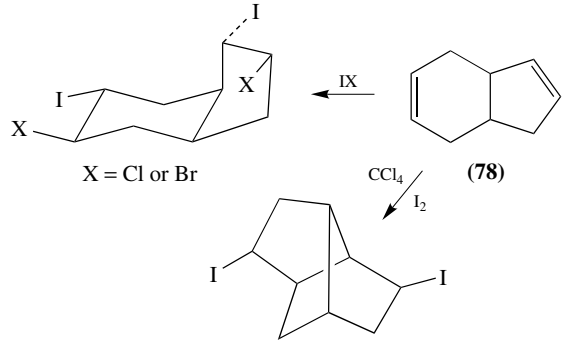
Steric factors during the nucleophilic attack have been invoked to explain the absence of addition products and the high tendency to undergo proton elimination.

The predominance of steric over electronic factors has been also used to explain the product distribution obtained by addition of I_2 in pyridine which takes place exclusively at the least substituted cyclopentene double bond of **79**. Under similar conditions the reaction of the unsubstituted diene **78** occurs by direct addition at the cyclohexene double bond[98].

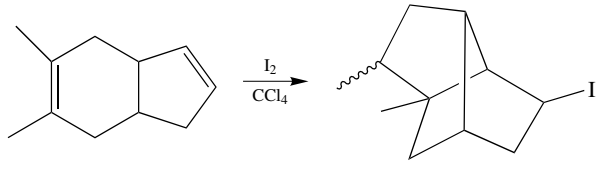
It is noteworthy that iodine addition in pyridine to **79** takes place regioselectively, with the iodine atom located exclusively in the product at C(7). Steric factors have been invoked again to explain the selectivity of the nucleophilic attack (equation 81).



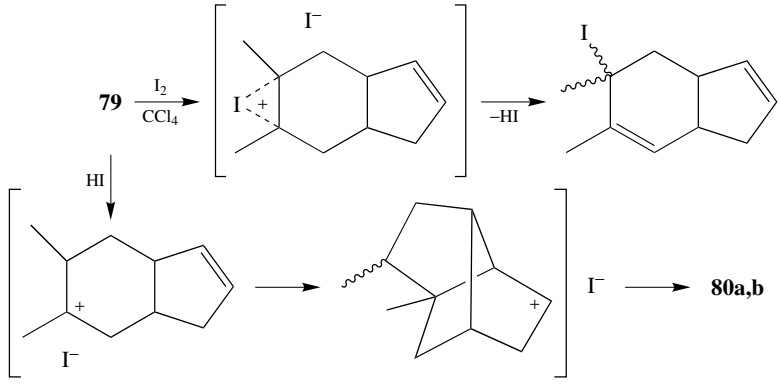
(77)


I
X
I
X
IX
X = Cl or Br
CCl4
I2
(78)

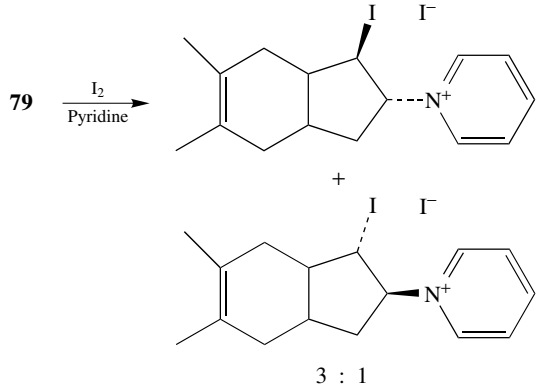
(78)


I2
CCl4
I
(79)
(80a,b)

(79)


79
I2
CCl4
I−
I
+
–HI
I
HI
+
I−
+
I−
80a,b

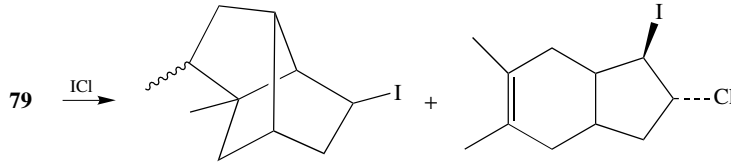
(80)


79
I2
Pyridine
I
I−
N+
+
I
I−
N+

(81)

3 : 1

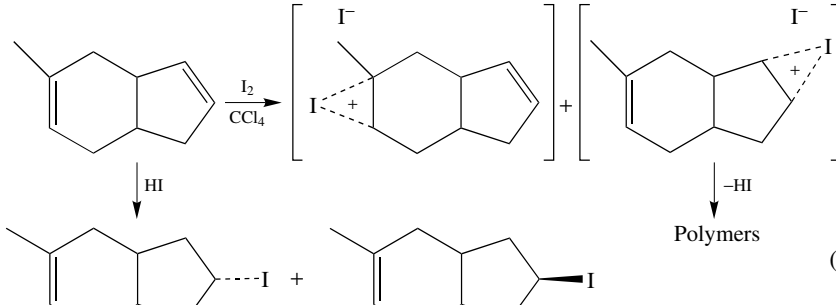
Finally, the addition of ICl gives a mixture of the tricyclic monoiodides **80a** and **80b** and of the product from addition of iodine and chlorine at the cyclopentene double bond (equation 82).



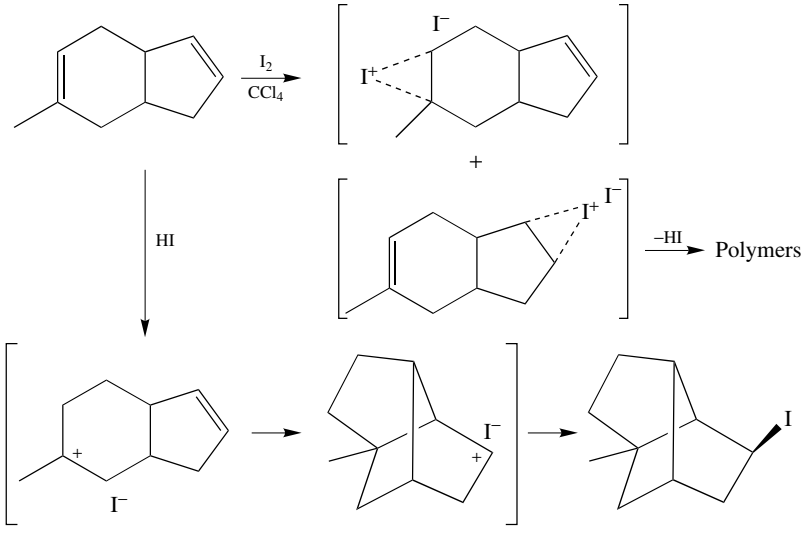
(82)

(80a,b)

By comparison, the direction of halogenation of monomethyl-substituted bicyclo[4.3.0] nona-3,7-dienes depends[99] considerably on the position of the methyl group. For a diene lacking a substituent at C(3), the reaction proceeds with retention of the initial structure (equation 83), whereas in the case of the 3-methyl substituted diene, it occurs through transannular cyclization giving a brexane type monoiodo derivative (equation 84).



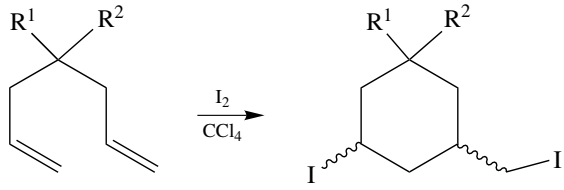
(83)



(84)

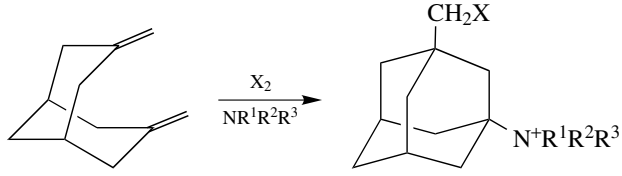
In both cases the electrophilic addition of HI, formed during the course of the reaction, is however the main pathway.

Reaction of iodine with non-conjugated dienes has been applied to the synthesis of cyclic compounds[100]. Although the reactions of 1,5-hexadiene, 1,6-heptadiene and 1,7-octadiene with I_2 in CCl_4 gave exclusively products arising from addition to the two double bonds, the introduction of dialkyl substituents into the 4-position of 1,6-heptadiene completely changed the reaction course in favor of cyclization (equation 85).



(85)

An easy cyclization arising from the intramolecular nucleophilic attack of the second double bond on the first formed intermediate has been also observed[101] in the reaction of 3,7-dimethylenebicyclo[3.3.1]nonane with iodine or bromine in the presence of amines. A series of halogenoadamantylammonium salts have thus been prepared in high yield and purity (equation 86).



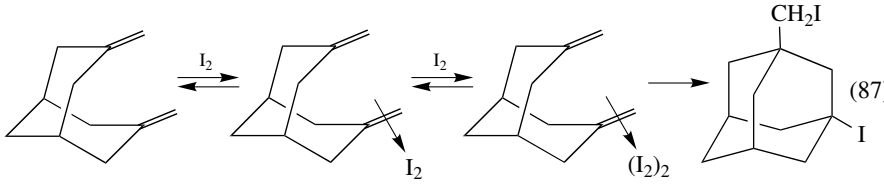
(86)

X = Br or I

$NR^1R^2R^3$ = pyridine, 2-methylpyridine, quinoline

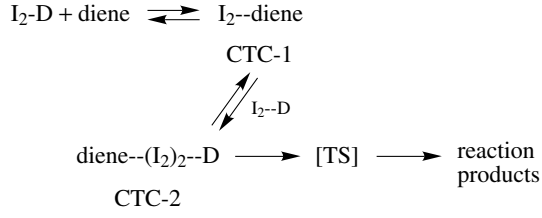
Although I_2 addition in non polar solvents generally follows a fourth-order rate law (third-order in iodine), the iodine addition in CCl_4 to this unconjugated diene is an overall third-order process (second order in halogen)[102–104]. Furthermore, a charge transfer band has been observed on mixing the reagents and the reaction rate is characterized by a negative temperature dependence and a large negative entropy of activation.

All these features have been initially interpreted[102–104] in terms of a molecular mechanism involving two successive alkene–iodine complexes of 1 : 1 and 1 : 2 stochiometries, the second of which evolves by internal nucleophilic attack of the uncomplexed double bond to the diiodo derivative (equation 87). The intramolecular attack of the second double bond has been regarded as rate determining, owing to the fact that the overall rate law is second order in iodine rather than the usual third order. Nevertheless, more



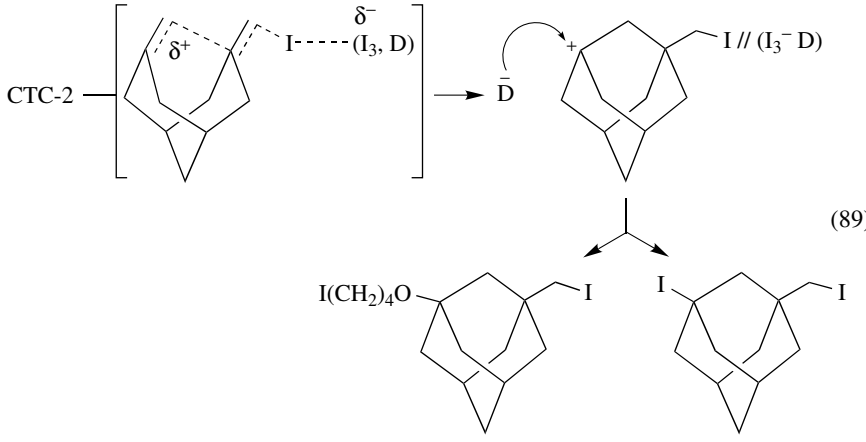
(87)

recently a molecular-ionic mechanism, characterized by a rate-limiting formation of an ion pair, has been suggested[105], in particular for transannular addition of iodine to 3,7-dimethylene- and 3-methylene-7-isopropylidenebicyclo[3.3.1]nonane in benzene, toluene, dioxane, diethyl ether and tetrahydrofuran. In all these solvents the reactions indeed follow a third-order rate law of the form $r = k_3[\text{diene}][I_2]^2$, with a reaction rate which is sensitive to both the electrostatic and electron-donor parameters of the medium. A reaction scheme involving the charge-transfer complexes CTC-1 and then CTC-2 which is additionally stabilized by one molecule of a donor solvent, D, has been proposed (equation 88).



(88)

The existence of an ion pair stabilized by a solvent molecule in the product-determining step of the reaction has been established by calculations and also supported by the product composition (equation 89). While the formation of the diiodo derivative is characteristic of all the cited solvents, in tetrahydrofuran this iodination takes place with the predominant formation of 1-iodomethyl-3-(4-iodobutoxy)adamantane (equation 89).



(89)

V. ELECTROPHILIC SULFUR AND SELENIUM

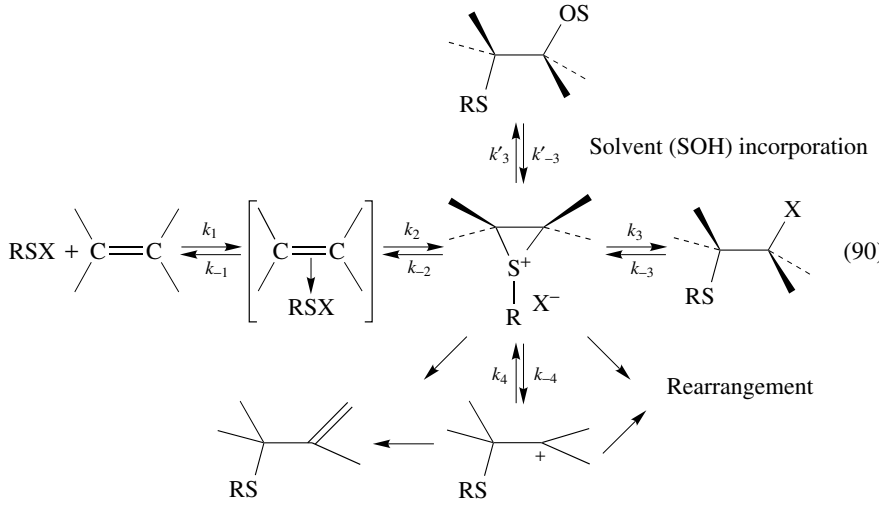
A. Sulfenyl Halides and Related Compounds

1. General aspects

Electrophilic addition of sulfenyl compounds at carbon–carbon double bonds, extensively studied and reviewed[2,4,7b,106], finds numerous synthetic applications owing to the regio- and stereoselectivity of the addition[2b]. The most common types of agents for the electrophilic addition of sulfur to double and triple bonds are sulfenyl halides (RSX,

ArSX), and among these the most used anionic carrier of the sulfenylium ions is the chloride anion[7b]. However, sulfenyl bromides have been also used[107] whereas iodides and fluorides are unstable although they can be prepared *in situ*[108,109]. Other sulfenylating agents include mixed anhydrides of the sulfenic acid such as sulfenyl sulfonates[110,111], triflates[112] and carboxylates[113]. Furthermore, the sulfenylium ion may be associated with basic anionic nucleophiles, such as in sulfenamides, disulfides, thiosulfinates, thiosulfonates and sulfenic esters[114]. Finally, the sulfenylium ion may be linked to a neutral and poorly nucleophilic sulfide or disulfide. Thiosulfonium and bis-thiosulfonium ions have been widely used as excellent sulfenylating agents[115].

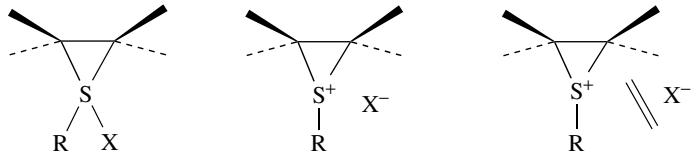
Sulfenyl chlorides and most of the other sulfenyl derivatives react with alkenes to give generally *anti* addition products with a high stereoselectivity. Although the mechanism of these reactions is still under study, it is usually accepted that sulfenyl transfer from the carrier to nucleophilic double bonds is consistent with the multistep mechanism reported in equation 90[7b].



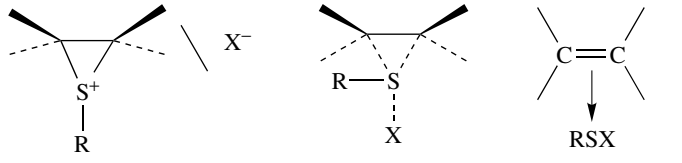
The regio-, stereo- and chemoselectivity of electrophilic additions of sulfenyl halides to alkenes, or reactions of preformed thiiranium ions with nucleophiles, as well as the role of solvent and 'doping' effect, have been interpreted by assuming the formation of a bridged intermediate characterized by different degrees of polarization of the S−Cl bond, depending on the reaction conditions[106]. In a general way it has been assumed that a continuum exists ranging from a completely covalent species, the sulfurane **81**, to the free ion **84**. Between these limits intimate and solvent-separated ion pairs (**82** and **83**, respectively) have been distinguished[2d].

The formation of the bridged intermediate has been represented as an S_N2-like displacement of the leaving group from the sulfenyl sulphur of **85**[116], or alternatively, as reported in equation 90 in agreement with the addition of other electrophiles to alkenes, it has been proposed that the reaction involves the initial formation of π-complex **86** in a rapid equilibrium with the reagents[7b].

As for the nature of the ionic intermediates, it is noteworthy that, independently of their representation, the bridged ions are not necessarily symmetrical species. The substituents at the ring carbons as well as at sulfur determine the amount of positive charge

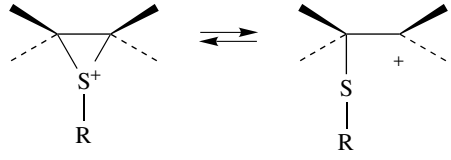


(81) **(82)** **(83)**



(84) **(85)** **(86)**

at this center and consequently on the ring carbons. Furthermore, the possibility of an equilibration of the bridged species with the open carbenium ion (equation 91) has been suggested[117].



(91)

As shown in equation 90, the ionic intermediate can follow several reaction routes. The product distribution is therefore controlled not only by the nature of the intermediate, whether bridged or weakly bridged, but also by association with its nucleophilic partner and by the rate ratios derived from the different reaction paths. All these factors depend on the alkene structure, the electrophile and the reaction conditions (solvent, added salts, temperature).

In agreement with the mechanism reported in equation 90, the reaction generally follows a second-order rate law (equation 92), first order in the sulfenyl halide and in the alkene, respectively.

$$dp/dt = k_{\text{obsd}}\ [\text{RSX}]\ [\text{Alkene}] \tag{92}$$

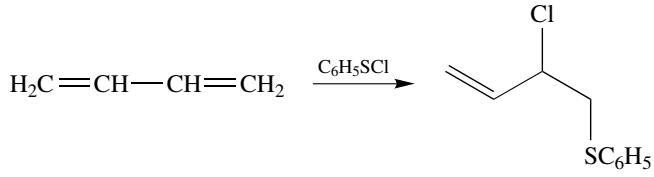
The alkene structure and the solvent polarity markedly affect the reaction rate. However, these effects are not easy to rationalize since, as shown in equation 90, one or more intermediates may be involved and each factor can influence the individual rate constants in a different way. It follows that only when the first step is rate determining can the observed rate constant k_{obsd} be interpreted straightforwardly.

2. Conjugated double bonds

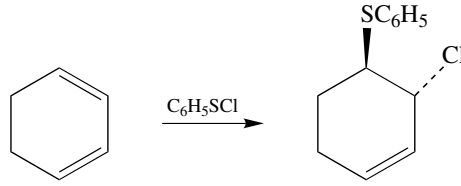
The sulfenylation of dienes as a distinct class of compounds has not been specifically reviewed, although several examples have been reported in early papers[2a,7b].

Generally, the addition of sulfenyl halides to conjugated dienes occurs, under kinetic control, at either double bond with *anti* stereospecificity to give 1,2-adducts with either

Markovnikov (M) or anti-Markovnikov (AM) regiochemistry (equation 93 and 94)[12]. A preferential attack of the electrophile on the least substituted double bond has often been observed[13]. The M adduct is the only one formed when the ionic intermediate has a high carbocationic character, and may be formed from bridged species when the nucleophilic step has a substantial S_N1 character. The AM product arises from an S_N2 process on the bridged intermediate.

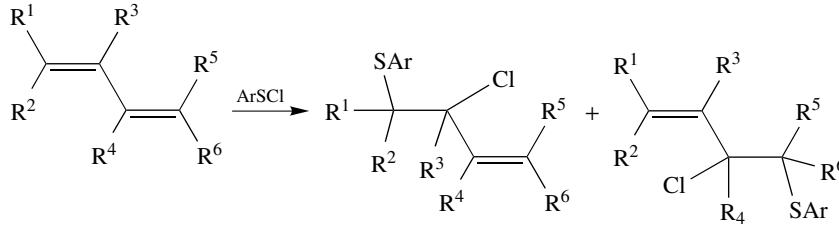


(93)



(94)

Except for the addition products to 1,3-butadiene, the initial products isomerize slowly to the 1,4-adducts[13]. Although small amounts of these compounds have been found among the addition of 4-chlorobenzenesulfenyl chloride to methyl substituted 1,3-butadienes (equation 95), it was not possible to establish whether they were formed under kinetic control or resulted from isomerization of the initially formed adducts. Therefore it is generally reported that arenesulfenyl chlorides react with dienes to give exclusively 1,2-adducts.

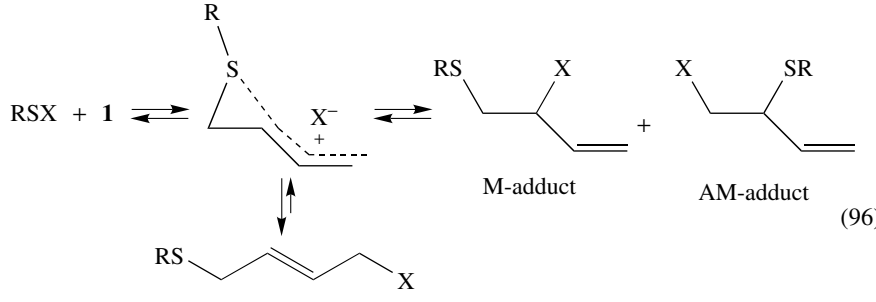


(95)

Kinetic studies carried out[12] on 1,3-butadiene and eleven of its methyl-substituted derivatives have shown that the addition of 4-chlorobenzenesulfenyl chloride in 1,1,2,2-tetrachloroethane to dienes follows the second-order rate law of equation 92. Furthermore, although substituent effects on rates and products are difficult to analyze quantitatively, owing to the presence of two possible sites of electrophilic attack, the authors concluded that the addition of arenesulfenyl chloride to 1,3-butadienes occurs through rate- and product-determining transition states resembling a thiiranium ion. The increase in rate caused by a methyl substituent on the β-double bond suggested charge delocalization in the rate-determining transition state and has therefore been considered as evidence for an unsymmetrically bridged transition state.

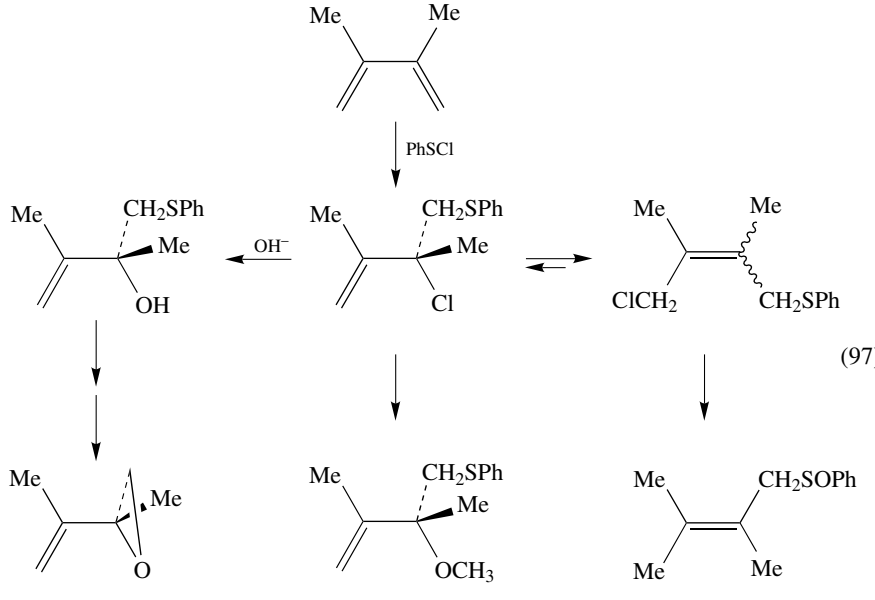
Finally, the possibility of obtaining 1,2- or 1,4-adducts, depending on reaction conditions, has been interpreted[2a], in agreement with the accepted mechanism of addition of

sulfenyl chlorides to alkenes, as reported in equation 96, as a classical example of kinetic vs thermodynamic control. The initially formed bridged but unsymmetrical ionic intermediate rapidly collapses to the 1,2-addition products. These compounds are, however, in equilibrium with the thiiranium chloride from which, through a slower reaction, the thermodynamically more stable 1,4-adduct may be formed.



(96)

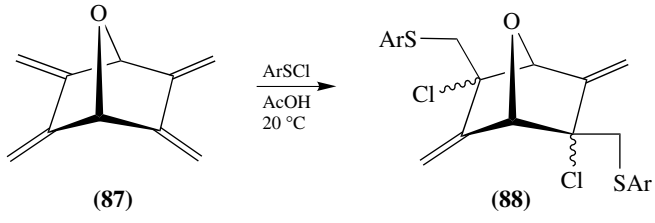
The possibility of obtaining, under kinetic control, a selective transformation of only one of the double bonds present in a dienic system, as well as the formation of 1,4-adducts under thermodynamic control, may find interesting applications. These two adducts may indeed be transformed into attractive synthetic intermediates, as shown in equation 97[118].



(97)

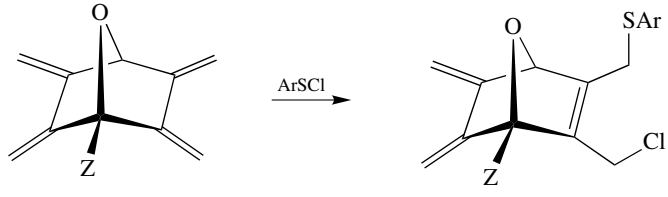
As far as the reactivity of polyenes is concerned, it is noteworthy that the stereochemistry of the addition of arenesulfenyl chloride to exocyclic tetraenes of type **87** depends on the substituent on the bridgehead carbon. The addition of arylsulfenyl chloride to the unsubstituted compound **87** proceeds with a high regio- and stereoselectivity[119]. This tetraene adds 2-nitrobenzenesulfenyl chloride to give exclusively the unstable bisadduct **88**, arising from a double 1,2-addition (equation 98)[120,121]. The regioselectivity of this

double addition has been interpreted in terms of either kinetic or thermodynamic control. The selectivity has been attributed in the former case, to a long-range effect of the monoadduct on the second electrophilic addition, and in the latter case it was attributed to the preferential stability of the bisadduct.



(87) **(88)** (98)

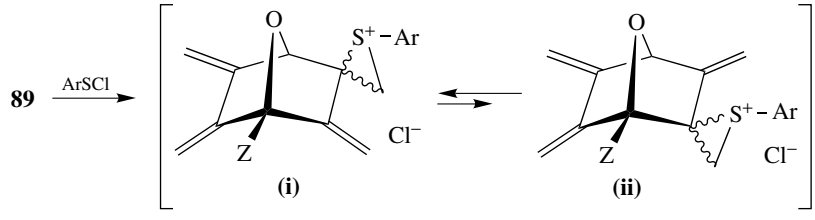
When an acetal moiety is introduced at one of the bridgehead centers, the reaction leads exclusively to a monoadduct[119]. In particular, in the presence of 1.5 equivalents of 2-nitrobenzenesulfenyl chloride, tetraene **89** gives a single derivative **90** corresponding to a 1,4-addition product (equation 99).



(89) **(90)** (99)

$Z = CH(OMe)_2$

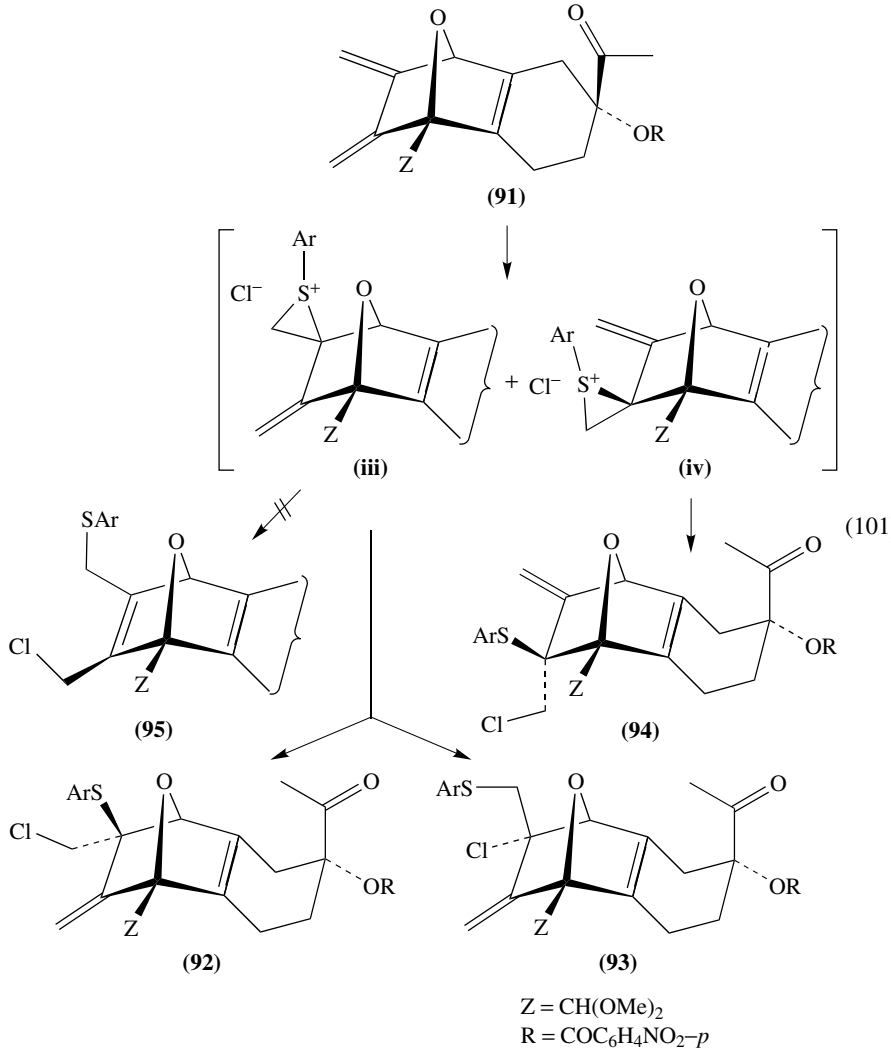
Although it was not possible to verify whether this product is formed under kinetic or thermodynamic control, the authors suggest[119] that if **90** arises from a kinetically controlled reaction, its formation could be rationalized on the basis of the stability of the involved intermediate. The bridged intermediate **i** is expected to be more stable than **ii** (equation 100) owing to the effect of the dimethoxymethyl substituent.



(100)

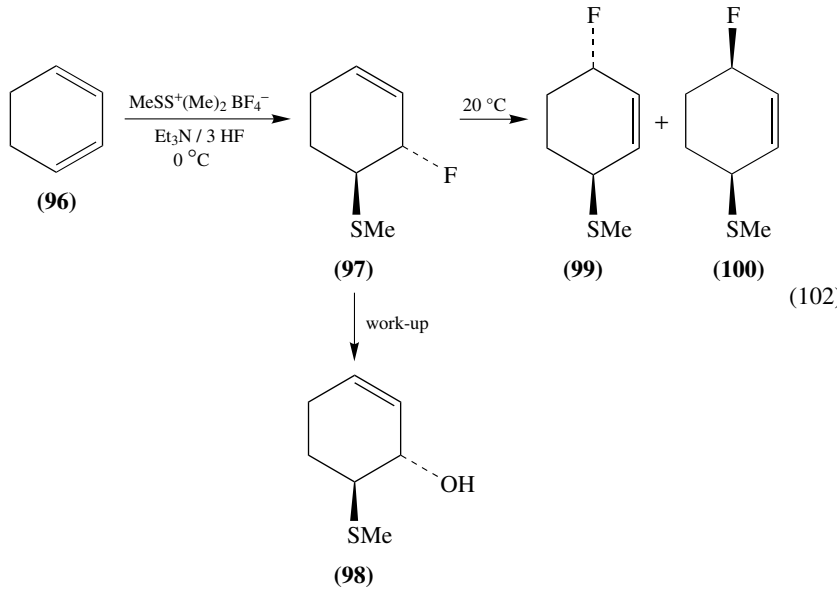
At variance with **89**, triene **91** gives a 17 : 51 : 31 mixture of monoadducts **92**, **93** and **94** (equation 101). This ratio does not change during the course of the reaction, indicating that these adducts are formed under kinetic control. The regioisomers **92** and **93**, corresponding to AM and M additions, may arise from a preferential electrophilic attack at the center remote from the electron-withdrawing acetal group, leading to the corresponding bridged thiiranium ion intermediate **(iii)** which is trapped by the chloride anion at the primary (giving **92**) or tertiary (giving **93**) carbon atom. Adduct **94** should

instead arise from the nucleophilic attack on the less stable intermediate **iv**. It is interesting to note that no 1,4-adduct **95** has been detected, in contrast with the stereochemical behavior of the reaction of tetraene **89**. This latter observation has been interpreted[119] in terms of enhanced strain, larger in bicyclo[2.2.1]hepta-2,5-diene derivatives than in 5,6-dimethylidenebicyclo[2.2.1]hept-2-ene systems. The increased strain could reduce the rate of transformation of intermediate **iii** into **95**, or make it unstable.



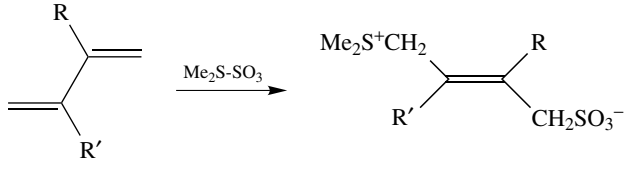
Sulfenyl fluorides are extremely unstable and therefore only few perhalosulfenyl fluorides have so far been reported[122]. The formal addition of the elements of methanesulfenyl fluoride to carbon–carbon double bonds has been obtained[123] by a one-pot reaction with dimethyl(methylthio)sulfonium tetrafluoroborate and triethylammonium tris(hydrofluoride). With this system also the addition to double bonds is highly stereoselective, at least

under kinetic control. With 1,3-cyclohexadiene **(96)**, *trans*-3-fluoro-4-(methylthio)cyclohexene **(97)** was found as the sole fluorinated product after 40 min at 0 °C, accompanied by 20% of **98**, which was formed during the work-up. Allylic rearrangement, giving the 1,4-adducts **99** and **100**, was reported only as a minor process when the reaction was continued for 4 h at 20 °C (equation 102).



(96) **(97)** **(99)** **(100)** **(98)** (102)

The complexes of sulfur trioxide with various nucleophiles (dioxane, pyridine etc.) are mild sulfonating reagents. Unlike other complexes of sulfur trioxide, dimethyl sulfide–sulfur trioxide readily adds to conjugated multiple bonds. Consequently, not only the sulfo group but also the dimethyl sulfide group add at the multiple bond. The reactions of dimethyl sulfide–sulfur trioxide complex with butadiene, isoprene and 2,3-dimethylbutadiene take place as conjugated 1,4-*E*-additions of dimethyl sulfide and sulfonate groups at the double bonds of the diene (equation 103).[124]

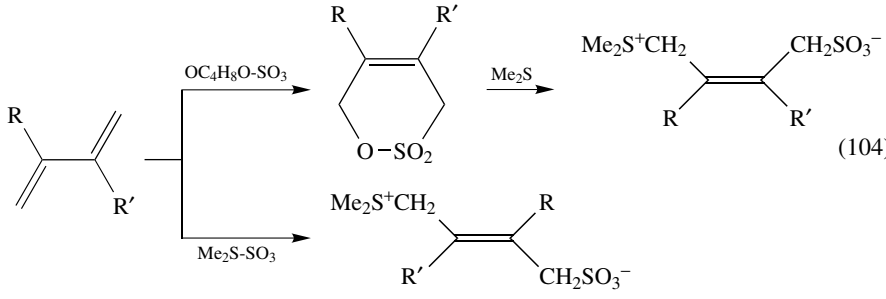


(103)

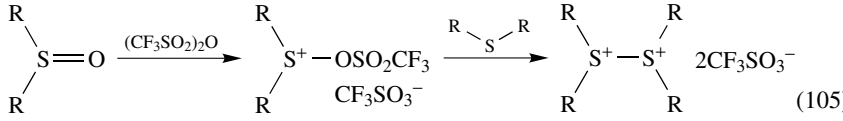
Cyclopentadiene forms a mixture of the 1,2- and 1,4-adducts in equal proportions. However, the 1,2-isomer rearranged completely into the thermodynamically more stable 1,4-isomer after prolonged standing in the solvent (alcohol or dichloroethane).

The different stereochemical outcome observed in the opening of sultones by the action of dimethyl sulfide and by that of $Me_2S–SO_3$ complex with the conjugated alkadienes has been considered as evidence against the intermediate formation of the sultones in the

latter reaction (equation 104).



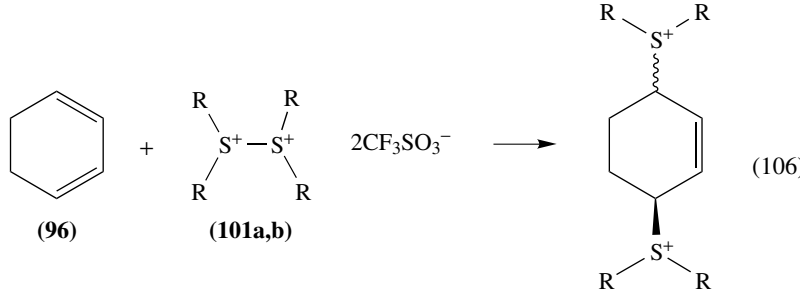
Unusual electrophilic compounds containing sulfur are the S^+-S^+ dications[125]. The reaction of dimethyl sulfide ditriflate with dimethyl sulfide leads to the formation of tetramethyldisulfonium ditriflate **(101a)**. The same procedure starting from tetrahydrothiophene ditriflate gives by reaction with tetrahydrothiophene the corresponding dication **101b** (equation 105).



(101a,b)

(a) $R = CH_3$; **(b)** $RR = -(CH_2)_4-$

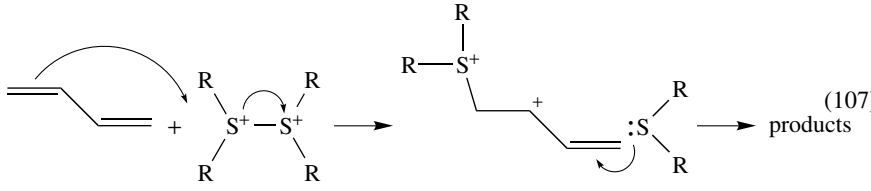
These dications react with alkenes to give 1,2-disulfonium salts, and with conjugated dienes to afford 1,4-adducts. Furthermore, while 1,4-disubstituted linear dienes yield complex mixtures of unidentified substances, 1,3-cyclohexadiene **(96)** produces a moderately stable salt **102** (equation 106). The formation of the kinetically controlled 1,2-addition product has never been observed.



(96) **(101a,b)** **(102)**

In view of the stereochemical behavior in the additions to alkenes and dienes, the authors suggest that the reaction proceeds via a stepwise electrophilic addition[126]. However, in this case the two sulfur atoms of the dithioether dication are positively charged. In the reaction with multiple bonds, therefore, one of these sulfur atoms should be an electrophilic center whereas the other one should simultaneously be a nucleophilic center. In

agreement with the generally accepted mechanism for an Ad_E path, this reaction should be a conjugated addition of a doubly charged sulfur electrophile (S^{+2}) and of a sulfide acting as nucleophile. The authors, however, believe that it is more correct to view this reaction as a nucleophilic substitution at the sulfur atom. The first step should therefore be the substitution of the sulfide moiety by the double bond to give a carbocation intermediate, followed by the trapping of the carbocation by the formed sulfide (equation 107).

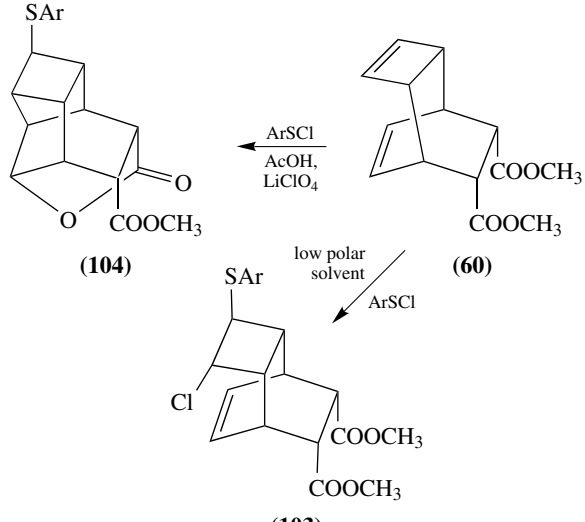


(107)

The possibility of trapping of the carbocation by a triflate anion followed by substitution of the triflate group by sulfide has also been suggested[126], at least for the addition of bicyclic dithioether dications to alkenes and alkynes.

3. Non-conjugated double bonds

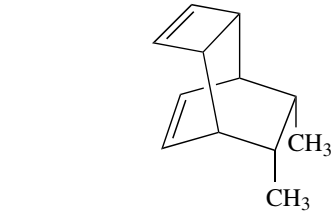
The addition of electrophilic reagents to tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives can give, depending on the electrophile or reaction conditions, products arising exclusively from *syn* or *anti* addition to the strained cyclobutene double bond, or involving transannular cross type participation of the second carbon–carbon double bond[127,128]. In particular, the addition of methanesulfenyl or aryl sulfenyl chlorides to diester **60** in non-polar solvents leads to the formation of the *anti* 1,2-addition product **103**, whereas the addition under 'doping conditions' ($AcOH + LiClO_4$) produces the cage δ-lactone **104** (equation 108)[128].



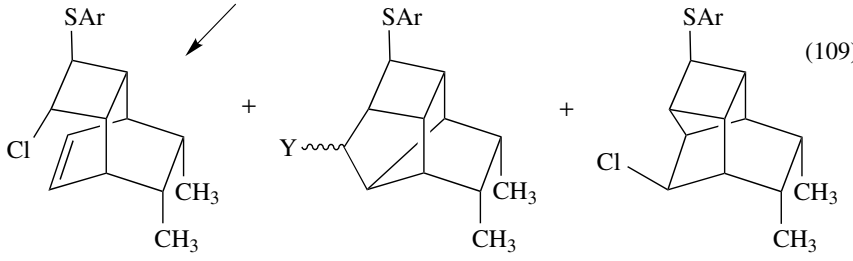
(108)

The addition of arylsulfenyl chlorides under doping conditions has also been investigated[127] with other compounds of this series where structural features did not permit lactone ring closure and therefore allowed other skeletal transformations.

Compound **62** on treatment with 2,4-dinitrobenzenesulfenyl chloride in acetic acid gave a mixture of compounds **105**, **106a**, **106b** and **107**, but in the presence of $LiClO_4$ only compounds **106a** and **106b** were isolated. On the other hand, the addition of ArSCl in an apolar solvent (CCl_4) yielded exclusively the *anti* addition product **105** (equation 109).



(62)



(109)

(105) **(106)** **(107)**

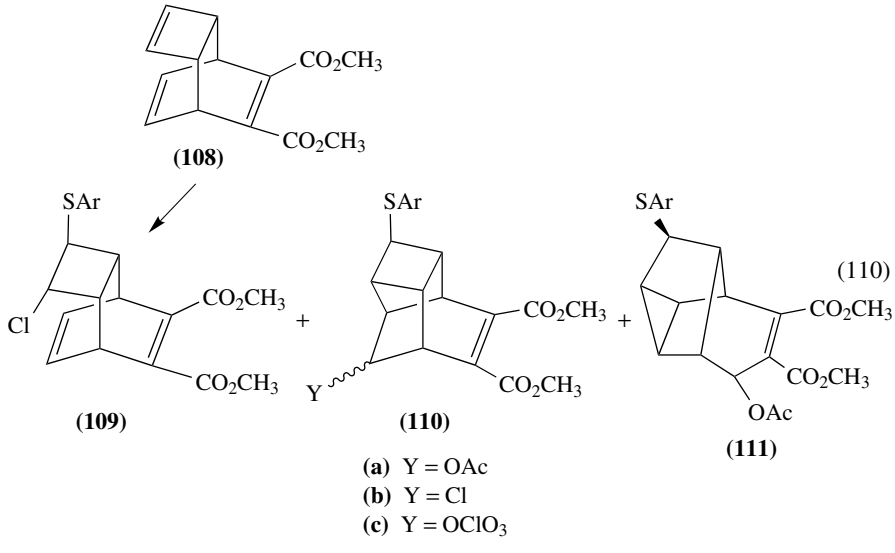
Ar = 2,4-$(O_2N)_2C_6H_3SCl$ **(a)** Y = OAc **(b)** Y = Cl

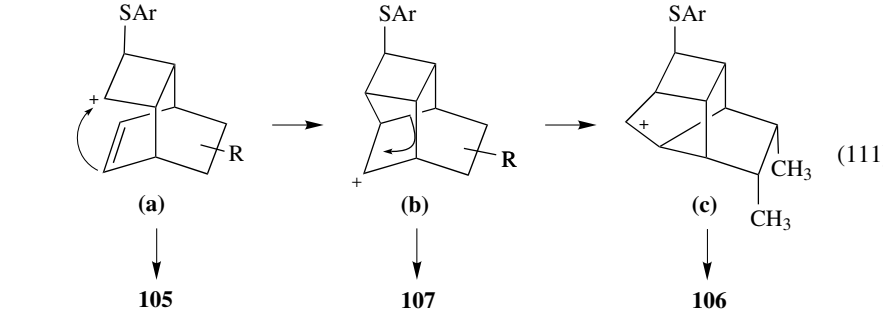
Similarly, compound **108** gave only the *anti* addition product **109** in CCl_4 and a mixture of compounds **109**, **110** and **111** in AcOH (equation 110). In the presence of $LiClO_4$ once again the 1,2-addition product was absent.

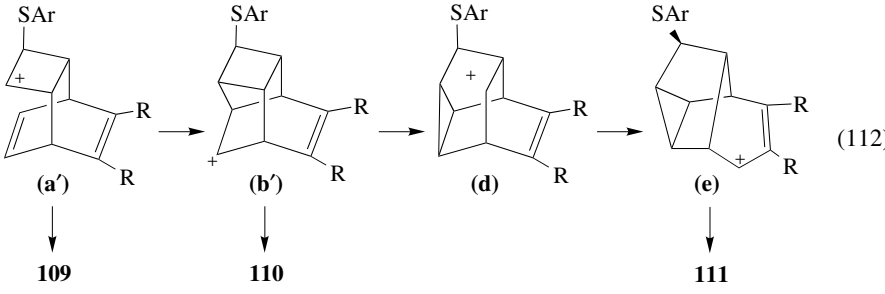
The change in solvent polarity thus leads to an appreciable variation in product composition, which is further changed under doping conditions. In the presence of $LiClO_4$ the products indeed arise exclusively from skeletal rearrangements and incorporation of external nucleophiles, solvent and perchlorate anion. The formation of ClO_4^--incorporated products can be increased by carrying out the reaction in non-nucleophilic solvents[129].

Skeletal rearrangements and incorporation of external nuclophiles were interpreted in terms of an ionic mechanism involving carbenium ions. Taking into account the structural features of the rearranged products, the authors propose[127] a reaction course involving an initial *exo* attack of the electrophile on the cyclobutene double bond. The primarily formed carbenium ions **a** or **a′**, arising respectively from **62** or **108**, which for the sake of simplicity are represented in the original work and in this review as pure carbenium ions, interact in a transannular fashion with the proximal double bond of the six-membered ring to give new cationic species, **b** or **b′**. The trapping of the latter intermediates gives **105**, **109** and **107** and **110**, respectively. However, both **b** and **b′** may undergo additional rearrangements, 1,2-shift of the C(2)−C(7) bond in diene **62** to give a cationic structure

of type **c**, affording compound **106**, or two subsequent 1,2-shifts of the C(8)−C(10) and C(5)−C(6) bonds in triene **108** which give, through intermediate **e**, compound **111** (equations 111 and 112).



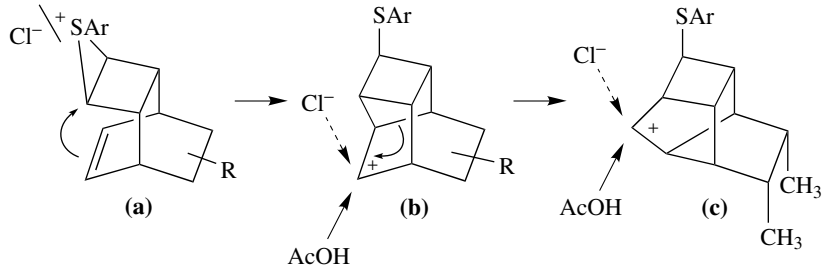




The different pathways followed by the two intermediates **b** and **b′** have been rationalized by assuming a possible participation of the third substituted double bond in the stabilization of the developing cationic center at C(10) in **d**.

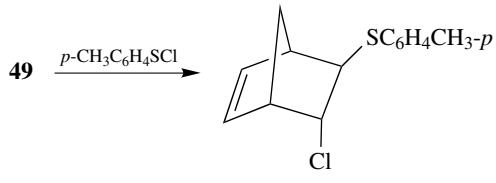
With this mechanistic scheme, the chemoselectivity of the addition and the formation of rearranged chlorides (but not acetates) have been chosen as criteria to differentiate the ion pair mechanism from the purely ionic one and, on the basis of both criteria, the authors suggest the involvement of a tight ion pair for the addition of ArSCl in AcOH to diene **62** and of solvent separated ion pairs to triene **108**. The effects related to the presence of added electrolytes, which favor the formation of rearranged acetates, have been considered in this work[127] as evidence that even a larger separation of ions, which should lead to more electrophilic species, is possible.

The involvement of ion pairs in the addition process has also been related to the stereochemical behavior. The remarkable difference in configuration between the rearranged chlorides and acetates has been rationalized, as shown in equation 113, on the basis of a *syn* internal attack of Cl^- on ion **c** and *anti* external attack of AcOH from the solvent pool.



(113)

The concept of stereocontrol by the ion pair mechanism in the electrophilic additions of sulfenyl chlorides has been further discussed[127] by Zefirov, using norbornadiene **(49)** as a substrate. The addition of sulfenyl chlorides to **49** has been reported to give a product distribution markedly dependent on the sulfenylating agent. In particular, it has been observed[129] that the addition of *p*-toluenesulfenyl chloride gives only the *anti* 1,2-addition product **112** (equation 114), whereas the addition of 2,4-dinitrobenzenesulfenyl chloride (DNBSC) yields, beside the 'normal' and 'inverted' *trans*-1,2-adducts, **112** and **113**, the single nortricyclic chloride **114** through homoallylic participation. Furthermore, when the reaction is carried out in the presence of $LiClO_4$, the addition of nitro- or dinitrobenzenesulfenyl chloride proceeds with the participation of the second double bond, giving the isomeric acetates **115** and **116** (equation 115).

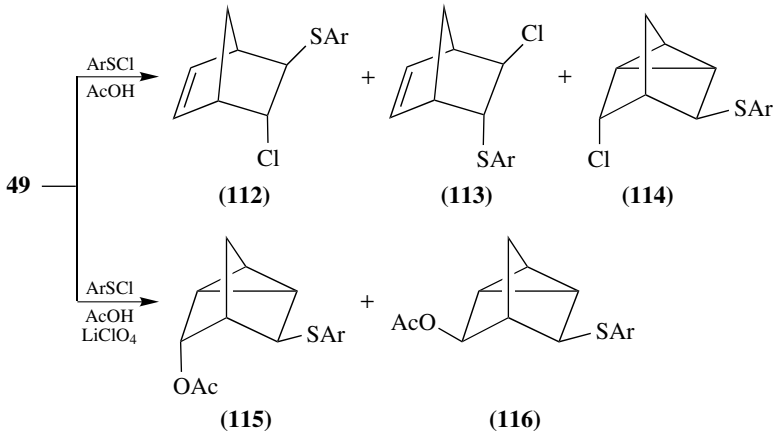


(112)

(114)

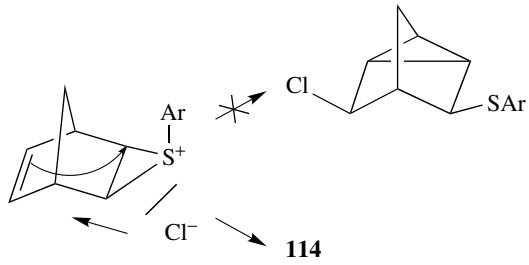
The non-stereospecific attack by nucleophiles has been regarded[127] as evidence for the involvement of a carbocation-like intermediate. The *endo* configuration of **114** has been attributed to the ion pair mechanism reported in equation 116, which should preclude the

formation of the product arising from an *exo* attack of the chloride anion.



(115)

Ar = 2,4-$(O_2N)_2C_6H_3SCl$

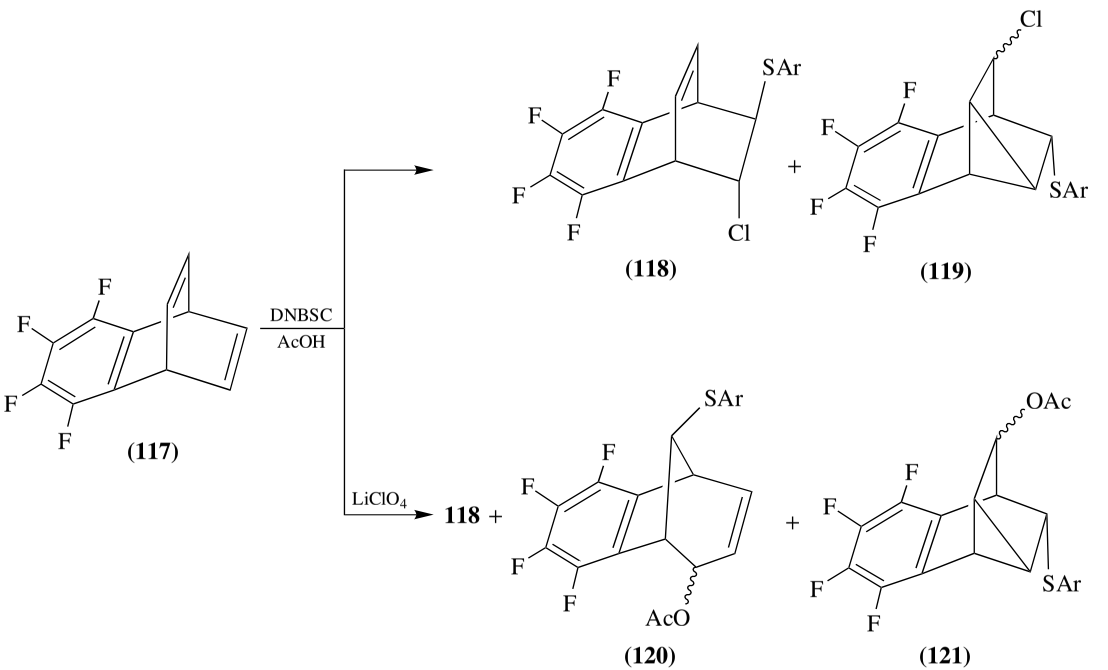


(116)

A dependence of the product distribution on $LiClO_4$ concentration has also been observed[130] in the addition of DNBSC to tetrafluorobarrelene (**117**). In the absence of added $LiClO_4$ this reaction gives the adduct **118** accompanied by a small amount of **119** (<2% yield). In the presence of $LiClO_4$ the products are chloride **118**, a mixture of the two isomeric acetates **120** and the tricyclic acetates **121** (equation 117). At high salt concentrations (0.2–0.25 M), the formation of the acetates **120** is dominant. Furthermore, a sharp non-linear increase in the content of doping-addition products at low concentrations of salt, followed by a more moderate increase at higher concentrations, has been observed[130].

Although the influence of $LiClO_4$ on the product distribution could be interpreted, in analogy with solvolysis, in terms of a 'special salt effect' which could be shown by internal return suppression at the stage of solvent separated ion pairs resulting from exchange between the ion pair counterion and ClO_4^-, the authors reject this interpretation on the basis of kinetic measurements. The addition of $LiClO_4$ indeed produces a significant acceleration of the reaction, which follows the equation for 'normal salt effect'. While underlining that the 'special salt effect' is kinetic in nature, whereas the 'doping addition' emphasizes products, the authors propose[130] a very similar mechanism (equations 118 and 119) for the doping effect to that reported for the special salt effect.

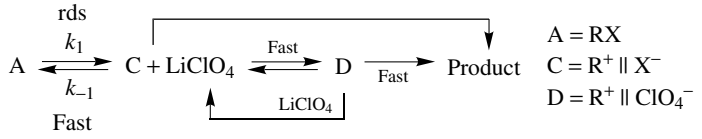
In both cases the product distribution is affected by the trapping of the first formed intermediate by the salt, but this trapping in the case of doping addition does not influence


F
F
F
F
(117)
DNBSC
AcOH
LiClO4
118 +
F
F
F
F
SAr
Cl
(118)
+
F
F
F
F
Cl
SAr
(119)
F
F
F
F
SAr
AcO
(120)
+
F
F
F
F
OAc
SAr
(121)

(117)

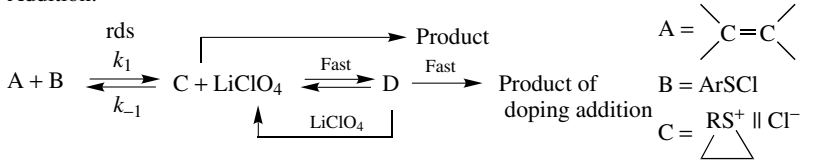
the total rate. The absence of the 'special' increase in rate therefore leads the authors to conclude that the reverse process, measured by k_{-1}, is relatively unimportant and the A + B → C transformation may be regarded as a non-reversible rate-limiting step. As remarked by the same authors, however, it is not possible to generalize this latter statement since the olefin structure and other factors can indeed markedly affect the return.

(a) Solvolysis:



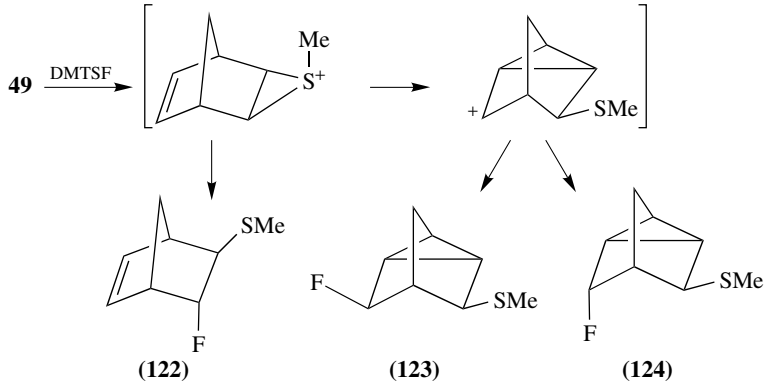
(118)

(b) Addition:



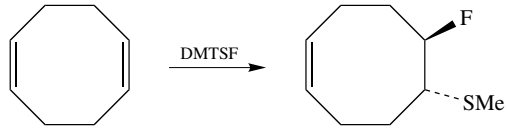
(119)

Finally, in contrast to the reactions reported above, **49** reacts[131] with dimethyl(methylthio)sulfonium fluoroborate (DMTSF) and triethylamine tris(hydrofluoride) in dichloromethane to give only 5% of the 1,2-addition product **122**. The main products, present in 73 : 27 ratio, are the *exo-exo* and *endo-exo* adducts **123** and **124**, formed by exclusive *exo* attack of the electrophile on the double bond, followed by transannular π-participation in the intermediate bridged cation and final addition of fluoride to the nortricyclic cation from both the *exo* or *endo* side (equation 120).



(120)

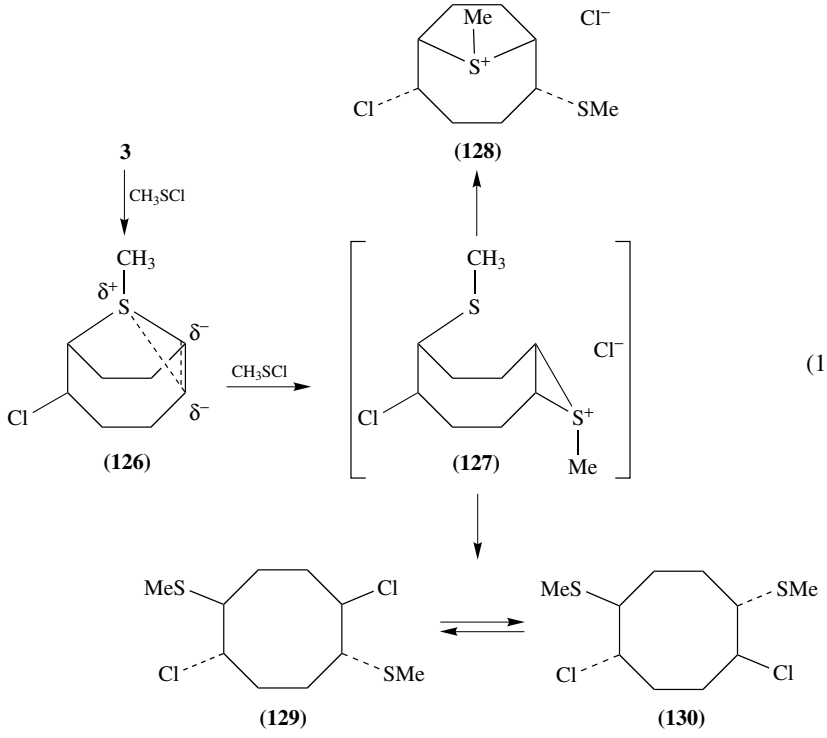
On the other hand, the addition of the same reagent to 1,5-cyclooctadiene **(3)** yields *trans*-5-fluoro-6-(methylthio)cyclooctene **(125)** as the sole product, without participation of the second double bond (equation 121).



(3) (125) (121)

Simple 1,2-additions to this compound have been observed[123,131,132] also in other sulfenylation reactions, and in other electrophilic additions involving strongly bridged intermediates. Although these results have been interpreted as evidence that additions of sulfenyl halides to symmetrical alkenes do not involve open carbenium ions before the product-determining step, the different behavior observed in the case of **49** suggests[123] that close proximity is necessary to have transannular participation of π-bonds, at least in additions of sulfenyl derivatives and of some other electrophiles carried out in the presence of efficient nucleophiles.

Finally, it is noteworthy that the reaction of methanesulfenyl chloride with **3** gives about 80–90% of the diadducts **128**–**130**, and only 8–13% of monoadduct **126**[20]. The remarkable propensity of **126** for diadduct formation has been attributed to the activation of the second double bond through a transannular overlapping of the sulfur orbitals with the π bond. Addition of the second mole of methanesulfenyl chloride probably involves an intermediate of type **127**. Attack by chloride ion on **127** gives compounds **129** and **130**. More interestingly, intramolecular ring opening by the methylthio group produces salt **128** (equation 122).



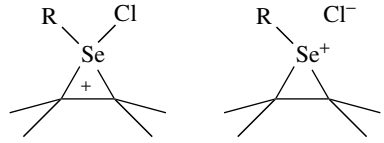
(122)

B. Selenenyl Halides and Related Compounds

1. General Aspects

The reaction of electrophilic selenium reagents with alkenes and alkynes has already been the subject of several reviews and mechanistic studies[2a,133]. Generally, the reactions involve selenic (Se^{II}) compounds; reactions of Se^{IV} were less extensively studied. Aryl, rather than alkyl, selenium derivatives are used in electrophilic reactions because of their lower volatility and toxicity. Diphenyl selenide (PhSeSePh) can be readily converted into benzeneselenenyl chloride or bromide by reaction with chlorine or bromine. These reagents can be further converted into useful Se^{II} electrophiles such as PhSeOAc, $PhSeN_3$, PhSeCN and $PhSeSO_2Ar$. In some cases these reagents can be isolated; in others they have been prepared and used *in situ* (PhSeF). The least reactive derivatives, such as PhSeSePh or $PhSeSO_2Ar$, require an appropriate coreagent such as strong protic or Lewis acids.

Areneselenenyl halides react with double bonds similarly to sulfenyl derivatives: 1,2-additions are generally *anti* stereospecific, in agreement with the involvement of a bridged intermediate [episelenurane **(a)** and/or seleniranium ions **(b)**], prior to the product-forming step.



(a) **(b)**

The regiochemistry of the addition depends on temperature and solvent. At low temperatures, under kinetic control, the AM products are favored while at room temperature or above, under thermodynamic control, the M adducts are generally formed.

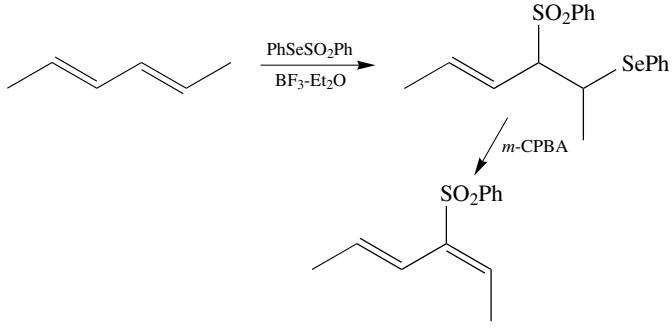
2. Conjugated double bonds

The addition of selenenyl derivatives to olefins has been shown to be of mechanistic interest and synthetic utility because of the versatility of the selenium functionalities[2a,133]. The possibility of modifying double bonds with seleno derivatives has been applied also to conjugated systems in order to obtain arylseleno dienes, or electron-deficient dienes, both being useful synthetic intermediates or building blocks.

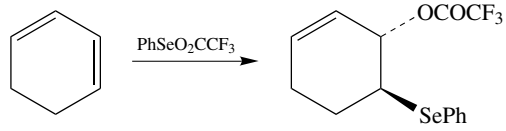
Selenosulfonylation of olefins in the presence of boron trifluoride etherate produces chiefly or exclusively M products arising from a stereospecific *anti* addition, from which vinyl sulfones can be obtained by stereospecific oxidation–elimination with *m*-chloroperbenzoic acid[134]. When the reaction is carried out on conjugated dienes, with the exception of isoprene, M 1,2-addition products are generally formed selectively from which, through the above-reported oxidation–elimination procedure, 2-(phenylsulfonyl)-1,3-dienes may be prepared (equation 123)[135]. Interestingly, the selenosulfonylation of butadiene gives quantitatively the 1,4-adduct at room temperature, but selectively 1,2-adducts at 0 °C. Furthermore, while the addition to cyclic 1,3-dienes, such as cyclohexadiene and cycloheptadiene, is completely *anti* stereospecific, the addition to 2,4-hexadienes is non-stereospecific and affords mixtures of *erythro* and *threo* isomers. For both (*E*,*E*)- and (*E*,*Z*)-2,4-hexadienes, the *threo* isomer prevails if the reaction is carried out at room temperature.

An *anti* stereospecific addition to 1,3-cyclohexadiene **(96)** has been observed also with benzeneselenenyl trifluoracetate (prepared by treatment of benzeneselenenyl bromide or

chloride with silver trifluoroacetate) which gives predominantly the *trans*-1,2-addition product **131** (equation 124). The small amount of a 1,4-adduct formed under these conditions[136] has been attributed to the lability of the first formed 1,2-adduct **(131)**.



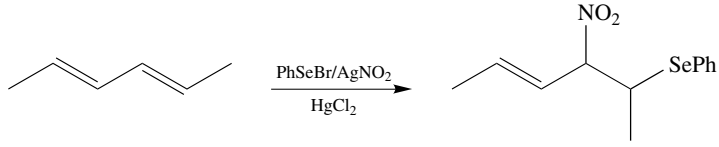
(123)



(124)

(96) **(131)**

The stereo- and regiospecific nitroselenylation of one of the double bonds of conjugated dienes was instead achieved by the addition of $PhSeBr/AgNO_2$ in the presence of $HgCl_2$ (equation 125)[137]. In all the examined cases 1,2-monoadducts with selenium in the 1-position were formed, the addition to (*E*,*E*)- and (*E*,*Z*)-2,4-hexadiene affording *erythro*- and *threo*-adducts respectively, showing that with this reagent the reaction exhibits a complete *anti* stereospecificity. Cyclic dienes, of course, give *trans*-adducts.



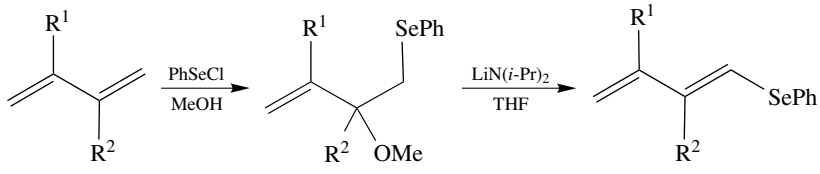
(125)

At variance with selenosulfonylation, however, attempts to prepare 2-nitro-1,3-dienes by oxidative elimination of selenium from the nitroselenylated products failed, probably owing to the lability of the products, which easily undergo further transformations. The expected 2-nitro-1,3-dienes have indeed been trapped as monoepoxy derivatives.

Finally, it has been shown that methoxyselenylation of conjugated dienes followed by treatment with lithium di-isopropylamide can be a convenient method for the preparation of 1-phenylseleno-1,3-dienes and their methyl-substituted homologues **134** (equation 126)[138].

With benzeneselenenyl chloride in methanol, Markovnikov-type 1,2-addition products **133a–d** are obtained in excellent yields. When isoprene is used as the conjugated diene, a mixture of two regioisomers **133b** and **133c** is formed. The main product is **133b** in the reaction at room temperature for 2 h, and **133c** when triethylamine is added to the reaction mixture. It is noteworthy that, as the above reported data show, although selenenyl halides react with alcohols to give the corresponding esters, the reaction of selenenyl chloride with methanol is generally much slower than its addition to a double bond. The comparison of

the rate constant $k_2 = 0.011\ M^{-1}\,s^{-1}$ for the reaction of benzeneselenenyl chloride with methanol with the rate constant $k_2' = 489\ M^{-1}\,s^{-1}$ for its reaction with ethylene gives a quantitative measurement of this reactivity difference, and indicates that the π orbital of a carbon–carbon double bond is a more efficient nucleophile than the oxygen of an alcohol in the nucleophilic displacement at bivalent selenium.

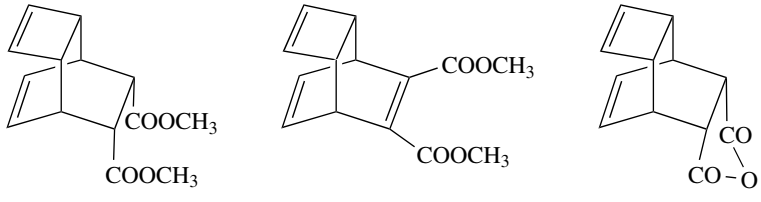


(132) **(133)** **(134)** (126)

(a) $R^1 = R^2 = H$
(b) $R^1 = Me$, $R^2 = H$
(c) $R^1 = H$, $R^2 = Me$
(d) $R^1 = R^2 = Me$

3. Non-conjugated double bonds

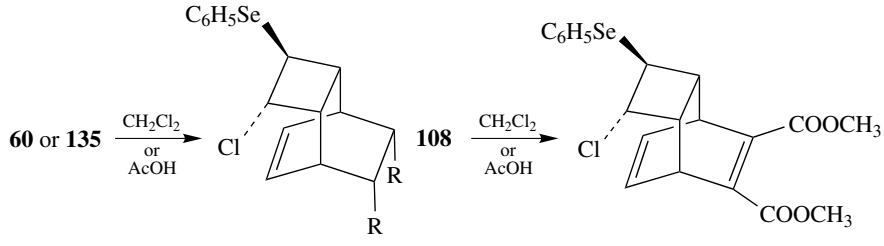
The addition of benzeneselenenyl chloride to strained tricyclo[4.2.2.0^{2,5}]deca-3,7-dienes **60**, **108** and **135** has been investigated in four media: methylene chloride, acetic acid, acetic acid/$LiClO_4$ and methanol[139]. Under conditions of kinetic control, only products of *exo-anti* attack, **136**–**138**, on the cyclobutene moiety are found both in methylene chloride and in acetic acid (equation 127), although during the course of the reaction of benzeneselenenyl chloride with **135** an *exo-syn* adduct, **139**, was observed as a transient product. The same results have also been obtained in acetic acid in the presence of $LiClO_4$, under 'doping conditions', except when the reaction was carried out on the tricyclotriene **108**, which gave as major product the cross-bonding adduct **140** arising from solvent incorporation (equation 128).



(60) **(108)** **(135)**

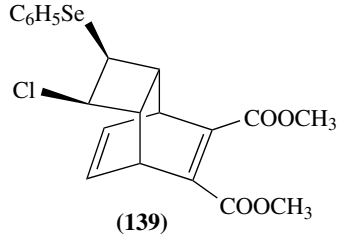
It is noteworthy that **108** reacts in AcOH with benzenesulfenyl chloride to give a 1 : 1 mixture of the sulfur analogues of **138** and **140**, but when the reaction is carried out in the presence of $LiClO_4$ a complex mixture of at least five products was detected. From this comparison the authors suggest that areneselenenylation is much less affected by the solvent than arenesulfenylation, and if the reaction profiles for the two product-forming processes are assumed to be similar, the difference in product distributions can be interpreted in terms of a more efficient bridging ability of selenium than that of sulfur. In the addition of selenenyl derivatives, the solvent-dependent product distribution has also

been rationalized in terms of an ion pair mechanism. A solvent polarity-dependent competition between bridged ionic intermediates, such as the seleniranium intimate ion pair **141**, which should give the *anti* 1,2-addition products by collapse before π-transannular participation, and a more loosely associated species, such as solvent-separated ion pairs **142**, the dissociated species **143** and the free carbenium ions **144**, more susceptible to give rearranged products, has been proposed (equation 129).

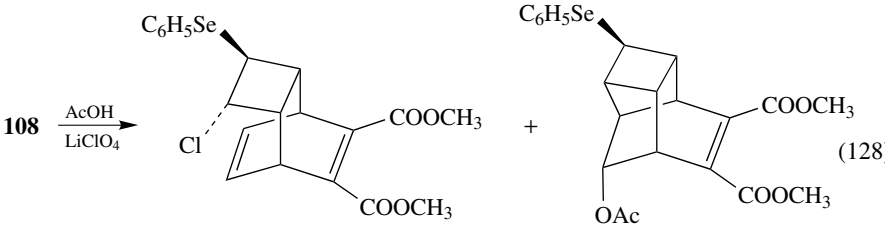


(136) R = $COOCH_3$
(137) RR = COOCO

(138) (127)



(139)

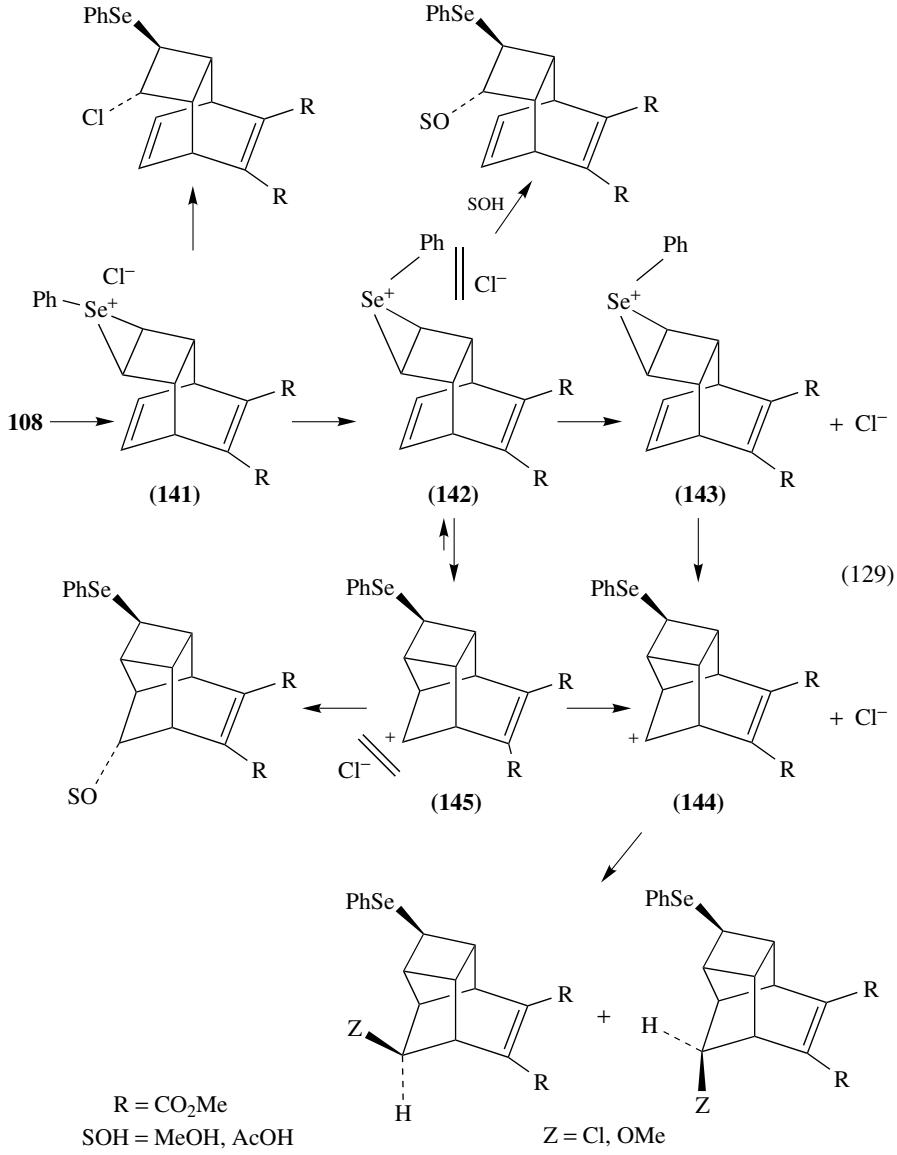


(138) **(140)** (128)

37 : 63

The same reaction scheme can also explain the stereochemical behavior of the addition of benzeneselenenyl chloride to **108** in methanol, which gives, in addition to the *trans* adduct **138**, the analogous methoxy derivative **146**, the cross-bonded chlorides **147** and **148**, and the analogous epimeric methoxy adducts **149** and **150** (equation 130).

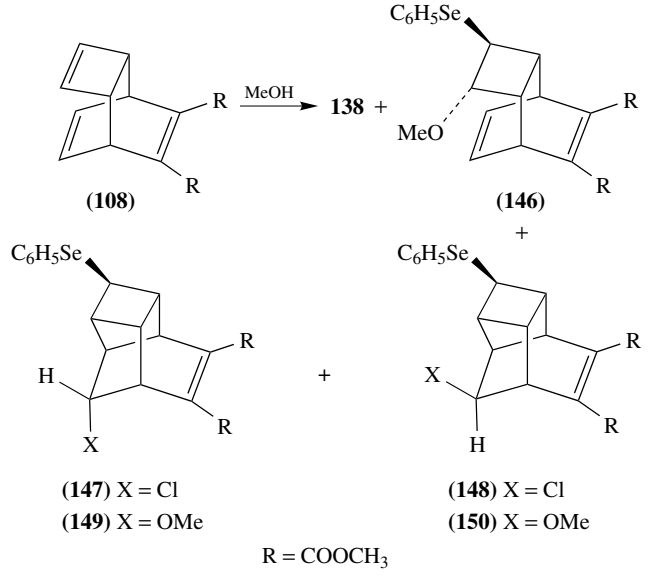
The formation of both isomeric chlorides **147** and **148** and the corresponding methoxy adducts **149** and **150** in methanol is at variance with the behavior observed in AcOH/$LiClO_4$, where only the acetoxy species **140** is formed. This has been interpreted by taking into account the possible role of a specifically solvated carbenium ion pair, such as **145**, prior to the formation of a free carbenium ion of type **144**.



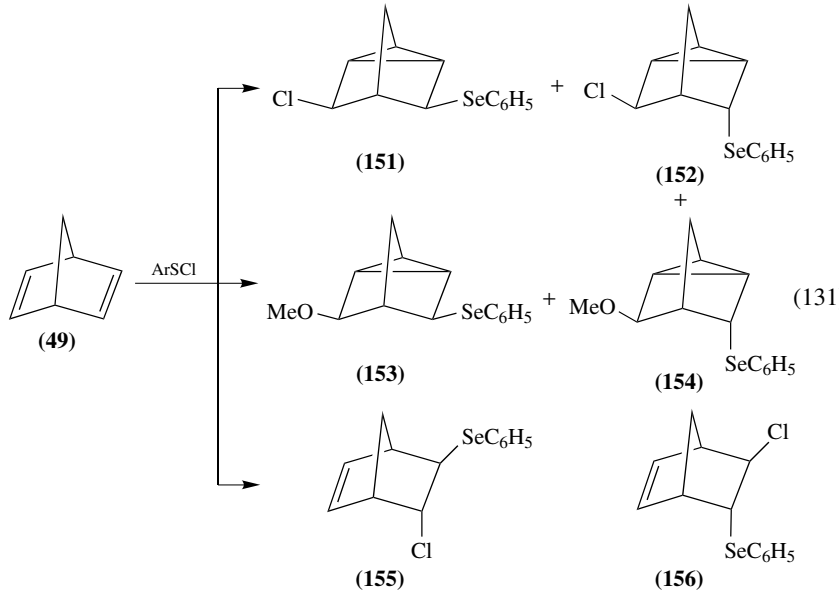
(129)

The involvement of at least three different forms of the seleniranium ion intermediate, i.e. tight and solvent-separated ion pairs and free ions, has been invoked also to rationalize the different chemical behavior observed in the addition of benzeneselenenyl chloride to bicyclo[2.2.1]hepta-2,5-diene **(49)** in methanol and in methylene chloride[140]. As stressed by the authors, the addition of benzeneselenenyl chloride to **49** shows a number of interesting trends. Four products (**151**–**154**), all resulting from homoallylic attack, were isolated from the reaction carried out in methanol (equation 131). Furthermore, it

is noteworthy that the reaction yields adducts arising from both *exo* and *endo* additions, with a predominant *endo* attack (*exo:endo* = 21 : 79). The same reaction carried out on norbornene proceeds exclusively with *exo* stereospecificity.



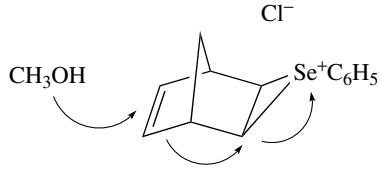
(130)



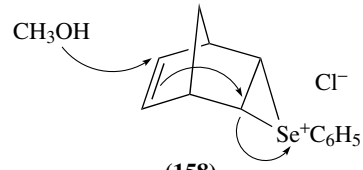
(131)

In chlorinated solvents the reaction of **49** also gives products of *exo* and *endo* attack (*exo:endo* = [**151** + **155**]/[**152** + **156**] = 39 : 61), but in this case compounds of simple 1,2-addition are found to predominate. Once again the solvent-dependent product

formation has been interpreted by assuming that in methylene chloride the collapse of intimate ion pairs to products occurs before the π participation of the homoallylic double bond becomes important. The exclusive formation of nortricyclenes in methanol should be a consequence of the preferential solvent attack upon the homoallylic double bond of the first formed ion pairs **157** and **158**.



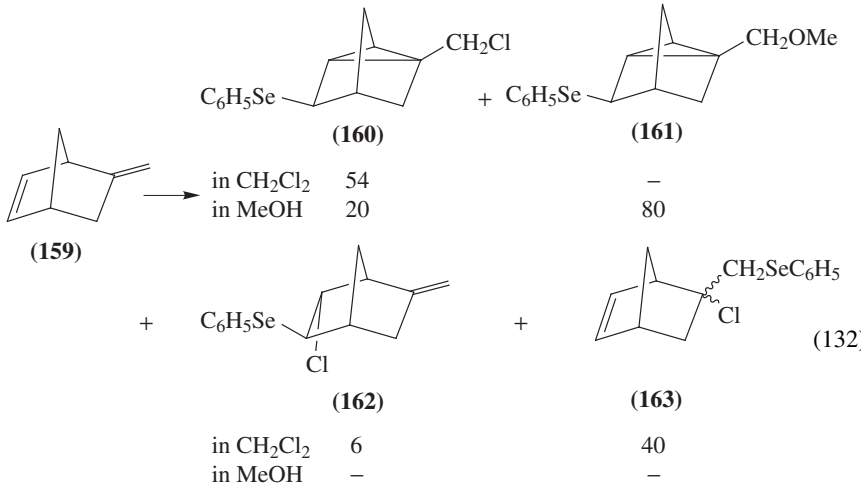
(157)



(158)

A mechanism of this type could explain the high ratio of methoxy/chloro adducts (**151** : **152** : **153** : **154** : **155** : **156** = 8 : 0 : 0 : 0 : 31 : 61) (in CH_2Cl_2) and 2 : 3 : 19 : 76 : 0 : 0 (in MeOH) since the solvent molecules do not have to enter the sterically hindered surrounding of the selenium in order to react.

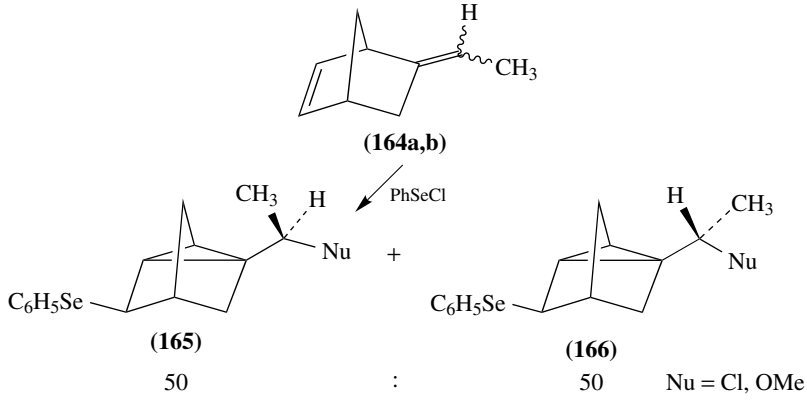
A solvent-dependent chemoselectivity, pointing to a dependence of the relative reactivities of the 1,2- and 1,1-disubstituted double bonds on solvent polarity and nucleophilicity, has been observed in the reaction of benzeneselenenyl chloride with 2-methylenebicyclo[2.2.1]hept-5-ene **(159)** which gives products **160**–**163**[140]. In methylene chloride the reaction occurs with a moderate chemoselectivity, attack on the *endocyclic* bond being preferred over that on the *exocyclic* one in a 60 : 40 ratio. In methanol, the addition is completely chemoselective and the attack occurs exclusively on the *endocyclic* double bond (equation 132). It may be further noted that **162** and **163** isomerize and solvolyze at high temperatures, leading to the homoallylic products **160** and **161**.



(132)

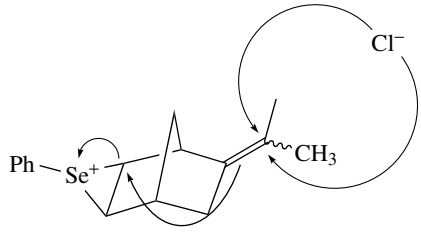
The transformation of **163** into **160** and **161** has been interpreted in terms of a reversible addition sequence, in which **159** and benzeneselenenyl chloride are regenerated and then react to give the more stable adducts **160** and **161**.

Finally, in the case of the geometrical isomers **164a,b**, only products from an *exo* addition to the *endocyclic* double bond followed by homoallylic rearrangement are observed[140], both in methanol and in methylene chloride. The electrophilic attack is *exo* specific, while the subsequent nucleophilic trapping by methanol or chloride proceeds non-stereospecifically giving equal amounts of **165** and **166** (equation 133).

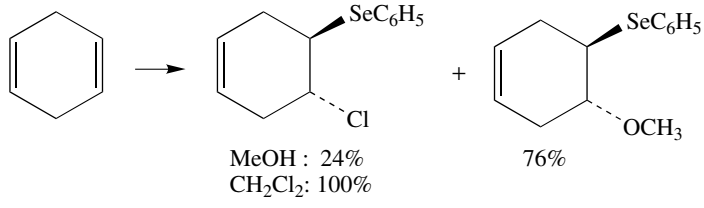


(133)

The absence of further products, particularly those resulting from β-attack on the seleno moiety and those arising from Wagner–Meerwein rearrangements, points to a mechanism involving a non-configurationally selective attack by Cl^- or methanol upon the seleniranium intermediate, as demonstrated below for Cl^-.



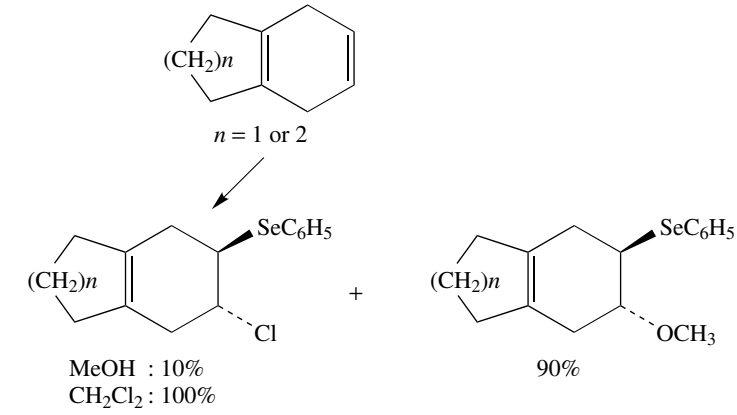
It is noteworthy that, at variance with norbornadiene derivatives, the addition of benzeneselenenyl chloride to 1,4-cyclohexadienes gives only products of *anti* 1,2-addition without any π participation (equations 134 and 135)[140].



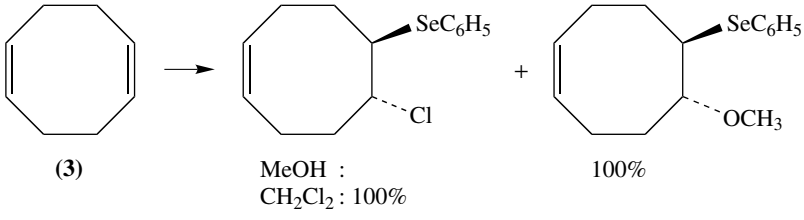
(134)

The same stereochemical behavior has also been observed in the addition of benzeneselenenyl chloride to 1,5-cyclooctadiene **(3)** (equation 136). However, **3** reacts with

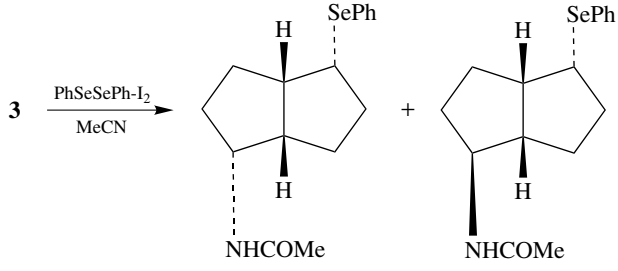
'benzene selenenyl iodide', prepared *in situ* by reaction of phenyl diselenide with iodine, in MeCN at room temperature to give the bicyclo[3.3.0]octane derivatives **167** and **168** (equation 137). The nucleophile, the solvent and/or the counterions therefore affect the possibility of obtaining products arising from π participation[21].



(135)

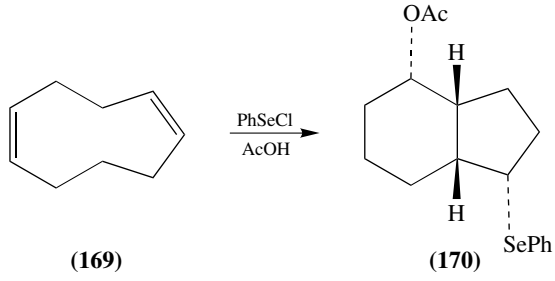


(136)



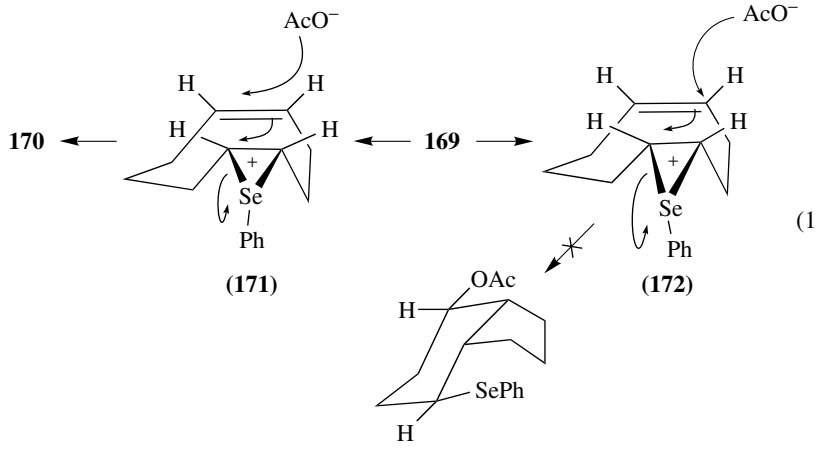
(137)

The larger (*Z*,*Z*)-1,5-cyclononadiene **(169)** reacts[141] stereoselectively with PhSeCl in AcOH to give the substituted hydrindan **170** (equation 138). In consideration of the *anti* addition mode of selenenyl reagents to double bonds, the transannular reactions of **169** have been rationalized on the basis of the two reaction intermediates, **171** or **172**, which are liable to place the PhSe- and AcO- groups in a *cis*-1,4-relationship and *trans* to the bridgehead hydrogen (equation 139). The preferential formation of **170** has thus been attributed to the fact that the pathway via **172** should involve a boat transition state.



(138)

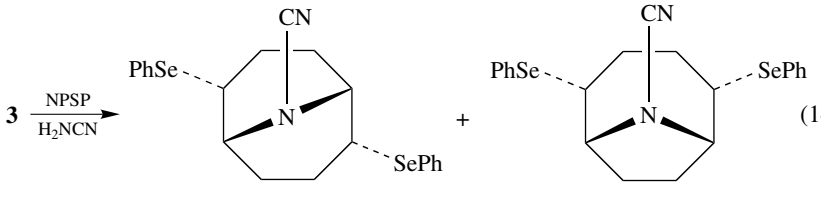
(169) **(170)**



(139)

(171) **(172)**

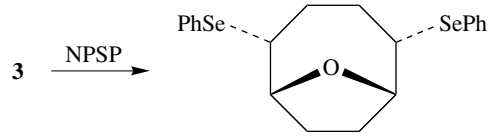
Finally, it must be mentioned that phenylselenation of some diolefins may provide a suitable method for the construction of heterocycles containing two phenylseleno groups. For instance, **3** reacts[142] with *N*-(phenylseleno)phthalimide (NPSP) in the presence of cyanamide (H_2NCN) to give the regioisomeric 9-azabicyclo[3.3.1]- and 9-azabicyclo [4.2.1]-nonanes, **173** and **174**, as the result of a combined process of inter- and intramolecular nucleophilic addition of cyanamide (equation 140).



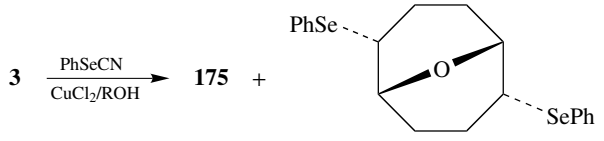
(140)

(173) **(174)**

Analogously, when the reaction of *N*-(phenylseleno)phthalimide or *N*-(phenylseleno) succinimide with **3** is carried out in methylene chloride in the presence of 2–3 equivalents of water, compound **175** can be obtained in high yield (equation 141)[16]. A mixture of isomeric cyclic ethers **175** and **176** was obtained also by treatment of **3** with phenylselenocyanide, in the presence of copper(II) chloride (equation 142)[143].

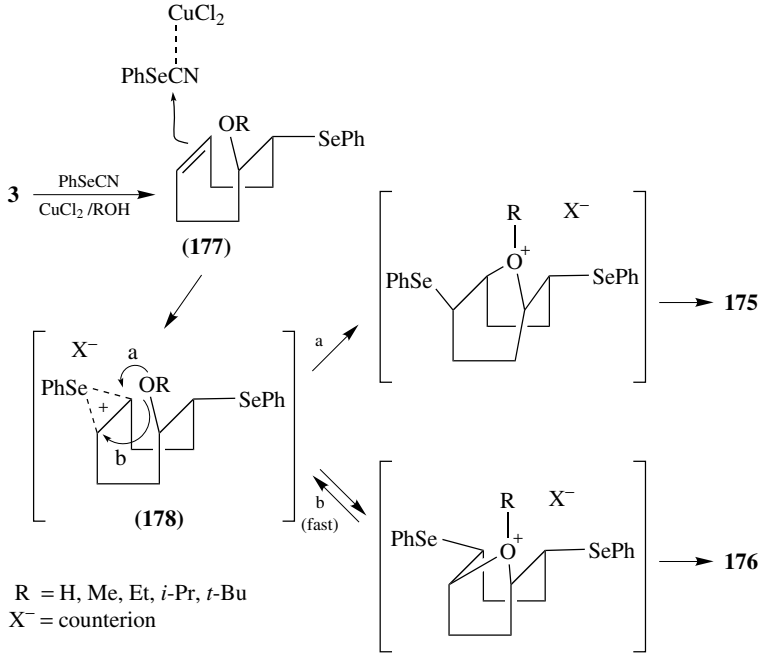


(175) (141)



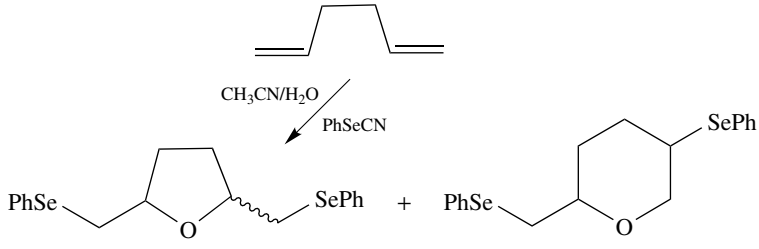
(176) (142)

The isomer ratio has been found to depend on the solvent, and a suitable choice of solvent results in the selective formation of one of the two isomers. This behavior has been explained by considering[143] that the first step of this reaction should be the oxyselenation of one double bond to produce **177**. In the subsequent transannular reaction of an alkoxy or hydroxy group with the seleniranium ion formed at the other double bond of **178**, the formation of an oxonium ion having a [4.2.1] framework is kinetically favored (path b). When R is hydrogen, it is removed prior to the isomerization in the chosen solvent (aqueous THF) to give **176** as the sole product. When R is an alkyl group reluctant to undergo elimination (Me > Et > *i*-Pr > *t*-Bu), an isomerization to a thermodynamically more stable intermediate having a [3.3.1] framework occurs to give **175** as the major product (path a, equation 143).



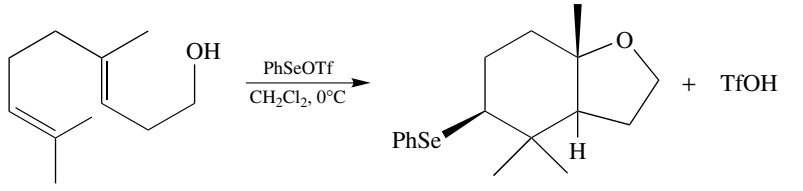
(143)

Interestingly, attempts to apply this cyclization reaction to linear diolefins using an alcoholic solvent give unsatisfactory results. Cyclic ethers have instead been obtained in aqueous acetonitrile. Under these conditions 1,5-hexadiene gives a 91 : 9 mixture of 2,5-bis[(phenylseleno)methyl]tetrahydrofuran and 2-[(phenylseleno)methyl]-5-(phenylseleno) tetrahydropyran in 86% yield (equation 144).

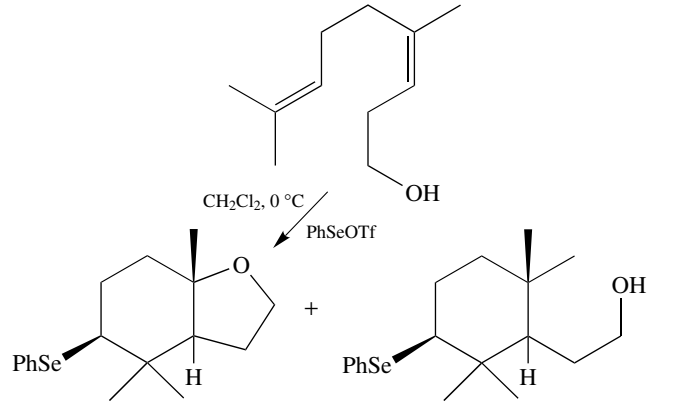


(144)

Similarly, electrophilic cyclizations of dienols and trienols, such as homogeraniol and homonerol, were carried out without addition of strong acid, using benzeneselenenyl triflate[18,144] as the organoselenium reagent (equations 145 and 146).



(145)



(146)

VI. ELECTROPHILIC MERCURY

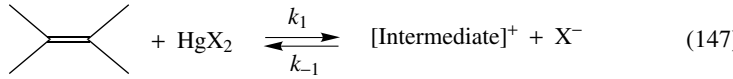
A. General Aspects[2a,145]

Addition of electrophilic mercury(II) salts to carbon–carbon double bonds in nucleophilic solvents (i.e. oxymercuration, solvomercuration etc.) is a well documented methodology in organic synthesis[146]. In these reactions a mercuric salt, usually the chloride or

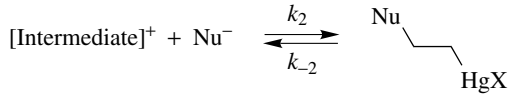
acetate but sometimes the trifluoroacetate or nitrate, is added in a suitable solvent. The products are 1 : 1 adducts, whose composition depends upon the solvent and any added nucleophile.

Mercuration usually occurs without rearrangement of the carbon skeleton and gives products arising from an almost complete Markonikov addition, with only a few exceptions. The product stereochemistry depends widely upon the structure of the alkene; generally *anti* addition is obtained although mercuration of strained alkenes can occur by *syn* addition.

The solvomercuration reaction is thought to be a two-step process. In the first step (equation 147), electrophilic attachment of mercury ion to the alkene produces a positively charged intermediate. In the second step (equation 148), a nucleophile (generally a solvent molecule) reacts with the intermediate leading to the organomercury compound.



(147)



(148)

Generally, mercuration reactions are overall second order, first order in the alkene and first order in the mercuric salt (equation 149)

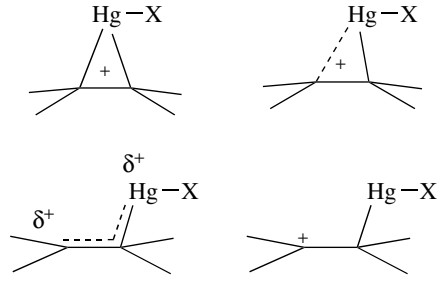
$$\text{rate} = (k_1 k_2 / k_{-1})\ [\text{alkene}]\ [\text{Hg salt}] \tag{149}$$

Substituent effects on the solvomercuration reaction differ markedly from those on many other electrophilic additions and these have been explained by assuming that the *formation* of the intermediate is often rate limiting in electrophilic additions whereas the *reaction* of the ionic intermediate with nucleophiles is rate limiting in solvomercuration[147]. In other words, the solvomercuration involves a fast pre-equilibrium formation of an intermediate, followed by rate-limiting attack of the nucleophile on this species.

Steric control has been invoked to explain the kinetic substituent effects as well as the *syn* stereoselectivity observed in these additions, for example to *trans*-cyclooctene and *trans*-cyclononene. In these cyclic compounds, one side of the π-bond is more shielded by the rest of the molecule and hence *anti* attack by a nucleophile is difficult.

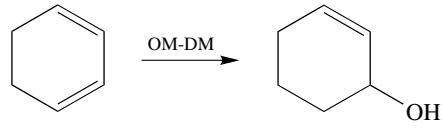
A symmetrically bridged 'mercurinium' ion, which might be described as a resonance hybrid, has been proposed as the intermediate by analogy with other electrophilic additions[148,149]. However, evidence has been presented both for and against the involvement of this intermediate in the mechanism of mercuration. Furthermore, CNDO/2 calculations have revealed[150] that there is only a shallow energy minimum on the potential energy surface associated to a shift of the mercury atom along the C−C axis, as shown below, so that asymmetrical ions might be lower in energy for asymmetrically substituted alkenes.

On the basis of theoretical and experimental results a symmetrical mercurinium ion, with most of the positive charge on mercury, has therefore been proposed in reactions of symmetrically substituted alkenes[151], while asymmetrical mercurinium ions or weakly bridged mercury-substituted carbocations have been proposed when there is a substituent, such as an aryl group, on the double bond[152]. Finally, with substituents highly capable of stabilizing carbocations, fully open intermediates have been proposed[151].



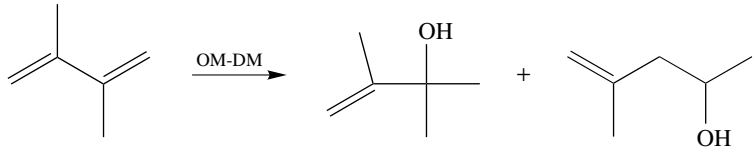
B. Conjugated Double Bonds

The possibility of converting alkenes into alcohols through a pair of reactions known as oxymercuration–demercuration (OM-DM) affords a convenient synthetic procedure for the hydration of carbon–carbon double bonds. However, little is known concerning the oxymercuration of dienes. The first studies related to the addition of mercury salts to conjugated double bonds, carried out using the standard OM-DM procedure [mercuration with an equimolar amount of $Hg(OAc)_2$ in THF–water followed by reduction of the oxymercurial with $NaBH_4$], provided information only about the regioselectivity of the reaction and about the applicability of the method[153]. Selecting as models of symmetrically conjugated dienes 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene, and as models of asymmetrically conjugated dienes 2-methyl-1,3-butadiene and *trans*-1,3-pentadiene, H. C. Brown and his coworkers showed[153] that Markovnikov hydration products are generally formed in these reactions, in yields often approaching 50%. In particular, it has been shown that 1,3-cyclohexadiene was readily converted into the allylic derivative, 2-cyclohexen-1-ol (equation 150), in contrast to a previous report[154] in which the formation of the isomeric homoallylic alcohol, 3-cyclohexen-1-ol, was observed.



(150)

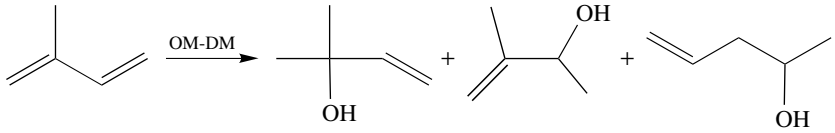
2,3-Dimethyl-1,3-butadiene underwent reaction to give the expected product 2,3-dimethyl-3-buten-2-ol besides a product containing a rearranged carbon structure, whose formation has been attributed to a radical process occurring during the demercuration step (equation 151).



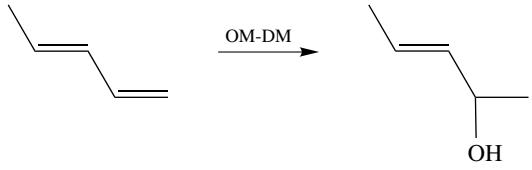
(151)

A very low yield characterized instead the reaction of isoprene. From this olefin, only 16% of the expected 2-methyl-3-buten-2-ol has been isolated besides a small amount of the isomeric 3-methyl-3-buten-2-ol and of a rearranged alcohol, 4-penten-2-ol (equation 152). Finally, *trans*-1,3-pentadiene was converted to 3-penten-2-ol in 56% yield (equation 153), the electrophilic attack occurring at the position predicted on the basis of the relative

reactivities of 1-pentene and *trans*-2-pentene toward mercury electrophiles.



(152)



(153)

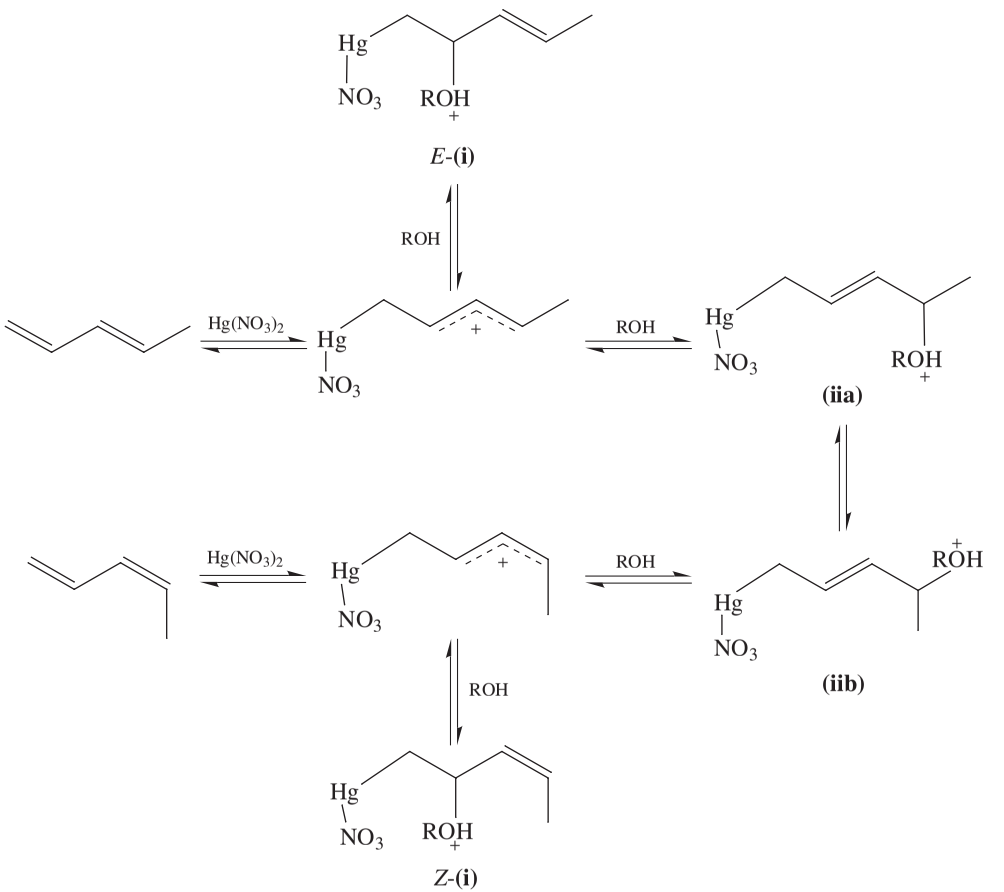
Subsequent isolation of solvomercuration products has supplied information about the stereoselectivity of the mercury addition and at the same time has shown that these reactions can give 1,2- and/or 1,4-addition products. In particular, the identification by ^{1}H NMR spectroscopy of a 1,4-adduct from 1,3-pentadiene and mercury(II)nitrate in methanol has provided[155] the first direct evidence that oxymercuration of conjugated dienes can proceed by 1,4-addition. Furthermore, the observed *Z*,*E*-isomerization of the diene has shown that the 1,4-oxymercuration is a reversible process.

On the basis of equation 154, the 1,2-adduct should be formed faster than the 1,4-adduct, the latter being obtained under conditions of thermodynamic control. The 1,2- and 1,4-adducts arise by deprotonation of **i** and **ii**, respectively. Rotation around the C(3)−C(4) bond of the 1,4-adduct **(iia ⇌ iib)** should provide a pathway for the ready isomerization of the diene. The involvement of an intermediate 1,4-adduct has been also reported[156] to rationalize the formation of 1,4-cycloamination products in the 'one-pot' reaction of linear and cyclic 1,3-dienes with primary aromatic amines and mercury(II) oxide-tetrafluoroboric acid (equations 155 and 156).

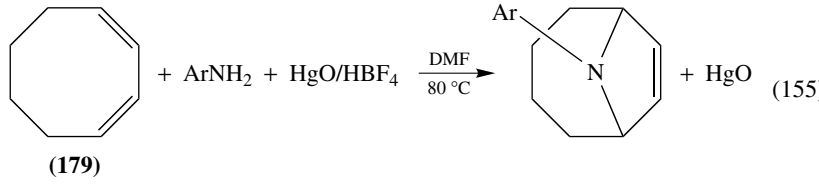
Considering that β-aminomercury(II) tetrafluoroborates are polar enough to undergo nucleophilic attack by the lone electron pair of an amine, ether or alcohol in the case of the 1,3-cyclooctadiene, **179**, it has been assumed that the first formed 1,4-adduct can give the reaction product by displacement of mercury by amine with direct participation of the nucleophile in an assisted breakage of the *anti* C−Hg bond (path a) or by spontaneous reduction of mercury in the intermediate allylic organomercurial (path b) (equation 157).

An alternative hypothesis, that the reaction product arises from a first formed 1,2-adduct, from which the same ionic intermediate may be generated (equation 158), has been ruled out by considering the directive effect of the conjugated double bonds on oxymercuration, which favors the attack of mercury at the terminal positions of conjugate π-systems.

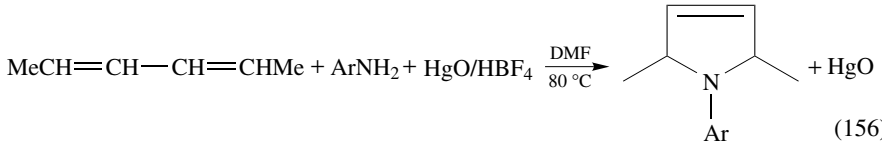
Furthermore, more recent work about the monoalkoxymercuration of a series of conjugated dienes with different mercury salts has shown[157] that the alkoxymercuration of these compounds proceeds in two steps, the first being the formation of 1,2-adducts in which, with the exception of the mercuration of α-terpinene, the alkoxy group occupies the allylic position. The 1,2-alkoxymercurials are in equilibria with the corresponding 1,4-regioisomers, which are easily solvolyzed owing to the allylic character of the C−Hg bond. Moreover, the 1,2-adducts are stable when derived from mercury(II)acetate. With more ionic salts, such as tetrafluoroborate or nitrate, the 1,2-adducts are rapidly transformed into the 1,4-adducts, only that of *trans*-piperylene being characterizable at room temperature. Finally, the 1,4-adducts undergo fast decomposition to the corresponding


Hg
NO3
ROH
+
E-(i)
ROH
Hg(NO3)2
Hg
NO3
+
ROH
Hg
NO3
ROH
+
(iia)
Hg(NO3)2
Hg
NO3
+
ROH
Hg
NO3
ROH
+
(iib)
ROH
Hg
NO3
ROH
+
Z-(i)

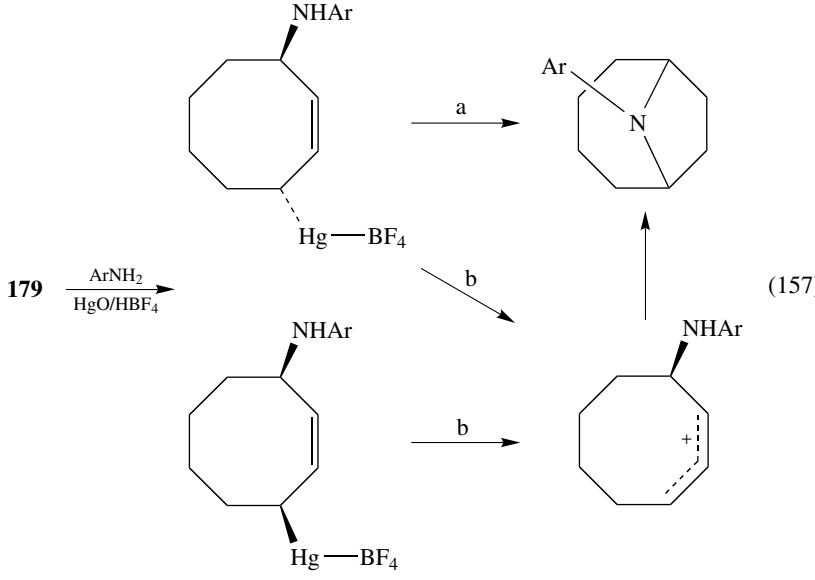
(154)



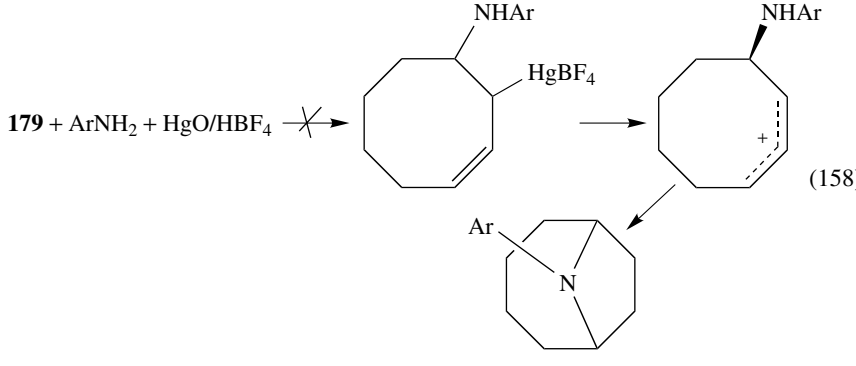
(179) (155)



(156)



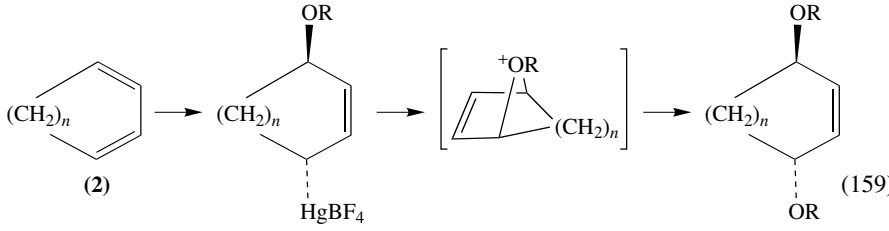
(157)

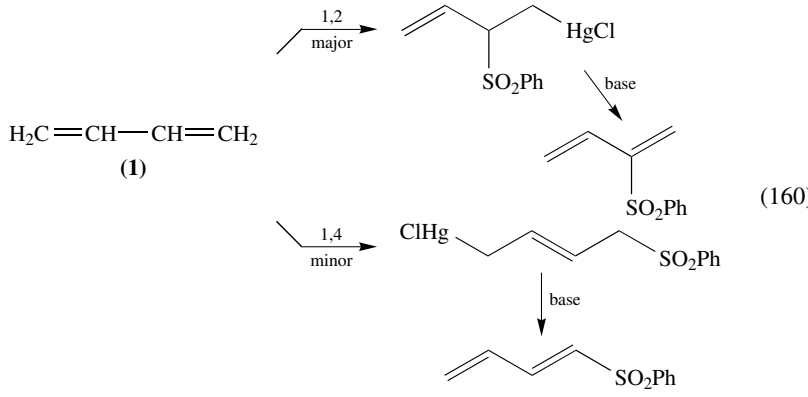


(158)

1,4-diethers. Their formation has been suggested to proceed by solvolytic cleavage of the allylic C−Hg bond in the 1,4-adducts, probably via formation of the corresponding allyl cation. The higher reactivity of the 1,4-adducts arising from cyclic dienes, and in particular that of the *trans* adduct arising from 1,3-cyclooctadiene, has been attributed to the participation of the oxygen lone pair in the displacement of mercury (equation 159). When the ring size decreases, the possibility of an anchimerically assisted displacement of mercury by oxygen is less important for geometrical reasons, the oxymercurial becomes more stable and the steroselectivity in the diether formation decreases. With respect to the stereochemistry of the diethers, most reactions occur with a reasonably high degree of stereoselectivity, always affording the *trans*-isomer as the major product.

Finally, the phenylsulfenylmercuration (using preformed mercury benzenesulfinate complex) of 1,3-dienes has also been reported[158] to give 1,2- and 1,4-mercury adducts (equation 160). In most cases the reaction proceeds regioselectively to give 2-(phenylsulfonyl)-1,3-dienes.





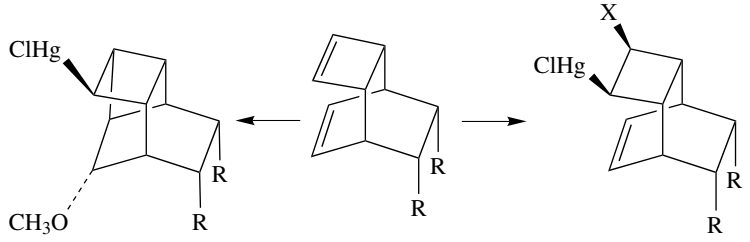
(160)

However, the reaction of 1,3-cycloheptadiene is less regioselective. Isoprene and *E*,*E*-2,4-hexadiene afford 1,2-/1,4-adducts in ratios of 87 : 13 and 83 : 17, respectively. The high selectivity for 1,2-addition (>95%) to 1,3-pentadiene is opposite to the corresponding oxymercuration of the same diene, which has been reported[159] to give mainly 1,4-adducts. The different regiochemistry has therefore been explained by assuming that sulfomercuration occurs under kinetic control whereas oxymercuration occurs under thermodynamic control.

C. Non-conjugated Double Bonds

The stereochemistry and the mechanism of the electrophilic additions to tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives have been studied frequently, although some unambiguous

structural assignments of the products were made. In particular, methoxymercuration of diester **60** has been investigated by Cookson[160] and the tetracyclic structure **180** has been assigned to the solid reaction product. Subsequently, the same reaction was reinvestigated by Mehta and Pandey[93]. A tricyclic structure **181** has been attributed to the reaction product on the basis of the NMR data (equation 161).

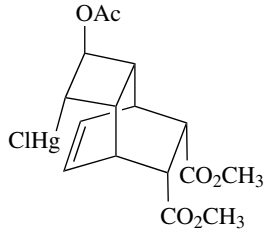


(161)

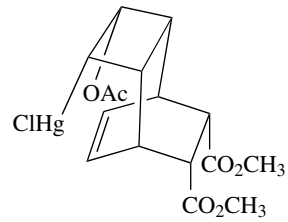
(180) R = $COOCH_3$ **(60)** R = $COOCH_3$ **(181)** R = $COOCH_3$; X = OCH_3
(62) R = CH_3 **(182)** R = $COOCH_3$; X = OH
(63) R = CH_2OCH_2 **(183)** R = $COOCH_3$; X = N_3
(184) R = CH_3; X = OCH_3
(185) R = CH_2OCH_2; X = OCH_3

A similar structure has furthermore been attributed[93] to the hydroxy- and azidomercuration products **182** and **183**. Methoxymercuration of the dimethyl compound **62** and of the ether **63** proceeded rapidly and smoothly to furnish again the *syn* methoxy mercurials **184** and **185** (equation 161). The rate of methoxy- and hydroxymercuration of these dienes increased markedly on going from **60** to **63** and **62**, in agreement with a strong transannular reactivity depression of the cyclobutene ring as a result of the substituent change. Therefore, considering that oxymercuration of simple olefins generally occurs with *anti* stereospecificity the exclusive formation of *syn* products in oxymercuration of **60**, **62** and **63**, and the consistent absence of compounds arising from either carbenium ion rearrangement or transannular participation have been rationalized[93] in terms of the 'twist strain' theory.

More recently the formation of an *endo trans*-adduct **186** has been reported[161] for the reaction of **60** with $Hg(OAc)_2$ in acetic acid, while in tetrahydrofuran an *endo cis*-isomer **187** has also been obtained[162].

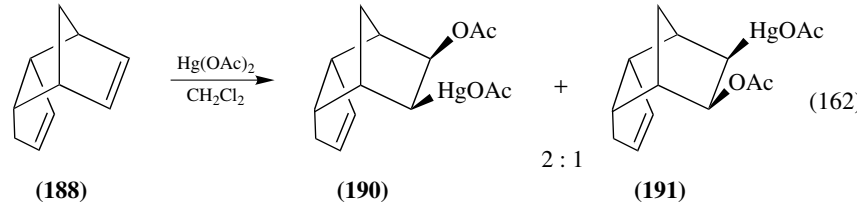


(186)

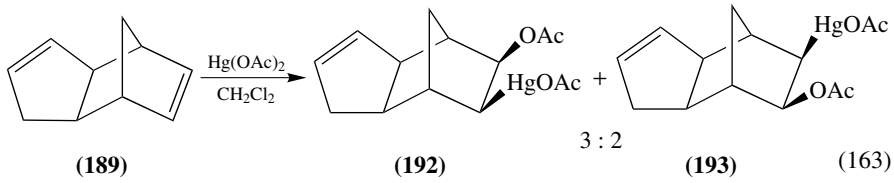


(187)

Nevertheless, the selective formation of *exo-syn* adducts has been observed in the mercuration of norbornadiene[163] and its derivatives **188** and **189**[164].



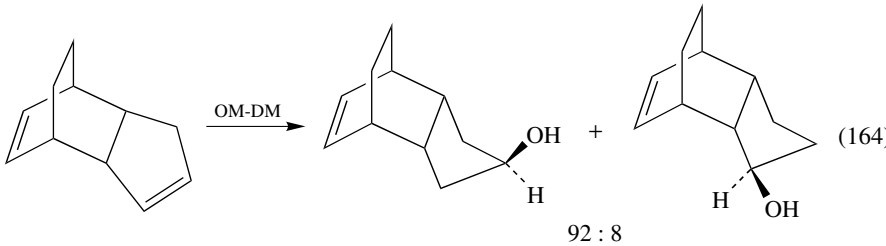
(188) (190) (191) (162)



(189) (192) (193) (163)

Oxymercuration in dichloromethane at room temperature afforded the adducts **190** and **191** from **188** (equation 162), and **192** and **193** from **189** (equation 163), the electrophilic mercury attack preferentially occurring at the C(3) carbon atom. A similar selectivity was previously observed also in OM-DM of **188**[165].

OM-DM reaction of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene **(194)** was found[166] to proceed with high regio- and stereoselectivity, giving mainly 4-*exo*-hydroxy-*endo*-tricyclo [5.2.2.0^{2,6}]undec-8-ene **(195)** together with **196** (equation 164). Saturation of the 8,9-ethylenic bond in **194** resulted in a large reduction in reactivity as well as in stereoselectivity.



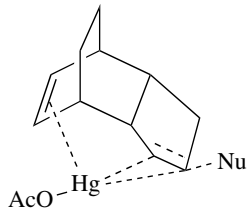
(194) (195) (196) (164)

These results have been interpreted in terms of *trans* addition of mercuric ion and nucleophile where the attack of the mercuric ion takes place from the more hindered side of the diene molecule. A transition state **197**, involving an *endo* attack of mercuric ion with some stabilization by coordination to the 8,9-ethylenic bond to the mercury atom, has been proposed to support the suggested mechanism. Analogously, and in sharp contrast to the results obtained[167] in the mercuration of norbornadiene which reacts with mercury salts via the usual scheme of *exo-syn* addition, the principal pathway in the mercuration of bicyclo[2.2.2]octa-2,5-diene is the formation of *endo-syn* products (equation 165).

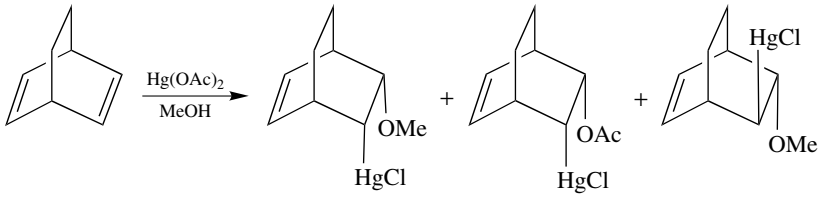
Therefore, although it is generally accepted that electrophilic mercuration of di- and polycyclic systems containing a double bond takes place in accordance with the *exo-syn* addition rule, at least a part of the reported results shows that the strain of the unsaturated system is insufficient to be the only determining factor for *syn* addition of mercury salts.

Finally, although mercuration–demercuration of dienes is a suitable method for synthesis of unsaturated alcohols and amines, 1,5-dienes cannot be used for this purpose

since these compounds undergo intramolecular cyclization to give five-membered cyclic systems, regardless of the diene/mercuric salt ratio employed.

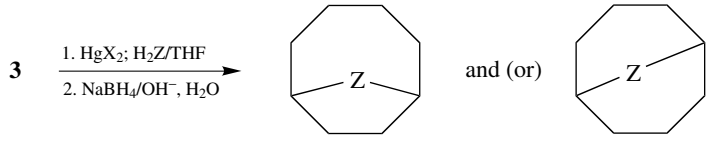


(197)



(165)

The mercuration–demercuration reaction of *cis,cis*-1,5-cyclooctadiene **(3)** has been widely studied in order to get some insight into the synthesis of 9-oxa and 9-azabicyclononane derivatives. However, the results of the reaction have often been the subject of some controversy since the ratio of the two isomeric bicyclo[3.3.1]- [**199** and **201**] and [4.2.1]- [**198** and **200**] nonanes, after reduction (equation 166), strongly depended on the reaction conditions of the mercuration step[168,169].

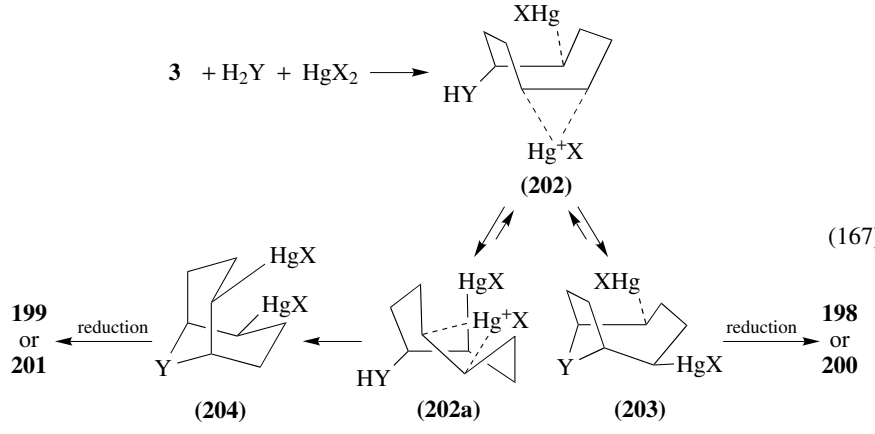


(166)

Z = O **(198)** **(199)**
Z = NAr **(200)** **(201)**

The ratio of the two products is primarily affected by the nature of the mercury(II) salt and also by the reaction conditions. Since the formation of these compounds could result from either a kinetically or a thermodynamically controlled mercuration process, a study of the mercuration of **3** in the presence of aromatic amines using various mercury(II) salts has been more recently carried out in order to determine the conditions under which aminomercuration is reversible, and the results have been compared to those of the oxymercuration[170].

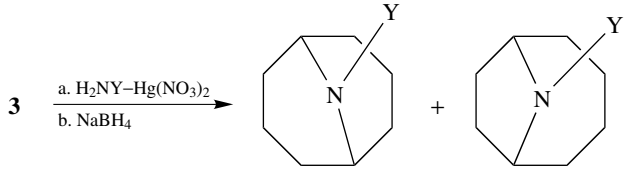
On the basis of these results, cyclization should proceed in two steps, the second one being the intramolecular amino (or oxy) mercuration of the second double bond. For geometric reasons, the reaction which leads to mercurial **203** from **202** is expected to be kinetically favored since it does not require any conformational change on going to the transition state, and hence this isomer should be obtained under kinetic control[170]. The mercurial **204**, arising from the intermediate **202a**, in equilibrium with **202**, should give instead the more stable [3.3.1]isomer **201** (or **199**), which should therefore predominate under thermodynamic control, i.e. in reversible aminomercuration of **3** (equation 167).



(167)

It has therefore been established[170] from the product distributions that, while the oxymercuration is reversible, unless a base (e.g. sodium acetate) is added to the reaction medium, and gives almost exclusively the more stable compound **199**, the aminomercuration takes place to give the kinetically controlled adduct **200**, or under thermodynamic control the aminomercurial **201**. Reactions are kinetically controlled when the mercurating species is a mercury(II) salt deriving from a weak acid such as mercury(II) acetate. Conversely, they are thermodynamically controlled with the covalent mercury(II) chloride. In the latter case, the presence of a strong acid in the medium allows the thermodynamically controlled product to be obtained.

Analogously, mixtures of *N*-alkoxycarbonyl- and *N*-tosyl-9-azabicyclo[3.3.1]- and [4.2.1]nonanes were obtained by reaction of **3** with carbamates or *p*-toluenesufonamide in the presence of mercury(II) nitrate followed by *in situ* demercuration with sodium borohydride (equation 168)[171,172].

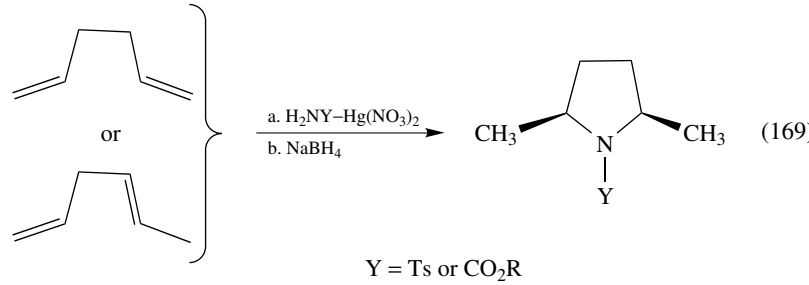


(168)

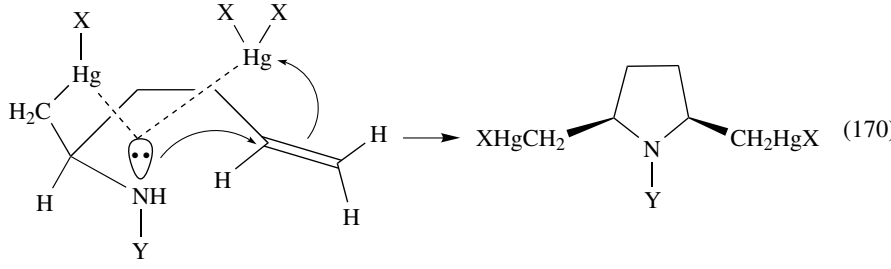
In contrast, the amido and the sulfamidomercuration–demercuration of acyclic 1,4- and 1,5-dienes yield saturated nitrogen-containing heterocycles (equation 169)[172].

It is noteworthy that a complete stereoselectivity toward the *cis*-isomer, which is opposite to that found in aminomercuration of the same dienes[173] characterizes these reactions. The following mechanism has therefore been proposed to rationalize the stereochemical behavior. After the addition to one of the double bonds, the electron pair of the nitrogen should interact with the mercury atom. In a second step, another mercury(II) ion from an additional molecule of mercury(II) nitrate is similarly complexed by the electrons of the nitrogen atom, requiring an approach from that same side and resulting in a *cis*

configuration of both mercurial groups (equation 170).



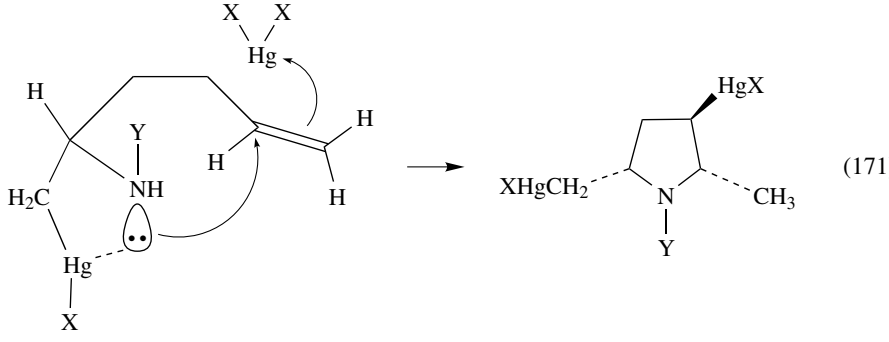
(169)



(170)

The preliminary electronic interaction seems to be required since, if the first mercury atom is absent, a *trans* addition takes place. Furthermore, a possible important role of the basicity of the nitrogen has been underlined taking into account that aminomercuration of 1,4- and 1,5-hexadienes with aromatic amines leads mainly to the *trans* isomer.

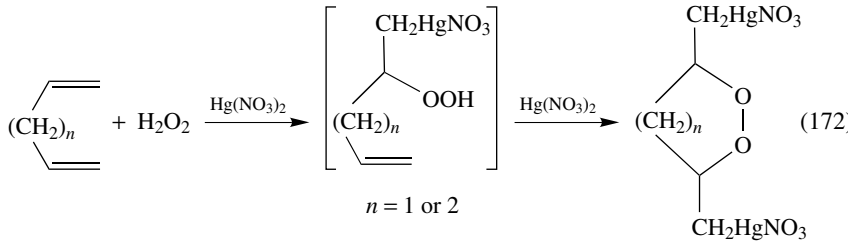
Considering the monoaminomercuration–demercuration of 1,4-hexadiene with *N*-methylaniline leads to *N*-methyl-*N*-(1-methylpent-3-enyl)aniline, the stereoselective synthesis of *N*-alkoxycarbonyl or *N*-tosyl *cis*-2,5-dimethylpyrrolidine from the same diene has been explained[172] on the basis of an initial amidomercuration reaction on the terminal bond followed by the second addition of mercury(II) salt to the internal double bond, on the less sterically hindered site (equation 171).



(171)

Finally, cyclic secondary alkyl peroxides have been prepared in high yield via the reaction of dienes with hydrogen peroxide and mercury(II) nitrate followed by hydrogen

or bromodemercuration[174]. Hydroperoxymercuration of suitable dienes (1,4-penta- and 1,5-hexadiene) affords unsaturated hydroperoxides capable of cyclization by a subsequent intramolecular peroxymercuration (equation 172).



(172)

With mercury(II) nitrate, the five-membered ring peroxide was obtained as an approximately equimolar mixture of isomers, while the 1,2-dioxacyclohexane contained about three times as much *trans*- as *cis*-isomer. Peroxymercuration of alkyl-substituted 1,4-penta- and 1,5-hexadienes, followed by demercuration, afforded mixtures of isomeric cyclic alkyl peroxides in yields strongly dependent on the number and position of the substituents[175].

VII. CONCLUSIONS

More than twenty years ago, G. H. Schmid and D. G. Garratt in their review[2a] on electrophilic additions to carbon–carbon double bonds concluded: 'experimental verification is lacking for all the proposed mechanisms'. Today, this conclusion applies fairly well to the electrophilic reactivity of dienes and polyenes. Most of the present interpretations are mainly suggested by partial results on the 1,2-/1,4-addition competition. Despite the huge number of available results, the association of kinetic and product data which has been very successful in detailed mechanistic investigations of other reactions, e.g. solvolysis or electrophilic additions to monoenes, has never been attempted for diene reactions. Moreover, most of the present mechanisms used for rationalizing the outcome of diene and polyene reactions with electrophiles have been postulated by analogy to those suggested for the monoene reactions a long time ago, and are not necessarily reasonable. On the one hand, the electrophilic behavior of dienes and polyenes involving interactions between two or several π bonds or between a π bond and a developing positive charge can differ markedly from that of alkenes. The related problem of the structure of the ionic intermediates, bridged versus allylic cations, has been discussed at length qualitatively based on the product data but, e.g., it has never been tackled directly by spectroscopic techniques. On the other hand, many features of electrophilic additions to monoenes, in particular bromination and sulfenylation, have been reinvestigated in much detail in recent years[2d,3,7] but the mechanisms for the analogous reactions of dienes did not take any advantage of these advances. For example, the characterization of bromine–alkene charge transfer complexes and their involvement in the reaction pathway[7a,c] have not been extended to polyenes. The nucleophilic solvent assistance (preassociation mechanism) to ionization of these CTCs into ion pairs, which has been shown to be related to the stereochemistry of the monoene reactions[7d,176], has not been considered in the interpretations of the 1,2-/1,4-addition competition. The well-established independence of bromine bridging of the solvent[7d,177] is systematically ignored in the rationalizations of the products of polyene reactions. The reversibility of the ionization step and its relation to the rate of the product-forming step[7d,178], either a nucleophilic trapping controlled by the intermediate lifetime

or a rearrangement in the case of strained olefins[3c,179], was revealed to be essential to the understanding of the chemo-, regio- and stereoselectivity of the monoene reaction. All these questions would have to be tackled in order to reach consistent interpretations of the nature of the products obtained by electrophilic additions to dienes and polyenes under a large variety of reaction conditions. It must be emphasized that the most recent activity in the field was focused on the access to polyfunctionalized diene derivatives of interest in organic synthesis rather than on reaction mechanisms. Therefore, the challenge concerning electrophilic reactions of dienes and polyenes is in developing their potential in synthetic methodology, despite or because of their high versatility as regards their selectivity.

A large number of multistep syntheses of natural compounds, such as terpenes or steroids, involves at some stage an electrophilic addition to or a cyclization of polyunsaturated substrates[17]. Lab-scale preparations of some chemical intermediates of interest as building blocks in heterocyclic chemistry have been reported under the headings 'Electrophilic sulfur, selenium and mercury'. Moreover, the diene and polyene reactions with 'electrophilic oxygen' involving oxo- or peroxometal complexes as oxygen carriers, which are reviewed in a specific chapter of Vol. 1 of this book[180], are very promising in the context of organic synthesis. The electrophilic additions to allenes and cumulenes, a very important reaction for synthesis, described elsewhere in this series, are not included in this report since these unsaturated compounds cannot be viewed as conjugated π-systems and exhibit a very different behavior[181].

Many large-scale applications of electrophilic additions to polyenes, particularly in polymer industry, have also been mentioned in this report. Most of these industrial procedures involve catalytic activation of the electrophilic dienes and polyenes by complexation with transition metals. These extensions have opened the way to a new field of organometallic chemistry on the reactivity of metal–diene complexes[182], which can be viewed as resulting from the diene electrophilicity and as activation of conjugated systems toward nucleophilic attack. In this context, methodologies for obtaining regio- and stereocontrolled 1,4-additions have been proposed. The wide synthetic utility of this field in selective organic transformations is illustrated in the previous volume of this book in the chapter[183] 'Palladium-catalyzed oxidation of dienes'.

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IX. REFERENCES

1. See, for example, J. March, in *Advanced Organic Chemistry*, 4th edn., McGraw-Hill, New York, 1992.
2. For reviews of general literature, see:
   (a) G. H. Schmid and D. G. Garratt, in *The Chemistry of Double Bonded Functional Groups*, *Supplement A*, *Part 2* (Ed. S. Patai), Wiley, New York 1977, p. 725.
   (b) K. A. V'yunov and A. I. Ginak, *Russ. Chem. Rev. (Engl. Transl)*, **50**, 151 (1981).
   (c) P. B. D. de la Mare and R. Bolton, in *Electrophilic Additions to Unsaturated Systems*, Elsevier, New York, 1982.
   (d) G. H. Schmid, in *The Chemistry of Double Bonded Functional Groups*, *Supplement A2*, *Part 1* (Ed. S. Patai), Wiley, New York 1989, p. 699.
3. For reviews of specific aspects of electrophilic additions, see:
   (a) M. F. Ruasse, *Adv. Phys. Org. Chem.*, **28**, 207 (1993).
   (b) G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann (Eds.), *Houben–Weyl E21*, G. Thieme, Stuttgart, New York, 1996.

(c) L. Forlani, in *The Chemistry of Functional Groups: The Chemistry of Double-bonded Functional Groups, Supplement A3, Part 1* (Ed. S. Patai), Wiley, New York, 1997, p. 367.
(d) R. S. Brown, *Acc. Chem. Res.*, **30**, 131 (1997).
4. V. Kh. Kristov, Kh. M. Angelov and A. A. Patrov, *Russ. Chem. Rev. (Engl. Transl.)*, **60**, 69 (1991).
5. P. D. Bartlett and D. S. Tarbell, *J. Am. Chem. Soc.*, **58**, 466 (1936); I. Roberts and G. E. Kimball, *J. Am. Chem. Soc.*, **59**, 947 (1937).
6. W. K. Chang, P. Knittel, K. M. Koshy and T. T. Tidwell, *J. Am. Chem. Soc.*, **99**, 3395 (1977).
7. (a) G. Bellucci, C. Chiappe, R. Bianchini, D. Lenoir and R. Herges, *J. Am. Chem. Soc.*, **117**, 12001 (1995).
(b) G. Capozzi, G. Modena and L. Pasquato, in *The Chemistry of Sulphenic Acids and their Derivatives* (Ed. S. Patai), Wiley, New York, 1990, p. 403.
(c) G. Bellucci, C. Chiappe and R. Bianchini, in *Advances in Organobromine Chemistry II* (Eds. J. R. Desmurs, B. Gérard and M. J. Goldstein), Elsevier, New York 1995, p. 128.
(d) M. F. Ruasse, G. Lo Moro, B. Galland, R. Bianchini, C. Chiappe and G. Bellucci, *J. Am. Chem. Soc.*, **119**, 12492 (1997).
8. J. R. Chrétien, J. D. Coudert and M. F. Ruasse, *J. Org. Chem.*, **58**, 1917 (1993).
9. J. E. Nordlander, P. O. Owuor and J. E. Haky, *J. Am. Chem. Soc.*, **101**, 1288 (1979).
10. D. F. Shellhamer, R. J. Conner, R. E. Richardson and V. L. Heasley, *J. Org. Chem.*, **49**, 5015 (1984).
11. W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **33**, 2642 (1968).
12. G. H. Schmid, S. Yeroushalmi and D. G. Garratt, *J. Org. Chem.*, **45**, 910 (1980).
13. G. H. Heasley, V. L. Heasley, S. L. Manatt, H. A. Day, R. V. Hodges, P. A. Kroon, D. A. Redfield, T. L. Rold and D. E. Williamson, *J. Org. Chem.*, **38**, 4109 (1973).
14. J. Barluenga, J. M. Gonzales, P. J. Campos and G. Asensio, *Tetrahedron Lett.*, **29**, 6497 (1988).
15. G. E. Heasley, D. C. Hayse, G. R. McClug, D. K. Strickland, V. L. Heasley, P. D. Davis, D. M. Ingle, K. D. Rold and T. S. Ungermann, *J. Org. Chem.*, **41**, 334 (1976).
16. K. C. Nicolaou, D. A. Claremon, W. E. Barnette and S. P. Seitz, *J. Am. Chem. Soc.*, **101**, 3704 (1979).
17. N. Gnonlonfoun, *Bull. Soc. Chim. Fr.*, 862 (1988).
18. G. Haufe and M. Mühlstäd, *J. Prakt. Chem.*, **323**, 89 (1981).
19. H. C. Brown, P. J. Geoghegan Jr, J. T. Kurek and G. J. Lynch, *Organometal. Chem. Syn.*, **1**, 7 (1970).
20. W. H. Mueller, *J. Am. Chem. Soc.*, **91**, 1223 (1969).
21. A. Toshimitsu, S. Uemura and M. Okano, *J. Chem. Soc., Chem. Commun.*, 965 (1982).
22. S. Uemura, S. Fukuzawa, A. Toshimitsu, M. Okano, H. Tezuka and S. Sawada, *J. Org. Chem.*, **48**, 270 (1983).
23. G. Haufe, A. Wolf and K. Schulze, *Tetrahedron*, **42**, 4719 (1986).
24. G. W. Parshall, *Homogeneous Catalysis*, Wiley, New York, 1980; W. C. Drinkard, U.S. Patents 3, 496, 215; 3, 496, 218; *Chem. Abstr.*, **74**, 53092 (1971).
25. G. T. Martirosyan and A. T. Malkhasyan, *Zh. Vses. Khim. Ova im D. I. Mendeleeva*, **30**, 263 (1985); *Chem. Abstr.*, **104**, 6948c (1986).
26. M. J. Virnig, World Patent N° 90/12859 (1990); *Chem. Abstr.*, **114**, 104765s (1991); R. Kummer, W. Bertleff and M. Roeper, Eur. Pat. Appl. EP 293,818 (1987); *Chem. Abstr.*, **114**, 104765s (1991).
27. D. Y. Waddan, E. Puentes, A. F. Noels, R. Warin, A. J. Hubert and Ph. Teyssié, *J. Catal.*, **116**, 415 (1989).
28. K. Oyama and T. T. Tidwell, *J. Am. Chem. Soc.*, **98**, 947 (1976).
29. J. L. Jensen and D. J. Carré, *J. Org. Chem.*, **36**, 3180 (1971).
30. J. L. Jensen, V. Uaprasert and C. R. Fujii, *J. Org. Chem.*, **41**, 1675 (1976).
31. A. Bagno, G. Scorrano and R. A. More O'Ferrall, *Rev. Chem. Intern.*, **7**, 313 (1987).
32. J. L. Jensen and V. Uapraser, *J. Org. Chem.*, **41**, 649 (1976).
33. K. Okuyama, T. Sakagami and T. Fueno, *Tetrahedron*, **29**, 1503 (1973).
34. F. Stunneuberg, F. G. M. Niele and E. Drent, *Inorg. Chim. Acta*, **222**, 225 (1994).
35. E. Drent, Eur. Patent N° 457 387 (1991); *Chem. Abstr.*, **116**, P105627b (1992).
36. I. Mamalis, A. F. Noels, E. Puentes, R. Warin, Ph. Teyssié, A. J. Hubert, J. Grandjean, R. Hubin and D. Y. Waddan, *J. Catal.*, **102**, 357 (1986).

37. I. Mamalis, J. Grandjean, A. F. Noels, E. Puentes, D. Y. Waddan, A. J. Hubert and Ph. Teyssié, *Catalysis Today*, **1**, 59 (1987).
38. Y. Tanabe, *Hydrocarbon Process.*, **60**, 187 (1981).
39. G. M. Mkryan, E. E. Kaplanyan, N. T. Tatevosyan and F. K. Sugryan, *J. Org. Chem. USSR*, **9**, 1153 (1973).
40. E. E. Kaplanyan, N. T. Tatevosyan , E. M. Aivazyan and G. M. Mkryan, *J. Org. Chem. USSR*, **11**, 1350 (1975).
41. R. A. Kazaryan, E. E. Kaplanyan and G. M. Mkryan, *J. Org. Chem. USSR*, **12**, 1639 (1976).
42. G. M. Mkryan, E. E. Kaplanyan, N. T. Tatevosyan, E. M. Aivazyan and N. A. Papazyan, *J. Org. Chem. USSR*, **13**, 1690 (1977).
43. N. T. Tatevosyan, G. G. Mkryan, E. E. Kaplanyan and G. M. Mkryan, *J. Org. Chem. USSR*, **19**, 52 (1983).
44. L. M. Mascavage and D. R. Dalton, *Tetrahedron Lett.*, **32**, 3461 (1991).
45. L. M. Mascavage, H. Chi, S. La and D. R. Dalton, *J. Org Chem.*, **56**, 595 (1991).
46. J.-E. Bäckvall and O. S. Andell, *J. Chem. Soc., Chem. Commun.*, 260 (1984).
47. E. Puentes, I. Mamalis, A. F. Noels, A. J. Hubert, Ph. Teyssié and D. Y. Waddan, *J. Catal.*, **82**, 365 (1983).
48. E. Puentes, A. J. Noels, R. Warin, A. J. Hubert, Ph. Teyssié and D. Y. Waddan, *J. Mol. Catal.*, **31**, 183 (1985).
49. G. A. Tolstikov, F. Ya Kanzafarov, Yu A. Sangalov, L. M. Zelenova and E. M. Vyrypaev, *J. Org. Chem. USSR*, **17**, 203 (1981).
50. H. Mayr, *Angew. Chem., Int. Ed. Engl.*, **29**, 1371 (1990).
51. H. Mayr and H. Klein, *Chem. Ber.*, **117**, 2555 (1984).
52. H. Mayr, R. Schneider, B. Irrgang and C. Schade, *J. Am. Chem. Soc.*, **112**, 4454 (1990).
53. H. Mayr and H. Klein, *Chem. Ber.*, **115**, 3528 (1982); H. Mayr and W. Striepe, *J. Org. Chem.*, **48**, 1159 (1983); Azizur–Rabman, H. Klein, J. Dressel and H. Mayr, *Tetrahedron*, **44**, 6041 (1988); R. Pock and H. Mayr, *Chem. Ber.*, **119**, 2497 (1986).
54. I. Martin and E. Muks, *J. Chem. Res. (S)*, 52 (1996).
55. H. Mayr, W. Förner and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **101**, 6032 (1979); **102**, 3663 (1980).
56. S. T. Purrington, B. S. Kagan and T. B. Patrick, *Chem. Rev.*, **86**, 997 (1986).
57. D. F. Shellhamer, C. M. Curtis, R. H. Dunham, D. R. Hollingsworth, M. L. Ragains, R. E. Richardson and V. L. Heasly, *J. Org. Chem.*, **50**, 2751 (1985).
58. V. L. Heasly, G. E. Heasly, R. A Loghry and M. R. McConnell, *J. Org. Chem.*, **37**, 2228 (1972).
59. (a) E. Z. Said and A. E. Tipping, *J. Chem. Soc., Perkin Trans. 1*, 1986 (1972).
    (b) M. A. Bigdely, A. C. Pratt and A. E. Tipping, *J. Chem. Soc. Pak.*, **14**, 35 (1992).
60. G. E. Heasly, D. Smith, J. N. Smith, V. L. Heasly and D. F. Shellhamer, *J. Org. Chem.*, **45**, 5206 (1980).
61. S. S. Shvanov, G. A. Tolstikov, I. M. Miniakhmetov, S. I. Lomakina and L. M. Xbalilov, *Zh. Org. Khim.*, **26**, 973 (1990); *J. Org. Chem.* USSR, **26**, 837 (1990).
62. D. F. Shellhamer, V. L. Heasly, J. E. Foster, J. K. Luttrull and G. E. Heasley, *J. Org. Chem.*, **43**, 2652 (1978).
63. M. A. Hashem, P. Weyerstahl and B. S. Green, *Tetrahedron*, **40**, 211 (1984).
64. G. B. Sergeev, G. T. Martirosyan, S. K. Akopyan, V. V. Smirnov, M. I. Shilina and S. A. Mkhitaryan, *Dokl. Acad. Nauk SSSR*, **295**, 115 (1987); *Dokl. Akad. Nauk. SSSR* (Eng. Trans.), **7**, 304 (1987).
65. G. E. Heasly, V. M. McCully, R. T. Wiegman, V. L. Heasly and R. A. Skidgel, *J. Org. Chem.*, **41**, 644 (1976).
66. V. L. Heasly, R. K. Gipe, J. L. Martin, H. C. Wiese, M. L. Oakes, D. F. Shellhamer, G. E. Heasly and B. L. Robinson, *J. Org. Chem.*, **48**, 3195 (1983).
67. G. E. Heasley, W. E. Emery III, R. Hinton, D. F. Shellhamer, G. E. Heasly and B. S. Rodgers, *J. Org. Chem.*, **43**, 361 (1978).
68. S. Uemura, A. Onoe and M. Okano, *Bull. Chem. Soc. Jpn.*, **47**, 692 (1974).
69. R. P. Vignes and J. Hamer, *J. Org. Chem.*, **39**, 849 (1974).
70. V. L. Heasly, K. D. Rold, D. R. Titterington, C. T. Leach, R. T. Gipe, D. B. McKee and G. E. Heasly, *J. Org. Chem.*, **41**, 3997 (1976).
71. S. Uemura, A. Onoe and M. Okano, *J. Chem. Soc., Chem. Commun.*, 210 (1975).

72. G. Haufe, *Tetrahedron Lett.*, **25**, 4365 (1984).
73. H. Hopf, R. Hänel, P. G. Jones and P. Bubenitschek, *Angew. Chem., Int. Ed. Engl.*, **33**, 1369 (1994).
74. G. E. Heasley, J. McCall Bundy, V. L. Heasley, S. Arnold, A. Gipe, D. McKee, R. Orr, S. L. Rodgers and D. F. Shellhamer, *J. Org. Chem.*, **43**, 2793 (1978).
75. G. Bellucci, C. Berti, R. Bianchini, G. Ingrosso and K. Yates, *J. Org. Chem.*, **46**, 2315 (1981).
76. U. Husstedt and H. J. Schäfer, *Synthesis*, 966 (1979).
77. V. L. Heasley, C. N. Griffith and G. E. Heasley, *J. Org. Chem.*, **40**, 1358 (1975).
78. T. Negoro and Y. Ikeda, *Bull. Chem. Soc. Jpn.*, **58**, 3655 (1985).
79. A. Kondo, T. Yamane, T. Ashida, T. Sasaki and K. Kanematsu, *J. Org. Chem.*, **43**, 1180 (1978).
80. L. A. Paquette, D. R. James and G. Klein, *J. Org. Chem.*, **43**, 1287 (1978).
81. G. Alvernhe, D. Anker, A. Laurent, G. Haufe and C. Beguin, *Tetrahedron*, **44**, 3551 (1988).
82. A. Gregoric and M. Zupan, *Tetrahedron*, **33**, 3243 (1977).
83. G. Haufe, G. Alvernhe and A. Laurent, *Tetrahedron*, **27**, 4449 (1986).
84. A. A. Bobyleva, E. V. Golubeva, N. F. Dubitskaya, T. I. Pekhk and N. A. Belikova, *Zh. Org. Khim.*, **21**, 680 (1985); *J. Org. Chem. USSR*, **21**, 616 (1985).
85. E. V. Lukovskaya, A. A. Bobyleva, T. I. Pekhk and N. A. Belikova, *Zh. Org. Khim.*, **27**, 345 (1991); *J. Org. Chem. USSR*, **27**, 293 (1991).
86. V. L. Heasley, L. S. Holstein III, R. J. Moreland, J. W. Rosbrugh, Jr and D. F. Shellhamer, *J. Chem. Soc., Perkin Trans. 2*, 1271 (1991).
87. J. Barluenga, J. M. González, P. J. Campos and G. Asensio, *Tetrahedron Lett.*, **27**, 1715 (1986).
88. J. Barluenga, J. M. Martínez–Gallo, C. Nájera, F. J. Fañanás and M. Yus, *J. Chem. Soc., Perkin Trans. 1*, 2605 (1987).
89. A. Hassner and J. Keogh, *Tetrahedron Lett.*, **19**, 1575 (1975).
90. T. Sasaki, K. Kanematsu and Y. Yukimoto, *J. Org. Chem.*, **37**, 890 (1972).
91. T. Sasaki, K. Kanematsu and Y. Yukimoto, *J. Chem. Soc., Perkin Trans. 1*, 375 (1973).
92. T. Sasaki, K. Kanematsu and A. Kondo, *Tetrahedron*, **31**, 2215 (1975).
93. G. Mehta and P. N. Pandey, *J. Org. Chem.*, **40**, 3631 (1975).
94. R. C. Cambie, P. S. Rutledge, G. M. Stewart, P. D. Woodgate and S. D. Woodgate, *Aust. J. Chem.*, **37**, 1689 (1984).
95. J. N. Labows and D. Swern, *J. Org. Chem.*, **37**, 3004 (1972).
96. B. Rose, D. Schollmeyer and H. Meier, *Liebigs Ann./Recueil*, 409 (1997).
97. V. A. Andreev, T. I. Pekhk, S. N. Anfilogova, N. A. Belikova and A. A. Bobyleva, *Zh. Org. Khim.*, **27**, 1450 (1991); *J. Org. Chem. USSR.*, **27**, 1259 (1991).
98. A. A. Bobyleva, E. V. Lukovskaya, T. I. Pekhk, N. F. Dubitskaya and N. A. Belikova, *Zh. Org. Khim.*, **25**, 1671 (1989); *J. Org. Chem. USSR*, **25**, 1507 (1989).
99. V. A. Andreyev, I. V. Bakhtin, Ye. V. Lukovskaya, T. I. Pekhk, A. A. Bobyleva, S. N. Anfilogova and N. A. Belikova, *Neftekhimiya*, **33**, 156 (1993); *Petrol. Chem.*, **33**, 146 (1993).
100. H. J. Günther, V. Jäger and P. S. Skell, *Tetrahedron Lett.*, **21**, 2539 (1977).
101. B. E. Kogai, V. K. Gubernantorov and V. A. Sokolenko, *Zh. Org. Khim.*, **20**, 2554 (1984); *J. Org. Chem. USSR*, **20**, 2324 (1984).
102. Yu. A. Sergushev, P. A. Krasutskii, A. B. Khotkevich and A. G. Yurchenko, *Teor. Eksp. Khim.*, **22**, 743 (1986); *Chem. Abstr.*, **107**, 77080 (1987).
103. Yu. A. Sergushev, A. B. Khotkevich, V. B. Barabash, P. A. Krasutskii and A. G. Yurchenko, *Teor. Eksp. Khim.*, **20**, 732 (1984); *Chem. Abstr.*, **102**, 148475 (1985).
104. P. A. Krasutskii, Yu. A. Sergushev, A. G. Yurchenko and A. B. Khotkevich, *Teor. Eksp. Khim.*, **19**, 229 (1983); *Chem. Abstr.*, **99**, 69920 (1983).
105. A. B. Khotkevich, Yu. A. Sergushev, P. A. Krasutskii, O. V. Kaminskii and A. G. Yurchenko, *Teor. Eksp. Khim.*, **25**, 249 (1989); *Chem. Abstr.*, **111**, 193874 (1989).
106. W. A. Smit, N. S. Zefirov, I. V. Bodrikov and M. Z. Krimer, *Acc. Chem. Res.*, **12**, 282 (1979).
107. F. Capozzi, G. Capozzi and S. Menichetti, *Tetrahedron Lett.*, **29**, 4177 (1988).
108. K. C. Nicolau, W. E. Barnette and R. Magolda, *J. Am. Chem. Soc.,* **103**, 3472 (1981).
109. E. Kuehle, *The Chemistry of Sulfenic Acids*, G. Thieme, Stuttgart, 1973.
110. G. Capozzi, G. Melloni and G. Modena, *J. Chem. Soc. (C)*, 2617 (1970).
111. F. Dasgupta and P.I Garegg, *Carbohydr. Res.*, **177**, 13 (1988).
112. A. J. Havlik and N. Karasch, *J. Am. Chem. Soc.*, **78**, 1207 (1956).

113. G. H. Schmid and I. G. Csizmadia, *Int. J. Sulfur Chem.*, **8**, 433 (1973).
114. L. Benati, P. C. Montevecchi and P. Spagnolo, *Gazz. Chim. Ital.*, **121**, 387 (1991).
115. R. Laitinen, R. Steudel and R. Weiss, *J. Chem. Soc., Dalton Trans.*, 1095 (1986).
116. E. Ciuffarin and A. Fava, *Prog. Phys. Org. Chem.*, **6**, 81 (1968).
117. V. Lucchini, G. Modena and L. Pasquato, *Gazz. Chim. Ital.*, **127**, 1 (1997).
118. B. T. Golding, E. Pombo–Villar and C. J. Samuel, *J. Chem. Soc., Chem. Commun.*, 1444 (1985).
119. H. Mosimann, Z. Dienes and P. Vogel, *Tetrahedron*, **51**, 6495 (1995).
120. J.-M. Tornare and P. Vogel, *J. Org. Chem.*, **49**, 2510 (1984).
121. J.-M. Tornare and P. Vogel, *Helv. Chim. Acta*, **68**, 1069 (1985).
122. E. Kuele, *Synthesis*, 561 (1970); 563, 617 (1971).
123. G. Haufe, G. Alvernhe, D. Anker, A. Laurent and C. Saluzzo, *J. Org. Chem.*, **57**, 714 (1992).
124. T. V. Popkova, A. V. Shastin, T. Lazhko and E. S. Balenkova, *J. Org. Chem. USSR*, **22**, 2210 (1986).
125. V. G. Nenajdenko, N. E. Shevchenko and E. S. Balenkova, *Tetrahedron*, **54**, 5353 (1998).
126. V. G. Nenajdenko, N. E. Shevchenko and E. S. Balenkova, *J. Org. Chem.*, **63**, 2168 (1998).
127. N. S. Zefirov, A. S. Koz'min, V. N. Kirin, V. V. Zhdankin and R. Caple, *J. Org. Chem.*, **46**, 5264 (1981).
128. N. S. Zefirov, V. N. Kirin, A. S. Koz'min, I. V. Bodrikov, K. A. Potekhin and E. N. Kurkutova, *Tetrahedron Lett.*, 2617 (1978).
129. N. S. Zefirov, A. S. Koz'min and V. V. Zhdankin, *Tetrahedron*, **38**, 291 (1982).
130. V. K. Kartashov, E. V. Skorobogatova, E. Yu. Grudzinskaja, N. F. Akimkina, N. S. Zefirov and R. Caple, *Tetrahedron*, **41**, 5219 (1985).
131. B. M. Trost, M. Ochiai and P. G. McDougal, *J. Am. Chem. Soc.*, **100**, 7103 (1978).
132. G. H. Schmid, *Can. J. Chem.*, **46**, 3757 (1968).
133. *The Chemistry of Organic Selenium and Tellurium Compounds*, Vol. 1 (Eds. S. Patai and Z. Rappoport), Wiley, Chichester, 1986 and Vol. 2 (Ed. S. Patai), Wiley, Chichester, 1987.
134. T. G. Back and S. Collins, *J. Org. Chem.*, **46**, 3249 (1981).
135. J.-E. Bäckvall, C. Nájera and M. Yus, *Tetrahedron Lett.*, **29**, 1445 (1988).
136. H. J. Reich, *J. Org. Chem.*, **39**, 429 (1974).
137. C. Nájera, M. Yus, U. Karlsson, A. Gogoll and J.-E. Bäckvall, *Tetrahedron Lett.*, **31**, 4199 (1990).
138. A. Toshimitsu, S. Uemura and M. Okano, *J. Chem. Soc., Chem. Commun.*, 965 (1982).
139. D. G. Garratt, M. D. Ryan and A. Kabo, *Can. J. Chem.*, **58**, 2329 (1980).
140. D. G. Garratt and A. Kabo, *Can. J. Chem.*, **58**, 1030 (1980).
141. D. L. J. Clive, G. Chittattu and C. K. Wong, *J. Chem. Soc., Chem. Commun.*, 441 (1978).
142. C. G. Francisco, R. Hernández, E. I. León, J. A. Salazar and E. Suárez, *J. Chem. Soc., Perkin Trans. 1*, 2417 (1990).
143. A. Toshimitsu, T. Aoai, S. Uemura and M. Okano, *J. Org. Chem.*, **46**, 3021 (1981).
144. S. Murata and T. Suzuki, *Tetrahedron Lett.*, **31**, 6535 (1990).
145. J. Chatt, *Chem. Rev.*, **48**, 7 (1951).
146. R. C. Larock, *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, New York, 1986.
147. H. B. Vardhan and R. D. Bach, *J. Org. Chem.*, **57**, 4948 (1992).
148. H. J. Lucas, F. R. Hepner and S. Winstein, *J. Am. Chem. Soc.*, **61**, 3102 (1939).
149. D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.*, **92**, 7480 (1970).
150. R. Bach and H. F. Henneike, *J. Am. Chem. Soc.*, **92**, 5589 (1970).
151. I. C. Ambridge, S. K. Dwight, C. M. Rynard and T. T. Tidwell, *Can. J. Chem.*, **55**, 3086 (1977).
152. A. Lewis, *J. Org. Chem.*, **49**, 4682 (1984).
153. H. C. Brown, P. J. Geoghegan, G. J. Lynch and J. T. Kurek, *J. Org. Chem.,* **37**, 1941 (1972).
154. S. Moon, J. M. Takakis and B. H. Waxman, *J. Org. Chem.,* **34**, 2951 (1969).
155. A. J. Bloodworth, M. G. Hutchings and A. J. Sotowicz, *J. Chem. Soc., Chem. Commun.*, 578 (1976).
156. J. Barluenga, J. Pérez–Prieto and G. Asensio, *J. Chem. Soc., Chem. Commun.*, 1181 (1982).
157. J. Barluenga, J. Pérez–Prieto and G. Asensio, *J. Chem. Soc., Perkin Trans. 1*, 629 (1984).
158. O. S. Andell and J.-E. Bäckvall, *Tetrahedron Lett.*, **26**, 4555 (1985).
159. J.-E. Bäckvall, J. E. Nyström and R. E. Nordberg, *J. Am. Chem. Soc.*, **107**, 3676 (1985).

160. R. C. Cookson, J. Hudek and J. Marsden, *Chem. Ind. (London)*, 21 (1961).
161. N. S. Zefirov, A. S. Koz'min, V. N. Kirin, B. B. Sedov and V. G. Rau, *Tetrahedron Lett.*, **21**, 1667 (1980).
162. V. R. Kartshov, T. N. Solokova, E. V. Skorobogatova, Yu. K. Grishin, D. V. Bazhenov and N. S. Zefirov, *Zh. Org. Khim.*, **23**, 1801 (1987); *J. Org. Chem. USSR*, **23**, 1783 (1987).
163. E. Vedejs and M. F. Solom, *J. Org. Chem.*, **37**, 2075 (1972).
164. S. Uemura, H. Miyoshi, M. Okano, I. Morishima and T. Inubushi, *J. Organomet. Chem.*, **171**, 131 (1979).
165. P. Wilder, A. R. Portis, G. W. Wright and J. M. Shepherd, *J. Chem. Soc.*, **39**, 1636 (1974).
166. N. Takaishi, Y. Fujikura and Y. Inamoto, *J. Org. Chem.*, **40**, 3767 (1975).
167. V. R. Kartashov, T. N. Sokolova, I. V. Timofeev, Yu. K. Grishin, D. V. Bazhenov and N. S. Zefirov, *Zh. Org. Khim.*, **27**, 2077 (1991); *J. Org. Chem. USSR*, **27**, 1938 (1991).
168. H. Settler and E. F. Schwartz, *Chem. Ber.*, **101**, 2464 (1968).
169. V. Gómez–Aranda, J. Barluenga, G. Asensio and M. Yus, *Tetrahedron Lett.*, **16**, 3621 (1972).
170. J. Barluenga, J. Pérez–Prieto, A. M. Bayón and G. Asensio, *Tetrahedron*, **40**, 1199 (1984); J. Barluenga, J. Pérez–Prieto, G. Asensio, S. Garcia–Granda and M. A. Salvado, *Tetrahedron*, **48**, 3813 (1992).
171. J. Barluenga, C. Jiménez, C. Nájera and M. Yus, *J. Heterocycl. Chem.*, **21**, 1733 (1984).
172. J. Barluenga, C. Jiménez, C. Nájera and M. Yus, *J. Chem. Soc., Perkin Trans. 1*, 721 (1984).
173. J. Barluenga, C. Nájera and M. Yus, *J. Heterocycl. Chem.*, **18**, 1297 (1981).
174. A. J. Bloodworth and M. E. Loveitt, *J. Chem. Soc., Perkin Trans. 1*, 522 (1978).
175. A. J. Bloodworth and J. A. Khan, *J. Chem. Soc., Perkin Trans. 1*, 2450 (1980).
176. M. F. Ruasse, S. Motallebi and B. Galland, *J. Am. Chem. Soc.*, **113**, 3440 (1991).
177. M. F. Ruasse and J. E. Dubois, *J. Am. Chem. Soc.*, **97**, 1977 (1975).
178. R. S. Brown, R. Gedye, H. Slebocka–Tilk, J. M. Buschek and K. R. Kopecky, *J. Am. Chem. Soc.*, **106**, 4515 (1984); G. Bellucci, R. Bianchini, C. Chiappe, D. Lenoir and A. Attar, *J. Am. Chem. Soc.*, **117**, 6243 (1995); H. Slebocka–Tilk, S. Motallebi, R. W. Nagorski, P. Turner, R. S. Brown and R. McDonald, *J. Am. Chem. Soc.*, **117**, 8769 (1995).
179. V. Lucchini, G. Modena and L. Pasquato, *J. Am. Chem. Soc.*, **113**, 6600 (1991).
180. R. Neumann and A. Khenkin, in *The Chemistry of Dienes and Polyenes* (Ed. Z. Rappoport), Vol. 1, Wiley, Chichester, 1997, p. 889.
181. (a) S. Patai (Ed.), *The Chemistry of Ketenes, Allenes and Related Compounds*, Wiley, New York, 1980.
(b) W. Smadja, *Chem. Rev.*, **83**, 263 (1983).
(c) H. F. Schuster and G. M. Coppola, in *Allenes in Organic Synthesis*, Wiley, New York, 1988.
182. A. J. Pearson, in *Comprehensive Organic Synthesis* (Eds. B. M. Trost and I. Fleming), Vol. 4, Pergamon Press, Oxford, 1991, p. 585.
183. J.-E. Bäckvall, in *The Chemistry of Dienes and Polyenes* (Ed. Z. Rappoport), Vol. 1, Wiley, Chichester, 1997, p. 653.

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CHAPTER **8**

Nucleophilic additions to dienes, enynes and polyenes

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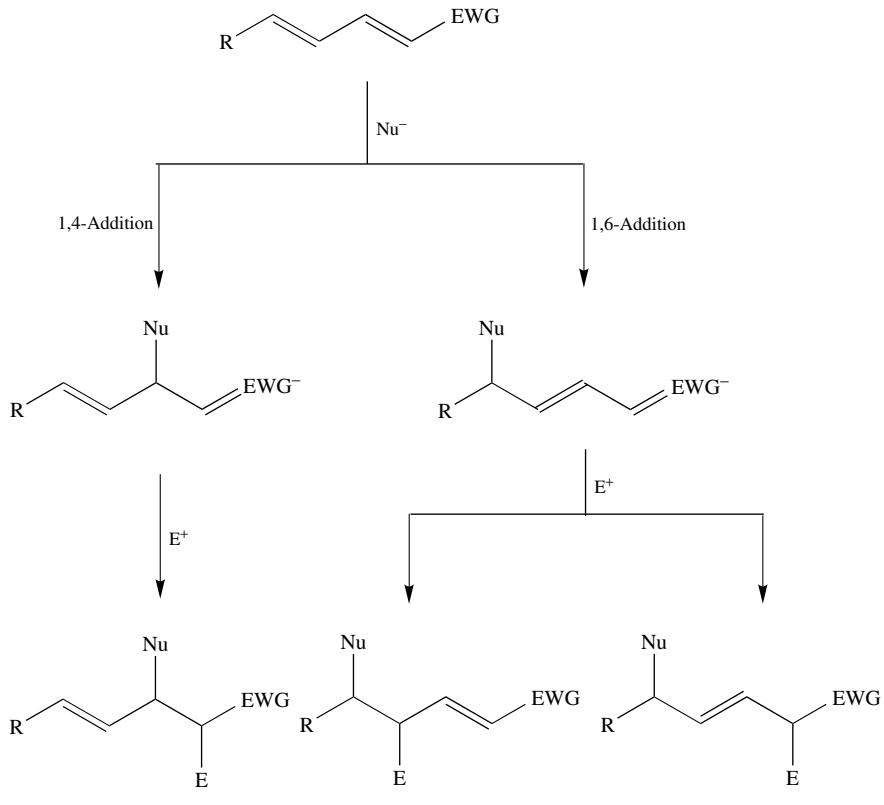
I. INTRODUCTION

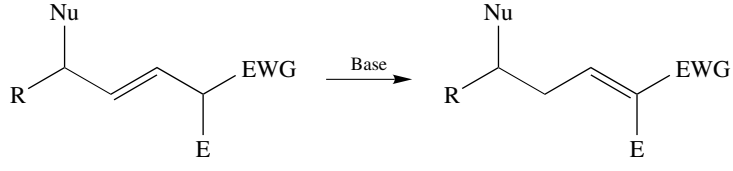
Due to their electron-rich π-systems, unsaturated hydrocarbons normally do not undergo nucleophilic but rather electrophilic additions. In order to activate a double bond for a nucleophilic attack, its electron density has to be decreased; this can be achieved by coordination to a metal, e.g. palladium(II)[1], or more conveniently by introduction of an electron-withdrawing group which acts as an intramolecular π-acceptor. Nucleophilic additions to these ambident acceptor dienes and polyenes substituted with electron-withdrawing groups (EWGs), can provide several isomeric products; hence, it is of particular importance to control the *regioselectivity* and *stereoselectivity* of these transformations (Scheme 1). Besides direct nucleophilic attack on the acceptor group, an activated diene may undergo a 1,4- or 1,6-addition; in the latter case, capture of the ambident enolate with a soft electrophile (E^+) can also take place at two different positions. Thus, the nucleophilic addition can produce three regioisomeric alkenes which may be formed as E/Z isomers. Depending on the nature of nucleophile and electrophile, the adducts also contain one or two centers of chirality.

The product distribution may depend on the reaction conditions if the nucleophilic attack is reversible (kinetic vs. thermodynamic control). An additional complication arises from



SCHEME 1

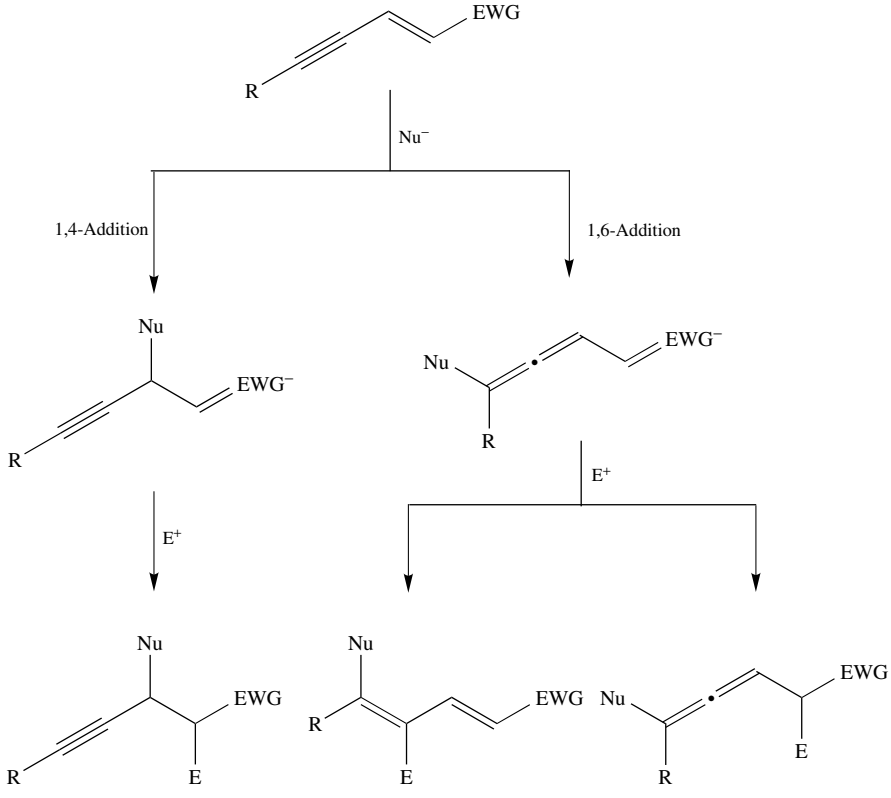
the fact that β,γ-unsaturated carbonyl compounds (and other acceptor-substituted alkenes of this type) are readily isomerized to the thermodynamically more stable conjugated isomers under basic conditions (equation 1, where EWG is a conjugating group, e.g., a carbonyl group).



(1)

Similar schemes can be developed easily for analogous reactions of acceptor-substituted polyenes. For example, a triene with an acceptor group in 1-position can form six regioisomeric products of Michael addition and electrophilic capture, and each of these exists as E/Z stereoisomers, diastereomers and/or enantiomers. Thus, reactions of this type are only useful if both the regio- and stereoselectivity can be controlled; fortunately, only one isomeric Michael adduct is formed in many cases. This is true in particular for polyunsaturated Michael acceptors which bear at least one triple bond besides one or more double bonds. An additional feature of the latter substrate type is that nucleophilic additions can

give rise to the formation of axial chirality (Scheme 2). For example, the addition of a nucleophile to an acceptor-substituted enyne may take place in a 1,4- or 1,6-fashion, and the ambident allenyl enolate formed in the latter case can trap a soft electrophile to furnish either an allene or a conjugated diene. Again, several stereoisomeric products can be obtained in each case.



SCHEME 2

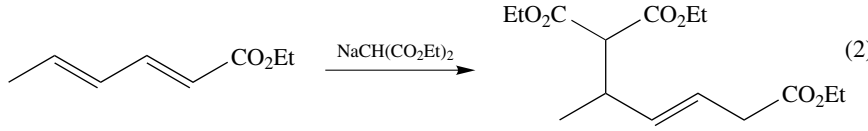
In this chapter, nucleophilic 1,*n*-additions ($n = 4, 6, 8, \ldots$) to acceptor-substituted dienes, enynes and polyenes are presented[2]. Addition reactions which obviously proceed via non-nucleophilic pathways (e.g. catalytic reductions, electrophilic or radical additions[3]), as well as 1,2-additions to the acceptor group, are not covered.

II. DIENES

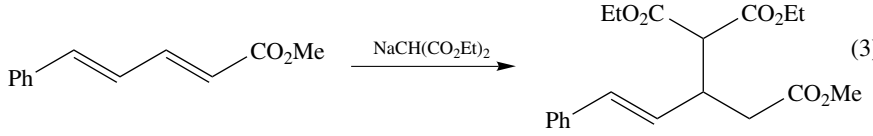
A. Carbon Nucleophiles

Early investigations of additions of soft carbon nucleophiles to simple Michael acceptors like ethyl sorbate date back to the beginning of the 20th century. Already in 1906, Vorländer and coworkers[4–6] described additions of malonate anion; whereas ethyl sorbate provided the 1,6-addition product[6] (equation 2), the 1,4-adduct was obtained from methyl 5-phenyl-2,4-pentadienoate[4] (equation 3). Thus, it seems that the regioselectivity

of the Michael addition is sensitive to the steric properties of the substrate. Similarly, phenyl-substituted 2,4-dienones reacted with sodium malonate under 1,4-addition[4,5]. The products were analyzed by oxidative degradation.

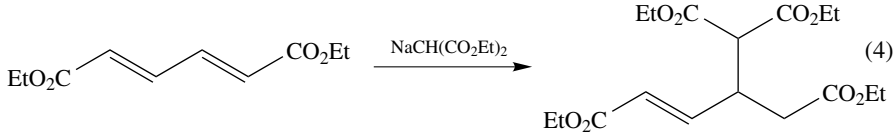


(2)



(3)

This work was repeated by several groups[7–11]; in the reaction of sodium dimethylmalonate with methyl sorbate, Farmer and Metha[9] observed small amounts of the 1,4-adduct besides the 1,6-addition product. Difficulties in conducting the transformations and analyzing the products are evident from reports on malonate additions to ethyl muconate[12–14]: depending on the reaction conditions, the expected 1,4-adduct (equation 4) or isomerization products formed by double bond displacement were isolated. Nucleophilic 1,4- and 1,6-addition reactions to 2,4-pentadienenitrile were also reported[15–17].



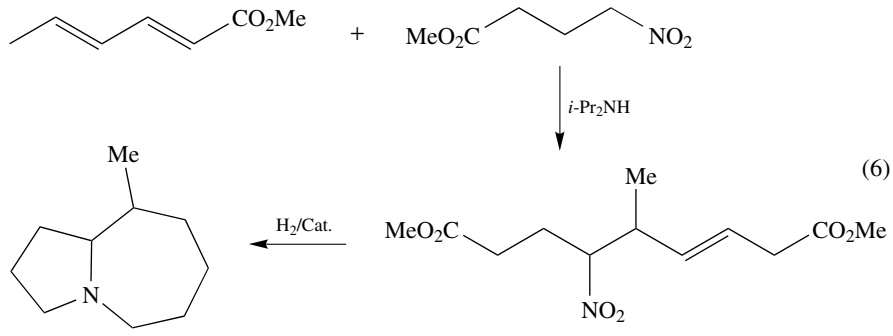
(4)

Michael additions to acceptor-substituted dienes are often followed by (spontaneous or induced) cyclizations. This was already noted by Vorländer and Groebel[4] who obtained a substituted 1,3-cyclohexanedione by treatment of 6-phenyl-3,5-hexadien-2-one with diethyl malonate (equation 5). Obviously, the 1,4-addition product which is formed initially then undergoes cyclization, ester hydrolysis and decarboxylation. Similarly, reaction of methyl sorbate with methyl 4-nitrobutyrate gave the 1,6-adduct which was reductively cyclized to 6-methyl-1-azabicyclo[5.3.0]decane[18] (equation 6).

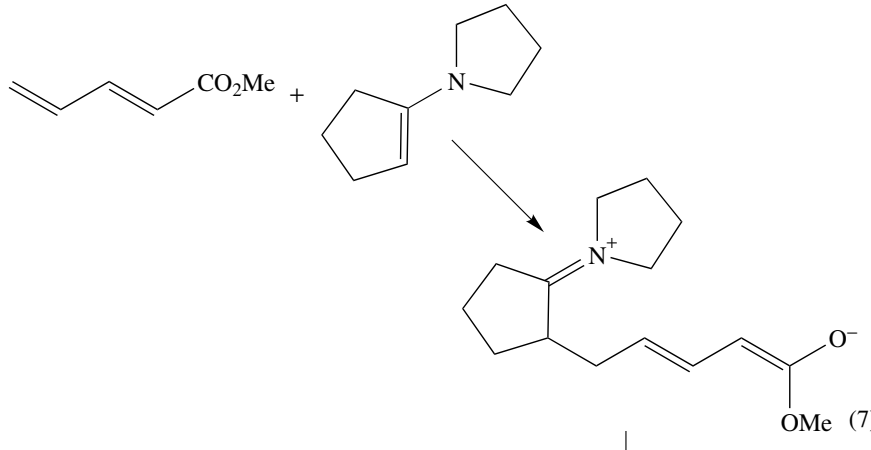
(5)

In 1965, Danishefsky and Cunningham[19] and Berchtold and coworkers[20] simultaneously reported 1,6-addition reactions of enanimes to conjugated dienoates; the zwitterionic intermediates cyclize spontaneously and eliminate an amine to furnish 1,3-cyclohexadienes

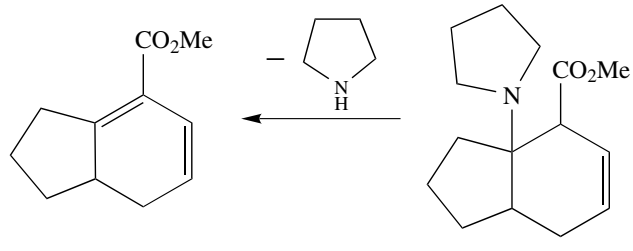
which can be oxidized easily to benzenes (equation 7). A similar approach was used by Heuschmann[21] who employed 1,3-dimethyl-2-methylenimidazolidine as nucleophile. Analogously, quinolines and isoquinolines were obtained when piperidone enamines were used for the 1,6-addition[22] (equation 8).



(6)



(7)



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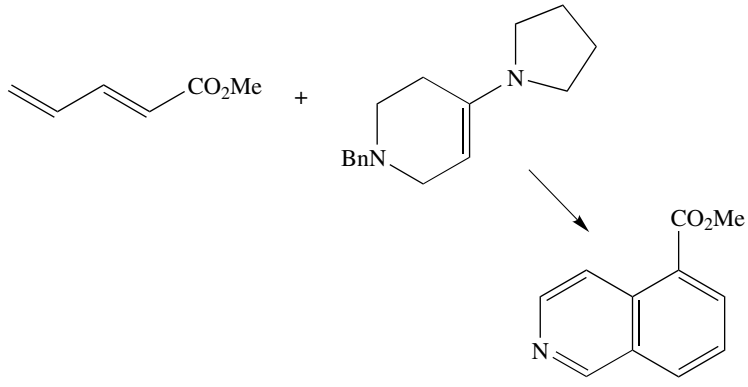
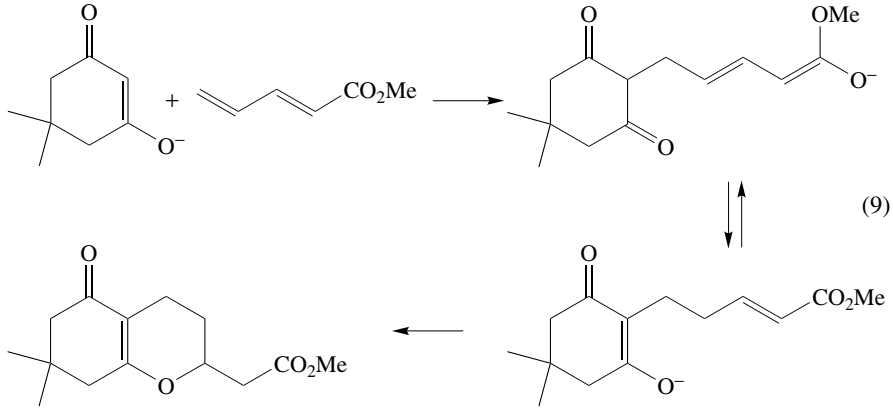


(8)

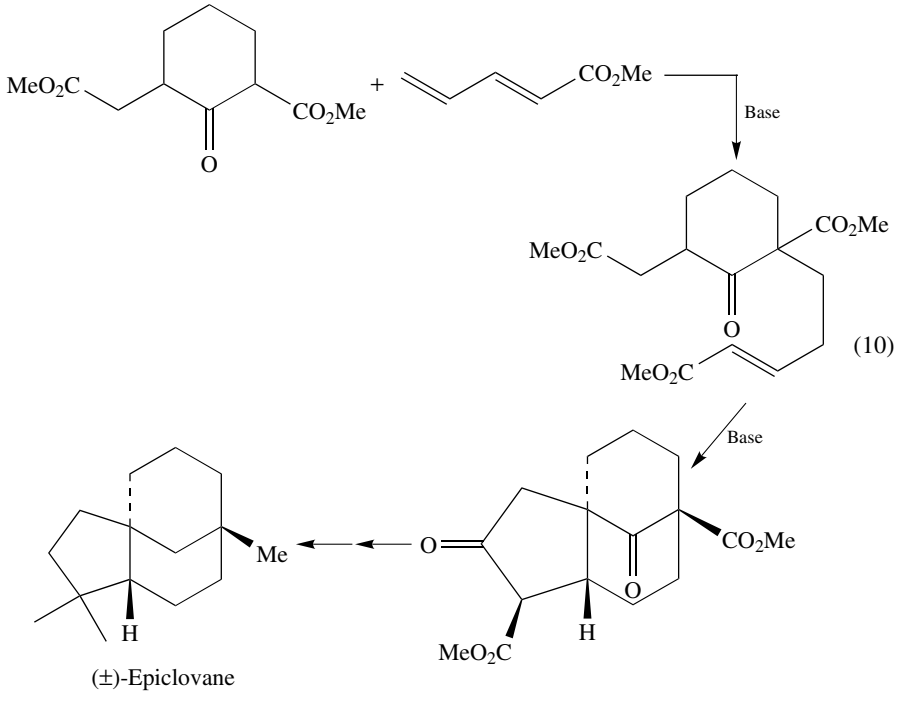
In a very similar manner, tandem 1,6- and 1,4-additions of β-dicarbonyl compounds to methyl 2,4-pentadienoate were utilized by Danishefsky and coworkers[23–25] for the formation of several bi- and tricyclic ring systems. For example, reaction of the enolate of dimedone with this ester gave the expected 1,6-addition product; protonation/deprotonation set the stage for a subsequent intramolecular 1,4-addition (equation 9)[23]. Likewise, a ketodiester was used to transform the pentadienoate in a one-pot procedure by consecutive 1,6- and 1,4-additions into a richly functionalized tricyclic product which was then converted into the natural product (±)-epiclovane[25] (equation 10). According to this principle, Irie and coworkers[26] obtained several decalin-2,7-diones by treatment of 2-methylen-2-cyclohexenones with dimethyl 3-oxoglutarate.



(9)

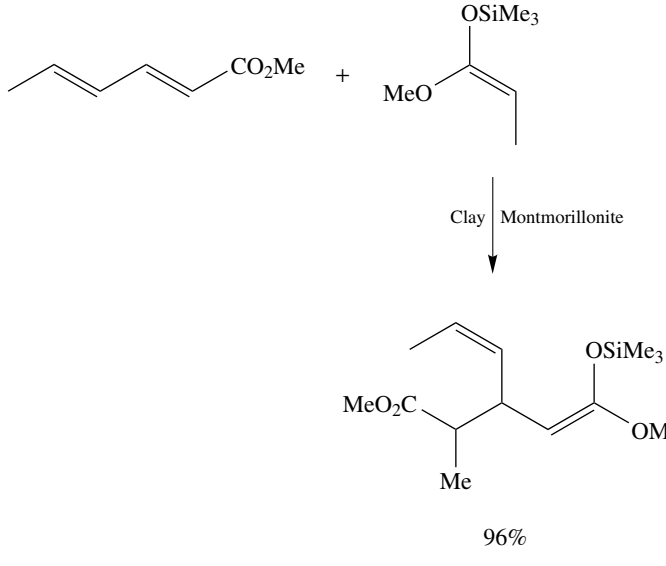
In contrast to these transformations, Michael additions of simple enolates to acceptor-substituted dienes often yield mixtures of 1,4- and 1,6-addition products[27–30]. For example, a 70 : 30 mixture of 1,4- and 1,6-adducts was isolated from the reaction of the lithium enolate of methyl propionate with methyl sorbate[30]. This problem can be solved by using the corresponding silyl ketene acetal in the presence of clay montmorillonite as acidic promoter: under these conditions, almost exclusive formation of the 1,4-addition product (*syn/anti* mixture) was observed (equation 11)[30]. Highly regioselective 1,4-additions

to activated dienes were also reported with allyltrimethylsilane/*n*-Bu_4NF[31] and tin(II) dienolates[32] as nucleophiles.



(10)

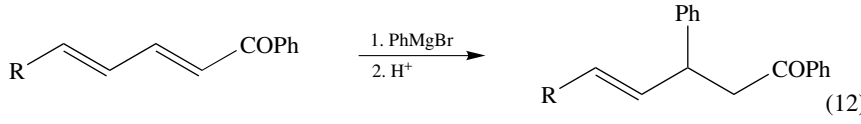
(±)-Epiclovane



(11)

96%

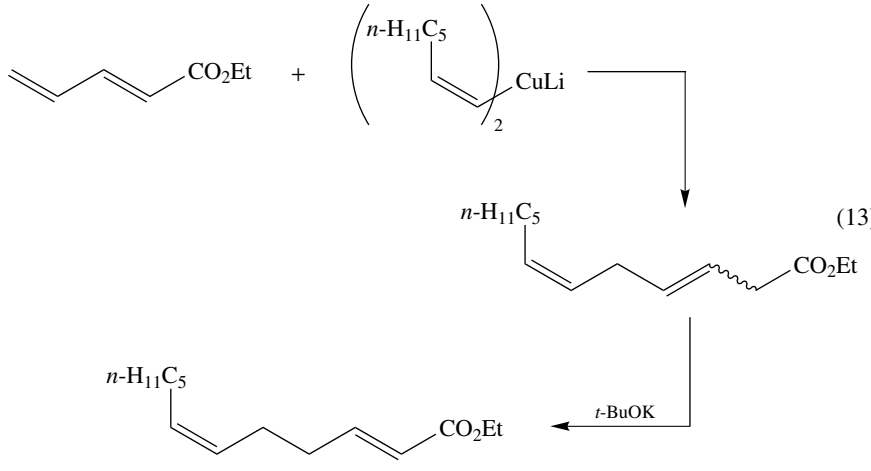
Simple organometallic reagents have to be used as nucleophiles in order to transfer unfunctionalized groups to a Michael acceptor. Already in 1926, Kohler and Butler[7] demonstrated that regioselective Michael additions of Grignard reagents to acceptor-substituted dienes are feasible. Treatment of 1-phenyl- and 1,5-diphenyl-2,4-pentadienone with phenylmagnesium bromide gave rise to the formation of the 1,4-addition products (equation 12). Likewise, organolithium compounds were found to add with high 1,4-regioselectivity to dienoic thioamides[33] and acylylides[34]. In contrast to this, 1-naphthyl-[35] and 2-styryloxazolines[36] react with Grignard and organolithium reagents under 1,6-addition. Analogously, 1,6-addition products were obtained from simple aromatic carbonyl compounds, such as benzaldehyde and benzophenone, and organolithium reagents when the carbonyl group was shielded by complexation with the sterically demanding Lewis acid aluminum tris(2,6-diphenylphenoxide)[37].



(12)

R = H, Ph

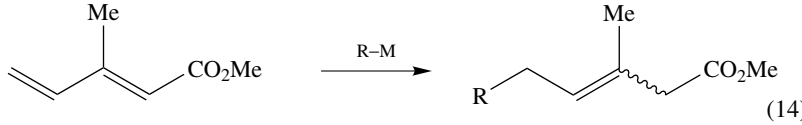
Subsequent studies by many different groups have shown that organocopper compounds are the reagents of choice for these transformations[38]. The major advantage of these nucleophiles is that the regioselectivity of the Michael addition can be controlled by 'tuning' of the reagent (see below); this feature distinguishes organocopper reagents from all other nucleophiles which can be used in additions to polyunsaturated substrates. The first example was reported by Näf and coworkers[39] who used lithium di-(*Z*)-1-heptenylcuprate in a Michael addition to ethyl 2,4-pentadienoate. The reaction proceeded with high regioselectivity to furnish a 1 : 1 mixture of ethyl (3*E*,6*Z*)- and (3*Z*,6*Z*)-3,6-dodecadienoate which was converted into the Bartlett pear constituent ethyl (2*E*,6*Z*)-2,6-dodecadienoate by basic isomerization (equation 13).



(13)

Subsequently, Corey and coworkers[40–42] described nucleophilic addition reactions of organocopper reagents and organocuprates to several acceptor-substituted dienes. The

choice of the reagent did not affect the regioselectivity, since exclusive 1,6-addition took place in all cases examined. However, organocopper reagents RCu reacted also stereoselectively to give the addition products with (*E*)-configuration whereas Gilman cuprates R_2CuLi yielded 1 : 1 mixtures of the *E*/*Z* isomers (equation 14)[41]. Similarly, propargylcopper reagents can be added regio- and stereoselectively to 2,4-dienoates[43].

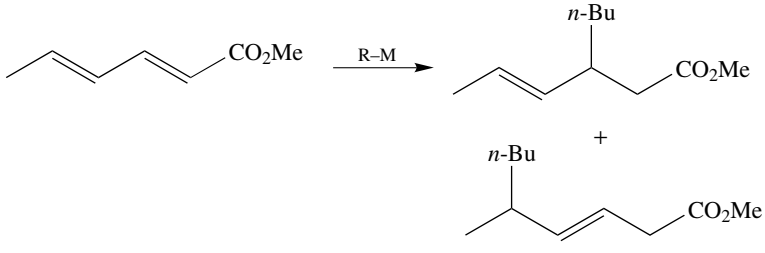


(14)

R-M = *n*-BuCu or $H_2C{=}CHCu$: *E* : *Z* = >95 : <5

n-Bu_2CuLi or $(H_2C{=}CH)_2CuLi$: *E* : *Z* ≈ 50 : 50

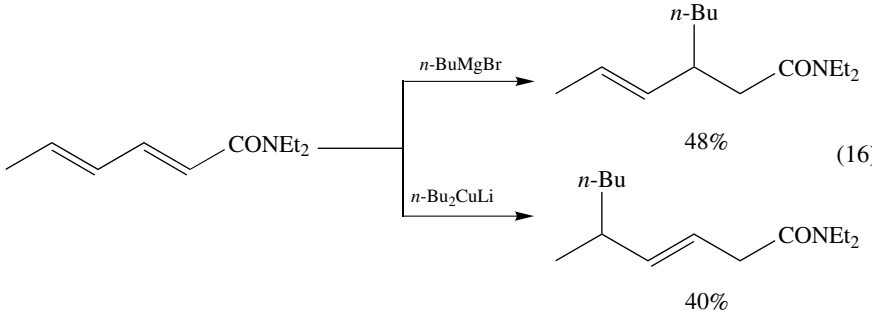
Whereas these and other reports[44–48] did not indicate the possibility of 1,4-cuprate additions to activated dienes, Yamamoto and coworkers[49,50] showed in their seminal contributions that this is indeed feasible: while the reaction of methyl sorbate with the Gilman cuprate *n*-Bu_2CuLi provided exclusively the 1,6-addition product, the reagent formed from butylcopper and the Lewis acid boron trifluoride led to the 1,4-adduct as the major product (equation 15). The synthetically very useful organocopper compounds RCu • BF_3[50] have been named Yamamoto reagents. In certain cases, the regioselectivity of these transformations can also be controlled by using different nucleophiles[31,51], for example with *N*,*N*-diethylsorbic amide as substrate (equation 16): whereas Gilman cuprates again reacted under 1,6-addition, the 1,4-adducts were obtained with Grignard reagents[51].



(15)

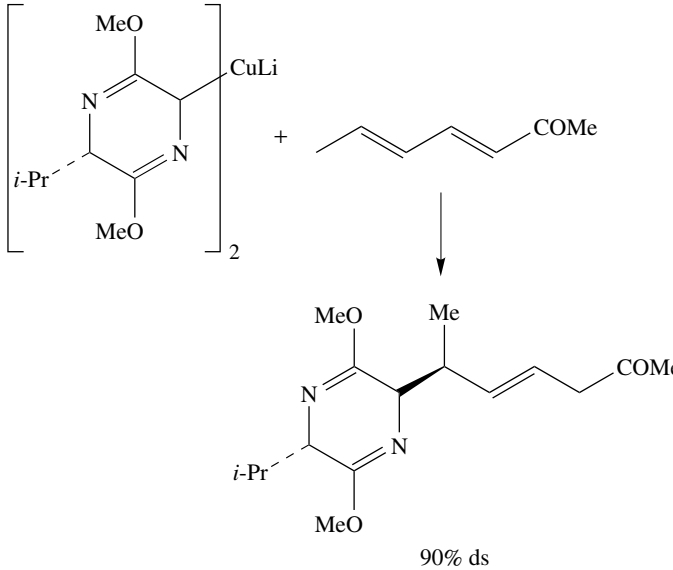
R-M = *n*-BuCu • BF_3: 93 : 7

n-Bu_2CuLi: <1 : >99



(16)

Nucleophilic 1,4- and 1,6-additions of cuprates and other organometallic reagents to acceptor-substituted dienes have been utilized extensively in target-oriented stereoselective synthesis[52–61]. Schöllkopf and coworkers[55] reported the diastereoselective 1,6-addition of a bislactim ether-derived cuprate to 3,5-heptadien-2-one (90% ds; equation 17). The corresponding reactions of dienoates were conducted with the lithiated bislactim ether and proceeded with diastereoselectivities of >99% ds (equation 18)[56]; the adducts could be converted easily into diastereo- and enantiomerically pure amino acid derivatives.

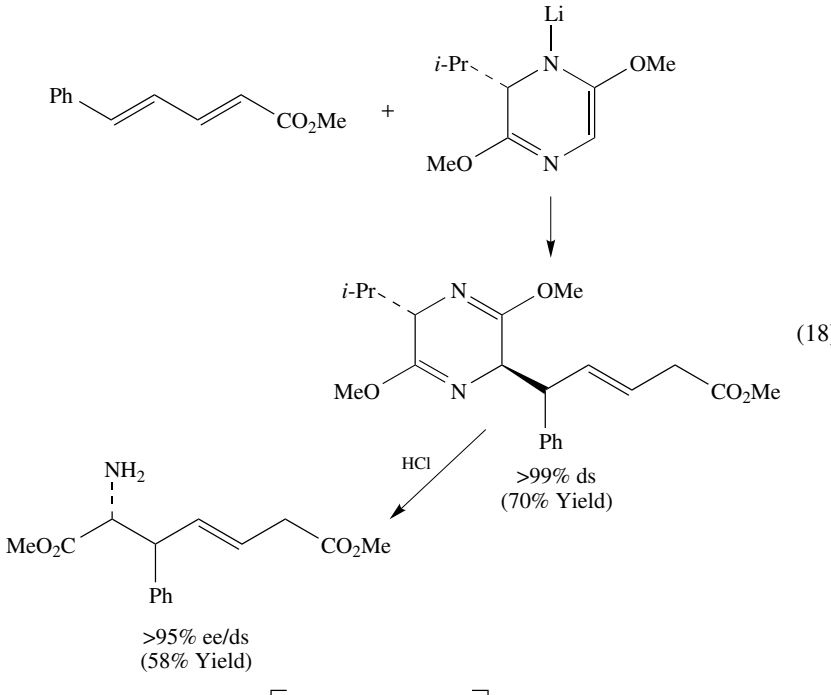


(17)

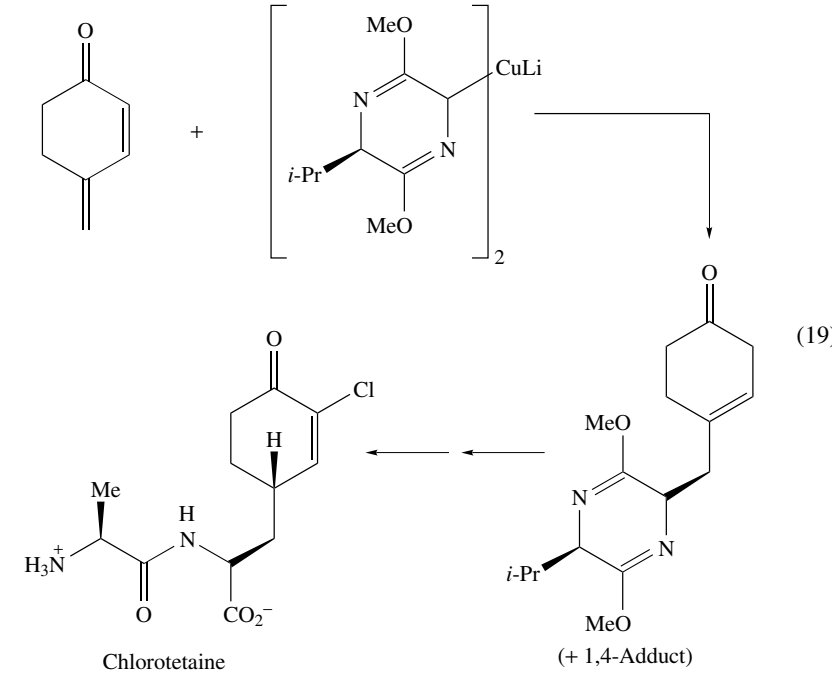
90% ds

The Schöllkopf bislactim ether cuprate was also used in the first total synthesis of the antimycotic dipeptide chlorotetaine (equation 19)[58]. In this case, however, the nucleophilic addition to 4-methylene-2-cyclohexenone did not proceed regioselectively since a 63 : 37 mixture of the 1,6- and 1,4-adduct was obtained. The 1,6-addition product was converted via several steps into diastereo- and enantioselectively pure chlorotetaine.

Most applications of stereoselective Michael additions of organometallic reagents to activated dienes are directed towards the synthesis of steroid hormones. Particularly interesting are estradiol derivatives bearing an alkyl chain in the 7α-position since these steroids were found to bind with high affinity and specificity to estrogen receptors; i.e. they are effective antiestrogenic agents[62] and may therefore be useful for the treatment of mammary tumors (breast cancer)[63]. The obvious way to introduce a group in the 7-position of a steroid backbone is a nucleophilic 1,6-addition to an acceptor-substituted doubly unsaturated $\Delta^{4,6}$-derivative, and many organometallic reagents (in particular organocopper compounds) do indeed react with the desired regioselectivity[63–88]. Here, the major challenge is the control of the diastereoselectivity of the Michael addition since the 7β-isomers are less effective enzyme inhibitors[63]. Addition reactions to tetrahydro-3*H*-naphthalen-2-ones, which can be considered as model substrates for $\Delta^{4,6}$-steroids, were examined by several groups[64–70]. Already in 1958, Yanagita and coworkers[64] observed a *trans*-selective 1,6-addition reaction of diethyl malonate to the 1,4a-dimethyl-substituted naphthalenone. In a series of papers, Marshall and coworkers[65–68] reported copper-catalyzed Michael additions to various bicyclic dienones; for example, treatment of

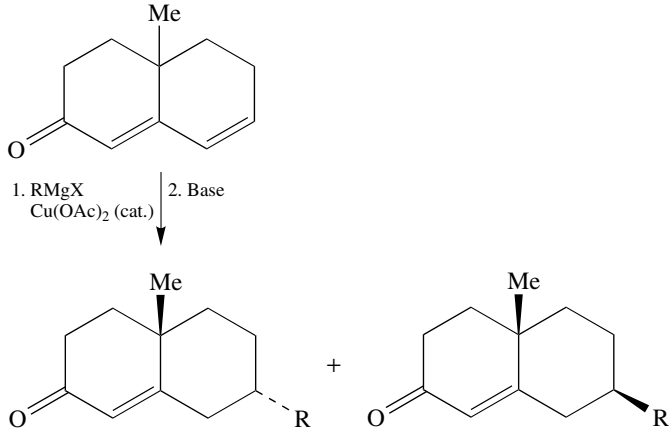

Ph
CO2Me
+
Li
i-Pr
N
OMe
MeO
N
i-Pr
N
OMe
MeO
N
CO2Me
Ph
HCl
>99% ds
(70% Yield)
NH2
MeO2C
CO2Me
Ph
>95% ee/ds
(58% Yield)

(18)


O
+
MeO
CuLi
N
N
i-Pr
MeO
2
O
MeO
N
N
i-Pr
MeO
(+ 1,4-Adduct)
O
Cl
H
Me
H
N
H3N+
O
CO2−
Chlorotetaine

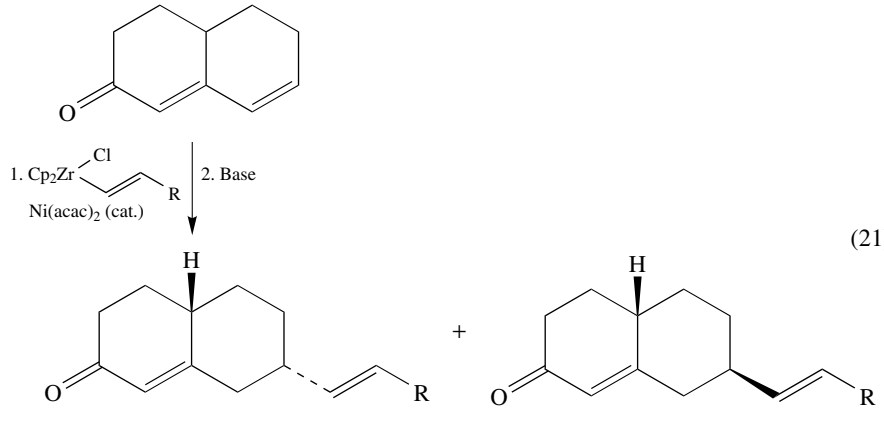
(19)

4a-methyl-4,4a,5,6-tetrahydro-3*H*-naphthalen-2-one with Grignard reagents in the presence of $Cu(OAc)_2$ furnished mixtures of 1,2- and 1,6-addition products. The 1,6-adducts consisted mainly of the *trans* isomer, and the diastereoselectivity increased with increasing steric bulk of the Grignard reagent (equation 20)[65]. In contrast to this, diastereoselectivities close to 1 : 1 were reported in the Cu(II)-catalyzed 1,6-addition of *n*-hexylmagnesium bromide[65] and the Ni(II)-catalyzed 1,6-addition of alkenylzirconium reagents to the unsubstituted naphthalenone (equation 21)[69]. The regioselectivity of cuprate additions to bicyclic dienones depends very strongly on the substitution pattern of the Michael acceptor[66].



(20)

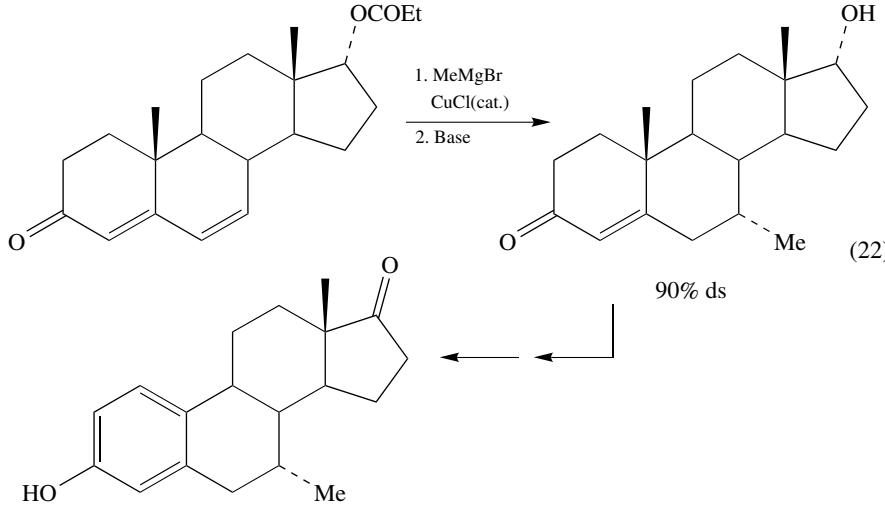
RMgX =		
MeMgI:	93	: 7
EtMgBr:	98	: 2
i-PrMgBr:	>99	: <1
t-BuMgCl:	>99	: <1

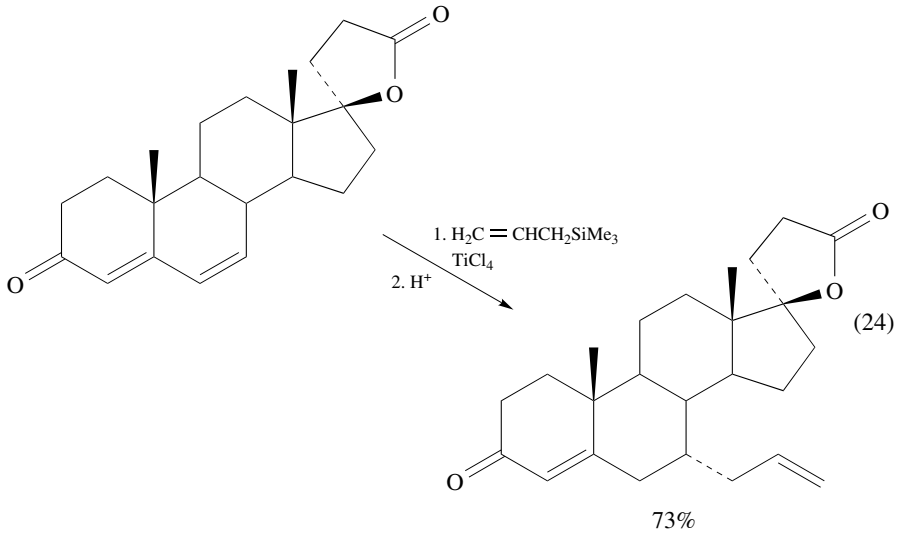


(21)

R =		
n-Bu:	59	: 41
t-Bu:	46	: 54

Early investigations of nucleophilic additions of organometallic reagents to $\Delta^{4,6}$-steroids were actually carried out before the discovery of the antiestrogenic behavior of the 7α -substituted steroids[71−78]. The interest in these transformations was prompted by the desire to prepare new, unnatural corticosteroids with possible interesting pharmacological activities. Campbell and Babcock[71] found in 1959 that the diastereoselectivity of the copper-promoted 1,6-addition of MeMgBr to $\Delta^{4,6}$-steroids depends strongly on the substitution pattern of the substrate: whereas 17β-hydroxy-17α-methyl-4,6-androstadien-3-one provided mainly the 7α-adduct, a mixture of both epimers was obtained from the substrate with an additional 11β-hydroxy group. The preference for the addition of methylmagnesium halides from the α-side was also observed by other groups[72−76]; for example, Wieland and Auner[75] reported an α -selectivity of 90% in the copper-catalyzed 1,6-addition of MeMgBr to 17β-propionyloxy-4,6-androstadien-3-one. The product was converted over several steps into 7α-methylestrone (equation 22). Interestingly, cross-conjugated $\Delta^{1,4,6}$-steroids also undergo 1,6-addition under these conditions[73−75]; here, attack of the nucleophile at C-1 seems to be disfavored because of repulsive steric interactions with the adjacent angular methyl group. Other possibilities to introduce a carbon nucleophile regio- and stereoselectively in the 7α-position of $\Delta^{4,6}$-steroids is the hydrocyanation with Et_2AlCN (equation 23)[77−80] and the Sakurai reaction with allyltrimethylsilane/$TiCl_4$ (equation 24)[81,82].





(24)

73%

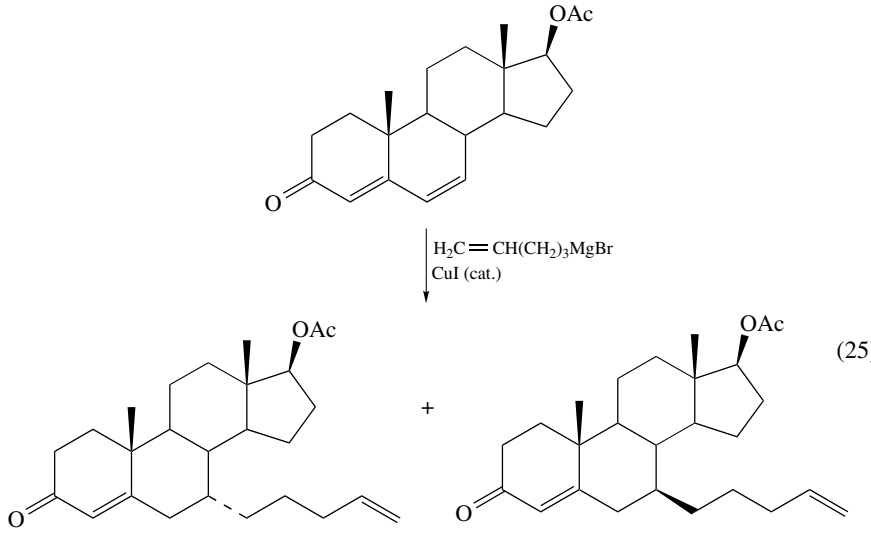
In contrast to these transformations, the introduction of longer alkyl chains by copper-promoted 1,6-addition reactions to $\Delta^{4,6}$-steroids normally proceeds with unsatisfactory $\alpha : \beta$ ratios[63,83–88]. In some cases, however, the diastereoselectivity could be improved by 'fine tuning' of the reaction conditions; for example, the ratio of α- and β-epimeric products in the copper-catalyzed 1,6-addition of 4-pentenylmagnesium bromide to 17β-acetoxy-4,6-androstadien-3-one rose from 58 : 42 to 82 : 18 upon variation of the number of equivalents of the nucleophile and the solvent composition (equation 25)[88].

B. H-, N-, O-, P-, Se- and S-Nucleophiles

Besides carbon nucleophiles, many other nucleophilic reagents can be added regioselectively to acceptor-substituted dienes. The simplest nucleophile is a hydride ion, its synthetic equivalent being a complex metal hydride or another reducing agent. In 1982, Camps ans coworkers[89] examined the reaction of sorbic acid with sodium dithionite; in this case, 1,6-reduction took place mainly to furnish 3-hexenoic acid as a mixture of E/Z isomers (equation 26). Likewise, reduction of methyl sorbate and other 2,4-dienoates under these conditions proceeded with high regioselectivities and good chemical yields to furnish the 1,6-reduction products (again as E/Z-mixtures). The reaction probably involves a nucleophilic attack of the sulfoxylate anion, followed by protonation of the resulting carbanionic species[89–91].

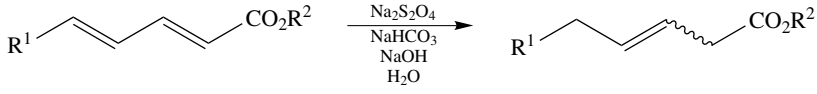
Complex hydrides have been used rather frequently for the conjugate reduction of activated dienes[92–95]. Just and coworkers[92] found that the reduction of α,β-unsaturated ketene *S*,*S*-acetals with lithium triethylborohydride provided mixtures of 1,4- and 1,6-reduction products which were transformed into enals by treatment with mercuric salts (equation 27). Likewise, tetrahydro-3*H*-naphthalen-2-ones can be reduced with L-Selectride® to the 1,6-reduction products[93–95]; this reaction has been utilized in the stereoselective synthesis of several terpenes, e.g. of (*R*)-(−)-ligularenolide (equation 28)[95]. Other methods for the conjugate reduction of acceptor-substituted dienes involve the use of methylcopper/diisobutylaluminum hydride[96] and of the Hantzsch ester

(3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine) in the presence of silica gel[97] as nucleophiles.



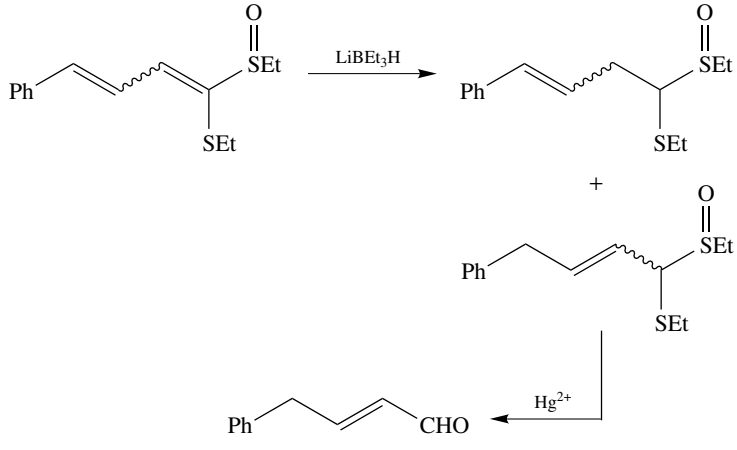
(25)

Eq. Grignard	Ratio THF / diethyl ether	α : β
12	1 : 9	58 : 42
12	1 : 4	60 : 40
12	1 : 1	78 : 22
4	1 : 1	82 : 18



(26)

R^1 = Me, *n*-C_5H_{11}, *n*-C_7H_{15}; R^2 = H, Me, Et



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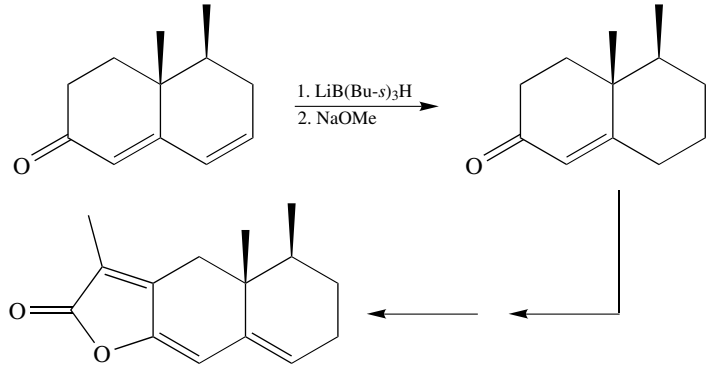
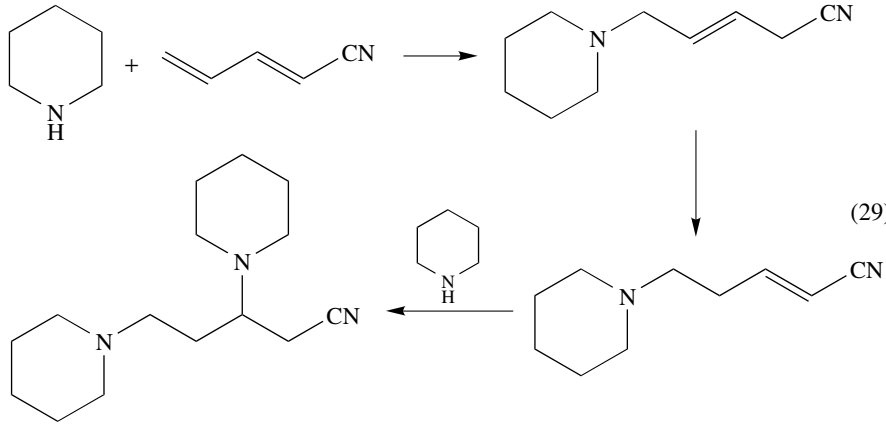


(28)

(*R*)-(−)-Ligularenolide

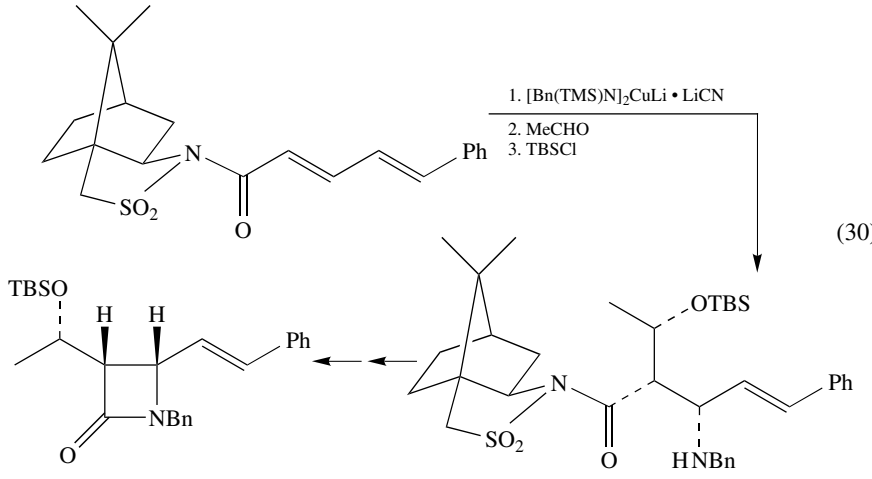
Nucleophilic additions of amines to acceptor-substituted dienes were examined as early as 1950. Frankel and coworkers[98] found that the reaction of 2,4-pentadienenitrile with various secondary amines proceeded regioselectively to furnish the 1,6-addition products (equation 29). In some cases, these could converted into the 2,4-diamino-substituted pentanenitriles by isomerization and 1,4-addition of a second molecule of amine. Analogous results were reported by other groups[17,99,100] and extended to hydrazine as nucleophile[101] and to vinylcyclobutenones[48] and dienoates[102−104] as Michael acceptors.



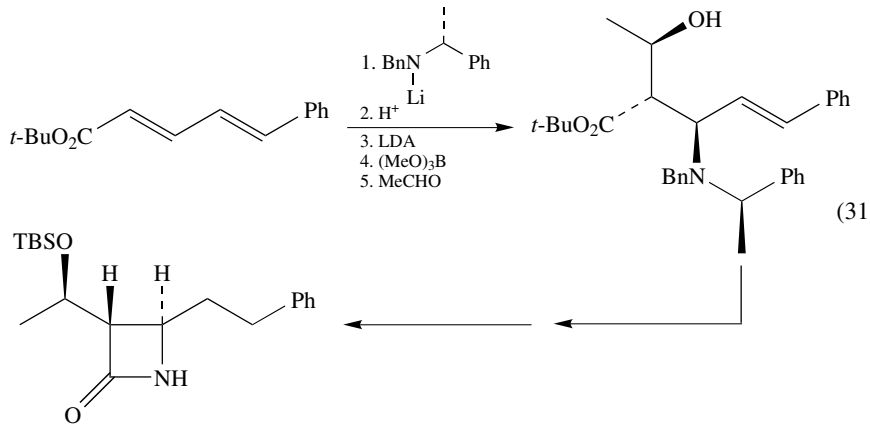
(29)

Recently, metalated amines were utilized in stereoselective addition reactions to activated dienes. In a series of papers, Yamamoto and coworkers[105−107] described new stereoselective syntheses of β-lactams utilizing 1,4-addition reactions of lithium amides and amidocuprates to 2,4-dienoic acid derivatives. For example, regio- and diastereoselective addition of the amidocuprate $[Bn(TMS)N]_2CuLi \bullet LiCN$ to a diene bearing a bornanesultam auxiliary, followed by trapping of the enolate with acetaldehyde and protection, provided the product with three contiguous stereogenic centers which could then be cyclized to the enantio- and diastereomerically pure β-lactam (equation 30)[105,107].

Alternatively, a chiral lithium amide was added regio- and diastereoselectively to an achiral 2,4-dienoate, and the 1,4-addition product formed could again be converted into the desired, stereochemically pure β-lactam (equation 31)[106].



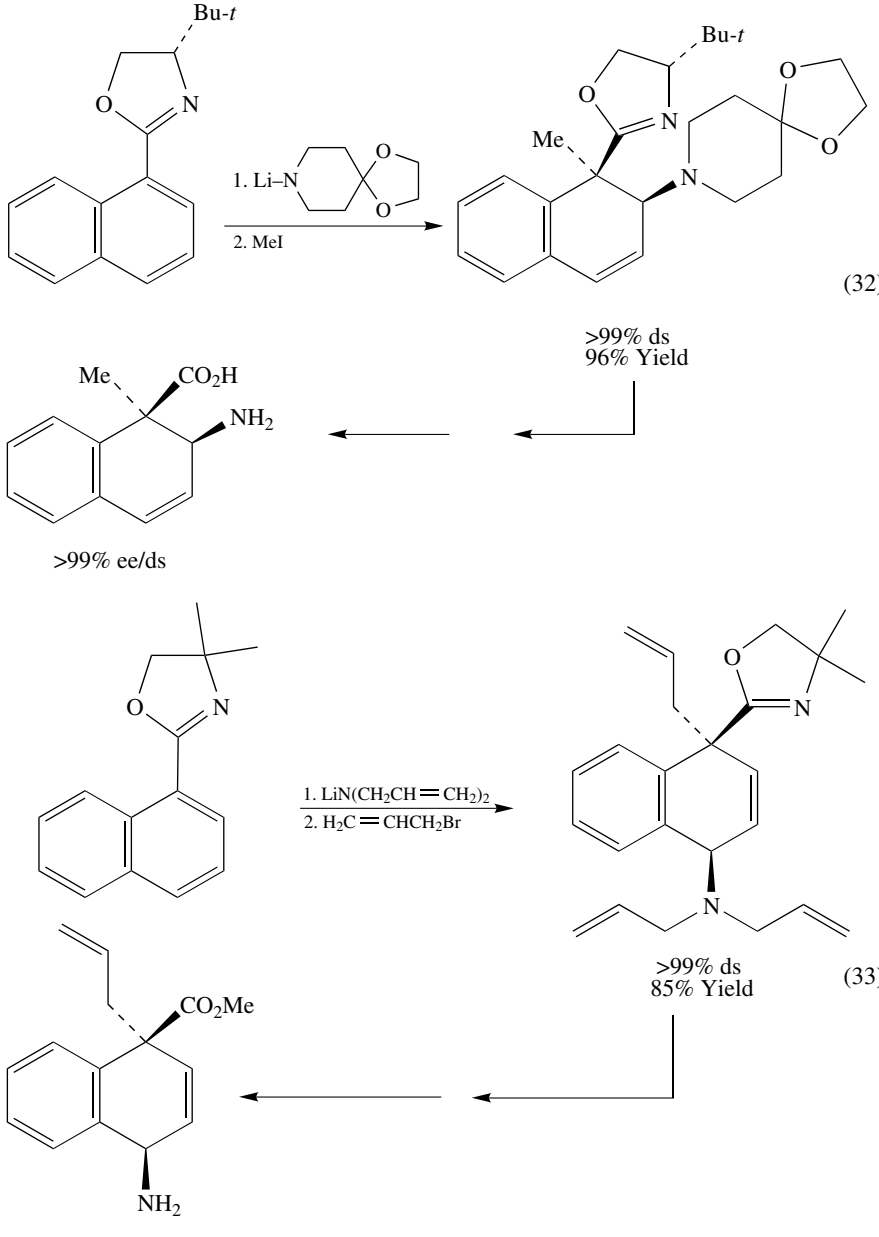
(30)



(31)

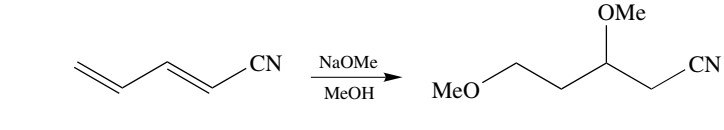
Diastereoselective 1,4- and 1,6-addition reactions of lithium amides to chiral naphthyloxazolines were used by Shimano and Meyers[108–110] for the synthesis of novel amino acids. For example, treatment of (*S*)-2-(1-naphthyl)-4-*t*-butyloxazoline with lithiated 1,4-dioxa-8-azaspiro[4.5]decane and iodomethane provided the diastereomerically pure 1,4-addition product with excellent yield; cleavage of the heterocyclic rings then gave the desired β-amino acid (>99% ee/ds; equation 32)[108,109]. In contrast to this, most acyclic lithium amides reacted with these oxazolines under 1,6-addition; the products were transformed smoothly to δ-amino acid derivatives (equation 33)[110].

The number of reports about addition reactions of oxygen nucleophiles to acceptor-substituted dienes is rather limited. Coffman[111] and Kurtz[17] examined the reaction of 2,4-pentadienenitrile with sodium methoxide and isolated the 2 : 1 adduct 3,5-dimethoxypentanenitrile formed by successive 1,6- and 1,4-additions (equation 34). Analogous treatment



of 4-chloro-3,5-hexadien-2-one resulted in the incorporation of three methoxy groups by 1,4-addition/elimination, 1,6-addition/isomerization and another 1,4-addition reaction (equation 35)[112,113]. Recently, Neuenschwander and coworkers[114] reported nucleophilic

1,6-additions of phenolate and other alcoholates to 2-aminopyrylium salts. An acid-catalyzed intramolecular 1,6-addition served for the stereoselective construction of a key intermediate in a synthetic approach to the natural quassinoid bruceantin (equation 36)[115].



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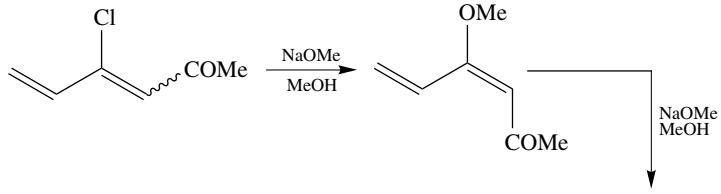

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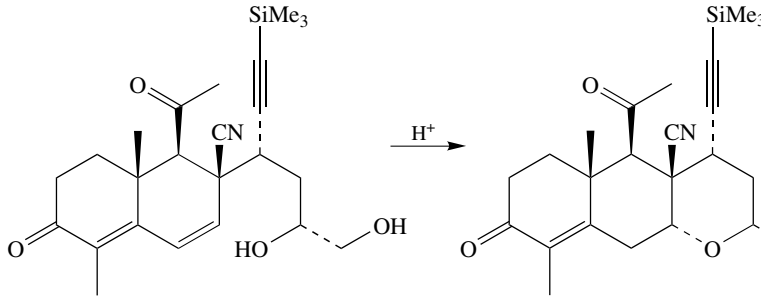
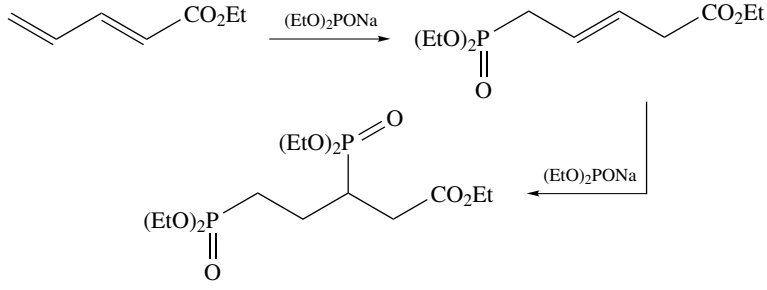


(36)

Like oxygen nucleophiles, phosphorus and selenium nucleophiles have been employed rarely in Michael additions to activated dienes. The reaction of phosphites with acceptor-substituted dienes was studied by several Russian groups[116–118]; again, 1,6-adducts and 2 : 1 addition products were formed (equation 37). The acid-catalyzed reaction of selenourea with sorbic acid was also reported to provide a 1,6-addition product[119] (equation 38).



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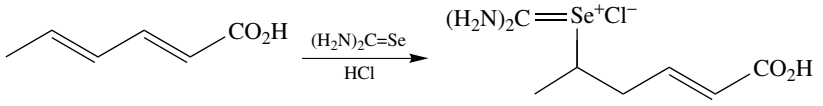
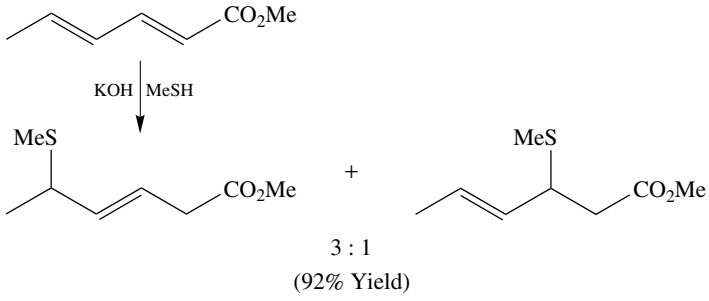


(38)

By far most of the reports on addition reactions of hetero-nucleophiles to activated dienes deal with sulfur-nucleophiles[17,48,80,120–137], in particular in the synthesis of 7β-sulfur-substituted steroids which, like their carbon-substituted counterparts (Section II.A), are of interest because of their ability to inhibit the biosynthesis of estrogens[80,129–137]. Early investigations[17,120–122] concentrated on simple acyclic Michael acceptors like methyl sorbate and 2,4-pentadienenitrile. Bravo and coworkers[120] observed the formation of a 3 : 1 mixture of the 1,6- and 1,4-adduct in the reaction of methyl sorbate with methanethiol in basic medium (equation 39). In contrast to this, 2,4-pentadienenitrile adds various thiols regioselectively at C-5, i.e. in a 1,6-fashion (equation 40)[17,121,122], and the same is true for reactions of this substrate with hydrogen sulfide (equation 41), sodium bisulfite and ethyl thioglycolate[17].



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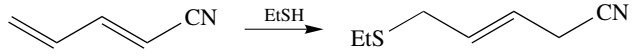

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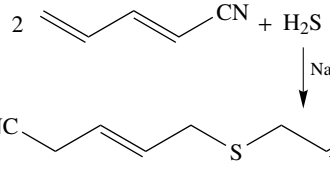
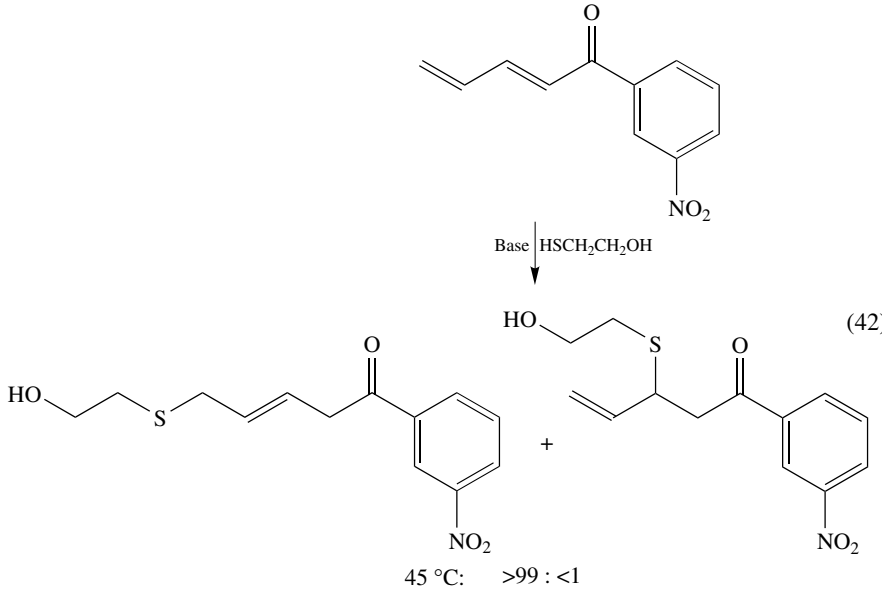


(41)

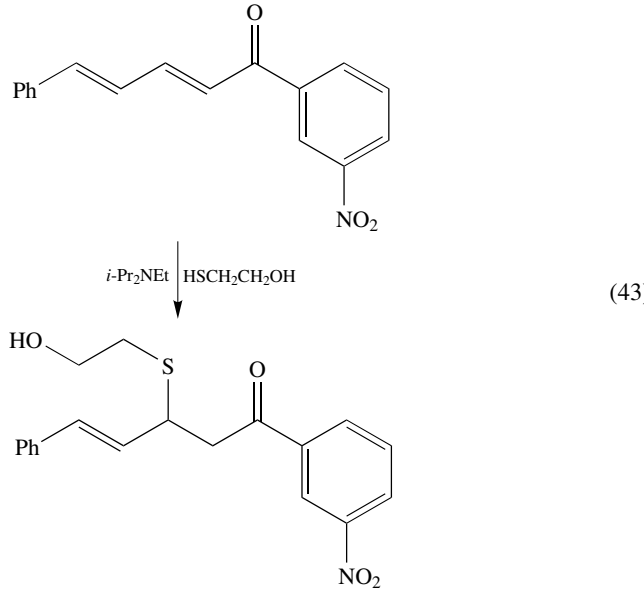
The regioselectivity of Michael additions of thiolates to 2,4-dienones can be altered drastically by variation of the reaction conditions and addition of Lewis acids to the reaction mixture. Lawton and coworkers examined the reaction of 2-mercaptoethanol with 1-(3-nitrophenyl)-2,4-pentadien-1-one and observed a high regioselectivity in favor of the 1,6-addition product at 45 °C (equation 42)[123,124]. Lowering of the reaction temperature caused an increase in the amount of 1,4-adduct, and at −40 °C, a product ratio of 40 : 60 was found. These events suggest that kinetic control favors the 1,4-addition product whereas the 1,6-adduct is thermodynamically more stable. If, however, the reaction was carried out with a complex of the dienone and titanium tetrachloride, only the 1,4-adduct was isolated after hydrolytic workup[123]. Obviously, this product is trapped as a metal chelate which prevents formation of the 1,6-adduct by retro-Michael/Michael addition. In the absence of the chelating Lewis acid, the 1,4-addition product can indeed be converted

into the 1,6-adduct by treatment with diisopropylethylamine. Introduction of a sterically demanding substituent, e.g. a phenyl group, at C-5 of the dienone, prevents the formation of the 1,6-addition product even in the absence of a Lewis acid (equation 43)[123].



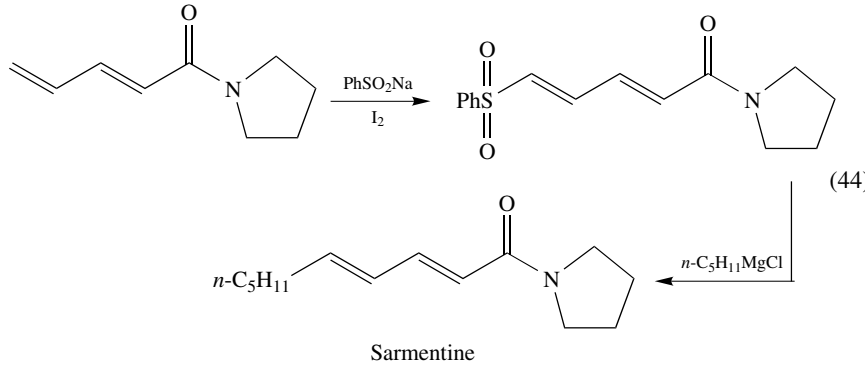
(42)

45 °C: >99 : <1
–40 °C: 40 : 60
$TiCl_4$, –40 °C: <1 : >99



(43)

Regioselective 1,6-addition reactions of sulfur nucleophiles to activated dienes were utilized by several groups for the synthesis of biologically relevant target molecules[125–128]. Nájera and coworkers[125] prepared several 5-tosyl-2,4-pentadienamides by 1,6-addition of sodium 4-toluenesulfinate to 2,4-pentadienamides, iodination and spontaneous dehydroiodination (equation 44). These transformations took place with complete control of the configuration of the olefinic double bonds. The products underwent 1,6-addition/elimination reactions with carbon and sulfur nucleophiles; with benzylthiolate, a double 1,6-addition could be realized. Treatment of the pyrrolidinyl derivative with pentylmagnesium chloride led directly to the natural product sarmentine, again with retention of the configuration of the double bonds. The 1,6-addition products of L-cysteine and various derivatives of this amino acid to trifluoroethyl 2-propyl-2,4-pentadienoate were prepared and identified as possible metabolites of the anticonvulsant agent valproic acid (2-propylpentanoic acid; equation 45)[126].



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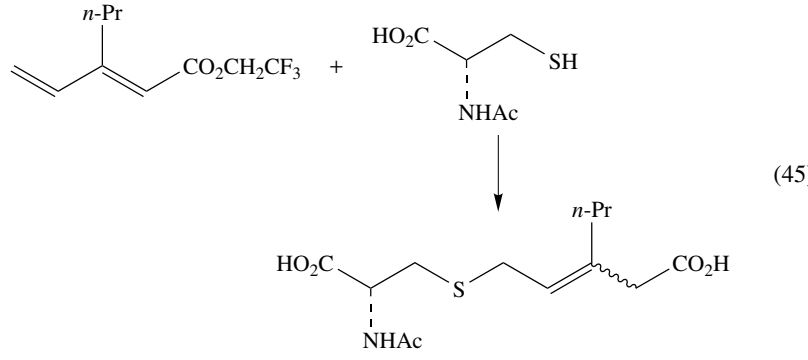
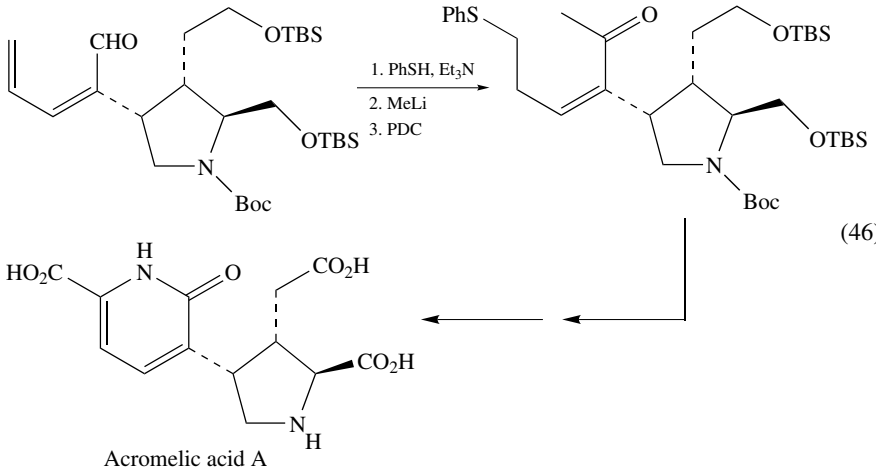


(45)

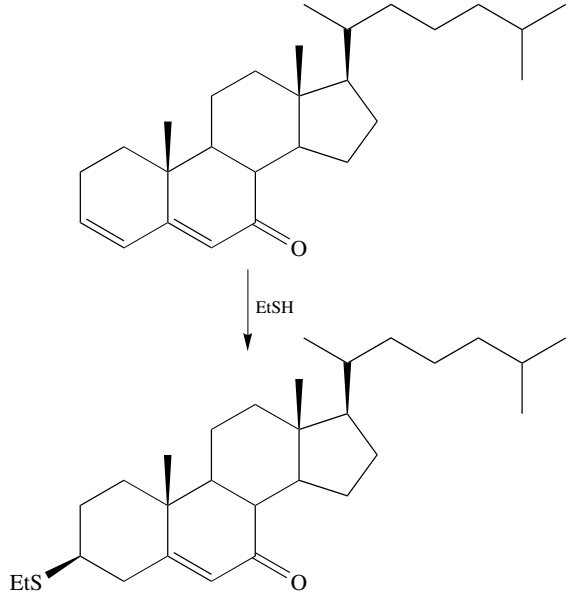
Structurally rather complicated target molecules can be synthesized with the aid of thiolate 1,6-addition reactions to acceptor-substituted dienes as well. For example, a richly functionalized proline derivative with a 2,4-pentadienal side chain was converted into the corresponding 6-phenylthio-3-hexen-2-one derivative by 1,6-addition of phenylthiolate, treatment of the adduct with methyl lithium and oxidation (equation 46)[127]. The product was transformed into acromelic acid A, the toxic principle of *clitocybe acromelalga ichimura*. Similarly, the 1,6-addition reaction of cesium triphenylmethylthiolate to methyl 2,4-pentadienoate served for the construction of the disulfide bridge of the macrobicyclic antitumor depsipeptide FR-901,228[128].



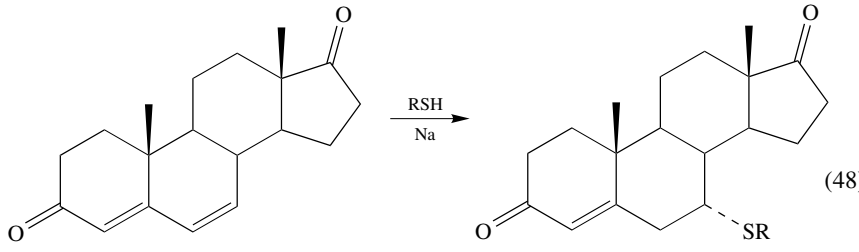
(46)

Acromelic acid A

The first 1,6-addition reactions of thiolates to steroid dienones were examined well before the discovery of the antiestrogenic properties of 7α-substituted steroids. Ralls and coworkers[129] and Djerassi and coworkers[130] studied thiol additions to $\Delta^{3,5}$-steroids; for example, the reaction of 3,5-cholestadien-7-one with ethanethiol was reported to proceed with high 1,6-regioselectivity and β-stereoselectivity (equation 47)[129]. In a series of papers, Brueggemeier and coworkers[131–137] described the synthesis and biochemical evaluation of numerous 7α-sulfur-substituted steroids which were prepared by Michael addition to steroid dienones. Thus, 4,6-androsta-3,17-dienone was treated with various

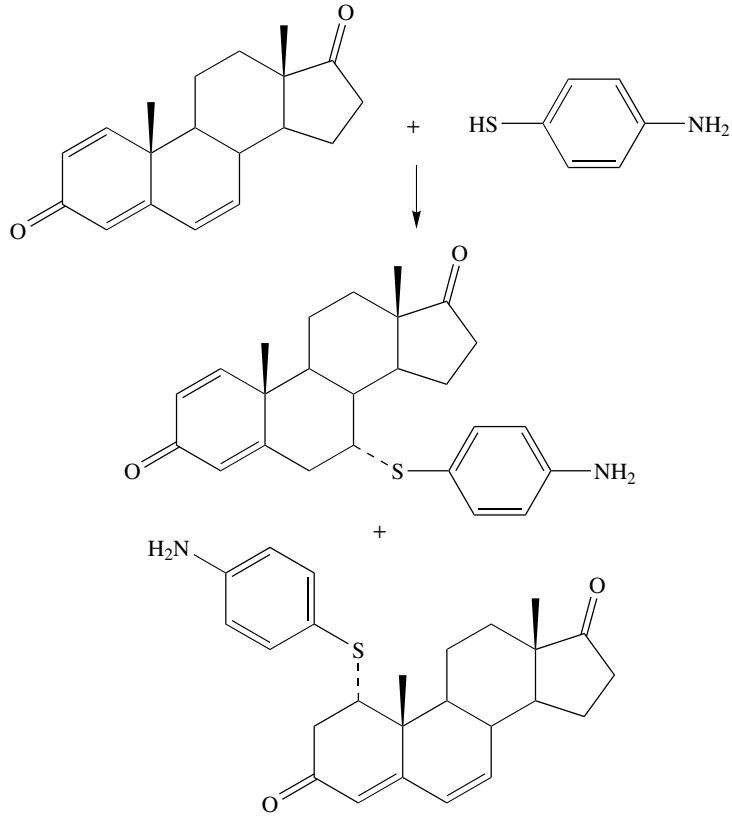


(47)



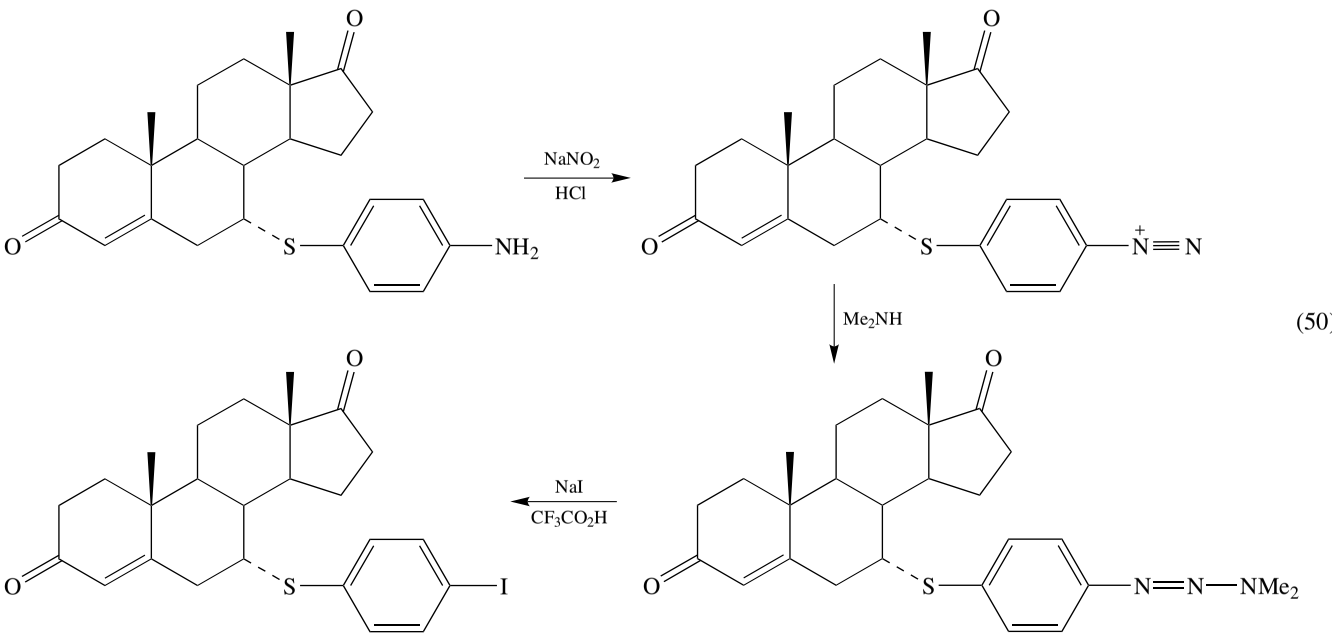
(48)

R = *n*-Bu: 58%
Ph: 84%
Bn: 98%
4-$H_2NC_6H_4$: 91%



(49)

aliphatic and aromatic thiols to furnish the 7α-substituted adducts with moderate to excellent yield (equation 48)[131−136]. The analogous reaction of $\Delta^{1,4,6}$-steroids gave mixtures of 1,6-adducts and 1,4-addition products resulting from attack of the thiolate at C-1 (equation 49)[134,137]. Subsequent functionalization provided steroids which were not directly accessible by 1,6-addition (equation 50)[132,133,136].

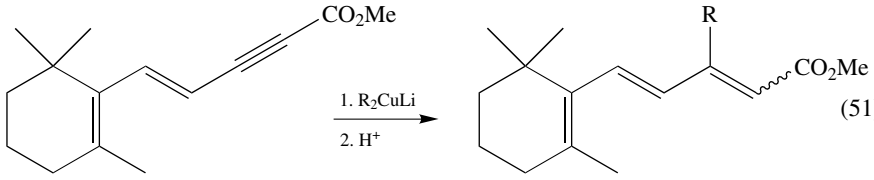


(50)

III. ENYNES

A. Carbon Nucleophiles

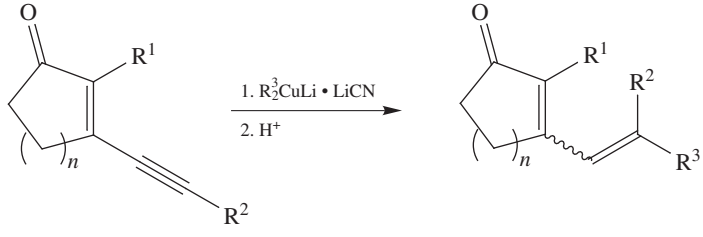
As in the case of addition reactions of carbon nucleophiles to activated dienes (Section II.A), organocopper compounds are the reagents of choice for regio- and stereoselective Michael additions to acceptor-substituted enynes. Substrates bearing an acceptor-substituted triple bond besides one or more conjugated double bonds react with organocuprates under 1,4-addition exclusively (equation 51)[138–140]; 1,6-addition reactions which would provide allenes after electrophilic capture were not observed (cf. Section IV).



(51)

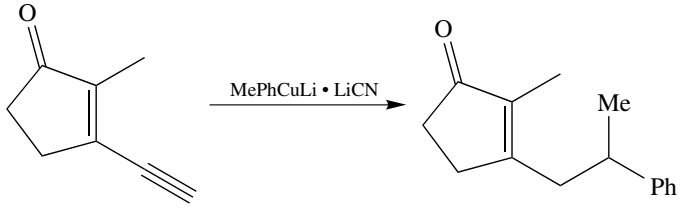
R = Et, *t*-Bu, Me_3Si

In contrast to these transformations, nucleophilic additions to enynes with an acceptor substituent at the double bond are highly rewarding from both the preparative and mechanistic point of view[38,141]. According to Scheme 2 (Section I), the outcome depends strongly on the regioselectivity of the nucleophilic attack and of the electrophilic trapping of the enolate formed. Recent investigations have demonstrated that the regio- and stereoselectivity of both steps can be controlled by the choice of the reactants, in particular by 'fine-tuning' of the organocopper reagent and the electrophile. The first example was reported by Hulce[142,143] who found that 3-alkynyl-2-cycloalkenones react with cuprates at the triple bond in a 1,6-addition and the allenyl enolate is protonated at C-4 with the formation of conjugated dienones as mixtures of *E*/*Z*-isomers (equation 52). As observed in other cuprate addition reactions[138,139], the *Z*-stereoselectivity rises with increasing size of the group R^3. Interestingly, substrates of this type can also undergo tandem 1,6-5,6-additions, indicating that the allenyl enolate formed by 1,6-cuprate addition is sufficiently electrophilic to react with another organometallic reagent in a carbometalation of the allenic double bond distal to the electron-releasing enolate moiety[144]. In this way, it is also possible to introduce two different groups at the terminus of the Michael acceptor, either by using two organometallic reagents successively or by employing a mixed cuprate (equation 53).



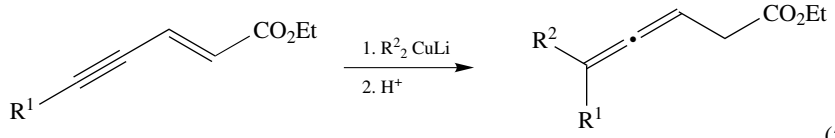
(52)

n = 1,2; R^1 = H, Me; R^2 = H, Ph, HMe_3Si; R^3 = Me, Et; *i*-Pr, *n*-Bu, *t*-Bu, Ph, CH═CH_2



(53)

More interesting in preparative terms would be the possibility of shifting the regioselectivity of the electrophilic quenching reaction towards formation of allenes, since the number of synthetic methods for the preparation of functionalized allenes has been rather limited[145]. Furthermore, a stereoselective reaction of this type would open up a route to these axially chiral compounds in enantiomerically enriched or pure form. Indeed, the Gilman cuprate $Me_2CuLi \bullet LiI$ and cyanocuprates $R_2CuLi \bullet LiCN$ ($R \neq Me$) in diethyl ether react regioselectively with variously substituted 2-en-4-ynoates in a 1,6-fashion (equation 54). Protonation with dilute sulfuric acid gives the β-allenic esters with alkyl, alkenyl, aryl and silyl substituents in good yield[146].



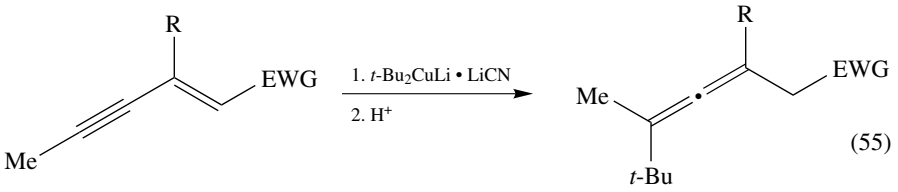
(54)

R^1 = Ph, R^2 = Me:	79%
R^1 = Ph, R^2 = *t*-Bu:	81%
R^1 = *n*-Bu, R^2 = Ph:	62%
R^1 = Me_3Si, R^2 = Me:	57%

The regioselectivity of the addition of organocuprates to acceptor-substituted enynes is hardly influenced by the nature of the acceptor substituent. Enynes containing ester, thioester, lactone and dioxanone as well as keto, sulfonyl, sulfinyl, cyano and oxazolidino groups react in a 1,6-manner to give the corresponding functionalized allenes (equation 55)[146–148]. Only 1-nitro-l-en-3-ynes are attacked at the C=C double bond with the formation of 1,4-adducts (equation 56)[148]. The differences in reactivity can be described qualitatively by the following reactivity scale: EWG = NO_2 > COR, CO_2R, COSR > CN, SO_3R, oxazolidino > SO_2R > SOR ≫ $CONR_2$. Remarkably, the regioselectivity of the cuprate addition to acceptor-substituted enynes is also insensitive to the steric properties of the substrate; enynes with *t*-butyl substituents at the triple bond undergo 1,6-addition, even when the cuprate itself is sterically demanding (equation 57)[147]. The reaction is therefore highly suitable for the preparation of sterically encumbered allenes.

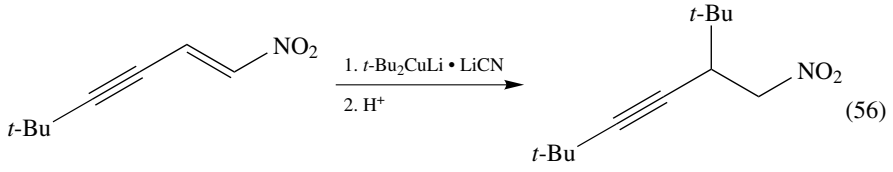
In order to achieve acceptable yields with the less reactive Michael acceptors, it is often necessary to use more reactive organocopper reagents or Lewis acid catalysis. Thus, the reaction of (1-penten-3-yn-1-yl) phenyl sulfone with five equivalents of Me_2CuLi alone gave no trace of addition product, whereas the analogous reaction with Me_3CuLi_2 provided the desired allene in 16% yield (equation 58)[148]. With two equivalents of Me_2CuLi in the presence of one equivalent of Me_3SiI the yield increased to 45%, while with added Me_3SiOTf the allene was isolated in 29% yield. Only amides fail to form 1,6-adducts

under these conditions.

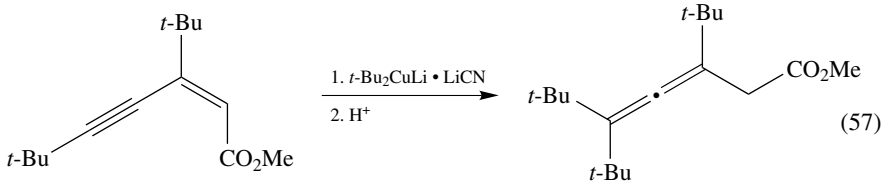


(55)

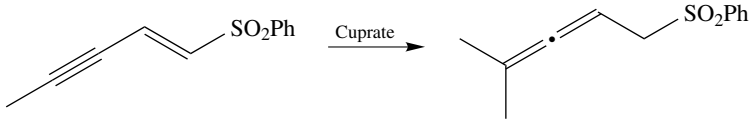
EWG = CN, R = Me:	79%
EWG = SO_2Ph, R = H:	91%
EWG = SO_3Et, R = H:	49%



(56)



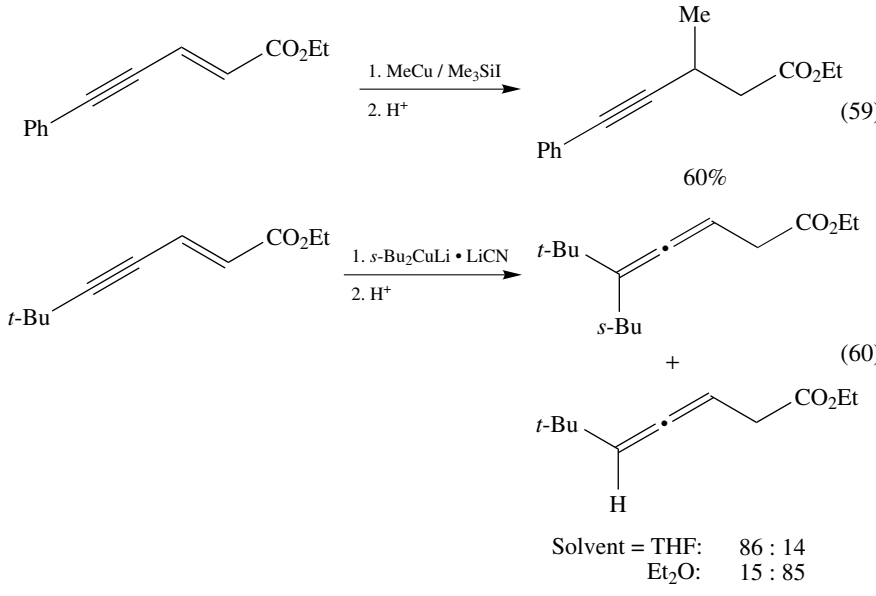
(57)



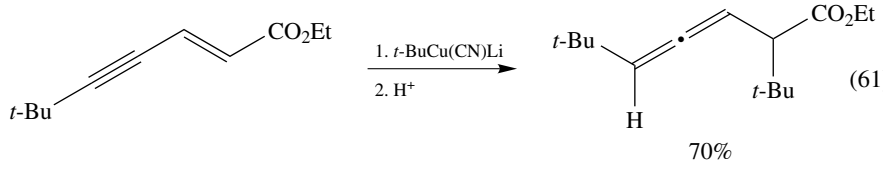
(58)

Me_2CuLi:	0%
Me_3CuLi_2:	16%
Me_2CuLi / Me_3SiI:	45%
Me_2CuLi / Me_3SiOTf:	29%

In contrast to the substrate, the organocuprate has a pronounced influence on the regioselectivity of the addition to acceptor-substituted enynes. While the Gilman cuprate Me_2CuLi • LiI and cyanocuprates R_2CuLi • LiCN ($R \neq Me$) add regioselectively in a 1,6-manner, the Yamamoto reagent RCu • BF_3[50] and the reagent combination RCu/Me_3SiI[149] lead to 1,4-adducts (equation 59)[38,146]. The behavior of the cyanocuprate *s*-Bu_2CuLi • LiCN towards 2-en-4-ynoates is particularly unusual since the reaction is very solvent-sensitive. In THF the 1,6-adduct is obtained as the major product, whereas in diethyl ether the 1,6-reduction product is the main component of the product mixture (equation 60)[150]. Other cyanocuprates of the stoichiometry R_2CuLi • LiCN react with acceptor-substituted enynes in THF very slowly under 1,6-addition or not at all[38]. A 1,6-reduction was also observed in the reaction of benzyl 3-methyl-2-penten-4-ynoate with Me_2CuLi/*n*-Bu_3P[141]. The reduction products may be formed by electron transfer from the cuprate or by hydrolysis of a stable copper(III) intermediate.

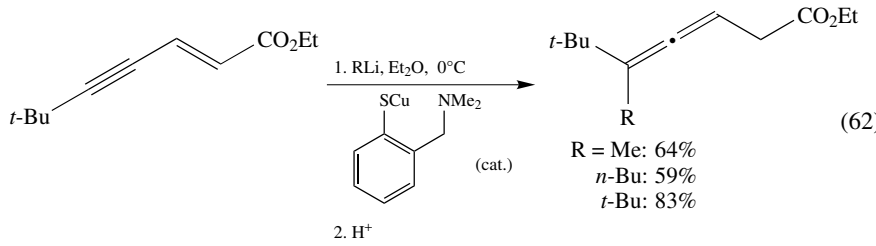


So-called 'lower order cyanocuprates' RCu(CN)Li do not generally react with acceptor-substituted enynes. An exception is the cuprate *t*-BuCu(CN)Li which undergoes anti-Michael additions with 2-en-4-ynoates and nitriles (equation 61)[151]. The mechanistic aspects of this very unusual reaction are unknown; radical intermediates and electron transfer steps have not been found.

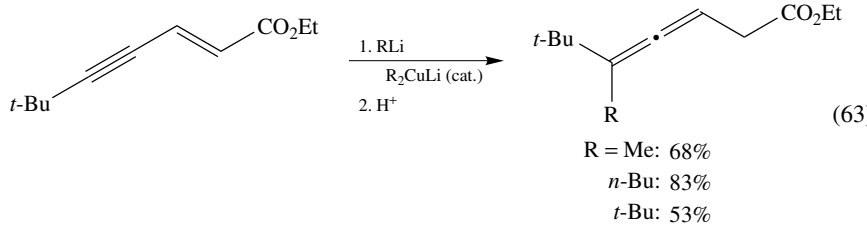


In analogy to copper-catalyzed 1,6-addition reactions of Grignard reagents to activated dienes (Section II.A), the 1,6-addition to acceptor-substituted enynes can also be conducted under catalytic conditions. However, only very carefully controlled reaction conditions lead to the 1,6-adduct as the major product, i.e. use of copper (2-dimethylaminomethyl)thiophenolate as catalyst and simultaneous addition of the substrate and an organolithium reagent to a suspension of the catalyst in diethyl ether at 0 °C (equation 62)[152]. Under these conditions variously substituted β-allenylcarboxylates are obtained with yields comparable to those of the stoichiometric cases. Other copper(I) salts and the use of Grignard reagents as the nucleophile led to very low yields of 1,6-addition products. A second catalytic version takes advantage of the fact that the products of the (stoichiometric) 1,6-cuprate addition, the lithium allenyl enolate and the organocopper compound are formed as independent species. The cuprate can be regenerated by addition of one equivalent of RLi such that it reacts with a further equivalent of the Michael acceptor. This procedure can, in principle, be repeated infinitely. The reaction is best conducted in a continuous mode by adding the substrate and the organolithium reagent

simultaneously to a solution of the cuprate (equation 63)[38].

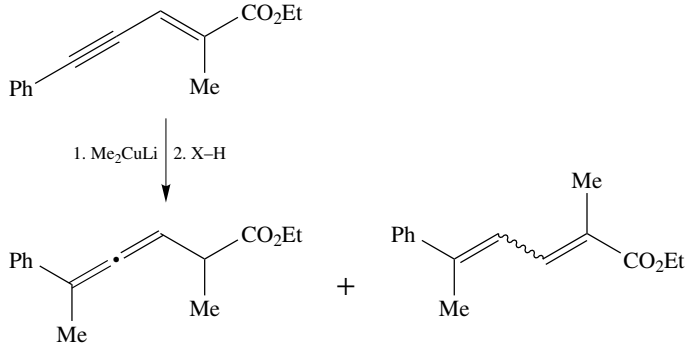


(62)



(63)

As mentioned repeatedly, a precondition for the successful preparation of allenes by 1,6-addition is that the allenyl enolate reacts regioselectively with an electrophile at C-2 (or at the enolate oxygen atom to give an allenylketene acetal; see Scheme 2). The regioselectivity of the simplest trapping reaction, the protonation of the allenyl enolate, depends on the steric and electronic properties of the substrate and the proton source. Whereas the allenyl enolates obtained from 3-alkynyl-2-cycloalkenones always provide conjugated dienones by protonation at C-4 (possibly via allenyl enols; see equation 52)[141–143], ester enolates are usually protonated at C-2 (equation 54), in particular when sterically demanding groups at C-5 block the attack of a proton at C-4 (equation 57)[38,146–148]. However, with a substituent at C-2 of the enolate, mixtures of allenes and conjugated dienes are formed, since now protonation at C-2 is sterically hindered. In the case of ester enolates this problem can be solved by using weak organic acids as proton source (equation 64).

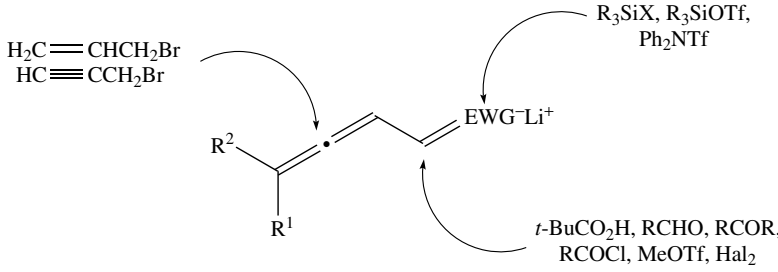


(64)

X-H = 2N H_2SO_4, 25 °C: 50 : 50
AcOH, 25 °C: 64 : 36
t-BuCO_2H, 25 °C: 82 : 18
t-BuCO_2H, –80 °C: > 99 : < 1

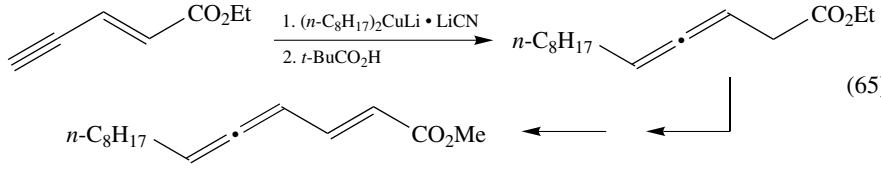
The optimal proton donor to conquer this problem of regioselectivity is pivalic acid (2,2-dimethylpropionic acid). At room temperature, an allene : diene ratio of 82 : 18 was observed, and at −80 °C only the desired allene was formed[146].

In contrast to protonation, the regioselectivity of the reaction of other electrophiles with allenyl enolates derived from 2-en-4-ynoates is independent of the steric and electronic properties of the reaction partners (Scheme 3)[38,148,152–154]. Hard electrophiles such as silyl halides and triflates react at the enolate oxygen atom to form allenylketene acetals, while soft electrophiles such as carbonyl compounds attack at C-2. Only allylic and propargylic halides react regioselectively at C-4 of the allenyl enolate to give substituted conjugated dienes; these reactions may also proceed via allenes which then undergo a Cope rearrangement. Again, cyclic allenyl enolates formed by cuprate addition to 3-alkynyl-2-cycloalkenones show a deviating behavior: treatment with iodomethane provided product mixtures derived from attack of the electrophile at C-2 and C-4, and the reaction with aldehydes and silyl halides took place at C-4 exclusively[141,155,156].



SCHEME 3

The synthesis of allenes by 1,6-addition of organocopper reagents to acceptor-substituted enynes has found a wide range of preparative applications. In addition to sterically encumbered allenes (equation 57)[147] and simple terpenes such as pseudoionone[146], allenic natural products can be prepared by this method (equation 65)[38]. Thus, 1,6-addition of lithium di-*n*-octylcuprate to ethyl 2-penten-4-ynoate, followed by regioselective protonation with pivalic acid, yielded the allene ethyl 2,3-tridecadienoate which can be converted easily into the insect pheromone methyl 2,4,5-tetradecatrienoate. Another application of the 1,6-addition in natural product synthesis relies on vinylallenes as diene components in the Diels–Alder reaction. The synthesis of the fungal metabolite (±)-sterpurene started with a 1,6-addition of lithium dimethylcuprate to a suitable enynoate and regioselective trapping with methyl triflate (equation 66)[157]. The vinylallene thus formed underwent an intramolecular [4 + 2]-cycloaddition upon brief heating in toluene, and the tricyclic product was converted into (±)-sterpurene in a few steps and also into several oxygenated metabolites.



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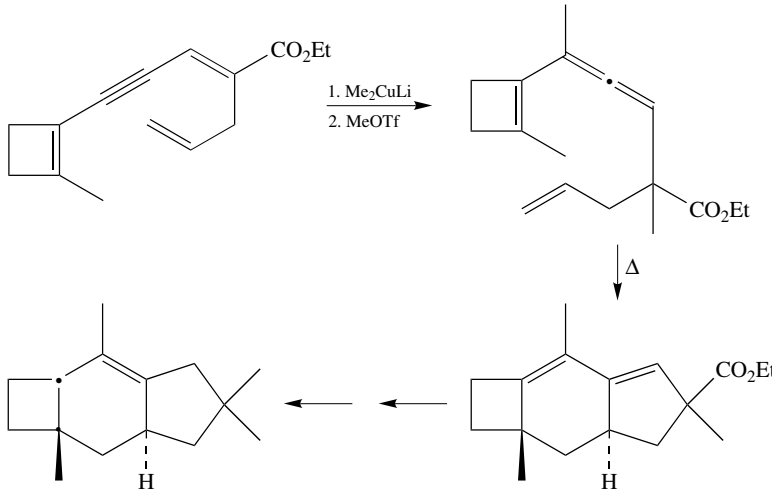
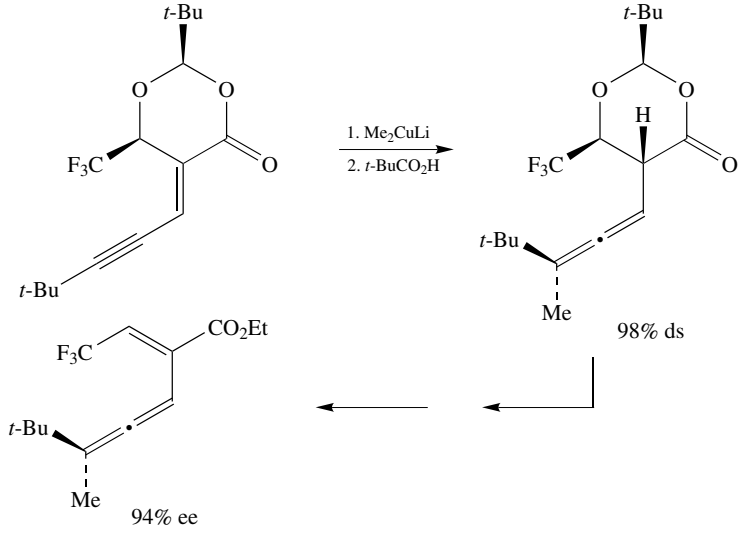


(66)

(±)-Sterpurene

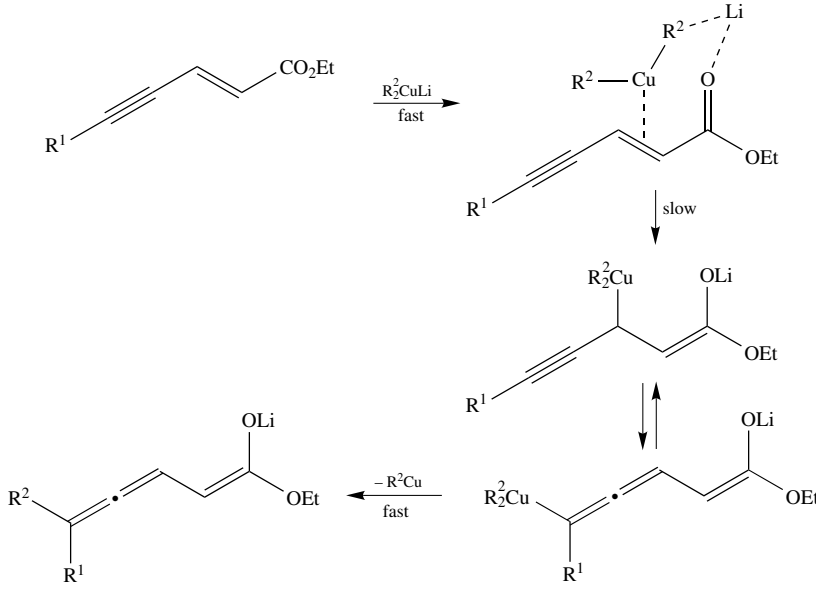
This Diels–Alder reaction is an example of how axially chiral allenes, accessible through 1,6-addition, can be utilized to form new stereogenic centers selectively. This is also possible by intermolecular Diels–Alder reactions of vinylallenes[158], aldol reactions of allenyl enolates[159] and Ireland–Claisen rearrangements of silyl allenylketene acetals[160]. In order to access the required allenes in enantiomerically enriched or pure form, the 1,6-cuprate addition has to be conducted not only regio- but also stereoselectively. This goal can be achieved by employing chiral 5-alkynylidene-1,3-dioxan-4-ones as Michael acceptor; here, the equatorial *t*-butyl group forces the molecule to adopt a very rigid conformation and the trifluoromethyl group protects the top face of the enyne unit, making the preferred point of attack the underside of the molecule (equation 67)[38,161].



(67)

Consequently, reaction with lithium dimethylcuprate and pivalic acid gave the desired allene with a diastereoselectivity of 98% ds, and the stereochemical information generated in this step remained intact even after further conversion into a chiral vinylallene.

In contrast to nucleophilic addition reactions to activated dienes, the mechanism of 1,6-cuprate additions to acceptor-substituted enynes is quite well understood, the main tools being kinetic and NMR spectroscopic investigations[38]. ^{13}C-NMR spectroscopic studies have revealed that these transformations proceed via π-complexes with an interaction between the π-system of the C=C double bond and the nucleophilic copper atom (a soft–soft interaction in terms of the HSAB principle), as well as a second interaction between the hard lithium ion of the cuprate and the hard carbonyl oxygen atom (Scheme 4)[162]. The use of ^{13}C-labeled substrates has confirmed that the cuprate does not interact with the triple bond, and it has also shed light on the structure of the metal-containing part of the π-complexes[163]. Further intermediates on the way from the π-complex to the allenyl enolate could not be detected spectroscopically; however, kinetic measurements have revealed that an intramolecular rearrangement of the π-complex occurs in the rate-determining step[164]. These experimental results can be explained by assuming that a σ-copper(III) species is formed which could be in equilibrium with an allenic copper(III) intermediate. Both intermediates can undergo reductive elimination to produce the 1,4- and 1,6-adduct, respectively. The experimental result of exclusive formation of the 1,6-addition product may indicate that the hypothetical equilibrium lies on the side of the allenic copper(III) species, or that the reductive elimination of the latter occurs much faster than from the first intermediate.

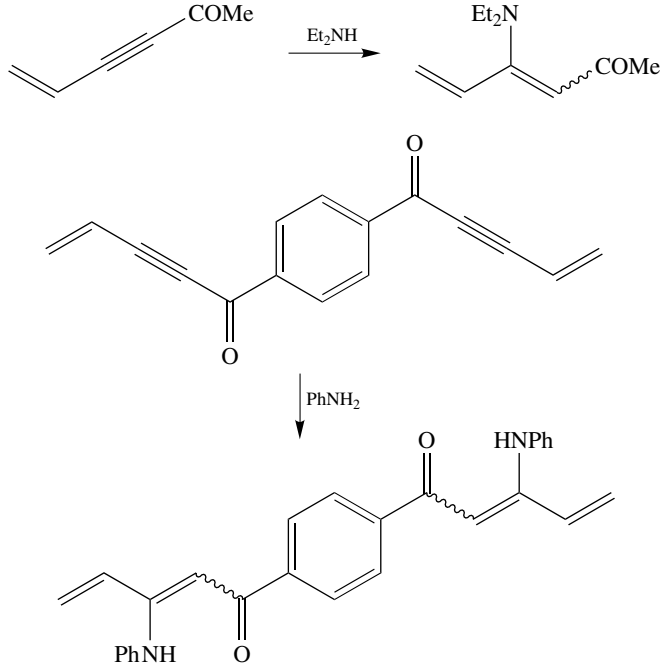


SCHEME 4

B. N-, O-, P-, S- and Si-Nucleophiles

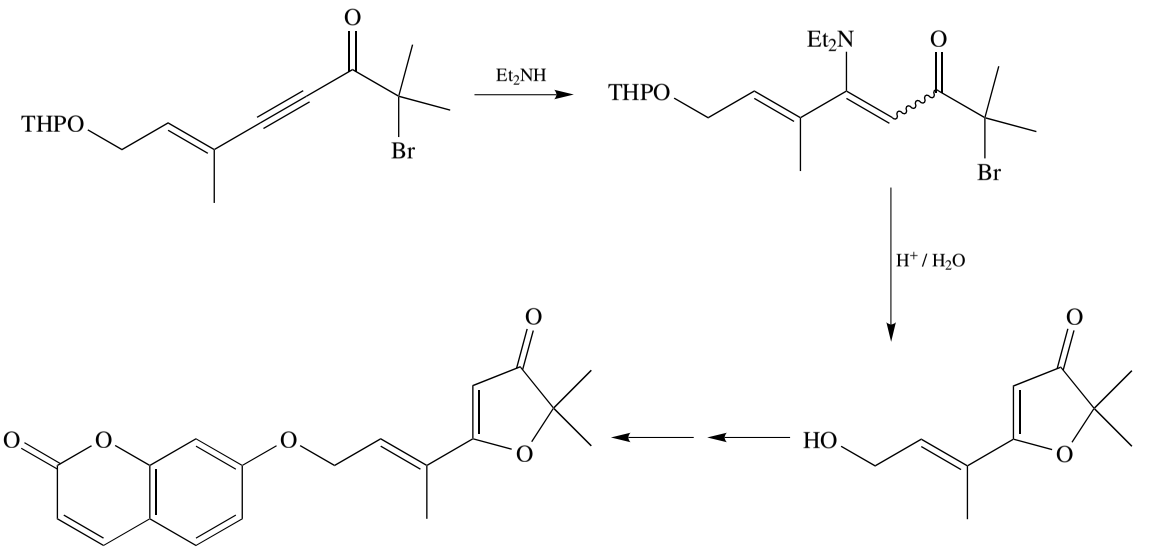
As demonstrated in Section III.A, activated enynes with an acceptor group at the triple bond react with carbon nucleophiles under 1,4-addition exclusively; the same is

true for their reactions with N−, O− and P-nucleophiles[165−174]. In 1946, Bowden and coworkers[165] reported the 1,4-addition of diethylamine to 5-hexen-3-yn-2-one (equation 68). Likewise, a Russian group synthesized several 1,4-adducts by treatment of 1-aryl-4-alken-2-yn-1-ones with aniline[166−168]; in one case, a double addition product was obtained (equation 69)[166]. The resulting aminodienones can be hydrolyzed easily to unsaturated 1,3-diketones[169]. Jackson and Raphael[170,171] employed this sequence in a synthesis of the 3(2*H*)-furanone natural product geiparvarin (equation 70); key steps were the 1,4-addition of diethylamine to a bromo-substituted enynone and the subsequent hydrolysis/cyclization to give the desired heterocycle.



Isolated instances of 1,4-addition reactions of other hetero-nucleophiles to 4-en-2-ynoic acids and derivatives have been reported[172−174]. Thus, treatment of methyl 4-methyl-4-penten-2-ynoate with phenolate provided the 3-phenoxy-substituted conjugated dienoate (equation 71)[172], and the 1,4-addition of water-soluble phosphines to 4-octen-2-ynoic acid afforded dienylphosphonium salts which were transformed into the corresponding phosphine oxides (equation 72)[174].

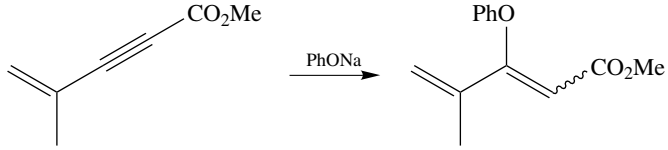
The number of reports on Michael additions of hetero-nucleophiles to enynes bearing an acceptor substituent at the double bond is also rather limited. Bowden and coworkers[165] found that 3-hexen-5-yn-2-one reacts with diethylamine under 1,6-addition to form the 6-amino-substituted dienone (equation 73). Similarly, 1,6-addition products were obtained by Russian groups from reactions of various primary and secondary amines with 2-en-4-ynoates and -nitriles[175−178]. However, enynoates and nitriles bearing *t*-butyl or trimethylsilyl groups at the triple bond were reported to react with methyl- and dimethylamine under 1,4-addition, indicating that the regioselectivity of the nucleophilic attack is



Geiparvarin

(70)

affected by the steric and electronic properties of the Michael acceptor (equation 74)[178,179].



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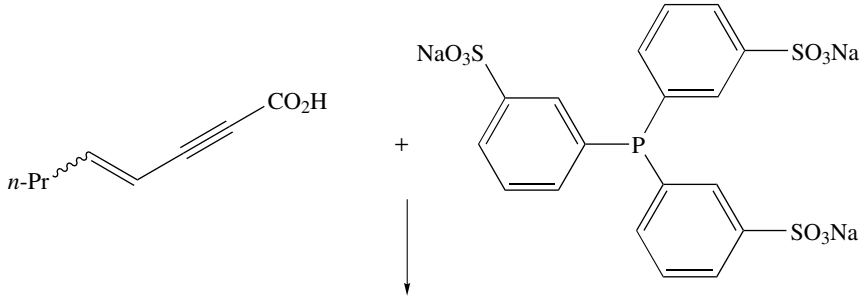

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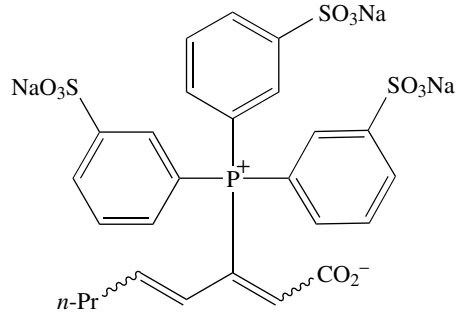
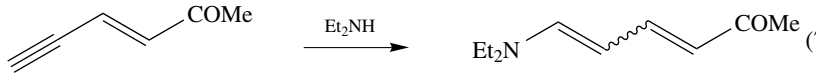
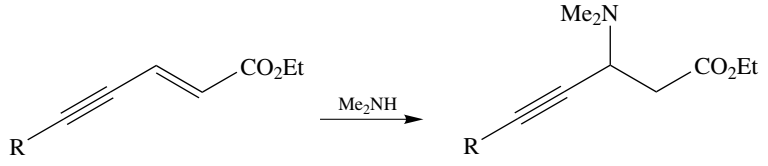




(73)

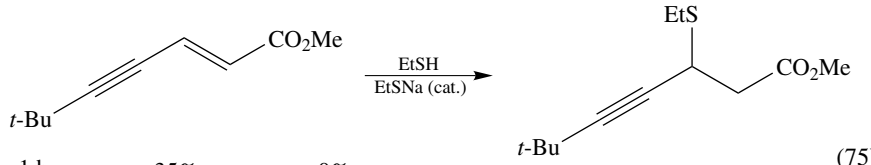


(74)

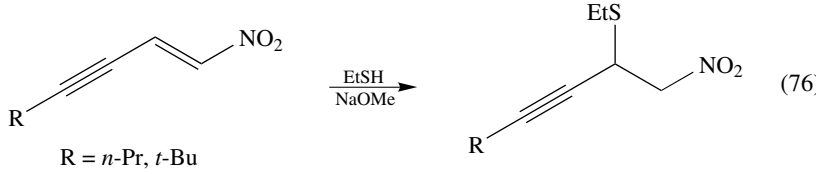
R = *t*-Bu, Me_3Si

In a thorough investigation of thiolate additions to acceptor-substituted enynes, Shustrova and coworkers[180,181] were able to demonstrate that the ratio of 1,4- and 1,6-addition depends on the reaction conditions, in particular on the duration of the experiment (equation 75): whereas only 1,4-adduct was observed in the reaction of methyl 6,6-dimethyl-2-hepten-4-ynoate and ethyl thiolate after 1 h, the product distribution shifted towards the 1,6-addition product with increasing reaction time, the latter being the sole

product after 48 h. This finding indicates that the Michael addition is reversible and that the (conjugated) 1,6-adduct is the thermodynamically most stable product. A 1,6-adduct was also obtained by treatment of a 3-alkynyl-2-cycloalkenone with lithium thiophenolate[141]. In contrast, treatment of 1-nitro-1-en-3-ynes with ethyl thiolate was reported to afford 1,4-addition products exclusively (equation 76)[182].



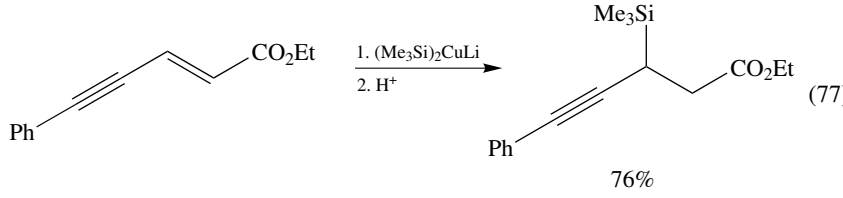
(75)



(76)

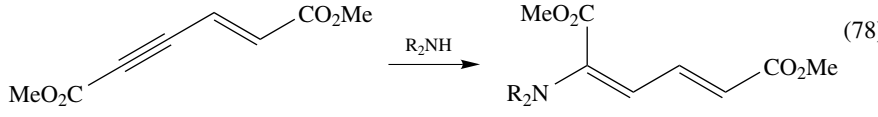
R = *n*-Pr, *t*-Bu

For the addition of silicon nucleophiles to activated enynes, silyl cuprates can be utilized. For example, treatment of ethyl 5-phenyl-2-penten-4-ynoate with $(Me_3Si)_2CuLi$ gave the 1,4-addition product with 76% yield (equation 77)[38].



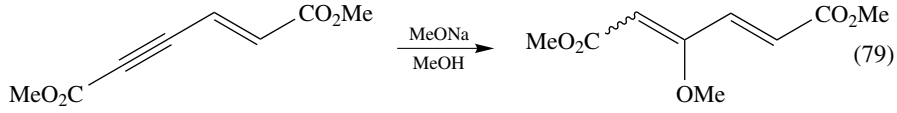
(77)

A particularly interesting Michael acceptor is dimethyl 2-hexen-4-ynedioate since it can react at either position of the double or triple bond to form 1,4- or 1,6-addition products. Winterfeldt and Preuss[183] treated this substrate with several secondary amines and observed exclusive attack at C-5 with formation of the 1,6-addition products (equation 78). In contrast to this, sodium methanolate added at C-4 to give the 1,4-adduct as a mixture of *E*/*Z* isomers (equation 79); with increasing reaction time, the product distribution was shifted towards the thermodynamically more stable *E*,*E*-product[184]. Acheson and

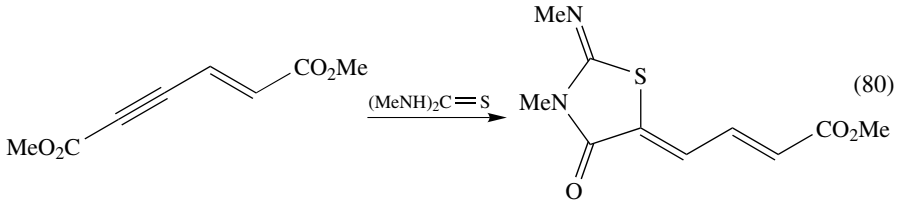


(78)

Wallis[185] examined reactions of dimethyl 2-hexen-4-ynedioate with thioureas and thioamides and observed addition at C-5 via the sulfur atom of these nucleophiles; the adducts often cyclize spontaneously to iminothiazolidinones (equation 80).



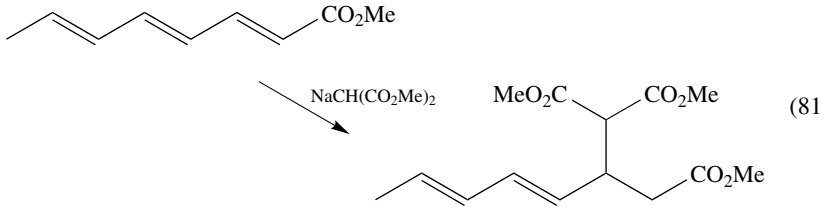
(79)



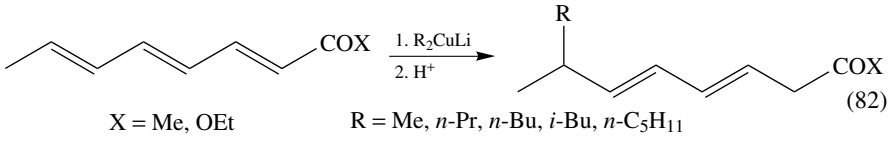
(80)

IV. POLYENES

Only few examples have been reported so far on nucleophilic addition reactions to acceptor-substituted polyenes[123,124,186–188]. In 1933, Farmer and Martin[186] examined the reaction of methyl 2,4,6-octatrienoate with sodium dimethyl malonate and isolated the 1,4-adduct as major product (equation 81). In contrast to this, 3,5,7-nonatrien-2-one and ethyl 2,4,6-octatrienoate react with organocuprates under 1,8-addition to provide the 4,6-dien-2-ones and 3,5-dienoates, respectively (equation 82)[187].



(81)

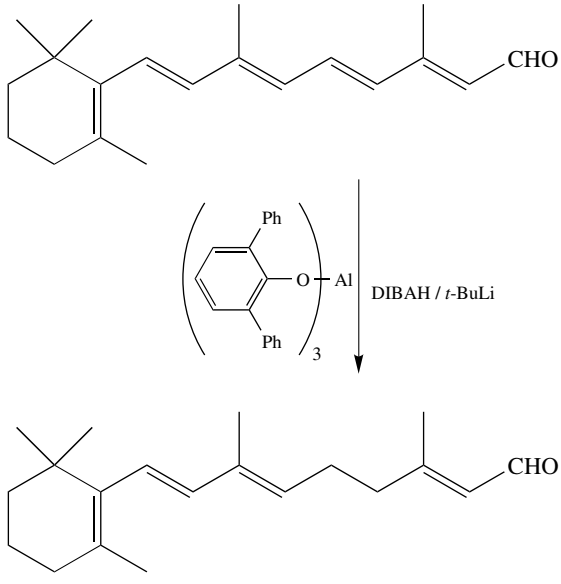


X = Me, OEt R = Me, *n*-Pr, *n*-Bu, *i*-Bu, *n*-C_5H_{11}

(82)

A case of a regioselective 1,6-reduction of retinal by treatment with the bulky Lewis acid aluminum tris(2,6-diphenylphenoxide) and DIBAH/*t*-BuLi as reducing agent was reported recently by Saito and Yamamoto (equation 83)[188]. In analogy to the Michael additions of thiolates to 2,4-dienones (Section II.B; equations 42 and 43), 1-(3-nitrophenyl)-2,4,6-heptatrien-1-one reacted with 2-mercaptoethanol with high 1,8-regioselectivity whereas the 1,4-addition product was formed in the presence of $TiCl_4$ (equation 84)[123]. Again, trapping of the 1,4-adduct as metal chelate seems to be responsible for this reversal

of regioselectivity. Consecutive 1,8-addition of 1,9-nonanethiol to 1-(3-nitrophenyl)-2-(2-hydroxyethylsulfonylmethyl)-2,4,6-heptatrien-1-one, sulfoxide elimination and intramolecular 1,4-addition led to the formation of an 18-membered macrocycle (equation 85)[124].

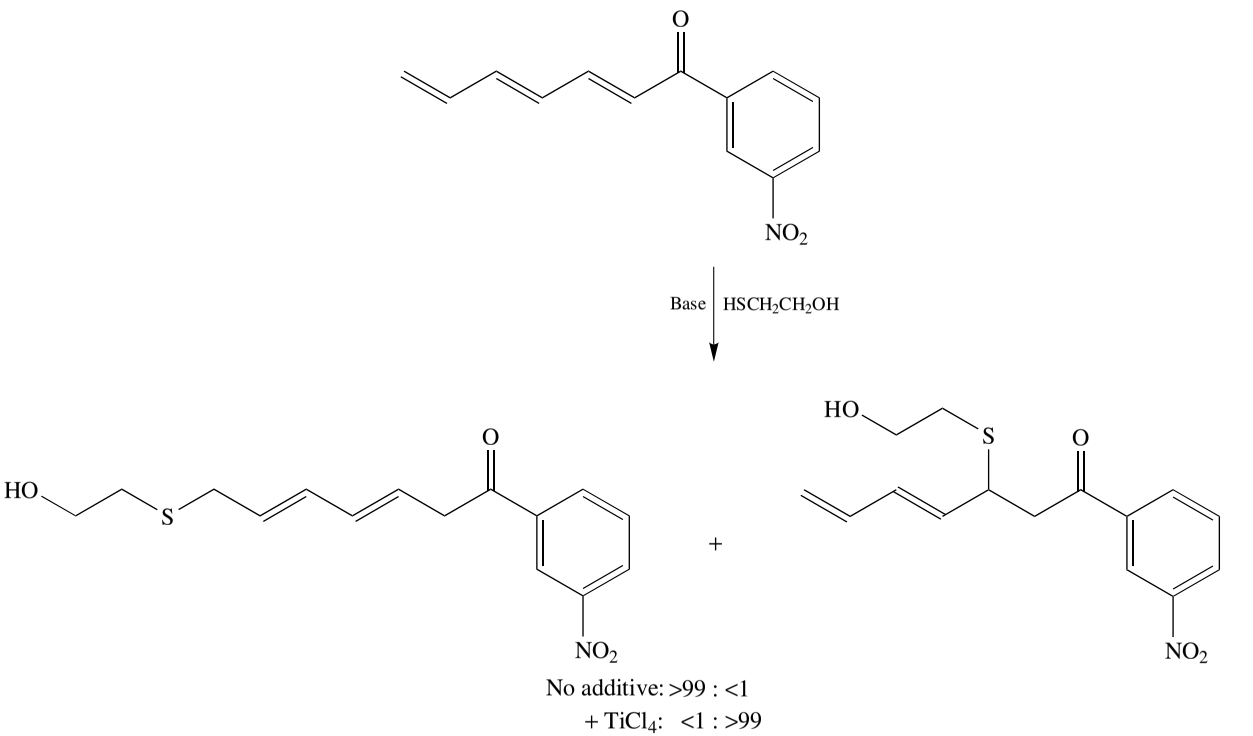


(83)

87%

In Section III it was demonstrated that the inclusion of a triple bond in polyunsaturated Michael acceptors serves to broaden the synthetic utility of these substrates in nucleophilic addition reactions. This is also true for activated dienynes, trienynes etc.; again, the position of the triple bond with respect to the acceptor substituent determines the regioselectivity of the nucleophilic attack. As already mentioned (Section III.A; equation 51), compounds bearing an acceptor-substituted triple bond besides several conjugated double bonds react with organocuprates regioselectively to give the 1,4-addition products. This selectivity has been exploited in the synthesis of several retinoids[138–140]; for example, addition of lithium diethyl- or di-*t*-butylcuprate to methyl 20-nor-13,14-didehydroretinoate afforded the 13-*cis*-substituted retinoates which were transformed into the corresponding retinals by reduction and reoxidation (equation 86)[138,139]. Likewise, treatment of 20-nor-13,14-didehydroretinal with hydrazoic acid furnished 13-nor-13-azidoretinal besides small amounts of the corresponding azirine (equation 87)[139,189]. Other examples for the addition of hetero-nucleophiles to acceptor-substituted dienynes involve the 1,4-addition of diethylamine to dimethyl 2,4-hexadien-6-ynedioate[190] and an intramolecular 1,8-thiolate addition observed in a bicyclic model compound for the enediyne antibiotic neocarzinostatin (equation 88)[191].

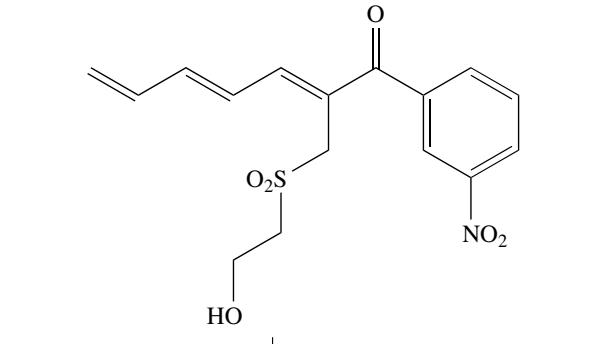
It was already noted that activated enynes bearing an acceptor substituent at the double bond react with organocuprates under 1,6-addition to provide functionalized allenes (see Section III.A)[38]. Interestingly, the preference of these reagents for triple bonds persists even when the distance between the acceptor group and the triple bond is increased by the introduction of further double bonds. For example, lithium dimethylcuprate attacked ethyl 8,8-dimethyl-2,4-nonadien-6-ynoate at the triple bond exclusively, and regioselective



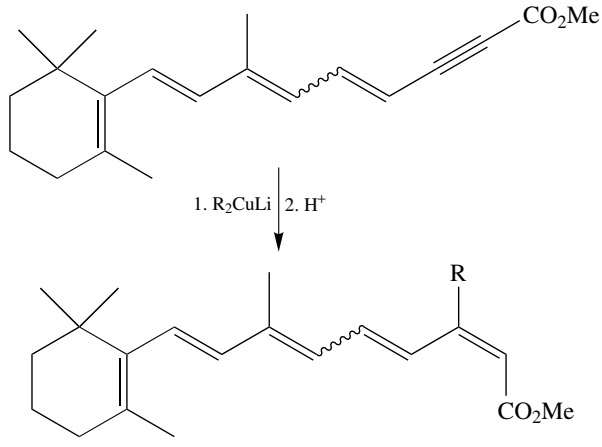
(84)

No additive: >99 : <1

+ $TiCl_4$: <1 : >99



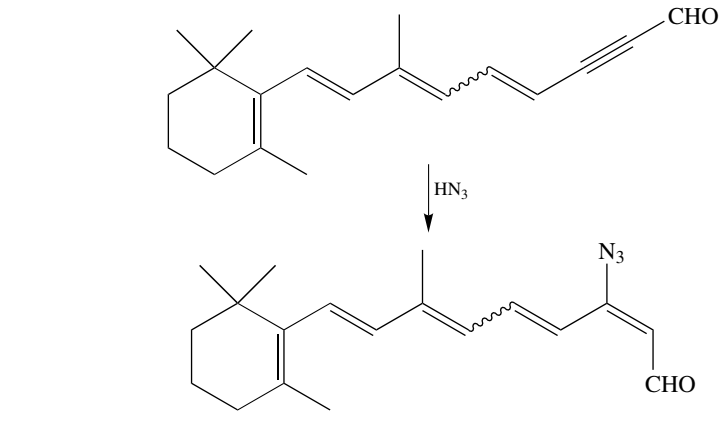
(85)



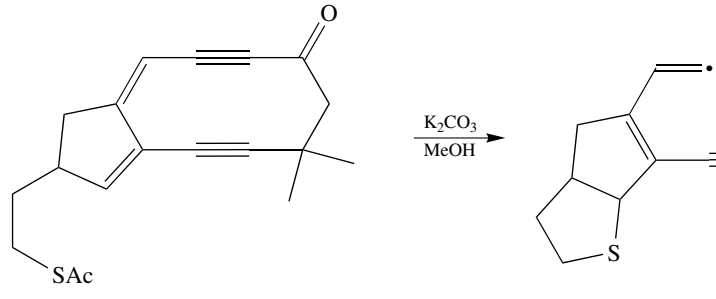
(86)

R = Et, *t*-Bu

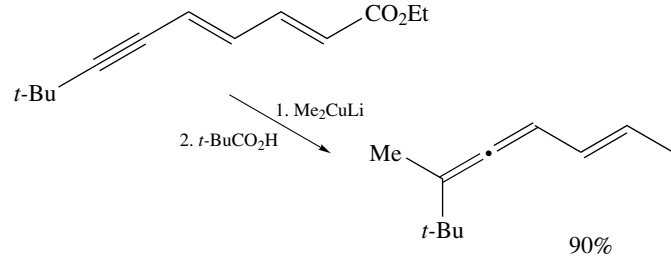
protonation with pivalic acid occurred at C-2 of the enolate, giving the 1,8-adduct as the only isolable regioisomer with 90% yield (equation 89)[38,158]. This vinylallene is well-suited as a diene in regio- and stereoselective Diels–Alder reactions. Analogously, ethyl 2,4,6-decatrien-8-ynoate reacted in a 1,10-fashion to give the 3,5,7,8-tetraenoate (equation 90), and even the 1,12-adduct could be obtained from a Michael acceptor



(87)



(88)

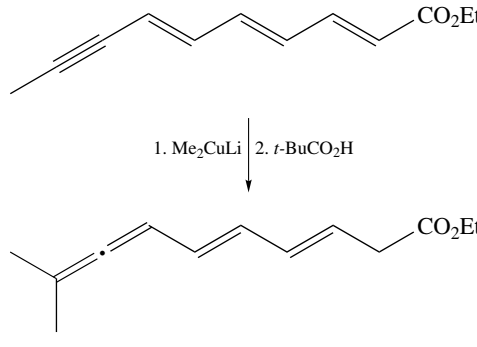


(89)

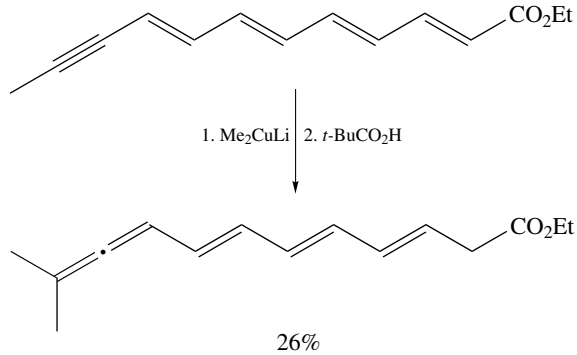
which contains four double bonds between the triple bond and the acceptor substituent (equation 91). In the latter case, however, the yield was only 26%; this is probably due to the reduced thermal stability of the addition products with increasing length of the conjugated π-system (the 1,12-adduct was the only isolable reaction product, apart from polymeric compounds)[38,158].

These transformations and those summarized in Section III.A make clear that Michael acceptors containing any combination of double and triple bonds undergo regioselective addition reactions with organocopper reagents. The following rule holds: *Michael acceptors with any given arrangement of conjugated double and triple bonds react regioselectively with organocuprates at the triple bond closest to the acceptor substituent*. Similar to the 1,6-cuprate addition to acceptor-substituted enynes (Scheme 4), these reactions start with the formation of a cuprate π-complex at the double bond neighboring the acceptor group[162] and may then proceed via an allenic σ-copper(III) intermediate which produces

the addition product by reductive elimination of RCu[38].



68% (90)



26% (91)

V. REFERENCES

1. J.-E. Bäckvall, in *The Chemistry of Dienes and Polyenes*, Vol. 1 (Ed. Z. Rappoport), Chap. 14, Wiley, Chichester, 1997, pp. 653–681.
2. Previous review: J. W. Ralls, *Chem. Rev.*, **59**, 329 (1959).
3. H. Zipse, in *The Chemistry of Dienes and Polyenes*, Vol. 1 (Ed. Z. Rappoport), Chap. 13, Wiley, Chichester, 1997, pp. 619–652.
4. D. Vorländer and P. Groebel, *Justus Liebigs Ann. Chem.*, **345**, 206 (1906).
5. D. Vorländer and H. Staudinger, *Justus Liebigs Ann. Chem.*, **345**, 217 (1906).
6. D. Vorländer, P. Weissheimer and F. Sponnagel, *Justus Liebigs Ann. Chem.*, **345**, 227 (1906).
7. E. P. Kohler and F. R. Butler, *J. Am. Chem. Soc.*, **48**, 1036 (1926).
8. E. H. Farmer and A. T. Healey, *J. Chem. Soc.*, 1060 (1927).
9. E. H. Farmer and T. N. Mehta, *J. Chem. Soc*. 1610 (1930).
10. J. Bloom and C. K. Ingold, *J. Chem. Soc.*, 2765 (1931).
11. D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 329 (1950).
12. E. H. Farmer, *J. Chem. Soc.*, 2015 (1922).
13. E. H. Farmer and T. N. Mehta, *J. Chem. Soc.*, 1762 (1931).
14. R. Robinson and J. S. Watt, *J. Chem. Soc.*, 1536 (1934).
15. J. L. Charlish, W. H. Davies and J. D. Rose, *J. Chem. Soc.*, 227 (1948).
16. J. L. Charlish, W. H. Davies and J. D. Rose, *J. Chem. Soc.*, 232 (1948).
17. P. Kurtz, *Justus Liebigs Ann. Chem.*, **572**, 23 (1951).
18. N. J. Leonard, D. L. Felley and E. D. Nicolaides, *J. Am. Chem. Soc.*, **74**, 1700 (1932).
19. S. Danishefsky and R. Cunningham, *J. Org. Chem.*, **30**, 3676 (1965).

20. G. A. Berchtold, J. Ciabattoni and A. A. Tunick, *J. Org. Chem.*, **30**, 3679 (1965).
21. M. Heuschmann, *Chem. Ber*., **121**, 39 (1988).
22. S. Danishefsky and R. Cavanaugh, *J. Org. Chem.*, **33**, 2959 (1968).
23. S. Danishefsky, G. Koppel and R. Levine, *Tetrahedron Lett.*, 2257 (1968).
24. S. Danishefsky, J. Eggler and G. Koppel, *Tetrahedron Lett.*, 4333 (1969).
25. S. Danishefsky, W. E. Hatch, M. Sax, E. Abola and J. Pletcher, *J. Am. Chem. Soc.*, **95**, 2410 (1973).
26. H. Irie, Y. Mizuno, T. Taga and K. Osaki, *J. Chem. Soc., Perkin Trans. 1*, 25 (1982).
27. A. Jellal and M. Santelli, *Tetrahedron Lett.*, **21**, 4487 (1980).
28. M. Santelli, D. El Abed and A. Jellal, *J. Org. Chem.*, **51**, 1199 (1986).
29. M. C. Roux-Schmitt, D. Croisat, J. Seyden-Penne, L. Wartski and M. Cossentini, *Pol. J. Chem.*, **70**, 325 (1996).
30. M. Kawai, M. Onaka and Y. Izumi, *Bull. Chem. Soc. Jpn.*, **61**, 2157 (1988).
31. G. Majetich, A. M. Casares, D. Chapman and M. Behnke, *Tetrahedron Lett.*, **24**, 1909 (1983).
32. R. W. Stevens and T. Mukaiyama, *Chem. Lett*., 851 (1985).
33. M. P. Cooke Jr. and R. Goswami, *J. Am. Chem. Soc*., **99**, 642 (1977).
34. Y. Tamaru, T. Harada, H. Iwamoto and Z. Yoshida, *J. Am. Chem. Soc.*, **100**, 5221 (1978).
35. A. I. Meyers and T. G. Grant, *J. Org. Chem.*, **57**, 4225 (1992).
36. J. A. Seijas, M. P. Vazquez-Tato, L. Castedo, R. Estevez and M. Ruiz, *J. Org. Chem*., **57**, 5283 (1992).
37. K. Maruoka, M. Ito and H. Yamamoto, *J. Am. Chem. Soc.*, **117**, 9091 (1995).
38. Review: N. Krause and A. Gerold, *Angew. Chem.,* **109**, 194 (1997); *Angew. Chem., Int. Ed. Engl.*, **36**, 186 (1997).
39. F. Näf, P. Degen and G. Ohloff, *Helv. Chim. Acta*, **55**, 82 (1972).
40. E. J. Corey, C. U. Kim, R. H. K. Chen and M. Takeda, *J. Am. Chem. Soc.*, **94**, 4395 (1972).
41. E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 1611 (1973).
42. E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6019 (1985).
43. B. Ganem, *Tetrahedron Lett.*, 4467 (1974).
44. S. F. Martin and P. J. Garrison, *Synthesis*, 394 (1982).
45. F. Barbot, A. Kadib-Elban and P. Miginiac, *J. Organomet. Chem.*, **255**, 1 (1983).
46. J. Bigorra, J. Font, C. Jaime, R. M. Ortuno and F. Sanchez-Ferrando, *Tetrahedron*, **41**, 5577 (1985).
47. J. Bigorra, J. Font, C. Jaime, R. M. Ortuno, F. Sanchez-Ferrando, F. Florencio, S. Martinez-Carrera and S. Garcia-Blanco, *Tetrahedron*, **41**, 5589 (1985).
48. H. Liu, L. M. Gayo, R. W. Sullivan, A. Y. H. Choi and H. W. Moore, *J. Org. Chem.*, **59**, 3284 (1994).
49. Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara and K. Maruyama, *J. Org. Chem*. **47**, 119 (1982).
50. Y. Yamamoto, *Angew. Chem.*, **98**, 945 (1986); *Angew. Chem. Int. Ed. Engl.*, **25**, 947 (1986).
51. F. Barbot, A. Kadib-Elban and P. Miginiac, *Tetrahedron Lett.*, **24**, 5089 (1983).
52. J. Lafontaine, M. Mongrain, M. Sergent-Guy, L. Ruest and P. Deslongchamps, *Can. J. Chem.*, **58**, 2460 (1980).
53. L. Novak, J. Rohaly, P. Kolonits, J. Fekete, L. Varjas and C. Szantay, *Liebigs Ann. Chem.*, 1173 (1982).
54. F. Näf, R. Decorzant and S. D. Escher, *Tetrahedron Lett.*, **23**, 5043 (1982).
55. U. Schöllkopf, D. Pettig, E. Schulze, M. Klinge, E. Egert, B. Benecke and M. Noltemeyer, *Angew. Chem.*, **100**, 1238 (1988); *Angew. Chem., Int. Ed. Engl.*, **27**, 1194 (1988).
56. D. Pettig and U. Schöllkopf, *Synthesis*, 173 (1988).
57. T. Kawamata, K. Harimaya and S. Inayama, *Bull. Chem. Soc. Jpn.*, **61**, 3770 (1988).
58. H. Wild and L. Born, *Angew. Chem.*, **103**, 1729 (1991); *Angew. Chem., Int. Ed. Engl.*, **30**, 1685 (1991).
59. S. Hanessian, A. Gomtsyan, A. Payne, Y. Hervé and S. Beaudoin, *J. Org. Chem.*, **58**, 5032 (1993).
60. P. Metz, U. Meiners, R. Fröhlich and M. Grehl, *J. Org. Chem.*, **59**, 3686 (1994).
61. K. Sabbe, C. D'Hallewyn, P. de Clercq, M. Vanderwalle, R. Bouillon and A. Verstuyf, *Bioorg. Med. Chem. Lett.*, **6**, 1697 (1996).
62. R. Bucourt, M. Vignau, V. Torrelli, H. Richard-Foy, C. Geynet, C. Secco-Millet, G. Redeuilh and E.-E. Baulieu, *J. Biol. Chem.*, **253**, 8221 (1978).

63. J. M. O'Reilly, N. Li, W. L. Duax and R. W. Brueggemeier, *J. Med. Chem.*, **38**, 2842 (1995).
64. M. Yanagita, S. Inayama, M. Hirakura and F. Seki, *J. Org. Chem.*, **23**, 690 (1958).
65. J. A. Marshall and H. Roebke, *J. Org. Chem.*, **31**, 3109 (1966).
66. J. A. Marshall, R. A. Ruden, L. K. Hirsch and M. Philippe, *Tetrahedron Lett.*, 3795 (1971).
67. J. A. Marshall and R. E. Conrow, *J. Am. Chem. Soc.*, **105**, 5679 (1983).
68. J. A. Marshall, J. E. Audia and B. G. Shearer, *J. Org. Chem.*, **51**, 1730 (1986).
69. F. M. Dayrit and J. Schwartz, *J. Am. Chem. Soc.*, **103**, 4466 (1981).
70. K. Utimoto, Y. Wakabayashi, T. Horiie, M. Inoue, Y. Shishiyama, M. Obayashi and H. Nozaki, *Tetrahedron*, **39**, 967 (1983).
71. J. A. Campbell and J. C. Babcock, *J. Am. Chem. Soc.*, **81**, 4069 (1959).
72. N. W. Atwater, R. H. Bible Jr., E. A. Brown, R. R. Burtner, J. S. Mihina, L. N. Nysted and P. B. Sollman, *J. Org. Chem.*, **26**, 3077 (1961).
73. R. Wiechert, U. Kerb and K. Kieslich, *Chem. Ber.*, **96**, 2765 (1963).
74. U. Kerb and R. Wiechert, *Chem. Ber.*, **96**, 2772 (1963).
75. P. Wieland and G. Auner, *Helv. Chim. Acta*, **50**, 289 (1967).
76. J. -C. Jacquesy, R. Jacquesy and C. Narbonne, *Bull. Soc. Chim. Fr.*, 1240 (1976).
77. W. Nagata, M. Yoshioka and M. Murakami, *J. Am. Chem. Soc.*, **94**, 4654 (1972).
78. W. Nagata, M. Yoshioka and T. Terasawa, *J. Am. Chem. Soc.*, **94**, 4672 (1972).
79. K. Nickisch, D. Bittler, H. Laurent, W. Losert, Y. Nishino, E. Schillinger and R. Wiechert, *J. Med. Chem.*, **33**, 509 (1990).
80. J. Grob, M. Boillaz, J. Schmidlin, H. Wehrli, P. Wieland, H. Fuhrer, G. Ribs, U. Joss, M. de Gasparo, H. Haenni, H. P. Ramjoué, S. E. Whitebread and J. Kalvoda, *Helv. Chim. Acta*, **80**, 566 (1997).
81. D. N. Kirk and B. W. Miller, *J. Chem. Res. (S)*, 278 (1988).
82. K. Nickisch and H. Laurent, *Tetrahedron Lett.*, **29**, 1533 (1988).
83. J. F. Grunwell, H. D. Benson, J. O. Johnston and V. Petrow, *Steroids*, **27**, 759 (1976).
84. A. J. Solo, C. Caroli, M. V. Darby, T. McKay, W. D. Slaunwhite and P. Hebborn, *Steroids*, **40**, 603 (1982).
85. B. Mühlenbruch, F. Kirmeier and H. J. Roth, *Arch. Pharm. (Weinheim)*, **319**, 177 (1986).
86. J. Bowler, T. J. Lilley, J. D. Pittam and A. E. Wakeling, *Steroids*, **54**, 71 (1989).
87. S. P. Modi, J. O. Gardner, A. Milowsky, M. Wierzba, L. Forgione, P. Mazur, A. J. Solo, W. L. Duax, Z. Galdecki, P. Grochulski and Z. Wawrzak, *J. Org. Chem.*, **54**, 2317 (1989).
88. A. N. French, S. R. Wilson, M. J. Welch and J. A. Katzenellenbogen, *Steroids*, **58**, 157 (1993).
89. F. Camps, J. Coll, A. Guerrero, J. Guitart and M. Riba, *Chem. Lett.*, 715 (1982).
90. F. Camps, J. Coll and J. Guitart, *Tetrahedron*, **43**, 2329 (1987).
91. F. Camps, J. Coll and J. Guitart, *J. Chem. Res. (S)*, 38 (1990).
92. G. Just, P. Potvin and G. H. Hakimelahi, *Can. J. Chem.*, **58**, 2780 (1980)
93. B. J. M. Jansen, J. A. Kreuger and A. de Groot, *Tetrahedron*, **45**, 1447 (1989).
94. H. J. Swarts, A. A. Haaksma, B. J. M. Jansen and A. de Groot, *Tetrahedron*, **48**, 5497 (1992).
95. L. H. D. Jenniskens and A. de Groot, *Tetrahedron Lett.*, **38**, 7463 (1997).
96. T. Tsuda, T. Hayashi, H. Satomi, T. Kawamoto and T. Saegusa, *J. Org. Chem.*, **51**, 537 (1986).
97. M. Fujii, K. Nakamura, S. Yasui, S. Oka and A. Ohno, *Bull. Chem. Soc. Jpn.*, **60**, 2423 (1987)
98. M. Frankel, H. S. Mosher and F. C. Whitmore, *J. Am. Chem. Soc.*, **72**, 81 (1950).
99. J. M. Stewart, *J. Am. Chem. Soc.*, **76**, 3228 (1954).
100. A. Lespagnol, E. Cuingnet and M. Debaert, *Bull. Soc. Chim. Fr.*, 1162 (1960).
101. F. Weigert, *J. Org. Chem.*, **43**, 622 (1978).
102. R. B. Zhurin and V. B. Vainer, *Zh. Org. Khim.*, **8**, 953 (1972); *J. Org. Chem. USSR*, **8**, 958 (1972).
103. R. B. Zhurin and V. B. Vainer, *Zh. Org. Khim.*, **8**, 959 (1972); *J. Org. Chem. USSR*, **8**, 964 (1972).
104. U. M. Dzhemilev, A. Z. Yakupova, S. K. Minsker and G. A. Tolstikov, *Zh. Org. Khim.*, **15**, 1164 (1979); *J. Org. Chem. USSR*, **15**, 1041 (1979).
105. Y. Yamamoto, N. Asao and T. Uyehara, *J. Am. Chem. Soc.*, **114**, 5427 (1992).
106. N. Asao, T. Shimada, N. Tsukada and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1660 (1993).
107. N. Asao, T. Uyehara, N. Tsukada and Y. Yamamoto, *Bull. Chem. Soc. Jpn.*, **68**, 2103 (1995).

108. M. Shimano and A. I. Meyers, *J. Am. Chem. Soc.*, **116**, 6437 (1994).
109. M. Shimano and A. I. Meyers, *J. Org. Chem.*, **60**, 7445 (1995).
110. M. Shimano and A. I. Meyers, *J. Org. Chem.*, **61**, 5714 (1996).
111. D. D. Coffman, *J. Am. Chem. Soc.*, **57**, 1981 (1935).
112. G. G. Melikyan, A. A. Tosunyan, E. V. Babayan, K. A. Atanesyan and S. O. Badanyan, *Zh. Org. Khim.*, **27**, 2039 (1991); *J. Org. Chem. USSR*, **27**, 1802 (1991).
113. G. G. Melikyan, A. A. Tosunyan and S. O. Badanyan, *Zh. Org. Khim.*, **27**, 2045 (1991); *J. Org. Chem. USSR*, **27**, 1808 (1991).
114. F. Fischer, D. Berger and M. Neuenschwander, *Angew. Chem.*, **110**, 2214 (1998); *Angew. Chem., Int. Ed. Engl.*, **37**, 2214 (1998).
115. S. Darvesh, A. S. Grant, D. I. Magee and Z. Valenta, *Can. J. Chem.*, **67**, 2237 (1989).
116. A. N. Pudovik and I. V. Konovalova, *Zh. Obshch. Khim.*, **28**, 1208 (1958); *J. Gen. Chem. USSR*, **28**, 1263 (1958).
117. V. A. Kukhtin and K. M. Orekhova, *Zh. Obshch. Khim.*, **30**, 1526 (1960); *J. Gen. Chem. USSR*, **30**, 1539 (1960).
118. L. M. Pevzner, V. M. Ignat'ev and B. I. Ionin, *Zh. Obshch. Khim.*, **55**, 2010 (1985); *J. Gen. Chem. USSR*, **55**, 1785 (1985).
119. E. G. Kataev and L. K. Konovalova, *Zh. Org. Khim.*, **3**, 949 (1967); *J. Org. Chem. USSR*, **3**, 912 (1967).
120. P. Bravo, G. Gaudiano, T. Salvatori, S. Maroni and M. Acampora, *Gazz. Chim. Ital.*, **98**, 1046 (1968).
121. M. de Malde, *Ann. Chim (Rome)*, **42**, 437 (1952).
122. R. B. Thompson, J. A. Chenicek and T. Symon, *Ind. Eng. Chem.*, **44**, 1659 (1952).
123. S. J. Brocchini and R. G. Lawton, *Tetrahedron Lett.*, **36**, 6319 (1997).
124. S. J. Brocchini, M. Eberle and R. G. Lawton, *J. Am. Chem. Soc.*, **110**, 5211 (1988).
125. M. C. Bernabeu, R. Chinchilla and C. Nájera, *Tetrahedron Lett.*, **36**, 3901 (1995).
126. W. Tang and F. S. Abbott, *J. Mass Spectrom.*, **31**, 926 (1996).
127. K. Hashimoto, K. Konno, H. Shirahama and T. Matsumoto, *Chem. Lett.*, 1399 (1986).
128. K. W. Li, J. Wu, W. Xing and J. A. Simon, *J. Am. Chem. Soc.*, **118**, 7237 (1996).
129. J. W. Ralls, R. M. Dodson and B. Riegel, *J. Am. Chem. Soc.*, **71**, 3320 (1949).
130. J. Romo, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, 1413 (1952).
131. R. W. Brueggemeier, E. E. Floyd and R. E. Counsell, *J. Med. Chem.*, **21**, 1007 (1978).
132. R. W. Brueggemeier, C. E. Snider and R. E. Counsell, *Cancer Res.*, **42**, 3334s (1982).
133. M. V. Darby, J. A. Lovett, R. W. Brueggemeier, M. P. Groziak and R. E. Counsell, *J. Med. Chem.*, **28**, 803 (1985).
134. R. W. Brueggemeier, P.-K. Li, C. E. Snider, M. V. Darby and N.E. Katlic, *Steroids*, **50**, 163 (1987).
135. R. W. Brueggemeier and N. E. Katlic, *Cancer Res.*, **47**, 4548 (1987).
136. H.-H. Chen and R. W. Brueggemeier, *Steroids*, **55**, 123 (1990).
137. S. Ebrahimian, H.-H. Chen and R. W. Brueggemeier, *Steroids*, **58**, 414 (1993).
138. L. Ernst, H. Hopf and N. Krause, *J. Org. Chem.*, **52**, 398 (1987).
139. H. Hopf and N. Krause, in *Chemistry and Biology of Synthetic Retinoids* (Ed. M. I. Dawson and W. H. Okamura), CRC Press, Boca Raton, 1990, pp. 177-199.
140. Y. L. Bennani, *J. Org. Chem.*, **61**, 3542 (1996).
141. Review: M. A. Fredrick and M. Hulce, *Tetrahedron*, **53**, 10197 (1997).
142. M. Hulce, *Tetrahedron Lett.*, **29**, 5851 (1988).
143. M. Cheng and M. Hulce, *J. Org. Chem.*, **55**, 964 (1990).
144. S. H. Lee and M. Hulce, *Tetrahedron Lett.*, **31**, 311 (1990).
145. H. F. Schuster and G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, 1984.
146. N. Krause, *Chem. Ber.*, **123**, 2173 (1990).
147. N. Krause, *Chem. Ber.*, **124**, 2633 (1991).
148. M. Hohmann and N. Krause, *Chem. Ber.*, **128**, 851 (1995).
149. M. Bergdahl, M. Eriksson, M. Nilsson and T. Olsson, *J. Org. Chem.*, **58**, 7238 (1993).
150. N. Krause and G. Handke, *Tetrahedron Lett.*, **32**, 7229 (1991).
151. A. Gerold and N. Krause, *Chem. Ber.*, **127**, 1547 (1994).
152. A. Haubrich, M. van Klaveren, G. van Koten, G. Handke and N. Krause, *J. Org. Chem.*, **58**, 5849 (1993).
153. S. Arndt, G. Handke and N. Krause, *Chem. Ber.*, **126**, 251 (1993).

154. N. Krause and S. Arndt, *Chem. Ber.*, **126**, 261 (1993).
155. S. H. Lee, M. Shih and M. Hulce, *Tetrahedron Lett.*, **33**, 185 (1992).
156. S. H. Lee and M. Hulce, *Synlett*, 485 (1992).
157. N. Krause, *Justus Liebigs Ann. Chem.*, 521 (1993).
158. U. Koop, G. Handke and N. Krause, *Liebigs Ann. Chem.*, 1487 (1996).
159. M. Laux, N. Krause and U. Koop, *Synlett*, 87 (1996).
160. M. Becker and N. Krause, *Liebigs Ann./Recueil*, 725 (1997).
161. G. Handke and N. Krause, *Tetrahedron Lett.*, **34**, 6037 (1993).
162. N. Krause, *J. Org. Chem.*, **57**, 3509 (1992).
163. N. Krause, R. Wagner and A. Gerold, *J. Am. Chem. Soc.*, **116**, 381 (1994).
164. J. Canisius, A. Gerold and N. Krause, *Angew. Chem.*, **111**, 1722 (1999); *Angew. Chem. Int. Ed. Engl.*, **38**, 1644 (1999).
165. K. Bowden, E. A. Braude, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946).
166. L. I. Vereshchagin, L. P. Kirillova, S. R. Buzilova, R. L. Bol'shedvorskaya and G. V. Chernysheva, *Zh. Org. Khim.*, **11**, 531 (1975); *J. Org. Chem. USSR*, **11**, 527 (1975).
167. L. I. Vereshchagin, E. I. Titova, L. G. Tikhonova, S. I. Demina and L. D. Gavrilov, *Zh. Org. Khim.*, **11**, 955 (1975); *J. Org. Chem. USSR*, **11**, 945 (1975).
168. L. D. Gavrilov, L. G. Tikhonova, E. I. Titova and L. I. Vereshchagin, *Zh. Org. Khim.*, **12**, 530 (1976); *J. Org. Chem. USSR*, **12**, 521 (1976).
169. A. S. Zanina, S. I. Shergina, I. E. Sokolov and R. N. Myasnikova, *Izv. Akad. Nauk, Ser. Khim.*, **44**, 710 (1995); *Russ. Chem. Bull.*, **44**, 689 (1995).
170. R. F. W. Jackson and R. A. Raphael, *Tetrahedron Lett.*, **24**, 2117 (1983).
171. R. F. W. Jackson and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 535 (1984).
172. V. F. Kucherov, A. I. Kuznetsova, M. V. Mavrov and E. F. Alekseev, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 484 (1962); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 446 (1962).
173. A. K. Chopra, G. P. Moss and B. C. Weedon, *J. Chem. Soc., Perkin Trans. 1*, 1371 (1988).
174. C. Larpent and H. Patin, *Tetrahedron Lett.*, **29**, 4577 (1988).
175. Z. A. Krasnaya, T. S. Smytsenko, E. P. Prokof'ev and V. F. Kucherov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2213 (1972); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2148 (1972).
176. E. P. Prokof'ev, Z. A. Krasnaya and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2218 (1972); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2153 (1972).
177. N. V. Koshima and F. Y. Perveev, *Zh. Org. Khim.*, **12**, 2074 (1976); *J. Org. Chem. USSR*, **12**, 2021 (1976).
178. F. Y. Perveev and I. I. Afonina, *Zh. Obshch. Khim.*, **41**, 345 (1971); *J. Gen. Chem. USSR*, **41**, 340 (1971).
179. N. N. Belyaev, L. I. Korchemkina and M. D. Stadnichuk, *Zh. Obshch. Khim.*, **49**, 2630 (1979); *J. Gen. Chem. USSR*, **49**, 2334 (1979).
180. T. A. Shustrova, N. N. Belyaev and M. D. Stadnichuk, *Zh. Obshch. Khim.*, **54**, 2781 (1984); *J. Gen. Chem. USSR*, **54**, 2492 (1984).
181. T. A. Shustrova, N. N. Belyaev and M. D. Stadnichuk, *Zh. Obshch. Khim.*, **55**, 1777 (1985); *J. Gen. Chem. USSR*, **55**, 1579 (1985).
182. K. B. Rall', A. I. Vil'davskaya and A. A. Petrov, *Zh. Org. Khim.*, **4**, 959 (1968); *J. Org. Chem. USSR*, **4**, 931 (1968).
183. E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).
184. E. Winterfeldt, W. Krohn and H. Preuss, *Chem. Ber.*, **99**, 2572 (1966).
185. R. M. Acheson and J. D. Wallis, *J. Chem. Soc., Perkin Trans. 1*, 1905 (1982).
186. E. H. Farmer and S. R. W. Martin, *J. Chem. Soc.*, 960 (1933).
187. F. Barbot, A. Kadlib-Elban and P. Miginiac, *J. Organomet. Chem.*, **345**, 239 (1988).
188. S. Saito and H. Yamamoto, *J. Org. Chem.*, **61**, 2928 (1996).
189. H. Hopf and N. Krause, *Tetrahedron Lett.*, **27**, 6177 (1986).
190. E. R. H. Jones, B. L. Shaw and M. C. Whiting, *J. Chem. Soc.*, 3212 (1954).
191. M. Hirama, M. Tokuda and K. Fujiwara, *Synlett*, 651 (1991).

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CHAPTER **9**

Synthetic applications of dienes and polyenes, excluding cycloadditions

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I. INTRODUCTION

The reactivity of polyenes is influenced by their substituents, and whether or not the multiple double bonds of the unsaturated hydrocarbon are conjugated or isolated from

one another. The π-system of a polyene may be fully conjugated, or there may be one or more pairs of conjugated double bonds isolated from the other π-bonds in the molecule, or, alternatively, each of the carbon–carbon double bonds in the polyene may be isolated from one another. Conjugated π-systems react differently with electrophiles than isolated double bonds. Addition of hydrogen to isolated double bonds has been previously discussed in this series and will not be addressed here[1]. Allenes and cumulenes constitute an important class of polyenes which will not be considered here as they have already appeared in this series[2] and in other more comprehensive reviews[3,4].

The reactions of dienes and other polyenes can be broadly classified as either addition reactions, coupling (or substitution reactions) or rearrangements (including metathesis reactions). This chapter will present recent examples from the literature of synthetic transformations involving polyenes. Cycloaddition and ring closing metathesis reactions appeared in volume one of this series and therefore will not be covered in this chapter. Citations for more detailed descriptions of the individual reactions discussed in this chapter and for more comprehensive reviews appear in the text.

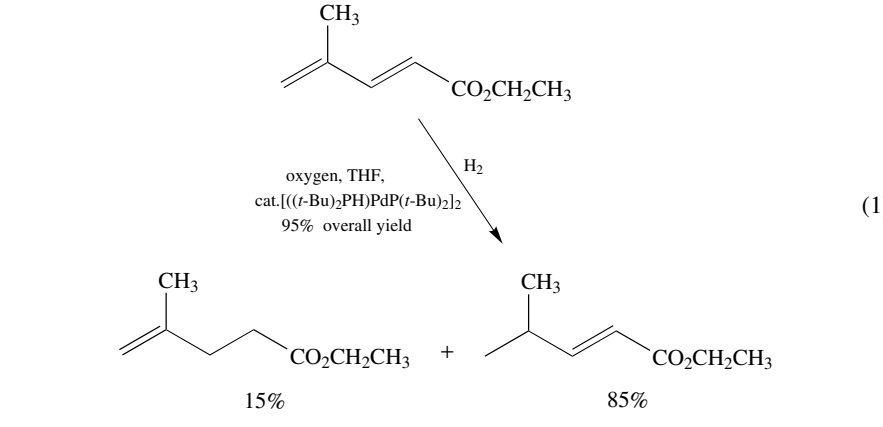
II. ADDITION REACTIONS

If the double bonds of a polyene are not conjugated with other π-systems in the molecule, addition to one of the π-bonds will proceed in a similar fashion to addition to a simple alkene. Usually addition to one of the bonds is preferred, because it is either more highly substituted and, as a result, has enhanced electron density, or because it has fewer substituents and is less hindered and more accessible to the electrophile. Alternatively, one of the double bonds of a polyene may be activated by the presence of a heteroatom at the allylic position.

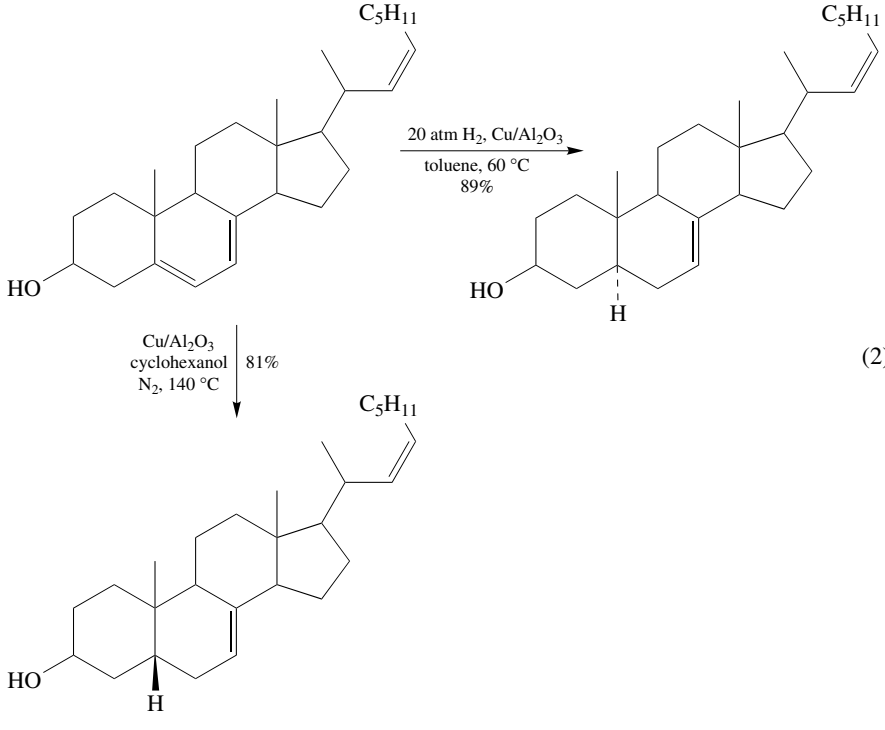
1,3-Dienes undergo both 1,2- and 1,4-addition to the carbons of the conjugated system to give the corresponding 1,2- and 1,4-substituted alkenes, respectively. The regioselectivity of the addition depends on the nature of the electrophile as well as on the reaction conditions. Deuteriation of conjugated dienes on cadmium monoxide, cobalt oxide (Co_3O_4) and chromium(III) oxide shows selectivity for 1,2-hydrogenation in the presence of the cadmium and cobalt oxides, and for 1,4-addition on chromium(III) oxide[5]. Selective 1,2-hydrogenation of simple and functionalized conjugated dienes using metal complexes as catalysts has been investigated[6]. The binuclear palladium complex, $[((t\text{-}Bu)_2PH)PdP(Bu\text{-}t)_2]_2$, has been used to catalyze the selective hydrogenation of conjugated diene esters, ketones and nitro compounds to the corresponding functionalized monoenes[7]. 1,2-Addition of hydrogen is selective for the double bond further from the electron-withdrawing group; thus, the major alkene formed on selective reduction of ethyl 4-methyl-2,4-pentadienoate is the α,β-unsaturated ester (equation 1). The reaction proceeds under mild conditions and in the presence of oxygen.

1,2-Hydrogenation of the conjucated cyclohexadienyl ring B of 3β-sterols has been accomplished using catalytic amounts of Cu/Al_2O_3[8]. Addition is selective for the double bond nearer the hydroxy group. In addition to regioselectivity, the stereochemistry of the epimer formed can be reversed by changing the hydrogenation conditions (equation 2).

Halogenation of conjugated dienes proceeds chiefly by 1,4-addition with molecular halogens (equation 3). 1,2-Addition is favored in the presence of pyridine–halogen complexes and amine tribromide salts (equation 4)[9]. The stereochemistry of 1,4-bromine addition with 2,4-hexadienes and cyclopentadiene is primarily *anti* in the presence of amine, but *syn* with molecular halogen in the absence of amine.



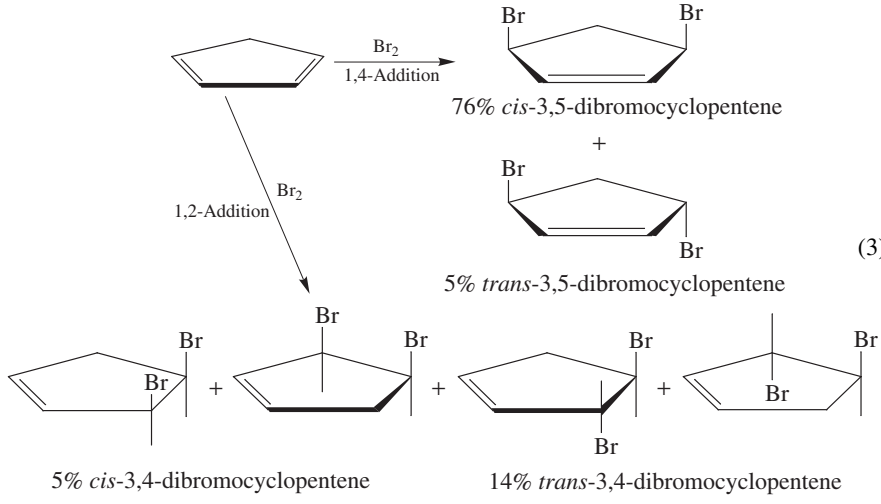
(1)

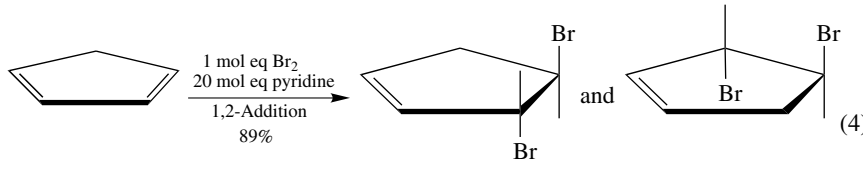


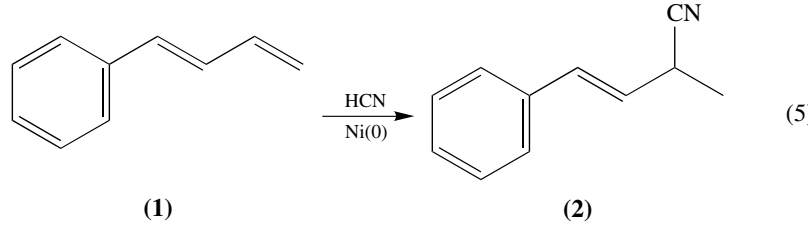
(2)

Hydrocyanation of aliphatic conjugated dienes in the presence of Ni(0) complexes gives diene rearrangement products and β,γ-unsaturated nitriles in 10–90% yields[10]. Dienes other than 1,3-butadiene do not produce terminal nitriles, implying that the more highly substituted π-allyl nickel complex is favored. Thus, reaction of 1-phenylbuta-1,3-diene **(1)** affords (*E*)-2-methyl-4-phenylbut-3-enenitrile **(2)** as the sole product (equation 5). The

use of chiral Ni complexes, however, displays only low levels of asymmetric induction.



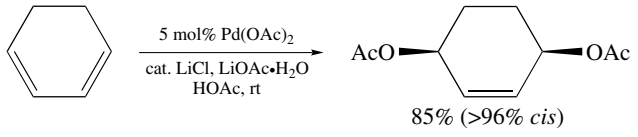


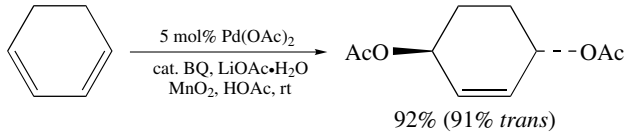


Stereo- and regioselective palladium-catalyzed oxidation of 1,3-dienes in acetic acid to give 1,4-diacetoxy-2-alkenes has been accomplished using MnO_2 and catalytic amounts of *p*-benzoquinone (BQ)[11]. The reaction can be made to take place with *cis*- or *trans*-1,4-diacetoxylation across the diene in cyclic systems as shown in equation 6.

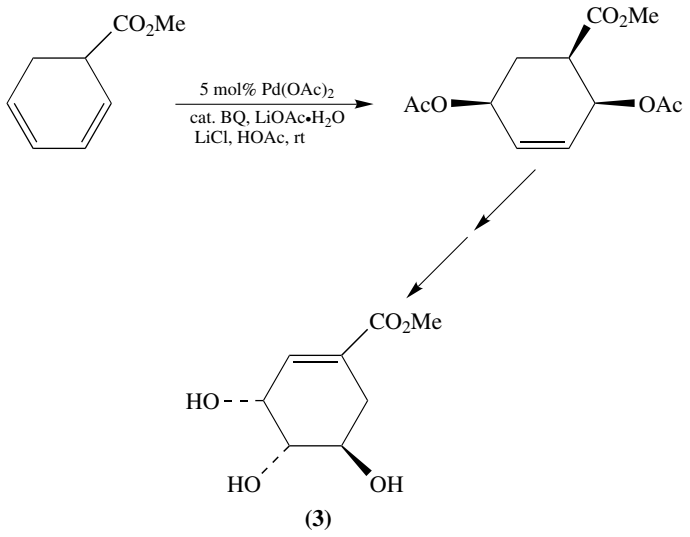
In acyclic systems the 1,4-relative stereoselectivity was controlled by the stereochemistry of the diene. Thus, oxidation of (*E*,*E*)- and (*E*,*Z*)-2,4-hexadienes to their corresponding diacetates affords *dl* (>88% *dl*) and *meso* (>95% *meso*) 2,5-diacetoxy-3-hexene, respectively. A mechanism involving a *trans*-acetoxypalladation of the conjugated diene to give an intermediate (π-allyl)palladium complex, followed by either a *cis* or *trans* attack by acetate on the allyl group, has been suggested. The *cis* attack is explained by a *cis* migration from a (σ-allyl)palladium intermediate. The diacetoxylation reaction was applied to the preparation of a key intermediate for the synthesis of *dl*-shikimic acid, **3**,

as shown in equation 7.





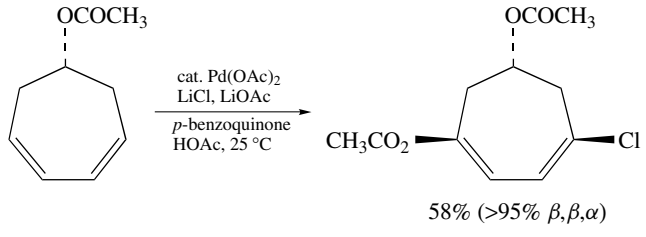
(6)



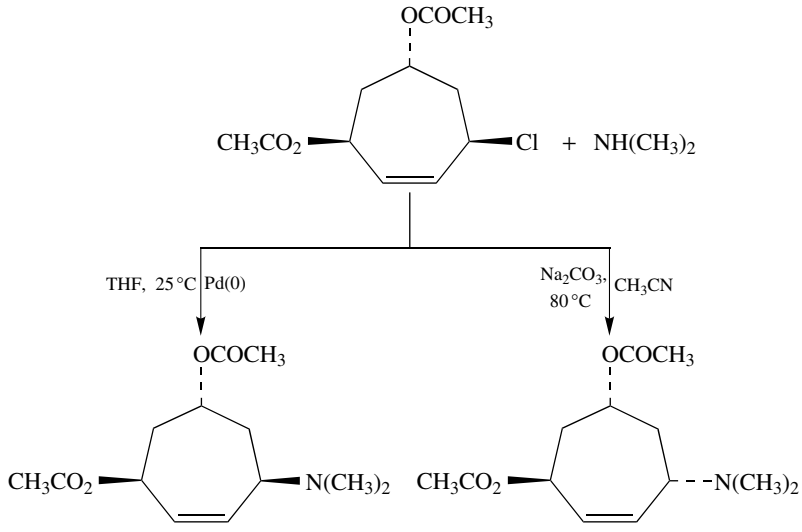
(7)

(3)

Amino alkenols have been prepared by palladium-catalyzed chloroacetoxylation and allylic amination of 1,3-dienes. 1,4-Acetoxychlorination is stereospecific and cyclic dienes give an overall *cis*-1,4-addition[12]. Acetoxychlorination of 6-acetoxy-1,3-cycloheptadiene afforded only one isomer as shown in equation 8. Sequential substitution of the allylic chloro group can occur with either retention or inversion, thereby allowing complete control of the 1,4-relative stereochemistry (equation 9).



(8)



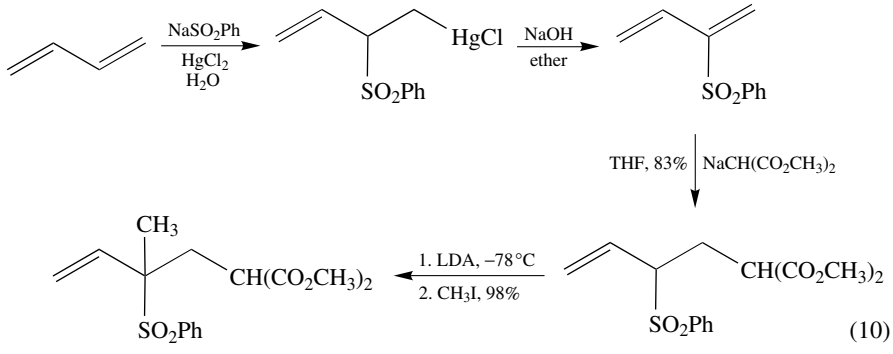
(9)

Using a similar approach, 1-acetoxy-4-diethylamino-2-butene and 1-acetoxy-4-benzylamino-2-butene were prepared. Treatment of 1,3-butadiene with LiCl–LiOAc in the presence of $Pd(OAc)_2$ and *p*-benzoquinone in acetic acid gave 91% 1-acetoxy-4-chloro-2-butene ($E/Z = 90/10$). Subsequent allylic amination with diethylamine, catalyzed by $Pd(PPh_3)_4$ in THF, produced mainly (*E*)-1-acetoxy-4-diethylamino-2-butene[13].

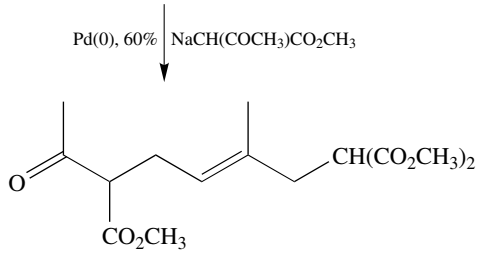
Allylic and dienyl sulfones have been prepared by conjugate addition to 1,3-dienes[14]. Phenylsulfonylmercuration of conjugated dienes gives mercury adducts which can be treated with base to afford phenylsulfonyldienes[15]. 2-(Phenylsulfonyl)-1,3-dienes can be stereo- and regioselectively functionalized via Michael addition of nucleophiles to give allylic sulfones. A key intermediate in the synthesis of a Monarch butterfly pheromone **4** was prepared by Bäckvall and Juntunen[16] by alkylation and subsequent palladium-catalyzed substitution of the allylic sulfone formed by Michael addition of dimethyl malonate to 2-(phenylsulfonyl)-1,3-butadiene (equation 10).

1- and 2-Nitro-1,3-dienes have been obtained from conjugated dienes by various methods[17–20]. Nitrodienes have proven to be useful synthetic intermediates and react with electron-rich alkenes to give nitronates[21–25]. Bäckvall has demonstrated that 2-nitro-1,3-dienes, prepared by a nitroselenation-elimination sequence, are useful intermediates in the preparation of unsaturated 1,4-dicarbonyl compounds (equation 11)[26].

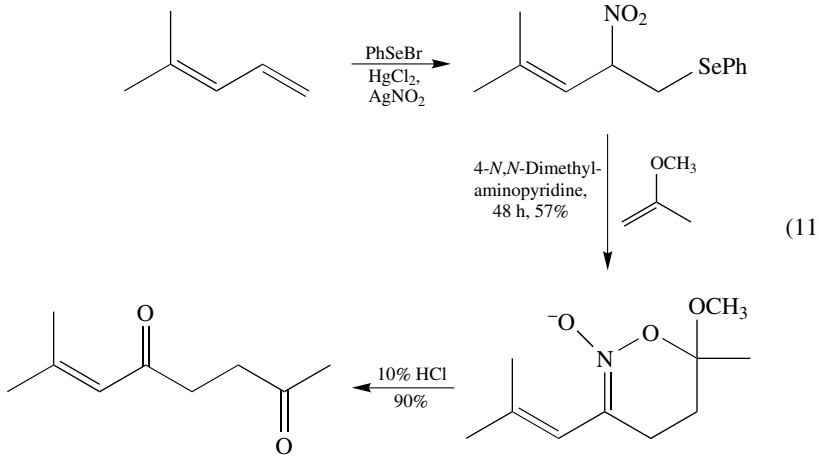
Ceric ammonium nitrate promoted oxidative addition of silyl enol ethers to 1,3-butadiene affords 1 : 1 mixtures of 4-(β-oxoalkyl)-substituted 3-nitroxy-1-butene and 1-nitroxy-2-butene[27]. Palladium(0)-catalyzed alkylation of the nitroxy isomeric mixture takes place through a common η^3 palladium complex which undergoes nucleophilic attack almost exclusively at the less substituted allylic carbon. Thus, oxidative addition of the silyl enol ether of 1-indanone to 1,3-butadiene followed by palladium-catalyzed substitution with sodium dimethyl malonate afforded 42% of a 19 : 1 mixture of methyl (*E*)-2-(methoxycarbonyl)-6-(1-oxo-2-indanyl)-4-hexenoate **(5)** and methyl 2-(methoxycarbonyl)-4-(1-oxo-2-indanyl)-3-vinylbutanoate **(6)**, respectively (equation 12).



(10)

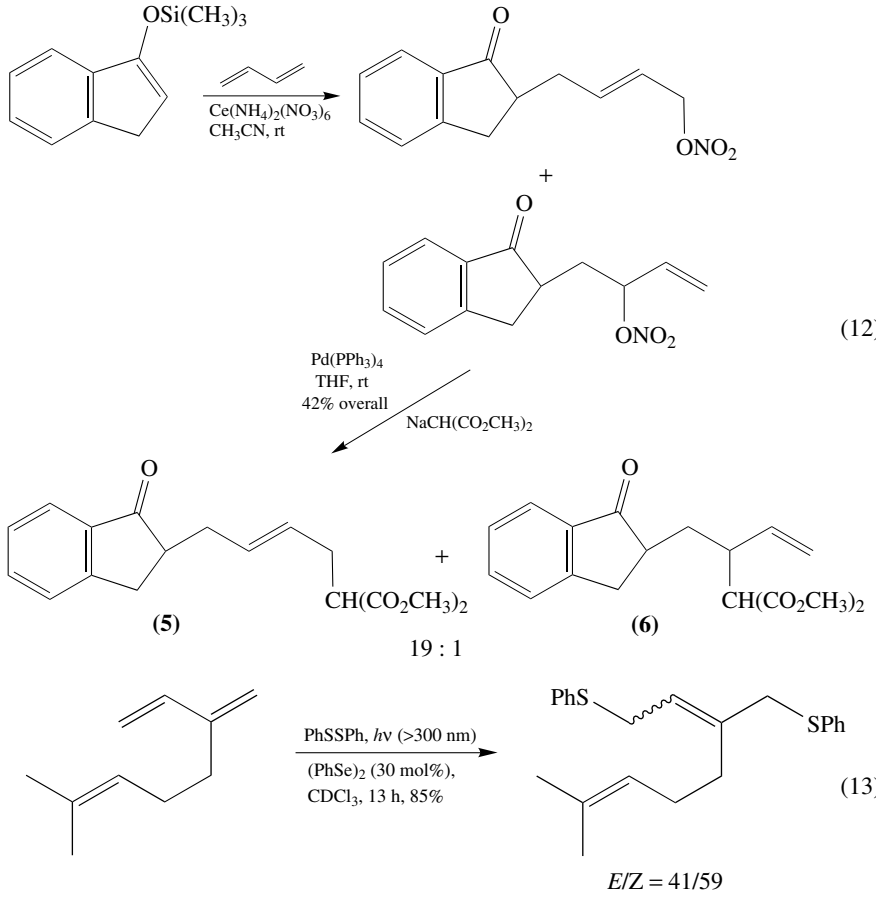


(4)



(11)

1,4-Dithiolation of conjugated dienes occurs on photolysis of disulfides in the presence of 1,3-dienes. However, the reaction is not clean and generally affords a polymeric mixture. Irradiation of diphenyl disulfides and 1,3-dienes in the presence of diphenyl diselenide was recently reported to provide the corresponding 1,4-dithiolation products selectively in good yields (equation 13)[28].



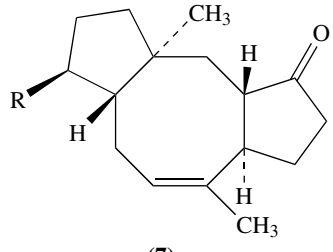
(12)

(13)

III. OXIDATION REACTIONS

Polyenes containing isolated double bonds undergo oxidation reactions similar to their alkene analogs. Thus, in the enantioselective synthesis of the tricyclic nucleus of ceroplastol I **(7a)**, Snider and Yang[29] prepared diene **8** which they transformed in four steps to diene **9** (equation 14). Osmylation of the diene with OsO_4 and 4-methylmorpholine N-oxide (NMO) generated the corresponding tetrol. Further oxidation of the tetrol with $NaIO_4$ gave keto aldehyde **10**. McMurry coupling of **10** afforded the tricyclic system **11** which, on deprotection of the silyl ether, was oxidized to the ketone to complete the synthesis of **7b**.

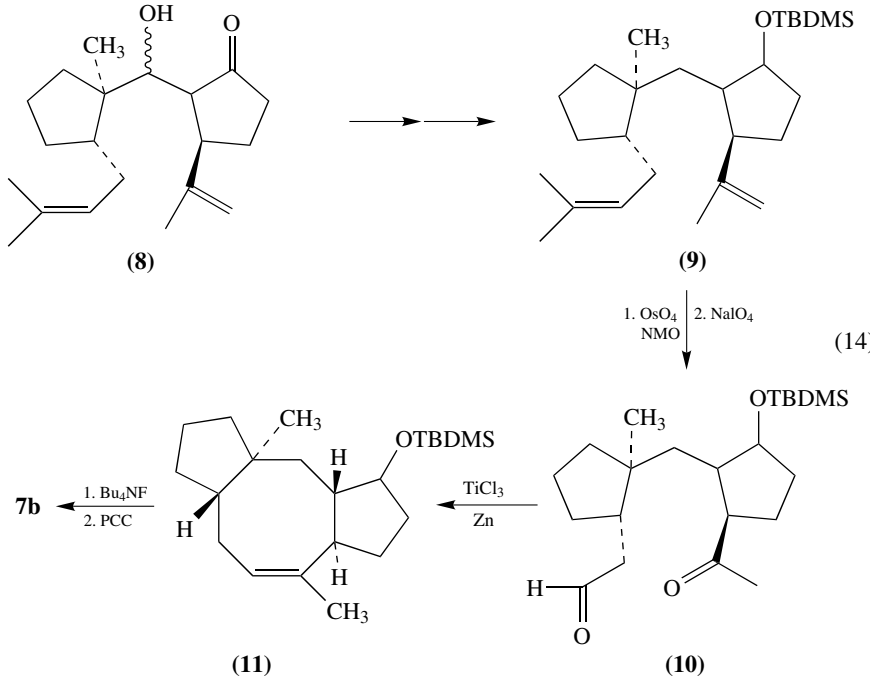
The regioselectivity of oxidation in nonconjugated polyenic systems is generally influenced by steric and electronic factors, or anchimeric effects. A comprehensive review of asymmetric epoxidation of allylic alcohols, including dienols and trienols, has recently been published[30]. The procedure first described by Katsuki and Sharpless[31] has proven to be one of the most effective methods for selectively epoxidating double bonds in polyfunctional systems with high stereo- and regioselectivities. Thus, epoxidation of pyrandienol **12** with titanium(IV) isopropoxide and (*R*,*R*)-(+)-diethyl tartrate (DET) selectively occurs at



(7)

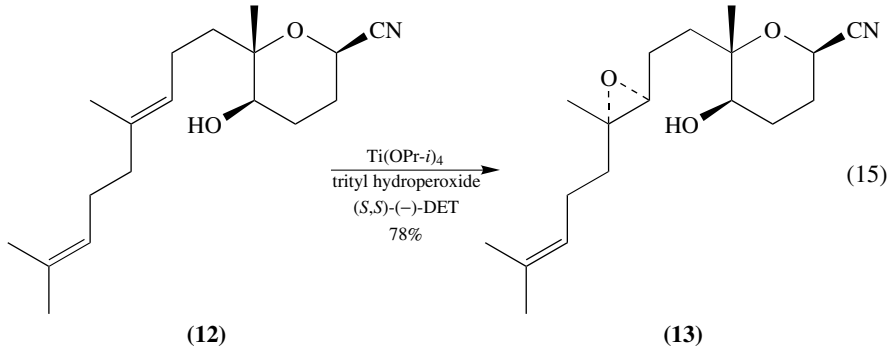
(7a) R = (*E*)-1,5-dimethyl-4-hexen-6-ol
(7b) R = H

the double bond nearest the pyran ring furnishing epoxide **13** exclusively (equation 15)[32]. The observed regio- and steroselectivity for this reaction is presumably due to anchimeric assistance by the hydroxy substituent on the pyran ring.



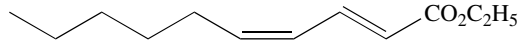
(14)

Asymmetric monoepoxidation of conjugated dienes has been accomplished via (salen)Mn(III)-catalyzed [salen = *N*,*N*′-bis(salicylidene)ethylenediamine] oxidation. The reaction exhibits regioselectivity for attack at *cis* double bonds of *cis,trans*-conjugated dienes, and affords *trans* epoxides as the major products from *cis* olefins[33]. Thus, diene **14** gave optically active *trans*-vinylepoxide **15** as the major product with 87% ee as shown in equation 16.

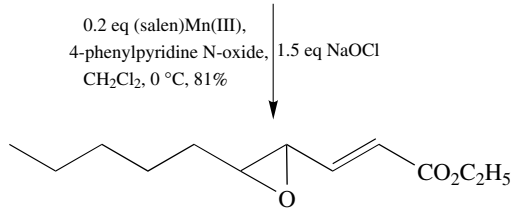


(15)

(12) **(13)**



(14)



(16)

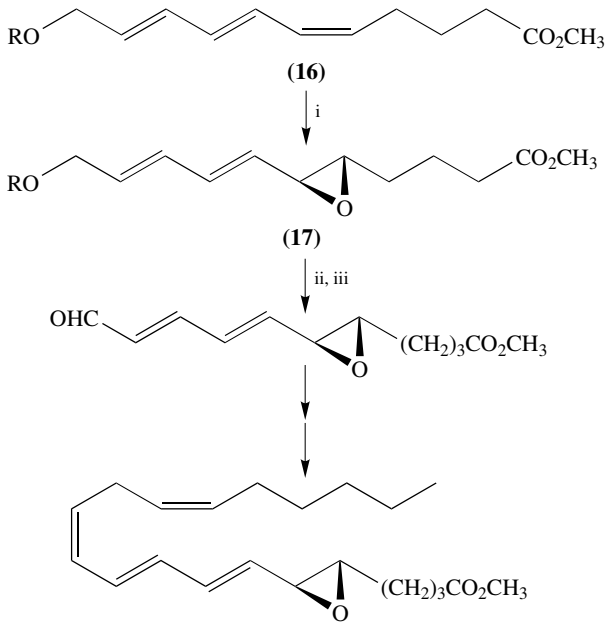
(15)

The successful application of this method was illustrated with a series of model dienes, and with the formal synthesis of leukotriene A_4 methyl ester, a complex polyene monoepoxide, from the intermediate epoxyundecadienoate **17** prepared by selective epoxidation of trienyl ester **16** (equation 17).

Asymmetric monoepoxidation of conjugated dienes has also been accomplished using a fructose-derived chiral ketone catalyst and oxone as the oxidant (equation 18)[34]. High regioselectivities and enantioselectivities are realized under these conditions. The regioselectivity of monoepoxidation of unsymmetric dienes can be regulated by using steric and electronic control. The reaction has been found to tolerate a variety of functional groups including hydroxyl groups, silyl ethers and esters.

A more unusual monoepoxidation was observed when 1-halo-1,3-cyclohexadienes were treated with aqueous solutions of potassium permangnate[35]. Oxidation of **18** resulted in formation of the unusual halo-epoxydiol **19** as the major oxidation product (equation 19). Hydrolysis of **19** with water in the presence of Al_2O_3 afforded the rare inosose **20** in high yield.

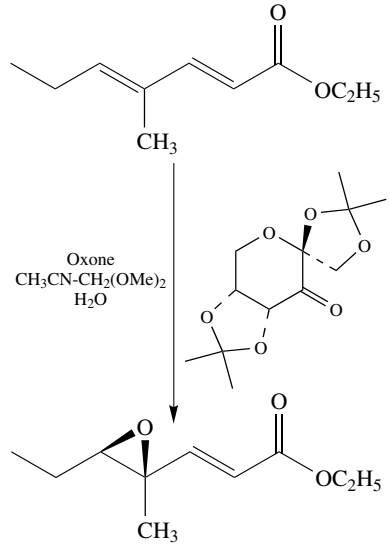
In an elegant synthesis of structurally simplified analogs of daphnane diterpene resiniferatoxin **(21)**, which possess the unusual 2,9,10-trioxatricyclo[4.3.1.0]decane system, cyclohexadiene was transformed into an endoperoxide[36]. Reaction of 1,3-cyclohexadiene with singlet oxygen generated *in situ* from oxygen and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine stereoselectively transformed the cyclic diene into *cis*-cyclohex-2-ene-1,4-diol (equation 20). Reduction of the reactive endoperoxide intermediate was accomplished with thiourea. Silylation of the diol followed by epoxidation with *m*-chloroperbenzoic acid (mCPBA) afforded mainly the *anti*-epoxide. Ring opening of the epoxide with an



(17)

Leukotriene A_4 methyl ester

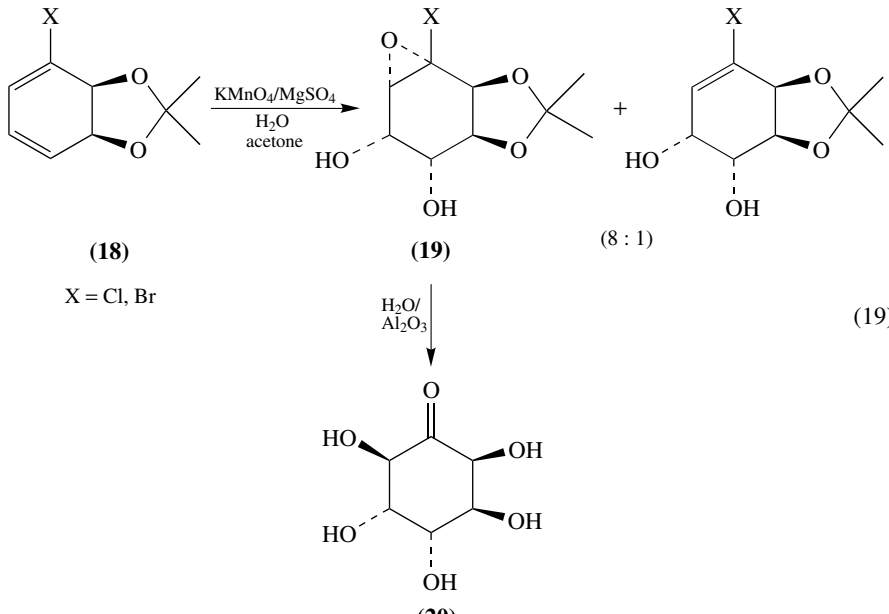
(i) 1.2 eq NaOCl, pH 11.3, 20 mol% 4-phenylpyridine-*N*-oxide, 4 mol% (salen)Mn(III); (ii) NH_3, CH_3OH; (iii) activated MnO_2



(18)

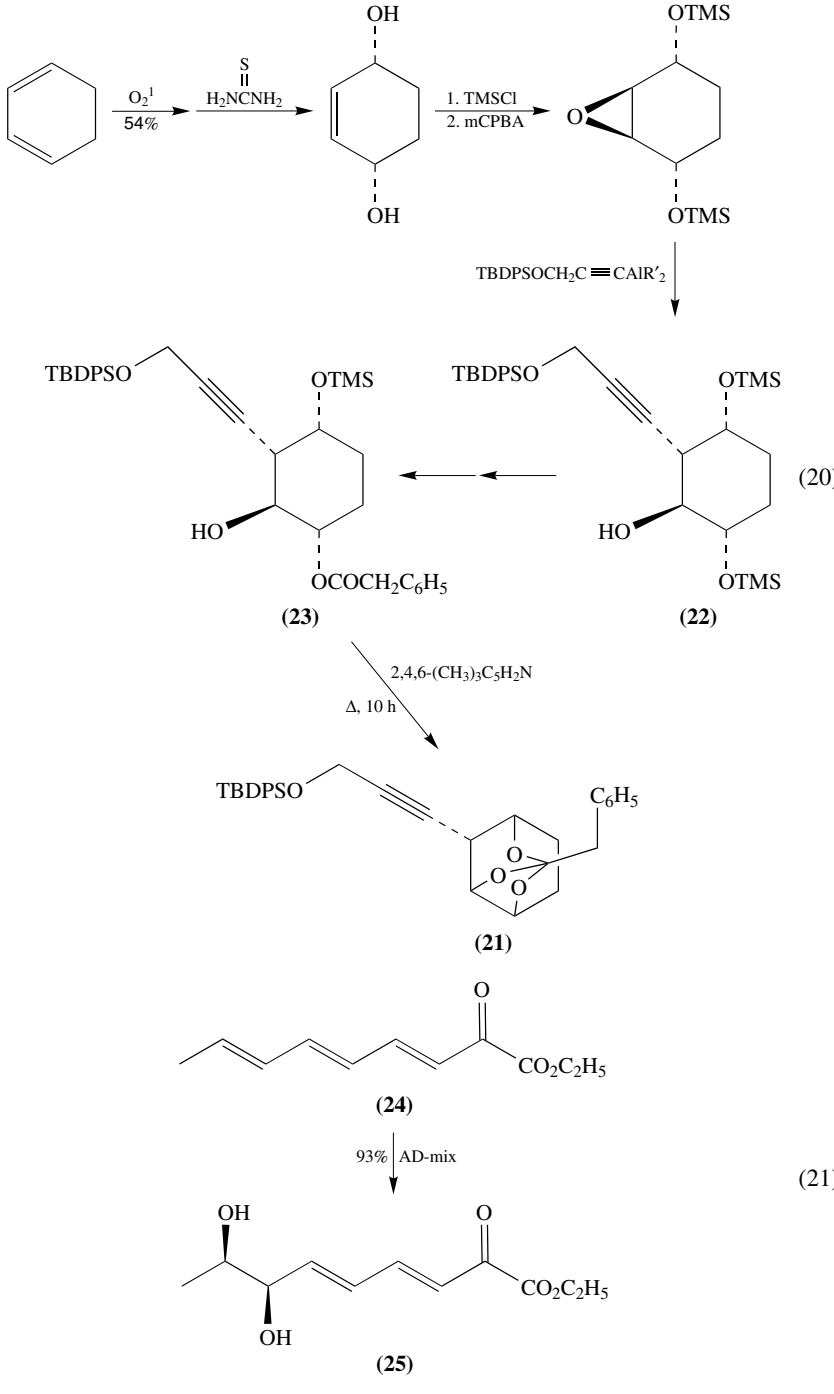
82% (95% ee)

alkynylalane produced intermediate **22** that was transformed in four steps to compound **23**. The desired trioxatricyclo[4.3.1.0]decane system, **21**, was acquired in 73% yield on refluxing **23** for 10 h in 2,4,6-trimethylpyridine.

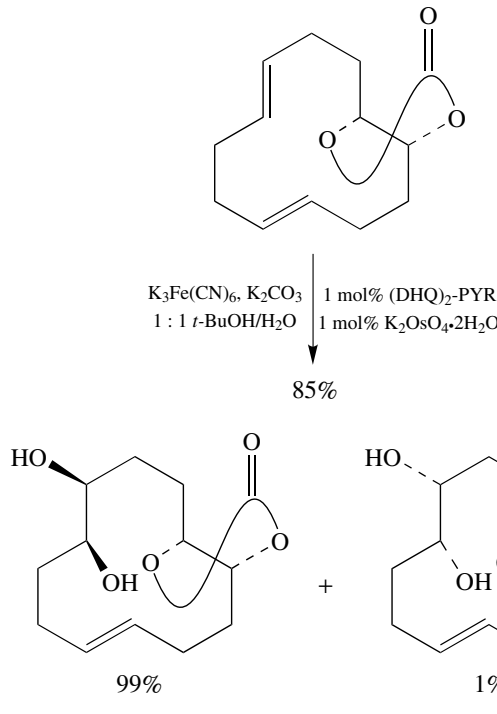


(19)

Conjugated dienes can be hydroxylated to the corresponding tetrols with catalytic amounts of osmium tetroxide in the presence of water, acetone and equimolar amounts of *N*-methylmorpholine[37]. High stereoselectivities were achieved for 1,4-disubstituted *trans*-1,3-butadienes. Less substituted 1,3-dienes or those with *cis* double bonds showed lower stereoselectivities for hydroxylation. Thus, while (*E*,*E*)-1,4-diphenyl-1,3-butadiene afforded 1,4-diphenyl-1,2,3,4-tetrahydroxybutane in 87% yield with a 16 : 1 preference for the 2,3-*anti* over the 2,3-*syn* isomer, hydroxylation of 1,3-butadiene resulted in an 80% yield of the corresponding tetrol with lowered selectivity (5 : 1 2,3-*anti* to 2,3-*syn* addition). Hydroxylation of (*E*,*Z*)-2,4-hexadiene resulted in only a 2 : 1 preference for *anti* versus *syn* addition. The reaction was also much less successful when applied to polyenes. However, catalytic osmylation of dienes and triene esters was found to proceed with high regio- and stereoselectivity when chiral esters of dihydroquinidines, such as 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine, are employed as ligands[38]. A typical asymmetric dihydroxylation procedure employs one mole percent ligand and one mole percent of $K_2OsO_4 \cdot 2H_2O$, generally referred to as an AD-mix[39]. Selective asymmetric dihydroxylation of polyenes has subsequently been realized using the Sharpless asymmetric dihydroxylation procedure[39]. In many cases excellent regioselectivities of stereoregular polyhydroxylated carbon chains were obtained. The observed selectivities were explained in terms of electronic and/or steric effects inherent to the substrate, superimposed on the substrate's favorable or unfavorable interactions with the binding pocket of the AD ligand. Thus, (*E*, *E*, *E*) ethyl 2-oxo-3,5,7-nonatrienoate **(24)** was selectively mono-dihydroxylated at the distal double bond to afford **25** in excellent yield with 95% ee (equation 21).


OH
OTMS
S
O_2[1]
54%
H_2NCNH_2
1. TMSCl
2. mCPBA
O
OH
OTMS
$TBDPSOCH_2C{\equiv}CAlR'_2$
TBDPSO
OTMS
HO
$OCOCH_2C_6H_5$
(23)
(22)
(20)
$2,4,6\text{-}(CH_3)_3C_5H_2N$
Δ, 10 h
C_6H_5
(21)
$CO_2C_2H_5$
(24)
93% AD-mix
(21)
(25)

Unexpectedly high enantioselectivities were also realized for medium and large ring dienes with *trans* double bonds using the pyrimidine (PYR) ligands (equation 22).



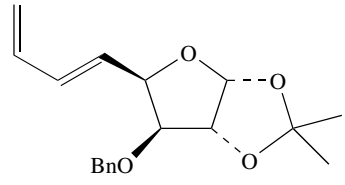
(22)

$(DHQ)_2$-PYR = Hydroquinone 2,5-diphenyl-4,6-pyrimidinediyl diethene

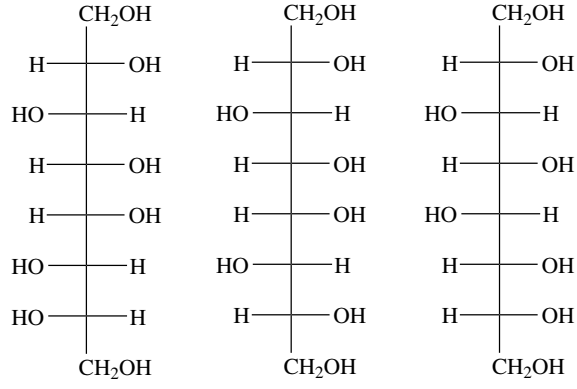
The diastereoselective synthesis of higher sugars was accomplished by *bis*-osmylation of sugar derived dienes using OsO_4-NMO[40]. As shown in equation 23, osmylation of diene **26** afforded diastereomeric sugars **27**, **28**, and **29** in 90% overall yield in a 6.6 : 1.2 : 1.0 ratio, respectively.

A stereoselective osmylation approach was applied to the synthesis of C(1)−C(7) and C(7)−C(13) subunits of erythronolide A[41]. A key synthon of the erythronolide A seco acid, **30**, was prepared in an enantiomerically pure form by utilizing a stereoselective osmylation of the chiral hydroxy (*Z*,*E*)-diene ester **31** and subsequent hydrogenation of the resulting butenolide **32** (equation 24).

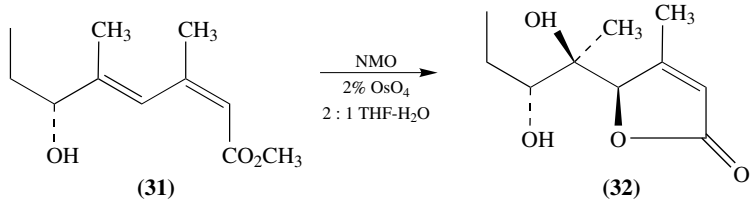
Regio- and stereoselective dihydroxylation of dienes functionalized at the allylic position with a benzene sulfone group has been reported[42]. Osmylation of dienic sulfones **33**, a potential key synthon for forskolin, occurred exclusively on the Δ^{6-7} double bound and preferentially from the α-face of the *trans*-fused bicyclic molecule, presumably due to a combination of steric and electronic factors (equation 25). While the reaction of diene sulfones proceeded sluggishly under catalytic conditions, treatment of **33a** with a stoichiometric amount of OsO_4 resulted in quantitative yield of diastereomeric diols **34a** and **35** in a 9 : 1 ratio, respectively. Protecting the hydroxy group of the dienol as its *t*-butyldimethylsilyl ether **(33b)** affords diol **34b** exclusively.



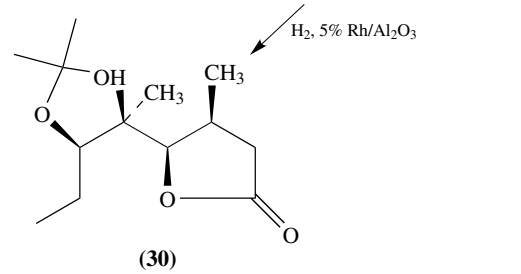
(26)



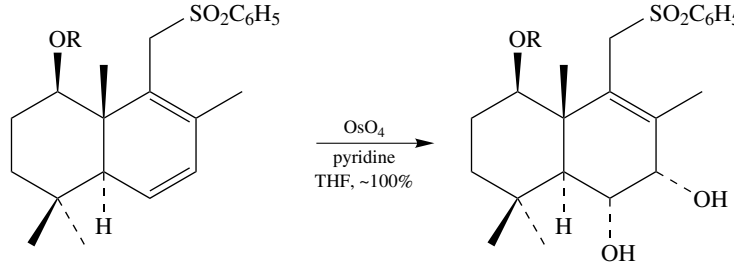
(27) **(28)** **(29)** (23)



(31) **(32)**



(30) (24)

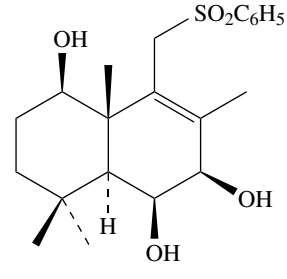


(33a) R = H
(33b) R = TBDMS

(34a) R = H
(34b) R = TBDMS

(25)

+

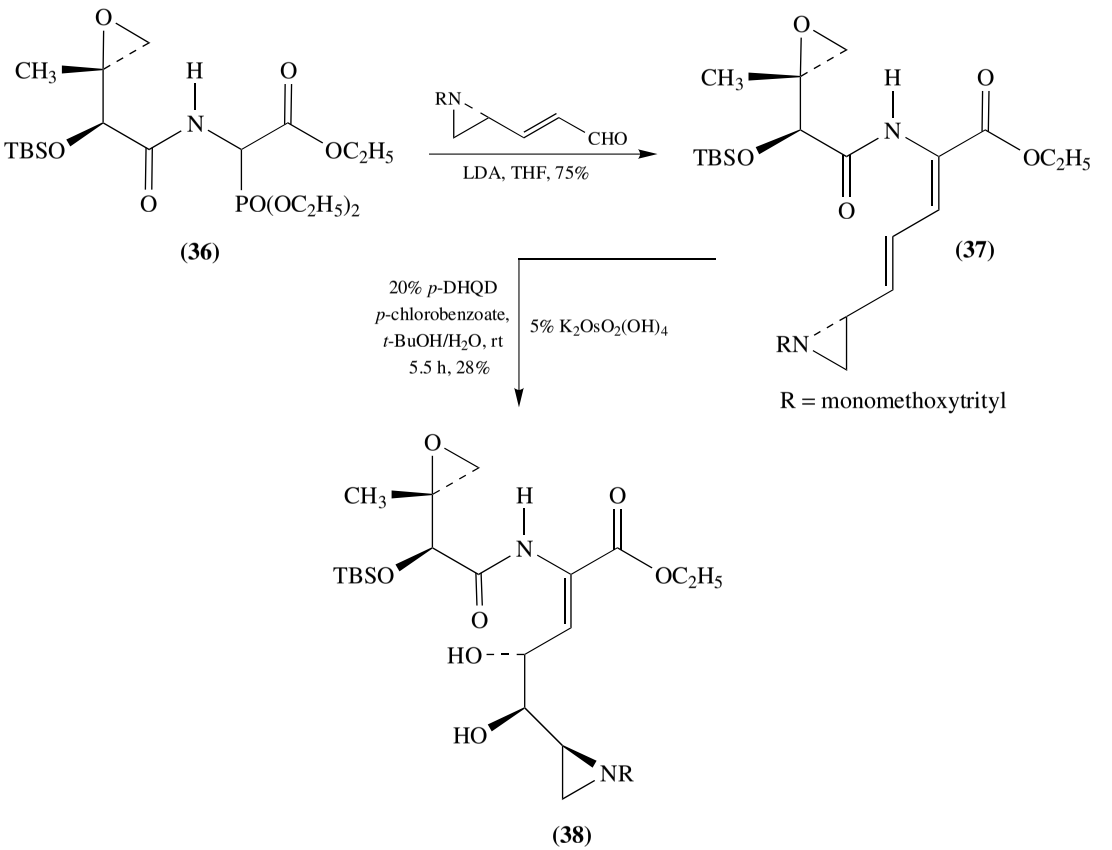


(35)

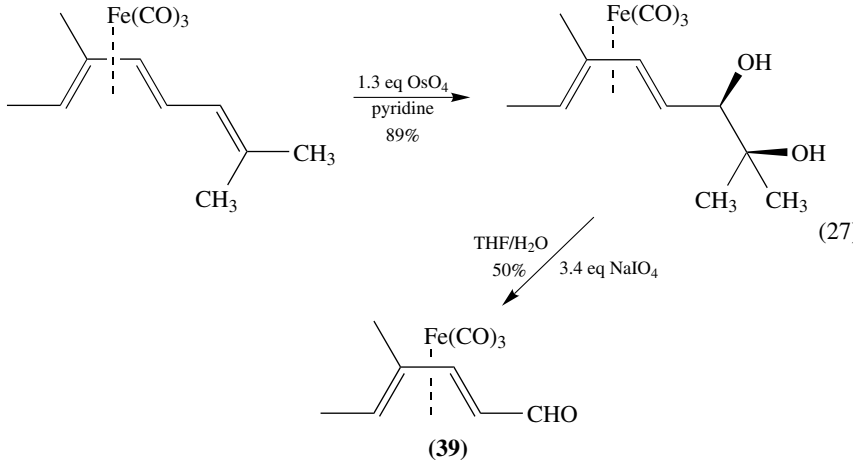
Sharpless' asymmetric dihydroxylation procedure was applied to the synthesis of the side chain of azinomycin A (equation 26)[43]. Horner–Emmons condensation of phosphonate **36** with a β-aziridine substituted acrolein afforded dehydroamino acid diene **37**. Treatment of the diene with catalytic amounts of an osmium reagent and dihydroquinidine (DHQD) *p*-chlorobenzoate resulted in asymmetric dihydroxylation, producing diol **38**. Diol **38** was further converted to the naphthyl ester.

Isolated double bonds can be oxidatively cleaved in systems containing a conjugated diene moiety if it is protected as a tricarbonyl(diene)iron complex[44]. Dienal **39** was acquired in 49% yield by a two-step osmylation–periodate cleavage sequence (equation 27). In contrast, ozonolysis of the polyene complexes is reported to lead to destruction of the complex.

Substituted 4,5-dihydro-5-vinylisoxazoles **(40)**, obtained by regio- and stereospecific cycloaddition of nitrile oxides to dienes, undergo smooth osmium-catalyzed *cis*-hydroxylation to give amino-polyol precursors (equation 28)[45]. The reaction is *anti* selective, the diastereomeric ratios ranging from 73 : 27 up to $\geqslant$99 : 1. Highest stereoselectivities were observed when R^3 was methyl. Thus, whereas osmylation of **40a** afforded a 78 : 22 mixture of **41a** and **42a**, respectively, in 80% overall yield, similar treatment of **40b** resulted in a 92 : 8 mixture of **41b** and **42b**, respectively, in 70% overall yield. The cycloaddition-osmylation sequence allows control of the relative configuration of up to 4 contiguous asymmetric centers.

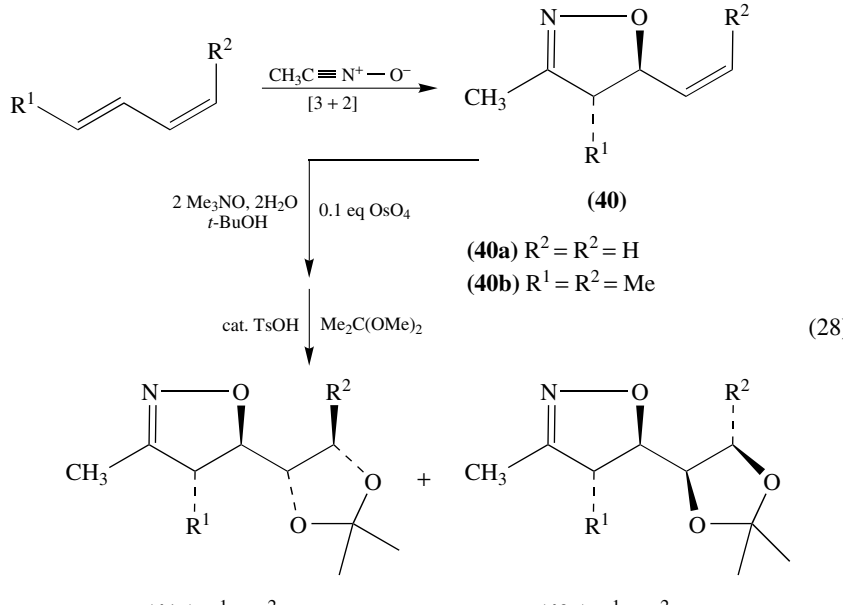

CH3
H
O
TBSO
N
OC2H5
O
PO(OC2H5)2
(36)
RN
CHO
LDA, THF, 75%
(37)
R = monomethoxytrityl
20% p-DHQD
p-chlorobenzoate,
t-BuOH/H2O, rt
5.5 h, 28%
5% K2OsO2(OH)4
HO
NR
(38)

(26)



(27)

(39)



(40)

(40a) $R^2 = R^2 = H$
(40b) $R^1 = R^2 = Me$

(28)

(41a) $R^1 = R^2 = H$
(41b) $R^1 = R^2 = Me$

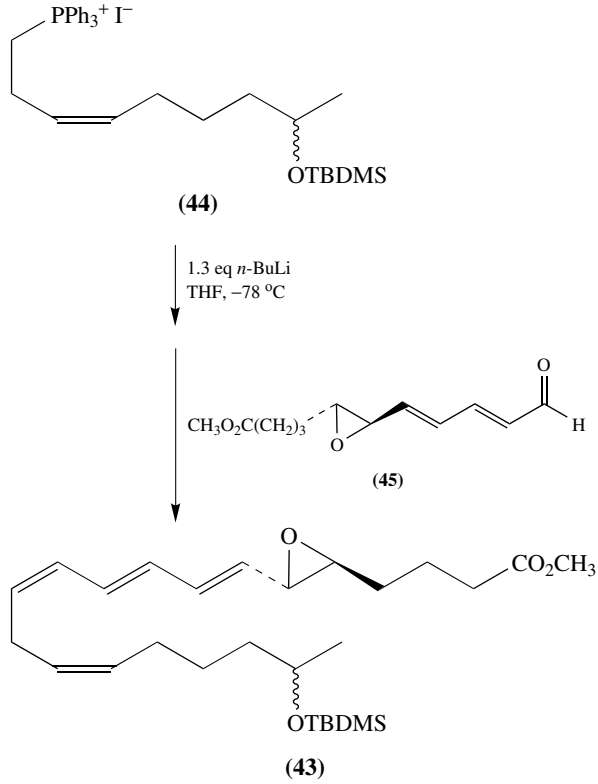
(42a) $R^1 = R^2 = H$
(42b) $R^1 = R^2 = Me$

IV. COUPLING REACTIONS

Polyenes are most often synthesized by cross-coupling reactions between unsaturated systems. Typically these reactions require an activated carbon, often in the form of an organometallic reagent. Enolates and phosphonium ylides, Wittig-type reagents, are also commonly employed in carbon–carbon bond formation. Pericyclic rearrangements also result in the generation of new carbon–carbon bonds and will be treated separately.

A. Wittig Reactions of Dienes and Polyenes

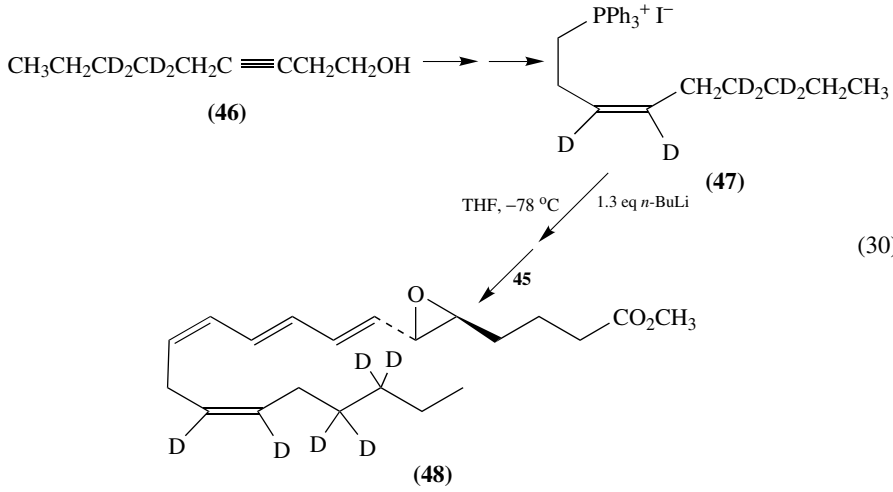
The Wittig reaction and its numerous derivations have undoubtedly proven to be one of the most useful and efficient methods for forming carbon–carbon double bonds[46]. The reaction of an organophosphorus reagent with an aldehyde or ketone has also been frequently employed to extend simple dienals and dienones into more elaborate polyene systems. A key step in the convergent synthesis of the TBDMS-protected leukotriene A_4 methyl ester, 19*R*,*S*-*t*-butyldimethylsiloxy-5*S*,6*S*-epoxyeicosa-7*E*,9*E*,11*Z*,14*Z*-tetraenoate **(43)**, was accomplished using a Wittig reaction between homoallylic phosphorus ylide **44** and C1–C11 chiral epoxy dienal **45**, derived from (−)-2-deoxy-D-ribose, shown in equation 29[47].



(29)

A similar approach had been reported earlier by Bestmann and coworkers[48] in their synthesis of hexadeuteriated leukotriene A_4 methyl ester. C-alkylation of the tetrahydropyranyl ether of 3-butyn-1-ol with 2,2,3,3-tetradeuterio-1-iodopentane, prepared in 4 steps from propargyl alcohol, and subsequent protective group removal afforded the tetradeuteriated acetylenic alcohol **46** (equation 30). Semideuteriation of the alkynol and further transformation by known methods produced the labeled key reagent 3,4,6,6,7,7-hexadeuterio-(*Z*)-(3-nonen-1-yl)triphenylphosphonium iodide **(47)**. Wittig olefination of epoxy dienal **45** with the labeled ylide generated from **47** completed the synthesis of

hexadeuteriated leukotriene A_4 methyl ester in 78% yield from **48**.



(30)

The Wittig reaction was employed to fuse diene **49** and aldehyde **50**, in the final stages of the stereoselective synthesis of epothilone B, a macrocyclic compound with potential antifungal properties (equation 31)[49].

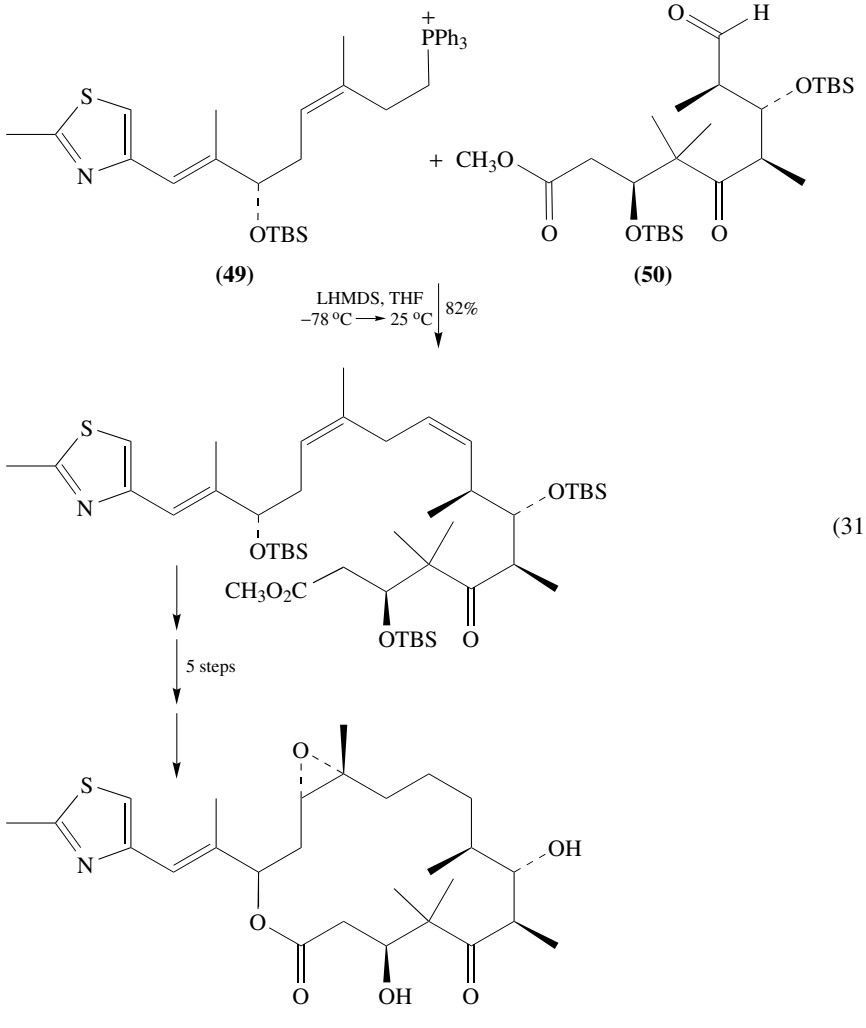
A series of conjugated polyenes capped with chromophores and containing an androstane spacer were synthesized by Wittig or Wittig-type olefinations from epi-androsterone **51**[50]. For example, vinyl carboxaldehyde **52**, prepared from **51** in 60% yield as shown in equation 32, was treated with 9-anthrylmethylphosphonium bromide and *n*-butyllithium to give diene **53**. Exocyclic diene **53** was subsequently oxidized to vinyl carboxaldehyde **54**. The androsterone vinyl aldehyde intermediate could either be treated with a tetraphenylporphyrinpolyenyl phosphonium ylide, or, as shown below, the phosphonium salt of the androsterone **(55)** could be reacted with TPP polyeneal **56**. The desired all-(*E*) isomer, **57**, was obtained from the (*E*)/(*Z*)-isomeric mixture by chromatographic purification.

B. Coupling Promoted by Organometallic Reagents

Main group and transition metals have been employed to couple unsaturated carbon chains, either by way of a σ-carbon–metal complex, in which the carbon can be either sp-, sp^2- or sp^3-hybridized, or via π-complexes of carbon–carbon bonds with the metal. While the Grignard reaction is perhaps still one of the most widely employed methods, requiring relatively mild reaction conditions and inexpensive reagents, many other organometallic reagents have been developed which are less sensitive to moisture or require only catalytic amounts of the metal. The Stille reaction is a highly acclaimed versatile synthetic technique which has been extensively reviewed[51]. In this reaction, allyl and vinyl stannanes react with organohalides or sulfonates in the presence of palladium catalysts to afford a cross-coupled unsaturated product. Intramolecular palladium-catalyzed additions of esters containing vinyl triflate and vinylstannane groups afford macrocyclic lactones[52,53].

The 20-membered all-*E* tetraene macrolide system **58** was prepared by intramolecular cyclization of vinyl stannane **59** in the presence of tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) and triphenylarsine, as shown in equation 33[54]. *E*,*E*-Dienamines have been

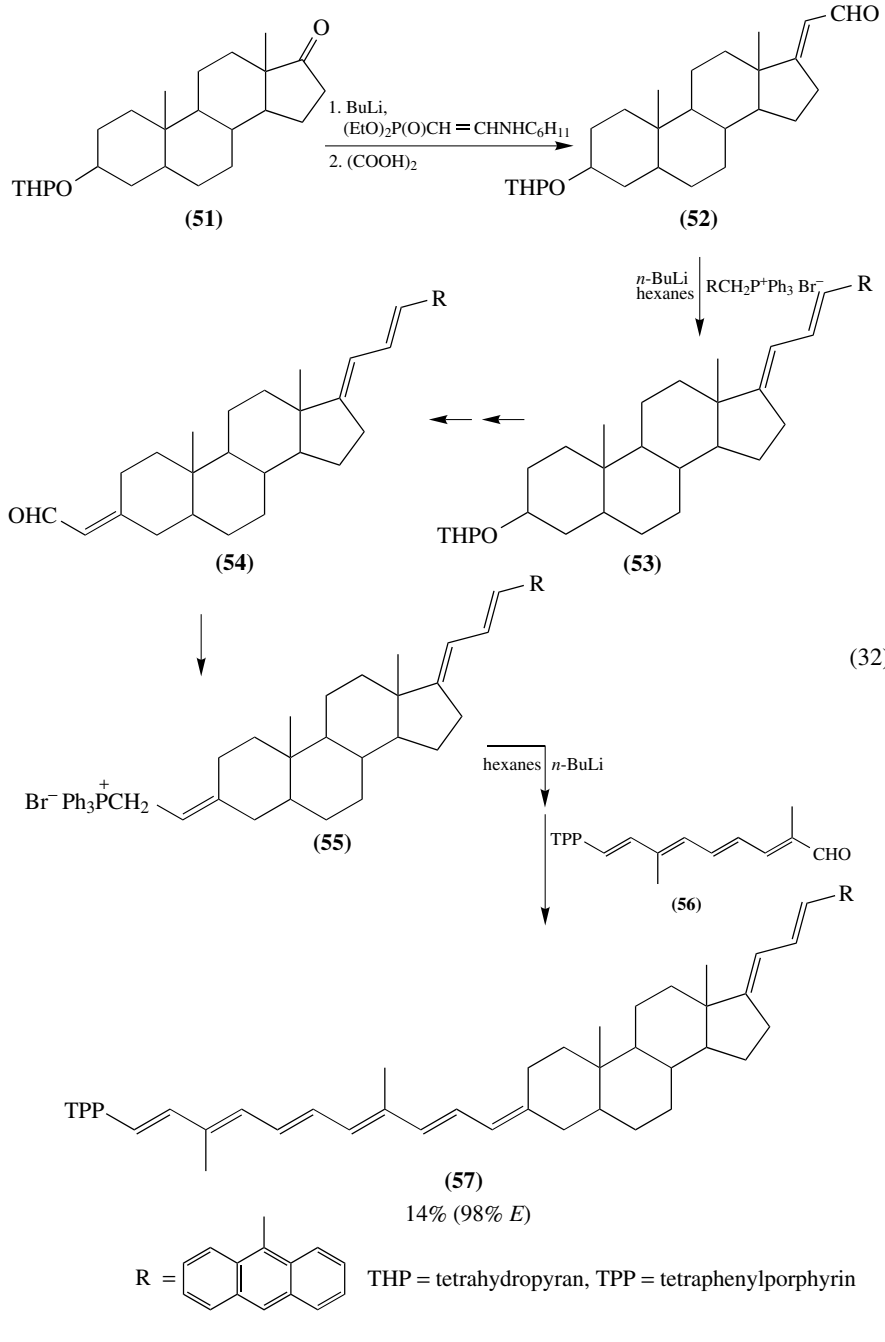
prepared by the palladium-catalyzed coupling of vinyl iodides with hydrostannylated FMOC-propargylamines, as shown in equation 34[55].



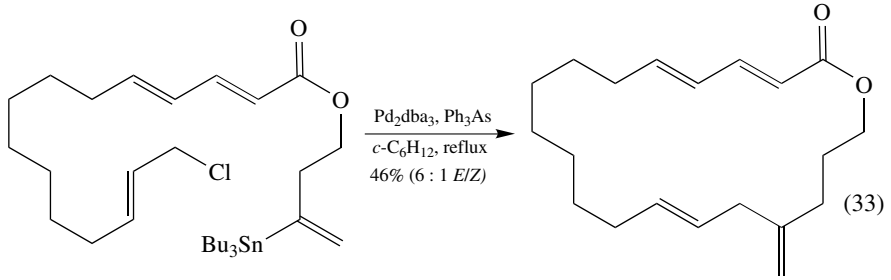
(31)

Epothilone B

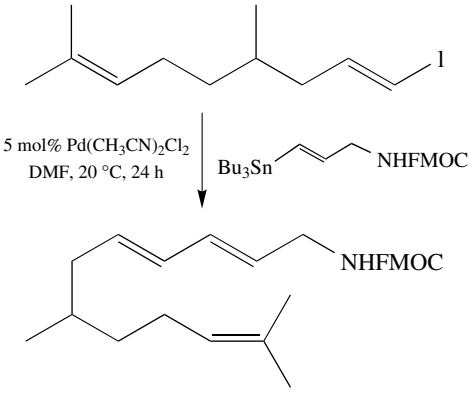
Stannylated dienyne **60** serves as an all-*E* 1,6-dimetallohexatriene equivalent[56]. Vinyl stannane **60** was prepared from stannyl enal **61** by Wittig coupling with the ylide derived from the known salt of **62**, affording **60** in high yields and usually with better than 90 : 10 *E*/*Z* selectivity (equation 35). Tin–lithium exchange followed by conversion to the organozinc derivative provides a reactive intermediate **63** which, in the presence of catalytic $Pd(PPh_3)_4$, was coupled with vinyl iodide **64** in THF. Removal of the acetylenic silyl moiety was accomplished with K_2CO_3 in EtOH at room temperature resulting in tetraenyne **65** in good overall isolated yield.


O
THPO
1. BuLi,
(EtO)2P(O)CH=CHNHC6H11
2. (COOH)2
CHO
THPO
(51)
(52)
n-BuLi
hexanes
RCH2P+Ph3 Br–
R
R
OHC
THPO
(54)
(53)
R
Br– Ph3P+CH2
(55)
hexanes
n-BuLi
TPP
CHO
(56)
R
TPP
(57)
14% (98% E)
R =
THP = tetrahydropyran, TPP = tetraphenylporphyrin

(32)

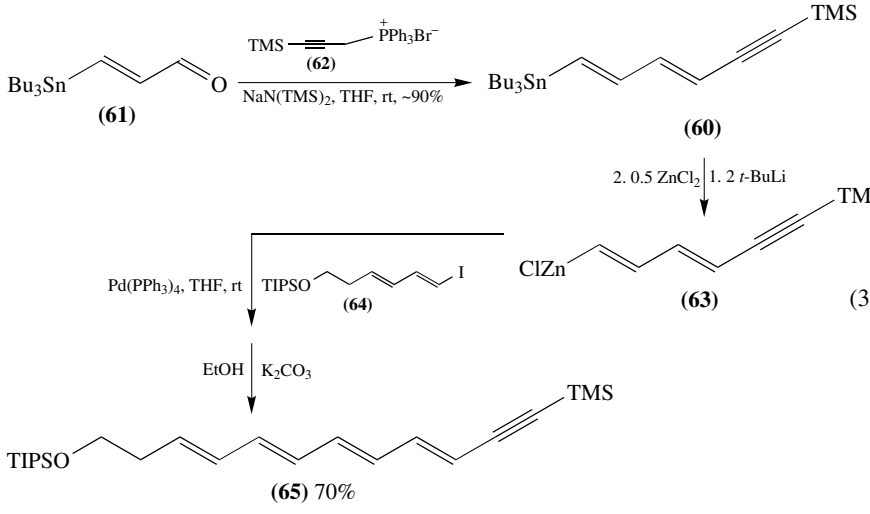


(59) (58) (33)



(34)

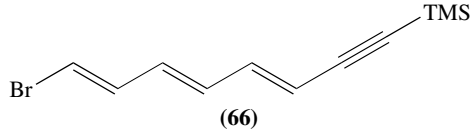
65% ($E : Z = 85 : 15$)
FMOC = 9-Fluorenylmethoxycarbonyl



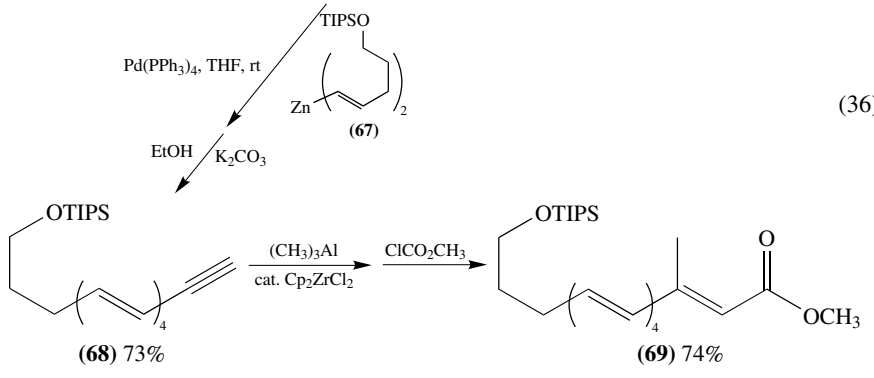
(35)

(65) 70%

Alternatively, bromo trienyne **66**, prepared by the Wittig reaction of TMS-capped propargyl ylide with *E*,*E*-5-bromo-2,4-pentadienal, could be coupled with dienyl zinc reagent **67**, as illustrated in equation 36[57]. Subsequent desilylation followed by treatment with trimethyl aluminum in the presence of catalytic Cp_2ZrCl_2 afforded the alane of tetraenyne **68** which, on exposure to chloroformate, gave essentially all-*E* polyene ester **69**.



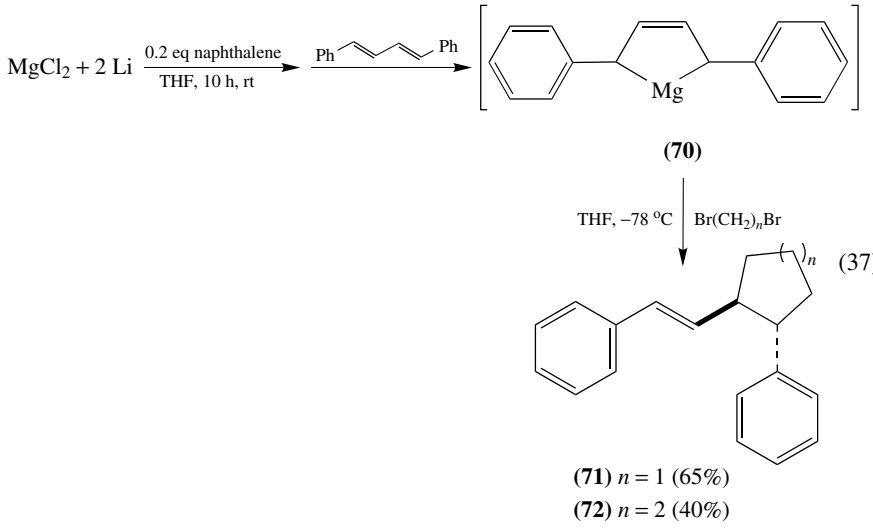
(66)



(36)

(68) 73% **(69)** 74%

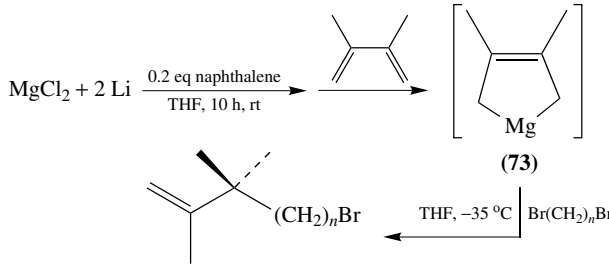
Magnesium complexes of 1,3-dienes have been used to form carbocycles and ω-bromoalkenes[58]. 1,4-Diphenyl-2-butene-1,4-diylmagnesium **(70)** was prepared by reacting (*E*,*E*)-1,4-diphenyl-1,3-butadiene with magnesium freshly generated by reducing anhydrous magnesium chloride with lithium in THF (equation 37). While **70** reacted with



(37)

(71) $n = 1$ (65%)
(72) $n = 2$ (40%)

1,3-dibromopropane and 1,4-dibromobutane to give carbocycles **71** and **72**, respectively, the magnesium complex of 2,3-dimethyl-1,3-butadiene, **73**, gave good yields of the corresponding brominated acyclic products **74** and **75** at low temperatures (equation 38). Cyclization was accomplished after refluxing the reaction mixture in THF for several hours.

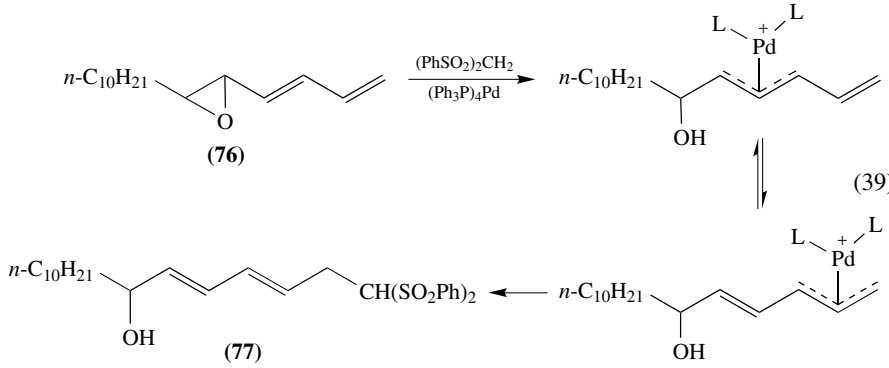


(38)

(74) $n = 1$ (72%)
(75) $n = 2$ (79%)

Manganese(III) has also proven to be effective in promoting carbon–carbon bond formation between alkenes or dienes with carbonyl compounds[59].

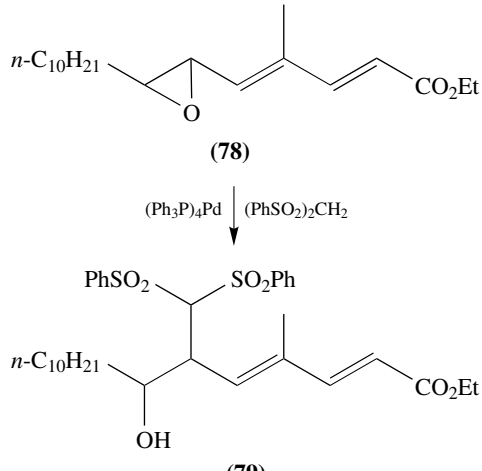
The regioselectivity in palladium-catalyzed alkylations has been attributed to the dynamic behavior of trihapto pentadienyl metal complexes[60]. For example, competing electronic and steric effects influence product formation in dienyl epoxides, but in palladium-catalyzed reactions steric factors were often found to be more important. Thus, alkylation of dienyl epoxide **76** with bulky nucleophiles such as bis(benzenesulfonyl)methane in the presence of $(Ph_3P)_4Pd$ occurred exclusively at the terminal carbon of the dienyl system producing allyl alcohol **77** (equation 39). However, the steric factors could be overcome by electronic effects when one of the terminal vinylic protons was replaced with an electron-withdrawing group. Thus, alkylation of dienyl epoxide **78** affords homoallylic alcohol **79** as the major product (equation 40).



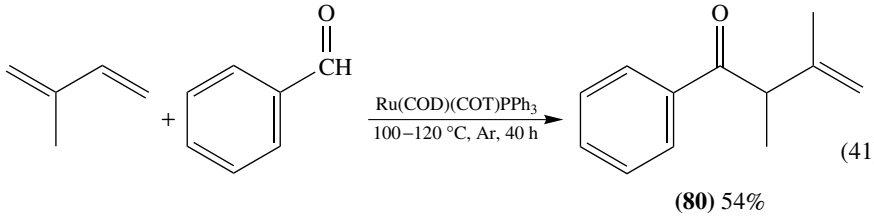
(39)

Ruthenium-catalyzed hydroacylation of 1,3-dienes with aromatic and heteroaromatic aldehydes occurs in relatively good yields to afford the corresponding β,γ-unsaturated ketones[61]. Isoprene and benzaldehyde were treated with 4 mol% Ru(COD)(COT) (COD = 1,5-cyclooctadiene, COT = 1,3,5-cyclooctatriene) and 4 mol% PPh_3 under argon for 40 hours to give 54% **80** (equation 41). The key intermediate is an acyl-η^3-(allyl)ruthenium complex which undergoes reductive elimination to give the corresponding

ketones. Aliphatic aldehydes, on the other hand, were not effective substrates in this reaction. Interestingly, carbon monoxide is not needed to suppress decarbonylation of aldehydes.



(40)



(41)

(80) 54%

V. DIMERIZATION REACTIONS

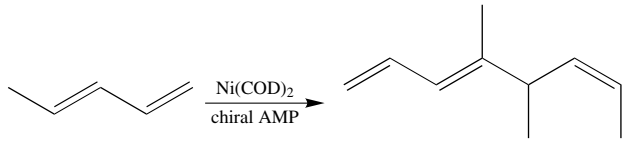
Dimerization of conjugated dienes and trienes is generally accomplished at elevated temperatures or in the presence of metal catalysts. Linear dimerization of butadiene occurs readily at room temperature on nickel catalysts bearing aminophosphinite (AMP) ligands, and the reaction rate is reportedly twice that observed in other nickel systems employing either morpholine, ethanol or P-methyloxaphospholidines as modifiers[62]. 1,3-Pentadiene dimerizes in the presence of 1 mol% nickel catalyst to give a diastereomeric mixture of 4,5-dimethyl-1,3,6-octatriene as shown in equation 42.

While linear dimerization of dienoic esters can also be accomplished with nickel-AMP systems, other functionalized dienes undergo little or no conversion. The reaction of methyl hexa-2,4-dienoate, **81**, furnishes diastereomeric trienoic diesters **(82)** in high yields (equation 43).

3-Methylene-1,4-pentadiene **(83)**, prepared by flash vacuum pyrolysis of 1,5-diacetoxy-3-(acetoxymethyl)pentane, dimerizes at 95 °C in benzene to give predominantly one isomer of 1,4,4-trivinylcyclohexene **(84)** as the major product (equation 44)[63].

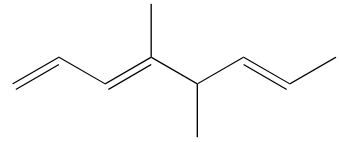
Similar investigations with the conformationally restricted triene **85** led the authors to conclude that dimerization proceeds by a two-step mechanism involving initial

formation of a diradical species, followed by rapid ring-closure to yield [4 + 2] dimer **86** (equation 45).



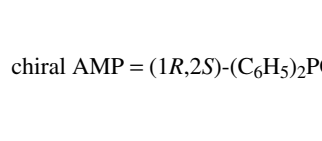
E,*Z*; ee = 90%

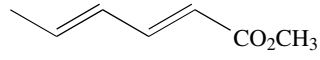
+



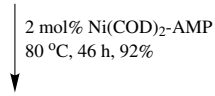
E,*E*; ee = 35%

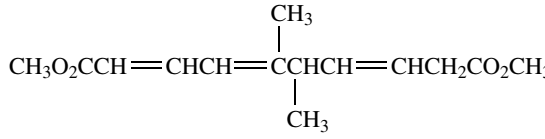
(42)





(81)

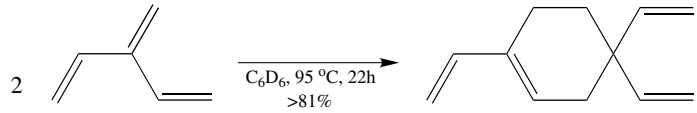




(43)

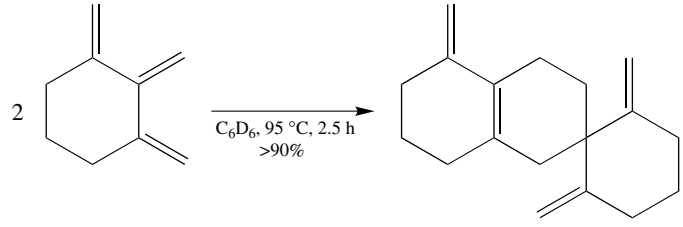
(82) 85% *E,E,E*; 13% *E,E,Z*

AMP = $(C_6H_5)_2POCH(C_6H_5)CH(CH_3)NHCH_3$



(44)

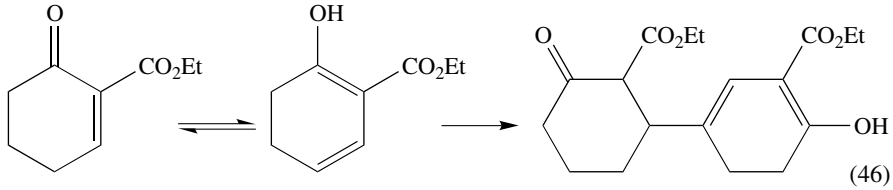
(83) **(84)**



(45)

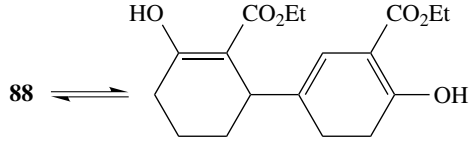
(85) **(86)**

Cycloalkenone-2-carboxylates tautomerize to conjugated dienols in the presence of either acids or bases. Iron(III) catalysts have also been found to promote enone–dienol equilibration, and, at room temperature, dimerization[64]. Thus, treating **87** with 1 mol% iron(III) chloride hexahydrate in methylene chloride at room temperature affords **88** in 81% yield (equation 46). The cyclohexadiene–cyclohexanone is in a rapid equilibrium with its triendiol tautomer, **89** (equation 47).



(46)

(87) **(88)**



(47)

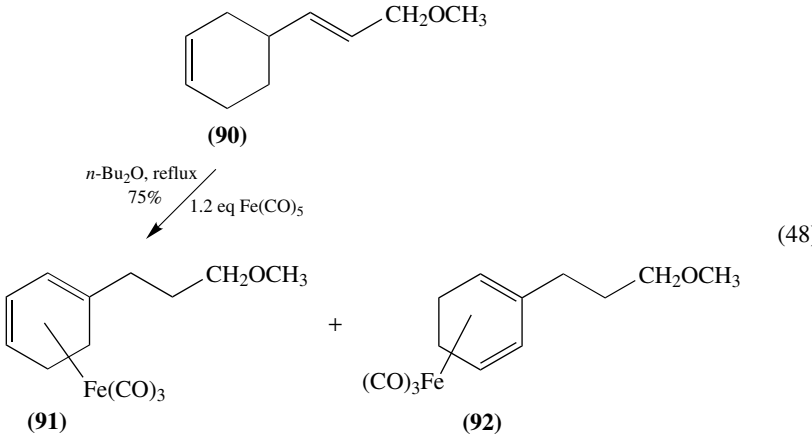
(89)

VI. PREPARATION OF METAL–POLYENE COMPLEXES

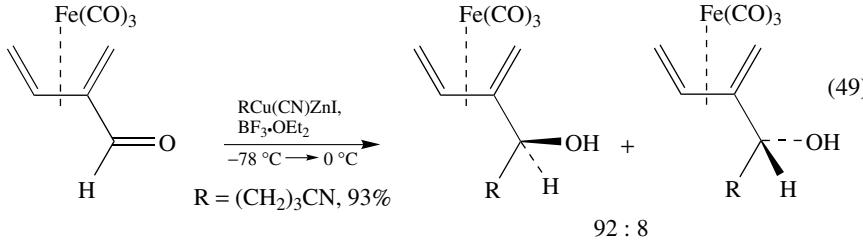
(η^4-Diene)tricarbonyliron complexes have found use as synthons for the preparation of functionalized dienes. Substituted 4-vinylcyclohexene derivatives are isomerized by pentacarbonyliron into a mixture of conjugated cyclohexadiene tricarbonyl iron complexes[65]. When the 4-vinyl cyclohexene **90** was refluxed with 1.2 equivalents of $Fe(CO)_5$ in di-*n*-butyl ether, a 3 : 1 mixture of cyclohexadiene isomers **91** and **92** was acquired in 75% overall yield (equation 48).

The diastereoselective formation of dienol tricarbonyliron complexes on treating (η^4-2,4-pentadienal)$Fe(CO)_3$ with functionalized zinc–copper reagents has been investigated (equation 49)[66]. Cyano-substituted complexes undergo intramolecular nucleophilic additions when treated with lithium diisopropylamide (LDA) as shown in equation 50.

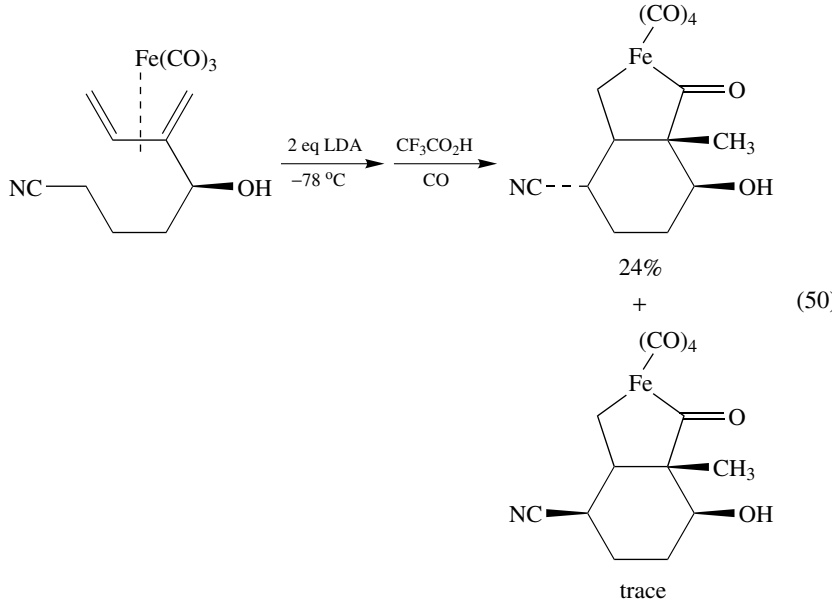
Acylation of terminal alkenes by (η^4-2,4-pentadienoyl chloride)$Fe(CO)_3$ proceeds in high yield in the presence of Lewis acid catalysts[67]. As shown in equation 51, the reaction generally produces a mixture of (η^4-diene)tricarbonyliron complexes of the β-chloroketone and β,γ-unsaturated ketone.


CH2OCH3
(90)
n-Bu2O, reflux
75%
1.2 eq Fe(CO)5
CH2OCH3
Fe(CO)3
(91)
+
CH2OCH3
(CO)3Fe
(92)
3 : 1

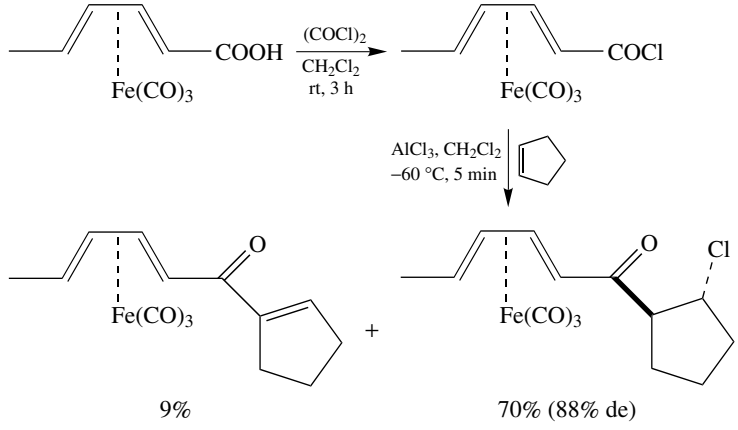
(48)


Fe(CO)3
O
H
RCu(CN)ZnI,
BF3•OEt2
−78 °C → 0 °C
R = (CH2)3CN, 93%
Fe(CO)3
OH
R
H
+
Fe(CO)3
OH
R
H
92 : 8

(49)


Fe(CO)3
NC
OH
2 eq LDA
−78 °C
CF3CO2H
CO
(CO)4
Fe
O
CH3
NC
OH
24%
+
(CO)4
Fe
O
CH3
NC
OH
trace

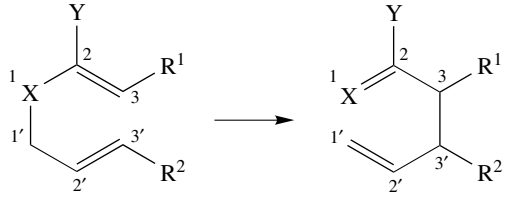
(50)



(51)

VII. REARRANGEMENTS

The popularity of [3,3]-sigmatropic rearrangements in organic synthesis derives from the ability of such reactions to generate stereogenic centers from the sp^2-hybridized carbons. The formation of these chiral centers can take place at a distance from other functional groups and chiral auxiliaries in the molecule[68]. The general equation for [3,3]-sigmatropic rearrangements and their asymmetric counterparts is depicted in equation 52.



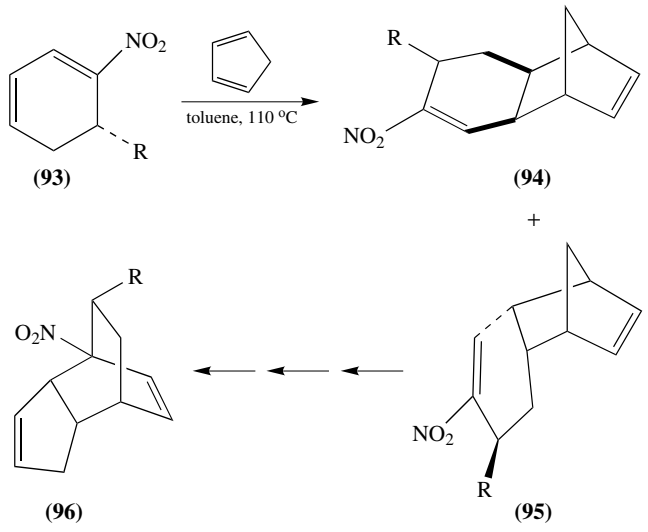
(52)

This section will focus on recent examples of asymmetric [3,3]-sigmatropic rearrangements involving dienes and polyenes. Attention will be given to Cope and Claisen rearrangements, as well as to several of their variants. For more exhaustive reviews of the subject, the reader is referred elsewhere[69,70].

A. Cope Rearrangement

Discovered in 1940, the Cope rearrangement is an all-carbon version of the [3,3]-sigmatropic rearrangement depicted in equation 52 (i.e. X and Y are carbon). Reactions in which X is a heteroatom (i.e. oxygen, nitrogen, sulfur) and Y is carbon are hetero variants, the most widely used being the Claisen rearrangement where X is oxygen[69]. Cope rearrangements can be performed thermally[68,69,71] or photochemically[72]. The Cope rearrangement of dienes has found utility in a number of regio- and stereoselective syntheses of ring systems[71,73,74]. Román and coworkers[71] have recently reported an enantioselective synthesis of 1-nitrotricyclo[5.2.2.$0^{2,6}$]undeca-3,8-dienes which involves an asymmetric

Diels–Alder reaction, followed in tandem by a Cope rearrangement (equation 53).



(53)

(a) R = *D*-manno-$(CHOAc)_4$-CH_2OAc
(b) R = *D*-manno-$(CHOH)_4$-CH_2OH
(c) R = CHO
(d) R = CH_2OH

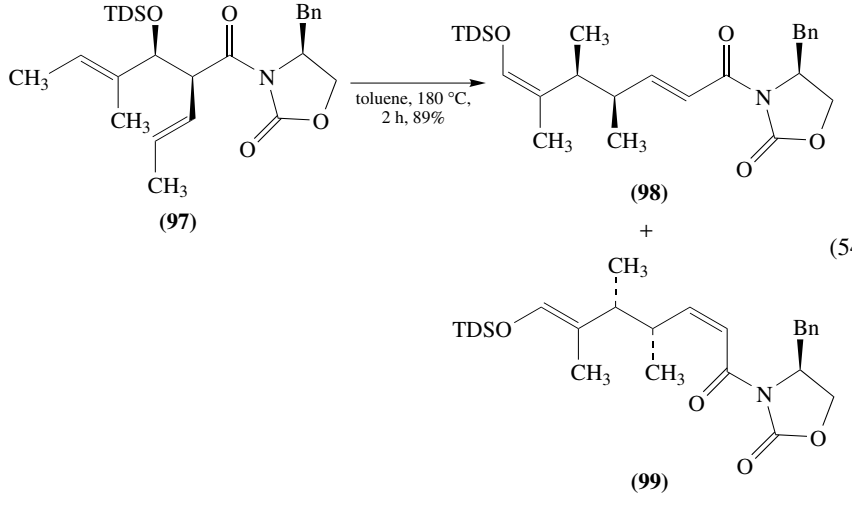
Nitrocyclohexadiene **93a** reacted with 4.0 equivalents of cyclopentadiene in toluene at 110 °C for 96 h, producing the 10-glyco-1-nitrotricyclo[5.2.2.$0^{2,6}$]undeca-3,8-diene **96a** in 70% yield. Subsequent treatment with potassium carbonate in a methanol–water (9 : 1) solution followed by oxidative cleavage of the sugar side chain with sodium metaperiodate afforded aldehyde **96c**. Reduction of the aldehyde with sodium borohydride produced alcohol **96d**.

Schneider and Rehfeuter[68] have reported that enantiomerically pure 1,6-disubstituted-1,5-dienes with an aldol substitution pattern can undergo stereoselective Cope rearrangements in good yield. For example, 1,5-diene **97** underwent Cope rearrangements in toluene in sealed flasks at 180 °C for 2 h to afford, after chromatography, an 89% yield of a 97 : 3 diastereomeric mixture of **98** and **99**, respectively (equation 54).

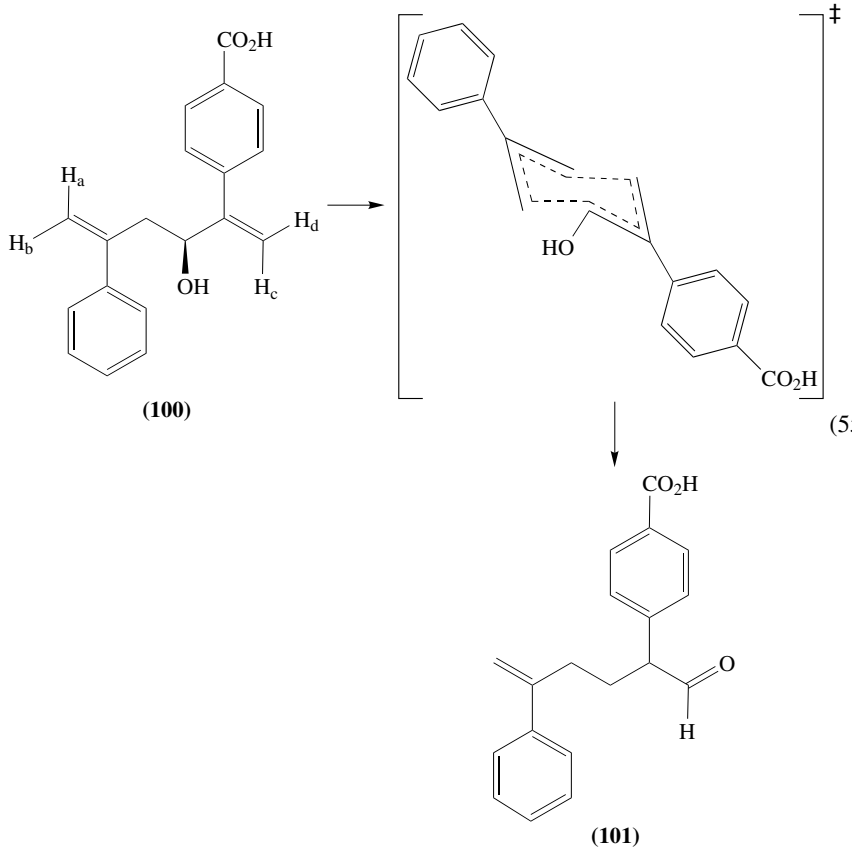
The oxy-Cope and anionic oxy-Cope rearrangements have found more widespread use in stereoselective synthesis than the Cope rearrangement[70,75–79]. Anionic oxy-Cope rearrangements can often be performed at or near room temperature. The rearrangement is compatible with many functional groups, and stereogenic centers are often introduced with a high degree of predictability[70].

An antibody, originally generated against a diaryl substituted cyclohexanol derivative, has been employed to catalyze the oxy-Cope rearrangement of hexadiene **100** to aldehyde **101** (equation 55)[80,81]. A rate enhancement of 5300-fold over the uncatalyzed reaction was achieved.

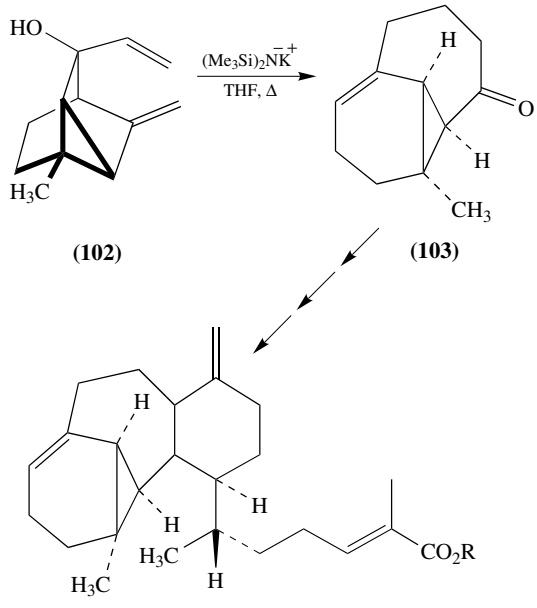
In the total synthesis of cerorubenic acid-III methyl ester **(105)**, diene **102** was converted to enantiopure tricyclic ketone **103** through an anionic oxy-Cope rearrangement (equation 56)[82]. Conversion of **102** to **103** afforded the entire ABC substructure of **104** and **105**, most notably the double bond occupying a bridgehead site.



(97) **(98)** **(99)** (54)



(100) **(101)** (55)

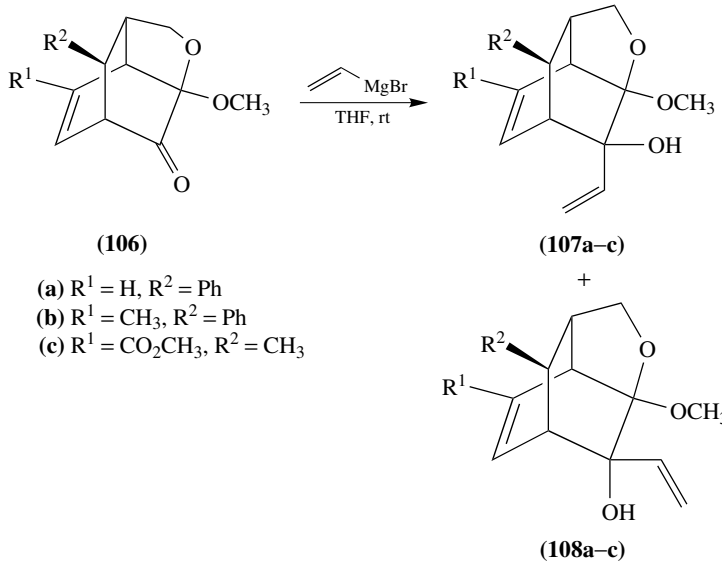


(102) **(103)**

(104) R = H
(105) R = Me

(56)

2-Vinylbicyclo[2.2.2]oct-5-en-2-ols **107a–c** and **108a–c**, bearing dialkoxy substituents at the C-3 position, underwent base catalyzed [3,3]- and [1,3]-sigmatropic rearrangements to yield a stereocontrolled route to *cis*-decalins and bicyclo[4.2.2]dec-7-en-4-ones (equation 57)[83]. Compounds **106a–c** were converted to diastereomeric alcohols **107a–c**



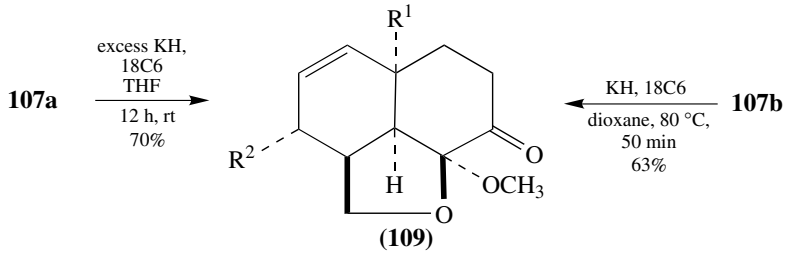
(106)

(a) R^1 = H, R^2 = Ph
(b) R^1 = CH_3, R^2 = Ph
(c) R^1 = CO_2CH_3, R^2 = CH_3

(107a–c)

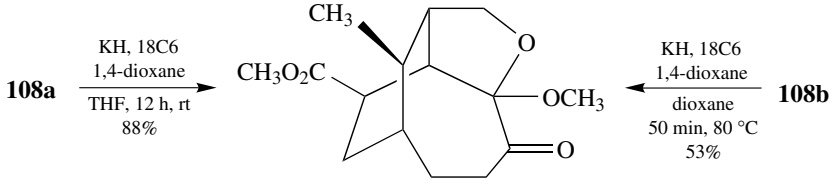
(108a–c)

(57)



(109)

(**a**) $R^1 = H$, $R^2 = Ph$
(**b**) $R^1 = CH_3$, $R^2 = Ph$



(110)

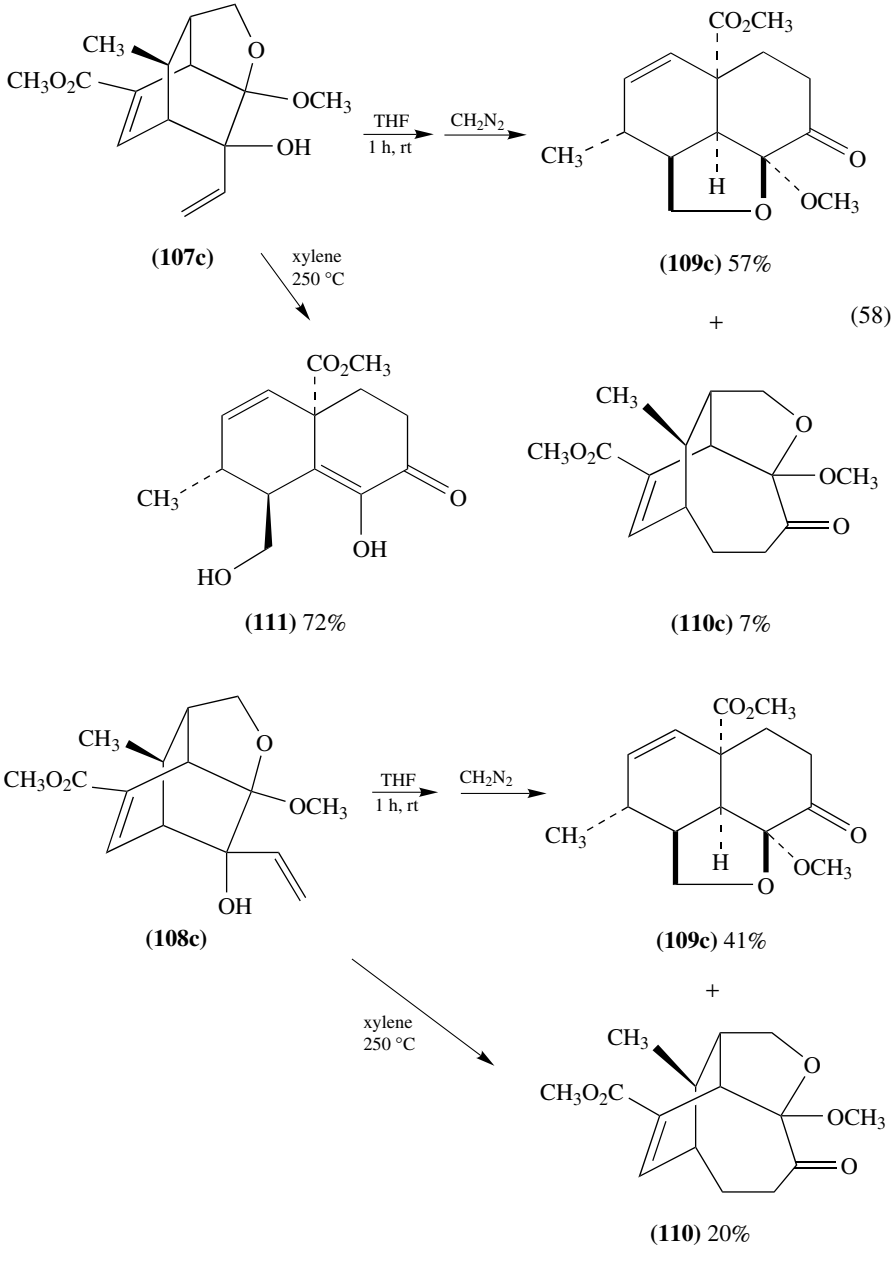
(a) $R^1 = H$, $R^2 = Ph$
(b) $R^1 = CH_3$, $R^2 = Ph$

and **108a–c** by treatment with vinylmagnesium bromide. Alcohols **107a** and **107b** underwent anionic oxy-Cope rearrangements on exposure to excess KH (5 equiv.) and in the presence of 18-crown-6 ether (3 equiv.) to produce compounds **109a** and **109b**, respectively. When subjected to similar conditions, however, alcohol **108a** and **108b** underwent [1,3]-rearrangement to yield the ring enlargement products **110a** and **110b**, respectively.

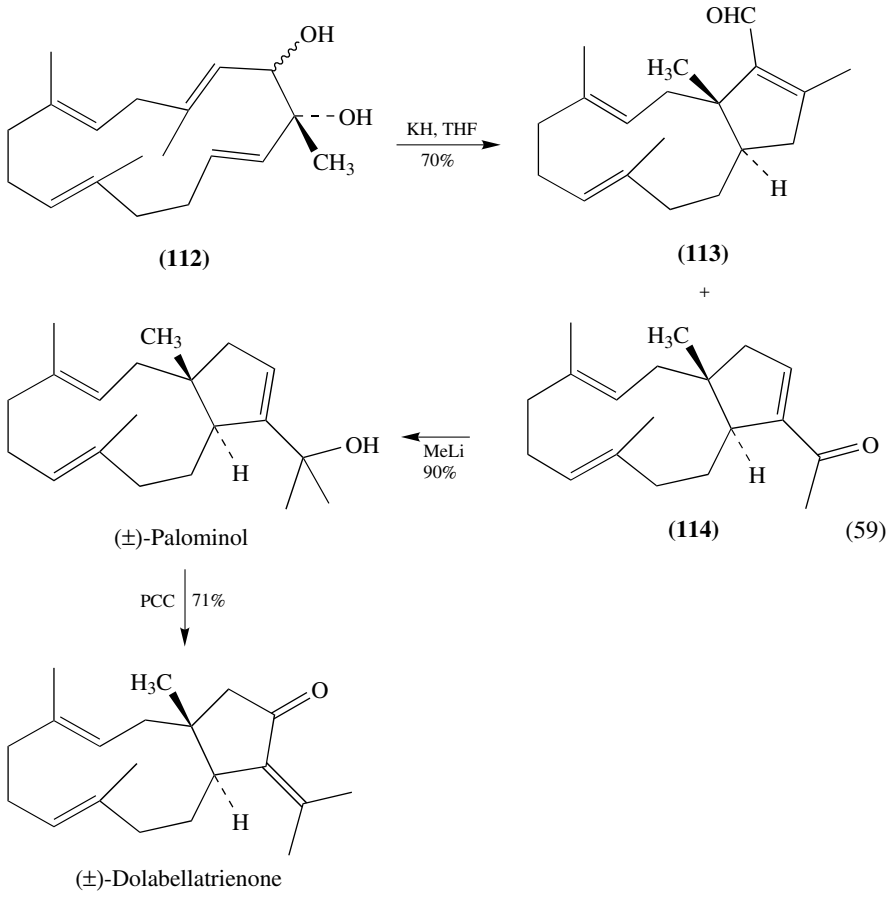
When R^1 was methoxycarbonyl **(106c)**, however, the reaction of each of the resulting diastereomeric bicyclic dienes, **107c** and **108c**, afforded products **109c** and **110c**. Interestingly, heating **107c** in a sealed tube resulted in a 72% yield of the fused-bicyclic enol **(111)**, presumably from hydrolysis of **109c**. On the other hand, heating **108c** produced only the ring enlarged product **110c** in 61% yield (equation 58).

In the synthesis of (±)-palominol and (±)-dolabellatrienone from farnesol, Corey and Kania[84] employed a dianion accelerated oxy-Cope rearrangement to form the 11,5-*trans*-fused ring system of the dolabellanes. Diol **112** was treated with potassium hydride in THF to afford a 1 : 1 mixture of products with *trans*-11,5-fused ring systems, **113** and **114** (equation 59). Bicyclic α,β-unsaturated methyl ketone **114** was then converted to (±)-palominol in 90% yield with methyllithium. Subsequent oxidation of (±)-palominol with PCC gave (±)-dolabellatrienone in 71% yield.

N-Glycosyl homoallylamines have been shown to undergo a stereocontrolled Lewis acid-catalyzed aza-Cope rearrangement to produce chain-extended amino sugars[85]. The reactions proceed in good to excellent yields with high stereoselectivity. Schiff base **115** was converted to *N*-galactosyl-*N*-homoallylamine **116** by $SnCl_4$-induced addition of allyltrimethylsilane or allyltributylstannane (equation 60).



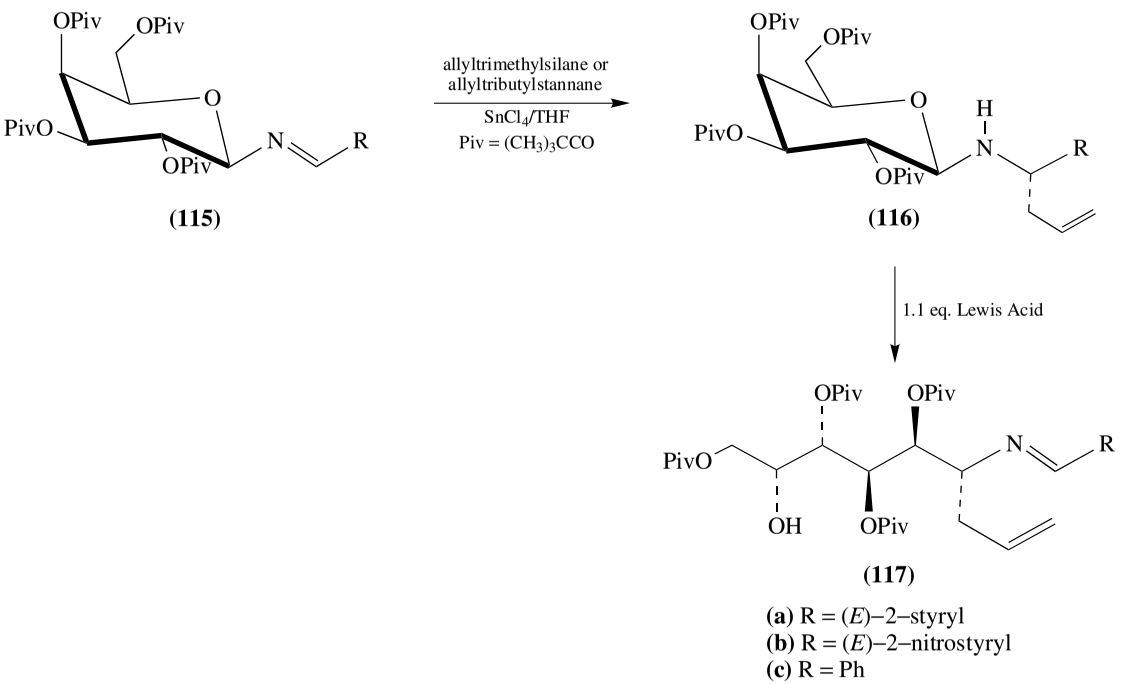
The mechanism involves conversion of *N*-homoallylamine **116a** to imine **117a** via a Lewis acid-catalyzed cationic aza-Cope rearrangement (equation 61). Various Lewis acids were tested with yields ranging from 40–99% with high diastereoselectivities.



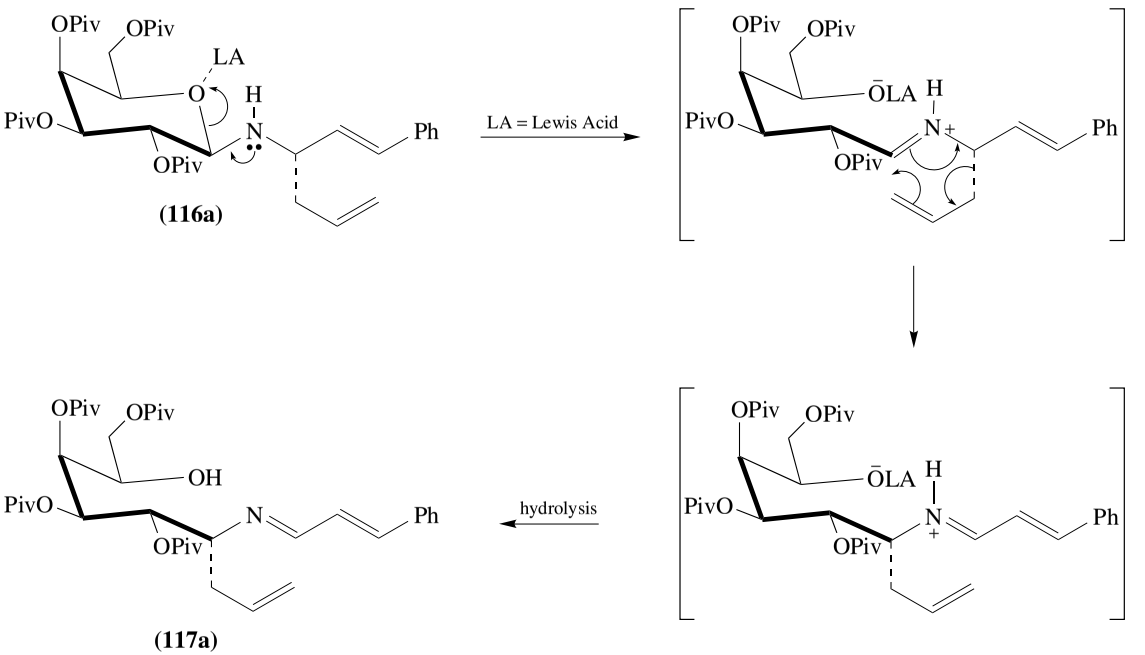
B. Claisen Rearrangement

The Claisen rearrangement, discovered in 1912, has proven to be a powerful tool for the stereoselective generation of C−C bonds[69]. It is widely employed in complex multistep syntheses (see, for example, References 86–89) and has inspired many variations, including the Carroll (1940), Eschenmoser (1964), Johnson (1970), Ireland (1972) and Reformatsky-Claisen (1973) reactions[69].

Sattelkau and Eilbracht[90] have exploited the Claisen rearrangement of allyl vinyl ethers in their synthesis of several spiro compounds. As shown below in equation 62, 7,9-dimethyl-1,4-dioxa-spiro[4,5]decan-8-one, **118**, was converted to α,β-unsaturated ester **119** which was reduced to allyl alcohol **120**[90b]. Allyl vinyl ether **121** underwent a rhodium-catalyzed Claisen rearrangement to afford 7*t*,13*t*-dimethyl-1,4-dioxa-(8rC^9)-dispiro[4.2.4.2]tetradecan-10-one **(122)** in 36% yield.

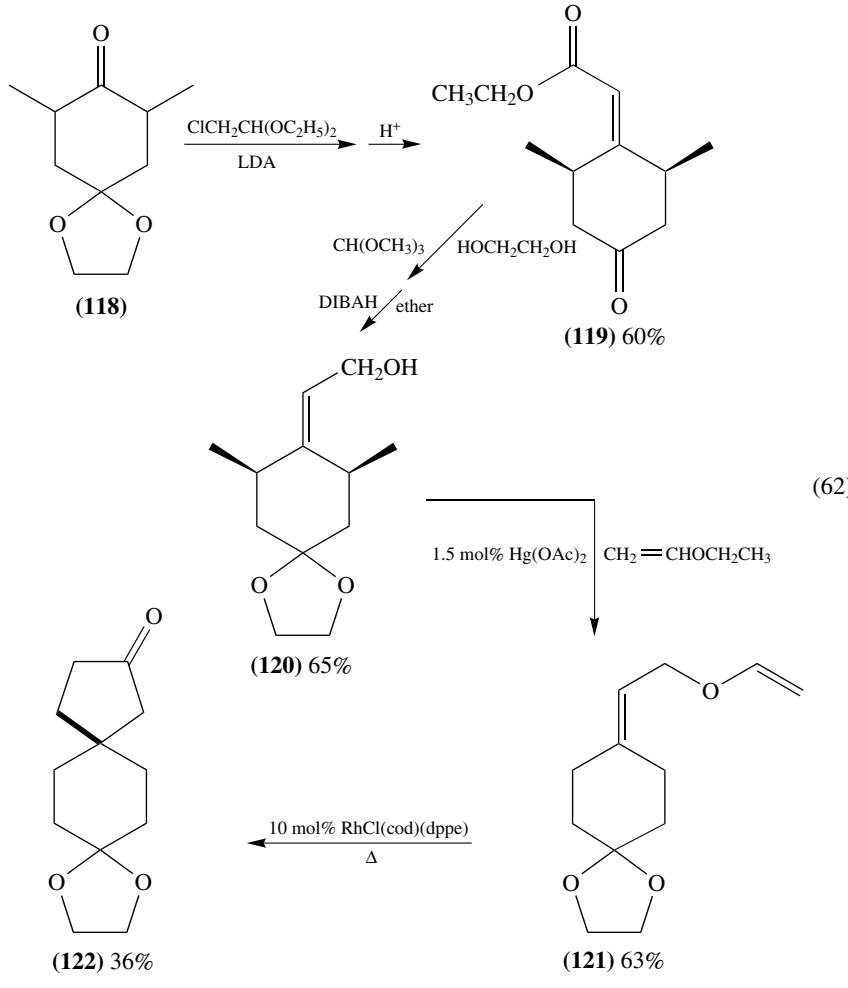

OPiv
OPiv
O
PivO
N
R
OPiv
(115)
allyltrimethylsilane or
allyltributylstannane
SnCl4/THF
Piv = (CH3)3CCO
OPiv
OPiv
O
H
PivO
N
R
OPiv
(116)
1.1 eq. Lewis Acid
OPiv
OPiv
PivO
N
R
OH
OPiv
(117)
(a) R = (E)–2–styryl
(b) R = (E)–2–nitrostyryl
(c) R = Ph

(60)


OPiv
OPiv
LA
O
H
N
PivO
OPiv
Ph
(116a)
LA = Lewis Acid
ŌLA
N+
hydrolysis
OH
(117a)

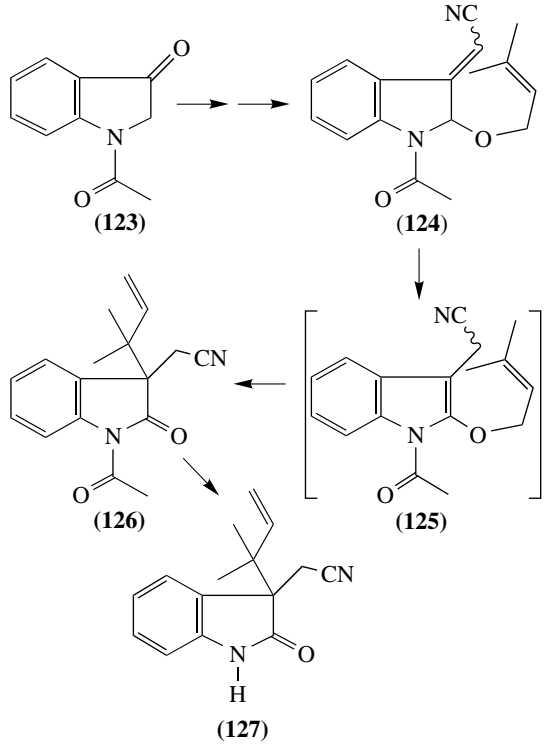
(61)

N-Acetyl indolin-3-one **123** was converted to 3-cyanomethyl-3-(1,1-dimethylallyl) indol-2-one, **127**, by a successive isomerization–Claisen rearrangement sequence (equation 63)[91]. *N*-Acetylindolin-3-one **123** was converted in two steps to a mixture of *E*- and *Z*-isomers of **124**. Isomerization of both isomers of **124** to **125** was accomplished with DBU. Claisen rearrangement of **125** afforded a 13% yield of **126**, which was subsequently deprotected to give 3-cyanomethyl-3-(1,1-dimethylallyl)indol-2-one, **127**, in 47% yield.

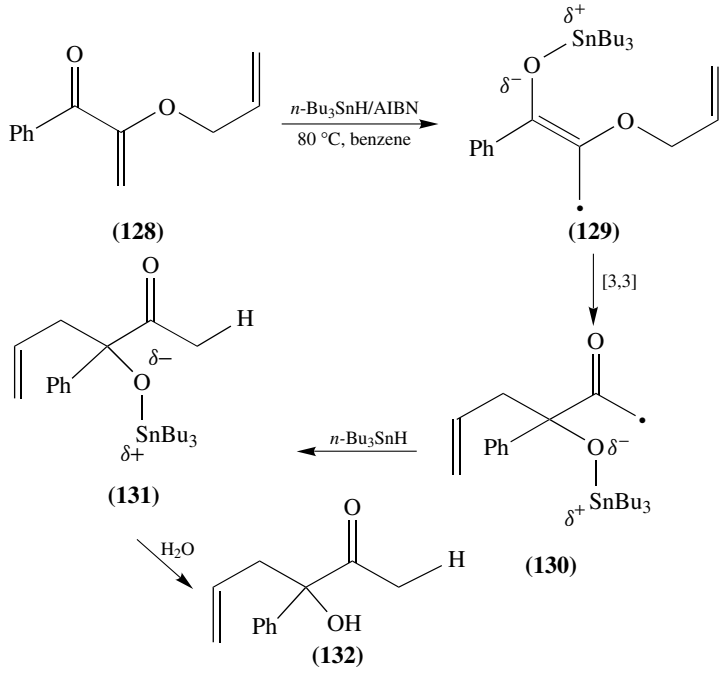


(62)

Ketyl radical anions generated from α-allyloxy-α,β-unsaturated ketones have been used to trigger [3,3]-sigmatropic rearrangements resulting in the formation of α-hydroxy-γ,δ-unsaturated methyl ketones (equation 64)[92]. It was postulated that formation of the tin(IV) enolate and allylic radical species **129** should induce a [3,3]-Claisen rearrangement to form the tin(IV) alkoxide radical **130**. This radical anion can undergo hydrogen atom abstraction to yield tin alkoxide **131** which, on quenching with water, affords alcohol **132**. To test this hypothesis, a series of six dienones were treated with tin hydride and AIBN. Refluxing

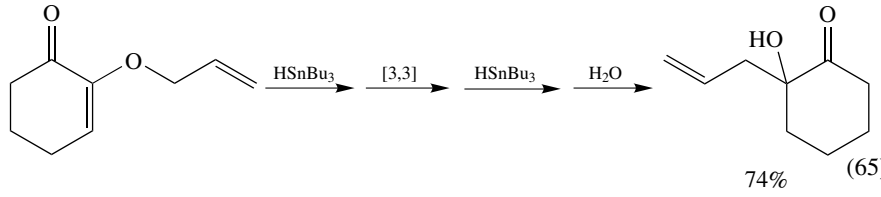

NC
O
N
O
O
(123)
(124)
CN
(126)
(125)
CN
(127)

(63)


Ph
O
O
n-Bu3SnH/AIBN
80 °C, benzene
δ+
SnBu3
δ−
(128)
(129)
[3,3]
H
δ−
Ph
SnBu3
δ+
n-Bu3SnH
(131)
(130)
H2O
OH
(132)

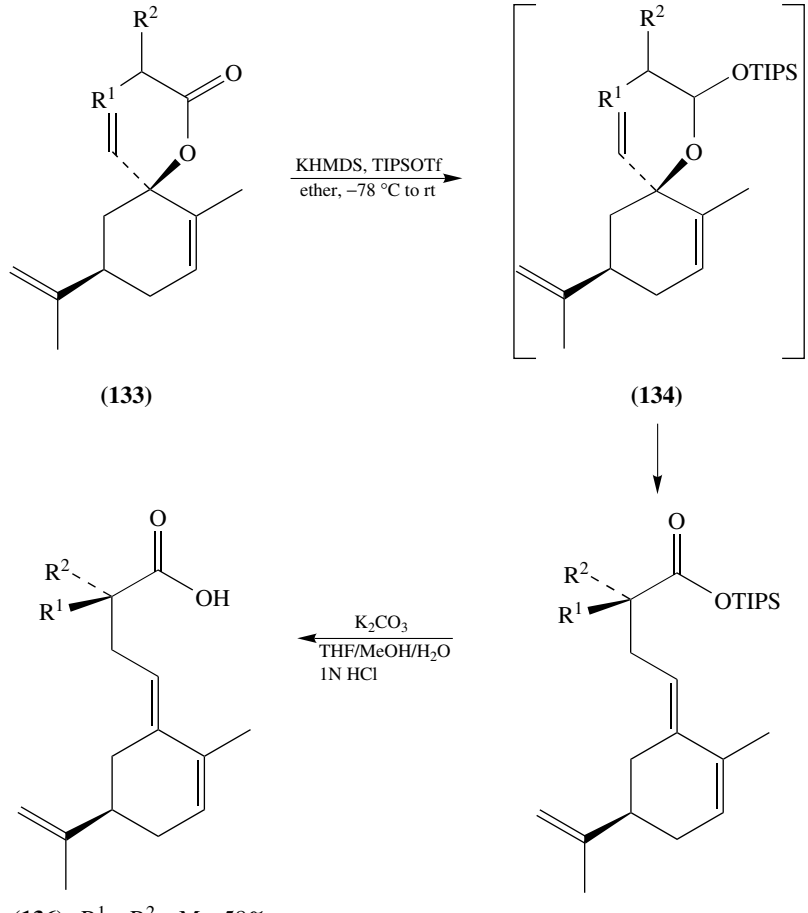
(64)

resulted in the corresponding α-hydroxy ketones in yields ranging from 51% to 74%. A typical example is shown in equation 65.



(65)

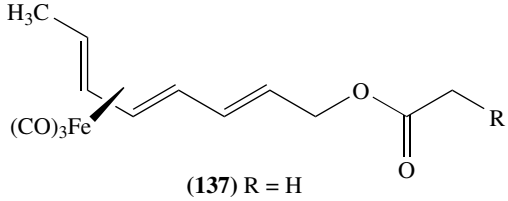
Alkylidene cyclohexenes were synthesized stereoselectively from bis-allyl silylketene acetals derived from cyclohexenones[93]. As shown in equation 66, Ireland Claisen rearrangement of ester **133** gave only *E*-diene **136**. Reaction of **133** with potassium



(66)

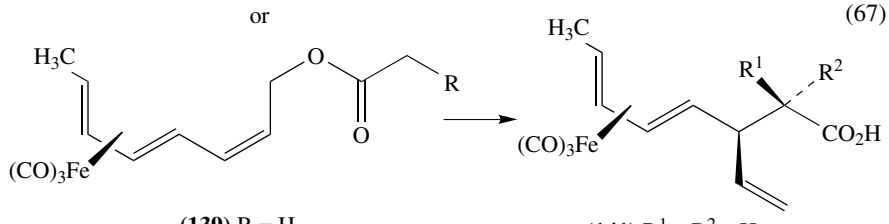
bis(trimethylsilyl)amide (KHMDS) and tris(isopropylsilyl)trifluoromethane sulfonate (TIPSOTF) in ether at −78 °C, followed by warming the reaction mixture to room temperature, afforded **135**, produced from the rearrangement of **134**. Hydrolysis of **135** yielded acid **136**.

Iron(tricarbonyl) was employed to control the diastereofacial selectivity in the enolate Claisen rearrangement of some trienylic esters[94]. Trienylic esters **137** and **139** underwent successful enolate Claisen rearrangements to afford **141** when treated with 1.05–1.15 equiv. of KHMDS in THF with 23% HMPA as cosolvent and 1.2 equiv. of TBDMSCl as an internal silylating agent (equation 67). Compound **137** yielded carboxylic acid **141** in 70–80% as a single diastereomer, while the yield from compound **139** was 45–50%. TBDMSOTf was used as an internal silylating agent for esters **138** and **140**. In contrast to the results obtained with **137** and **139**, inseparable mixtures of diastereomers **142** and **143** were obtained in 85–95% yield.



(137) R = H
(138) R = CH_3

or

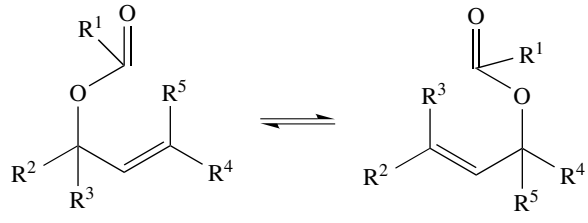


(67)

(139) R = H
(140) R = CH_3

(141) $R^1 = R^2 = H$
(142) $R^1 = H$, $R^2 = CH_3$
(143) $R^1 = CH_3$, $R^2 = H$

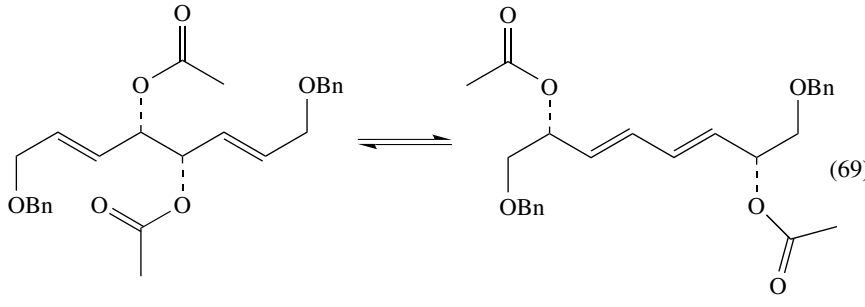
An interesting variation of the Claisen rearrangement is the hetero-Claisen rearrangement in which an allylic functionality containing a secondary hydroxyl group can be formed with controlled configuration of the allylic stereogenic center[95]. As depicted in equation 68, the rearrangement is a thermodynamically controlled equilibrium process.



(68)

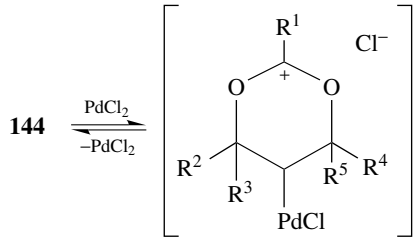
Using this hetero-Claisen rearrangement, Saito and coworkers[95] have recently shown that octadiene **144** can be converted to the rearranged product **145** with total retention of

stereochemistry of the chiral centers in **144** (equation 69). The reaction was performed at room temperature in methylene chloride with 20 mol% $PdCl_2(CH_3CN)_2$ as catalyst. Furthermore, other possible isomers, such as **146** and **147**, were not detected, even when the reaction was discontinued at an early stage. The reaction was postulated to proceed through a 1,3-dioxanium ion as shown in equation 70. This mechanism is commonly referred to as 'cyclization-induced rearrangement catalysis'.



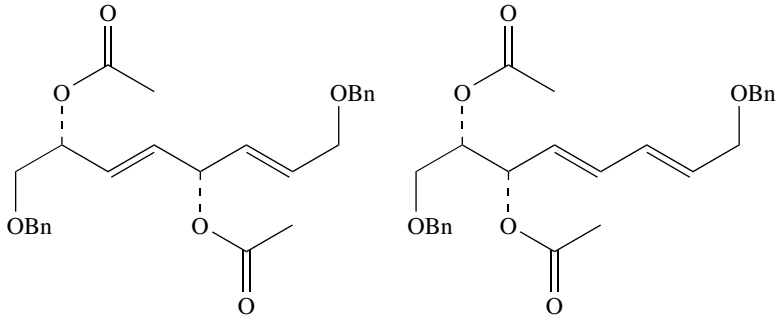
(69)

(144) **(145)**



(70)

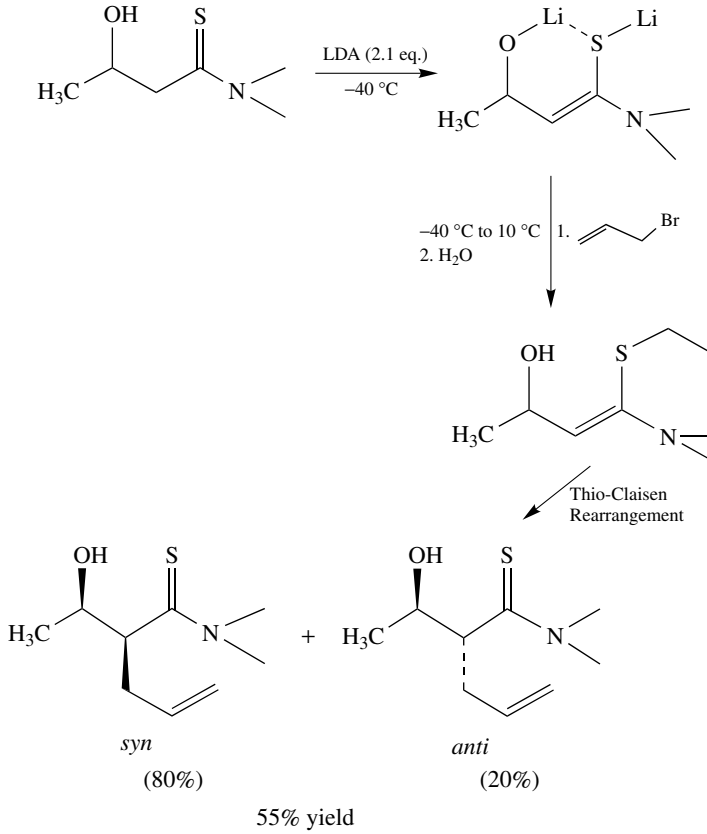
1,3-dioxanium ion



(146) **(147)**

(*Z*)-*S*-Allylic ketene aminothioacetals underwent thio-Claisen rearrangement at room temperature to give *N*,*N*-dimethyl *β*-hydroxy *α*-allylic thioamides[96]. *β*-Hydroxy-*N*,*N*,-dimethylthioamides were deprotonated with LDA to afford a chelated dianion with *Z*-configuration. Alkylation of this dianion gave the corresponding *Z* *α*-hydroxy *S*-allylic

ketene dimethylamino thioacetals. These compounds underwent [3,3]-sigmatropic rearrangement at room temperature to afford *syn N*,*N*-dimethyl β-hydroxy α-allylic thioamides in yields ranging from 30% to 70%. The preference for the *syn* over the *anti* diastereomer was generally found to be in excess of 4 : 1. An example is given in equation 71.



(71)

55% yield

VIII. REFERENCES

1. S. Mitsui and Kasahara, in *The Chemistry of Alkenes*, Vol. 2 (Ed. J. Zabicky), Interscience, New York, 1970, p. 569.
2. P. Blake, in *The Chemistry of Ketenes, Allenes, and Related Compounds*, Part 1 (Ed. S. Patai), Wiley, New York, 1980, p. 342.
3. W. Smadja, *Chem. Rev.*, **83**, 263–320 (1983).
4. S. R. Landor, *The Chemistry of Allenes*, Vol. 2, Academic Press, New York, 1982, p. 569.
5. T. Suzuki, K. Tanaka, I. Toyoshima, T. Okuhara and K. Tanaka, *J. Chem. Soc., Faraday Trans. 1*, **83**, 1213 (1987).
6. H. Takaya and R. Noyori, in *Comprehensive Organic Synthesis*, Vol. 8, (Ed. B. M. Trost), Pergamon Press, New York, 1991, p. 449.
7. I. S. Cho and H. Alper, *Tetrahedron Lett.*, **36**, 5673 (1995).
8. N. Ravasio, M. Gargano and M. Rossi *J. Org. Chem.*, **58**, 1259 (1993).
9. G. E. Heasley, J. M. Bundy, V. L. Heasley, S. Arnold, A. Gipe, D. Mckee, R. Orr, S. L. Rodgers and D. F. Shellhamer, *J. Org. Chem.*, **43**, 2793 (1978).

10. E. M. Campi, P. S. Elmes, W. R. Jackson, C. G. Lovel and M. K. S. Probert, *Aust. J. Chem.*, **40**, 1053 (1987).
11. J. E. Bäckvall, S. E. Byström and R. E. Nordberg, *J. Org. Chem.*, **49**, 4619 (1984).
12. J. E. Bäckvall, J. E. Nyström and R. E. Nordberg, *J. Am. Chem. Soc.*, **107**, 3676 (1985).
13. J. E. Nyström, T. Rein and J. E. Bäckvall, *Org. Synth.*, **67**, 105 (1989).
14. J. Barluenga, J. M. Martínez-Gallo, C. Nájera, F. J. Fañanás and M. Yus, *J. Chem. Soc., Perkin Trans. 1*, 2605 (1987).
15. O. S. Andell and J. E. Bäckvall, *Tetrahedron Lett.*, **26**, 4555 (1985).
16. J. E. Bäckvall and S. K. Juntunen, *J. Am. Chem. Soc.*, **109**, 6396 (1987).
17. A. J. Bloom and J. M. Mellor, *J. Chem. Soc., Perkin Trans. 1*, 2737 (1987).
18. A. Barco, S. Benetti, G. P. Pollini, G. Spalluto and V. Zanirato, *J. Chem. Soc., Perkin Trans. 1*, 390 (1991).
19. A. Barco, S. Benetti, G. P. Pollini, G. Spalluto and V. Zanirato, *Tetrahedron Lett.*, **32**, 2517 (1991).
20. C. Nájera, M. Yus, U. Karlsson, A. Gogoll and J. E. Bäckvall, *Tetrahedron Lett.*, **31**, 4199 (1990).
21. S. E. Denmark, M. S. Dappen and C. J. Cramer, *J. Am. Chem. Soc.* **108**, 1306 (1986).
22. S. E. Denmark, C. J. Cramer and J. A. Sternberg, *Helv. Chim. Acta*, **69**, 1971 (1986).
23. D. Seebach and M. A. Brook, *Can. J. Chem.*, **65**, 836 (1987).
24. A. Yoshikoshi and M. Miyashita, *Acc. Chem. Res.* , **18**, 284 (1985).
25. A. T. Nielsen and T. G. Archibald, *Tetrahedron*, **26**, 3475 (1970).
26. J. E. Bäckvall, U. Karlsson and R. Chinchilla, *Tetrahedron Lett.*, **32**, 5607 (1991).
27. A. B. Paolobelli, P. Ceccherelli and F. Pizzo, *J. Org. Chem.*, **60**, 4954 (1995).
28. A. Ogawa, O. Ryoichi, N. Sonoda and T. Hirao, *Tetrahedron Lett.*, **39**, 1577 (1998).
29. B. B. Snider and K. Yang, *J. Org. Chem.*, **57**, 3615 (1992).
30. T. Katsuki and V. S. Martin, *Org. React.*, **48**, 1–299 (1996).
31. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980).
32. E. J. Corey and D-C. Ha, *Tetrahedron Lett.*, **29**, 3171 (1988).
33. S. Chang, N. H. Lee and E. N. Jacobsen, *J. Org. Chem.*, **58**, 6939 (1993).
34. M. Frohn, M. Dalkiewicz, Y. Tu, Z-X. Wang and Y. Shi, *J. Org. Chem.*, **63**, 2948 (1998).
35. M. Mandel, T. Hudlicky, L. D. Kwart and G. M. Whited, *J. Org. Chem.*, **58**, 2331 (1993).
36. G. C. Bloomfield, T. J. Ritchie and R. Wrigglesworth, *J. Chem. Soc., Perkin Trans. 1*, 1229 (1992).
37. C. Y. Park, B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.*, **32**, 1003 (1991).
38. D. Xu, G. A. Crispino and K. B. Sharpless, *J. Am. Chem. Soc.*, **114**, 7570 (1992).
39. H. Becker, M. A. Soler and K. B. Sharpless, *Tetrahedron*, **51**, 1345 (1995).
40. K. Narkunan and M. Nagarajan, *J. Chem. Soc., Chem. Commun.*, 1705 (1994).
41. Y. G. Kim, K. Whang, R. J. Cooke and J. K. Cha, *Tetrahedron Lett.*, **31**, 3275 (1990).
42. M. Leclaire, P. Jean, L. Ricard and J. Y. Lallemand, *Synth. Commun.*, **28**, 4371 (1998).
43. R. W. Armstrong, J. E. Tellew and E. J. Moran, *Tetrahedron Lett.*, **37**, 447 (1996).
44. W. A. Donaldson and L. Shang, *Tetrahedron Lett.*, **37**, 423 (1996).
45. R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi and A. Restelli, *Helv. Chim. Acta*, **68**, 1217 (1985).
46. W. S. Wadsworth, *Org. React.*, **25**, 73–253 (1977).
47. A. Pastouret, J. P. Vidal, T. Durand, J. P. Girard and J. C. Rossi, *Bull. Soc. Chim. Fr.*, **130**, 206 (1993).
48. H. J. Bestmann, C. O. Meese and T. Roeder, *J. Labelled Compd. Radiopharm.*, **27**, 1325 (1989).
49. J. D. White, R. G. Carter and K. F. Sundermann, *J. Org. Chem.*, **64**, 684 (1999).
50. F. Effenberger and H. Stobel, *Chem. Ber.*, **126**, 1683 (1993).
51. V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React.*, **50**, 1–652 (1997).
52. J. K. Stille and M. Tanaka, *J. Am. Chem. Soc.*, **109**, 3785 (1987).
53. J. K. Stille, H. Su, D. H. Hill, P. Schneider, M. Tanaka, D. L. Morrison and L. S. Hegedus, *Organometallics*, **10**, 1993 (1991).
54. C. Boden and G. Pattenden, *Synlett*, 181 (1994).
55. A. S. Kende and R. J. DeVita, *Tetrahedron Lett.*, **31**, 307 (1990).
56. B. H. Lipshutz and C. Lindsley, *J. Am. Chem. Soc.*, **119**, 4555 (1997).

57. B. H. Lipshutz, B. Ullman, C. Lindsley, S. Pecchi, D. J. Buzard and D. Dickson, *J. Org. Chem.*, **63**, 6092 (1998).
58. H. Xiong and R. D. Rieke, *J. Org. Chem.*, **54**, 3247 (1989).
59. G. G. Melikyan, *Org. React.*, **49**, 427–675 (1997).
60. B. M. Trost, C. J. Urch and M. H. Hung, *Tetrahedron Lett.*, **27**, 4949 (1986).
61. T. Kondo, N. Hiraishi, Y. Morisaki, K. Wada, Y. Watanabe and T. Mitsudo, *Organometallics*, **17**, 2131 (1998).
62. P. Denis, A. Jean, J. F. Croizy, A. Morteux and F. Petit, *J. Am. Chem. Soc.*, **112**, 1292 (1990).
63. W. S. Trahanovsky and K. A. Koeplinger, *J. Org. Chem.*, **57**, 4711 (1992).
64. J. Christoffers, *J. Org. Chem.*, **63**, 4539 (1998).
65. J. Rodriguez, P. Brun and B. Waegell, *J. Organomet. Chem.*, **359**, 343 (1989).
66. J-L. Wang, C-H. Ueng, S-J. Cheng and M-C. P. Yeh, *Organometallics*, **13**, 4453 (1994).
67. S. Nakanishi, J. Nakanishi and T. Takata, *Synth. Commun.*, **28**, 1967 (1998).
68. C. Schneider and M. Rehfeuter, *Tetrahedron*, **53**, 133 (1997).
69. D. Enders, M. Knopp and R. Schiffers, *Tetrahedron: Asymmetry*, **7**, 1847 (1996).
70. L. A. Paquette, *Tetrahedron*, **53**, 13971 (1997).
71. E. Román, M. Baños, F. J. Higes and J. A. Serrano, *Tetrahedron: Asymmetry*, **9**, 449 (1998).
72. (a) H. Ikeda, A. Ishida, T. Takasaki, S. Tojo, S. Takamuku and T. Miyashi, *J. Chem. Soc., Perkin Trans. 2*, 849 (1997).
    (b) H. Ikeda, T. Minegishi, H. Abe, A. Konno, J. L. Goodman and T. Miyashi, *J. Am. Chem. Soc.*, **120**, 87 (1998).
73. H. M. L. Davies, D. G. Stafford, B. D. Doan and J. H. Houser. *J. Am. Chem. Soc.,* **120**, 3326 (1998).
74. P. D. Rao, C. Chen and C. Liao, *Chem. Commun.*, 155 (1998).
75. T. Lee and C. Liao, *Tetrahedron Lett.*, **37**, 6869 (1996).
76. C. Chen, M. E. Layton and M. D. Shair, *J. Am. Chem. Soc.*, **120**, 10784 (1998).
77. (a) L. A. Paquette and M. Zhao, *J. Am. Chem. Soc.*, **120**, 5203 (1998).
    (b) L. A. Paquette, Z. Gao and G. F. Smith, *J. Am. Chem. Soc.*, **120**, 2543 (1998).
    (c) L. A. Paquette, L. Sun, T. J. Watson, D. Friedrich and B. T. Freeman, *J. Am. Chem. Soc.*, **119**, 2767 (1997).
    (d) L. A. Paquette, L. H. Kuo and J. Doyon, *J. Am. Chem. Soc.*, **119**, 3038 (1997).
78. H. Y. Yoo and K. N. Houk, *J. Am. Chem. Soc.*, **120**, 205 (1998).
79. M. M. Bio and J. L. Leighton, *J. Am. Chem. Soc.*, **121**, 890 (1999).
80. A. C. Braisted and P. G. Schultz, *J. Am. Chem. Soc.*, **116**, 2211 (1994).
81. E. M. Driggers, H. S. Cho, C. W. Liu, C. P. Katzka, A. C. Braisted, H. D. Ulrich, D. E. Wemmer and P. G. Schultz, *J. Am. Chem. Soc.*, **120**, 1945 (1998).
82. L. A. Paquette and B. P. Dyck, *J. Am. Chem. Soc.*, **120**, 5953 (1998).
83. T. Lee, C. Liao and W. Liu, *Tetrahedron Lett.*, **37**, 5897 (1996).
84. E. J. Corey and R. S. Kania, *Tetrahedron Lett.*, **39**, 741 (1998).
85. S. Deloisy and H. Kunz, *Tetrahedron Lett.*, **39**, 791 (1998).
86. E. J. Corey and R. S. Kania, *J. Am. Chem. Soc.*, **118**, 1229 (1996).
87. L. A. Paquette, L. Sun, D. Friedrich and P. B. Savage, *J. Am. Chem. Soc.*, **119**, 8438 (1997).
88. J. Barluenga, R. Sanz, A. Granados and F. J. Fañanás, *J. Am. Chem. Soc.*, **120**, 4865 (1998).
89. J. Wang and C. D. Gutsche, *J. Am. Chem. Soc.*, **120**, 12226 (1998).
90. (a) T. Sattelkau and P. Eilbracht, *Tetrahedron Lett.*, **39**, 9647 (1998).
    (b) T. Sattelkau and P. Eilbracht, *Tetrahedron Lett.*, **39**, 1905 (1998).
91. T. Kawasaki, R. Terashima, K. Sakaguchi, H. Sekiguchi and M. Sakamoto, *Tetrahedron Lett.*, **37**, 7525 (1996).
92. E. J. Enholm, K. M. Moran, P. E. Whitley and M. A. Battiste, *J. Am. Chem. Soc.*, **120**, 3807 (1998).
93. X. Zhang and M. C. McIntosh, *Tetrahedron Lett.*, **39**, 7043 (1998).
94. W. R. Roush and A. B. Works, *Tetrahedron Lett.*, **38**, 351 (1997).
95. S. Saito, A. Kuroda, H. Matsunaga and S. Ikeda, *Tetrahedron*, **52**, 13919 (1996).
96. P. Beslin and B. Lelong, *Tetrahedron*, **53**, 17253 (1997).

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CHAPTER **10**

Rearrangements of dienes and polyenes

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I. INTRODUCTION

The rearrangements of dienes and polyenes are numerous and of different types. Many of these reactions have been known for a long time (see, e.g., the books in References[1–7] and reviews[8–11]), and they have not only been widely adopted for organic synthesis but also used as a basis for important theoretical generalizations and concepts. New synthetic methods were developed and our knowledge of organic reactions mechanisms was extended during the investigation of these rearrangements. It is sufficient to note that one of the outstanding achievements of theoretical organic chemistry in the last thirty years resulted from an analysis of cyclizations and rearrangements of diene systems, namely, the principle of conservation of orbital symmetry.

In general, the rearrangements of dienes and polyenes can be both thermal and photochemical reactions (the latters are not included in this chapter), and can be catalyzed by acids, bases, metal complexes and enzymes. They can be degenerate processes or occur with the introduction or elimination of functional groups, be accompanied by shifts of multiple bonds or by migrations of atoms or groups and they may lead to cyclizations.

Such a variety of transformations complicates attempts at a general classification of the field. Moreover, it is difficult even to specify the term 'rearrangement'. In this respect the interesting suggestion of Balaban and Fârcasiu is noteworthy[12]. According to them, 'rearrangements' are only the transformations which conserve neither the molecular nor the structural formula of the starting material (e.g. the pinacol rearrangement), while reactions which conserve the molecular but not the structural formula are named 'isomerizations' (e.g. dienone–phenol and Claisen rearrangements). The process which conserves both features is called 'automerization' (and a more common term now is 'degenerate rearrangements').

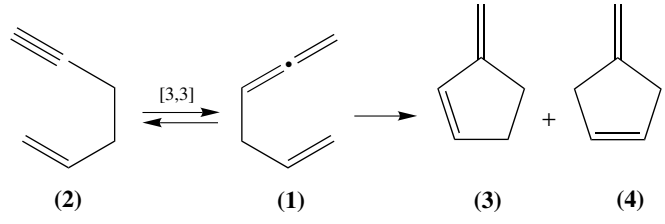
In view of the above we have arranged the material according to the structural features by using a subdivision into cumulated, conjugated and non-conjugated dienes and polyenes.

II. REARRANGEMENTS OF ALLENES AND CUMULENES

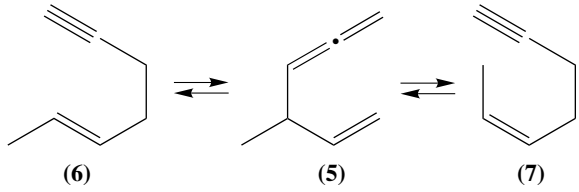
The title reactions are discussed in a series of reviews[13–15]. However, the most complete and detailed description of rearrangements involving allenes was presented in Huntsman's comprehensive survey[16], wherein the cumulated systems were considered as either the starting materials, the intermediates or the reaction products. More recently, very detailed reviews devoted to vinyl cations and containing numerous examples of rearrangements of cumulenes and other polyenes were published[17,18]. Therefore, this section will cover only relatively recent publications.

Generally, the rearrangements of allenes and cumulenes can lead to acetylene derivatives, to conjugated dienes and, in certain cases, to non-conjugated dienes[16]. A unique combination of all these transformations is presented by the rearrangements of 1,2,5-trienes **(1)** where a reversible [3,3]-sigmatropic rearrangement is accompanied by a slower cyclization to the methylenecyclopentene derivatives **3** and **4** (equation 1). The kinetics of various interconversions of methyl substituted 1,2,5-alkatriene homologues of **1** and 1-alken-5-ynes **(2)** are described in detail in a review[16]. In another example, the gas-phase pyrolysis of 4-methyl-1,2,5-hexatriene **5** at 310–320 °C for 20–90 min was recently reported[19]. Rate constants and Arrhenius parameters show that the reactions **5** → **6** and

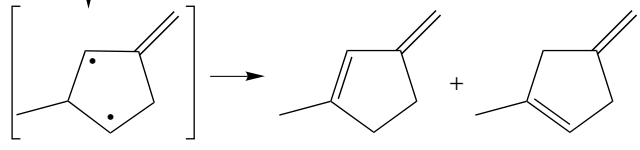
5 → **7** correspond to [3,3]-sigmatropic Cope-type rearrangements, whereas the cyclization of triene **5** to dienes **9** and **10** proceed via the diradical **8** (equation 2). The kinetic data are consistent with a concerted rearrangement of the 1,2,5-triene into its isomeric enynes but the authors do not exclude the possibility that for certain substituents the non-concerted process could become competitive. It should be noted that results were reported which exclude a cyclohexene-1,4-diyl diradical as an intermediate in the thermal acetylenic Cope rearrangement (i.e. the 'cyclization–cleavage' mechanism)[20] (see also Section IV.C.1).



(2) (1) (3) (4) (1)



(6) (5) (7) (2)



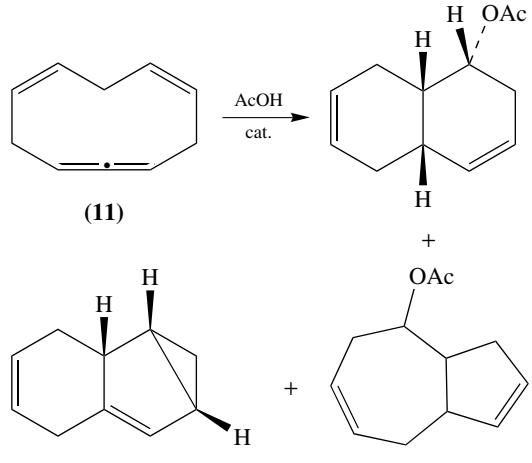
(8) (9) (10)

The cyclic 1,2,5-trienes **11** and **12** rearrange in the presence of ten different catalysts [e.g. $HgSO_4$, $Hg(OAc)_2$, AgOAc, CuOAc] in acetic acid to various unsaturated bicyclic derivatives[21] (equations 3 and 4). It is interesting that **13**, the cyclic allene isomer of **12**, forms with mercuric acetate in AcOH followed by reduction with $LiAlH_4$ only the alcohols **14** and **15** (in a ratio 92 : 8) rather than the rearranged product **16**. The authors suggest that the cyclopropyl ring stabilizes the cationoid intermediate and thus prevents it from rearrangement[21] (equation 5).

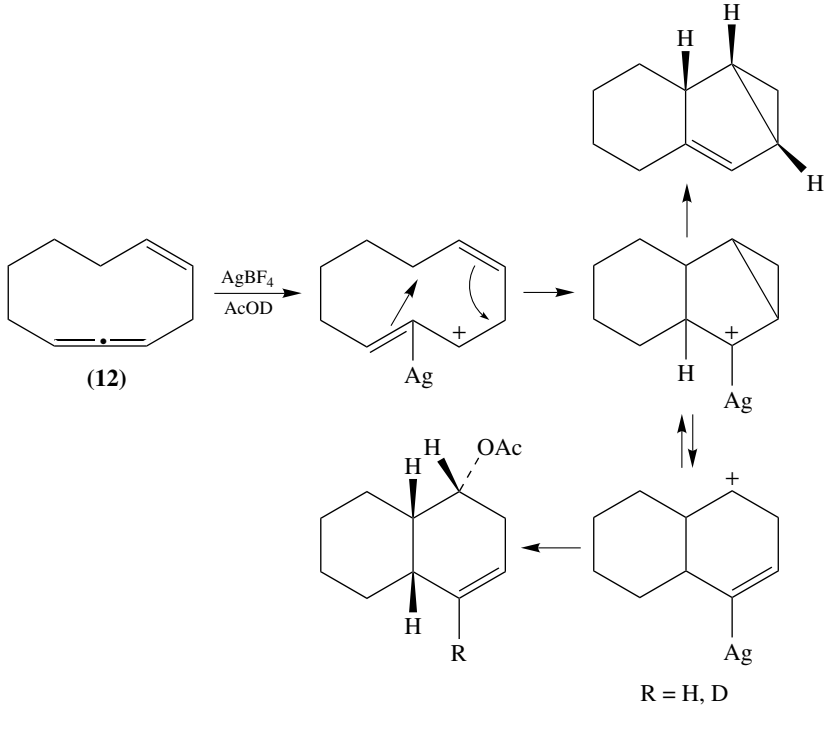
The cyclic diradical, 2-methylene-1,4-cyclohexadiyl (**18**), can be formed from the hepta-1,2,6-triene **17**[22,23]. Thermolysis of **17** gives 3-methylene-1,5-hexadiene **19** as a Cope rearrangement product, while the same treatment (155 °C, benzene) in the presence of SO_2 leads to sulfones **20** and **21** instead of **19** (equation 6). It was shown that sulfone **20** is obtained by reaction of SO_2 with the rearrangement product **19**, while sulfone **21** originates directly from the diradical **18**.

This finding confirms an opinion that, at least in some cases, diradicals such as **18** can be the actual intermediates in the non-concerted Cope rearrangement, so-called 'stepwise cyclization-then-cleavage' mechanism. Berson and coworkers who previously excluded diyl intermediate in the acetylenic Cope rearrangement[20] designed in their next work[24]

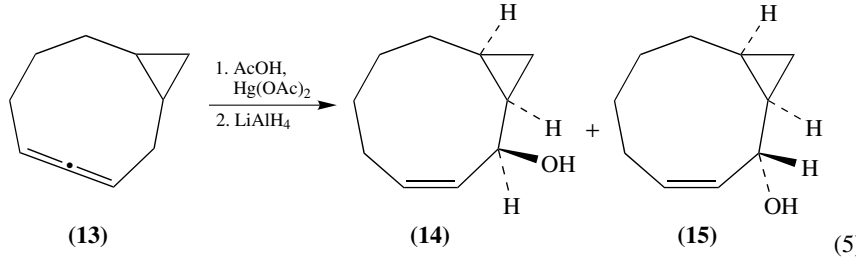
a new test structure to stabilize the possible diradical through conjugation and thereby encourage the stepwise path. Gas-phase pyrolysis of the enantiomerically pure test compound (*R*,*E*)-**22** (214–255 °C, 32–260 min) has resulted in the triene **23** (equation 7). Its stereochemical analysis had confirmed the possibility to divert the Cope rearrangement from its normally concerted mechanism into a stepwise one, proceeding via a conformationally mobile diradical intermediate[24].



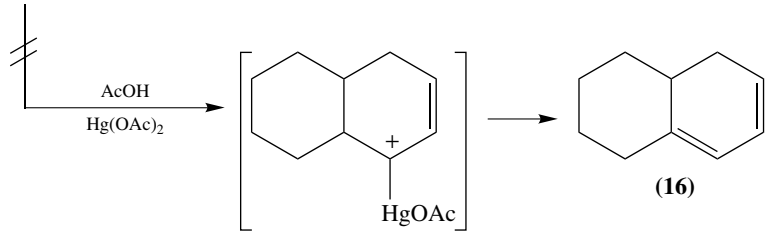
(3)



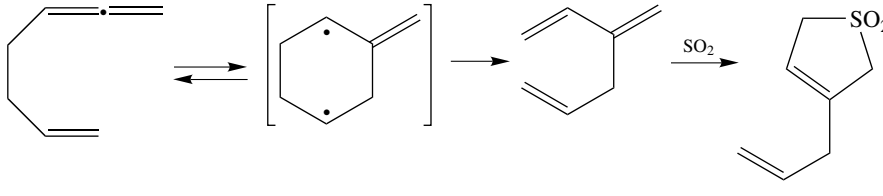
(4)



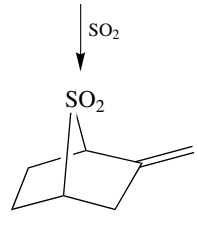
(13) **(14)** **(15)** (5)



(16)



(17) **(18)** **(19)** **(20)** (6)



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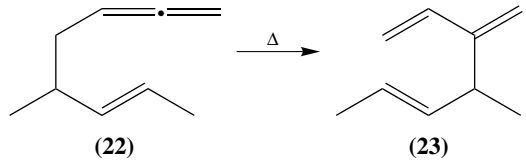
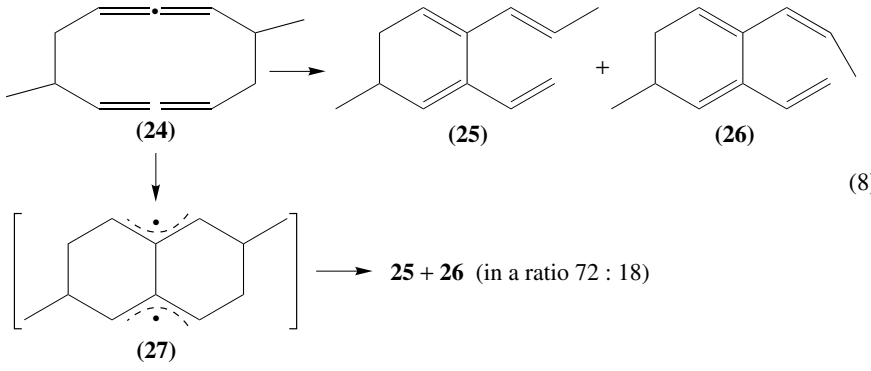


(22) **(23)** (7)

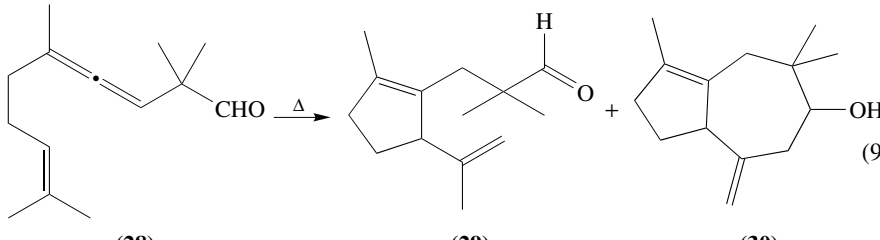
Another type of diradical intermediate species **(27)** in Cope rearrangement is formed during thermolysis of optically active *trans*-4,9-dimethyl-1,2,6,7-cyclodecatetraene **24**[25] which was studied in order to distinguish between concerted and stepwise mechanisms of Cope rearrangement. The transformation of optically active *trans*-**24** via a concerted mechanism would lead to optically active tetraenes **25** and **26**, while the participation

of diradical **27** will result in the loss of optical activity (equation 8). It was found that bis-allene *meso*-**24** undergoes thermolysis at 200 °C to form optically active products **25** and **26**. In contrast, the transformation of *rac*-**24** involves a competition between concerted and nonconcerted pathways. The different behavior of the two isomers can be explained by the boat and chair geometries, respectively, of the two transition states.

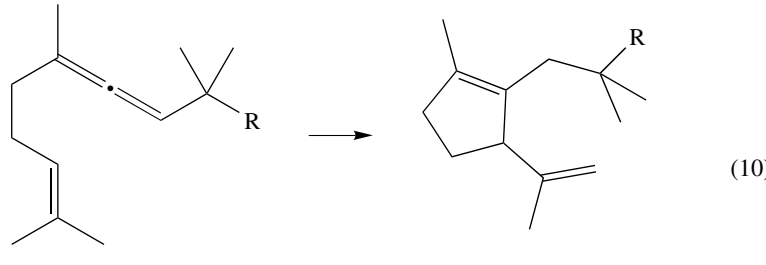


(8)

Thermolysis of the functionally substituted 1,2,6-trienes **28** and **31a–d** leads by Cope rearrangements to dienes **29, 30** and **32a–d** (equations 9 and 10), respectively[26]. The reactions of aldehyde **28** occur at a relatively high temperature (>170 °C) to furnish both **29** and **30**. Product **29** can be cyclized to **30** by heating. The similar thermolysis of the Shiff base **33** obtained from aldehyde **28** proceeds via two steps to afford the separable analogous products **34** and **35** (equation 11)[27].

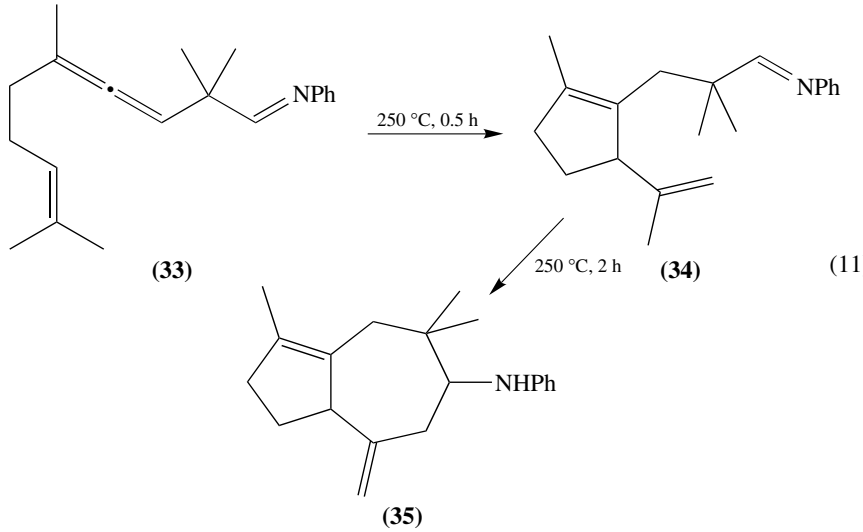


(9)



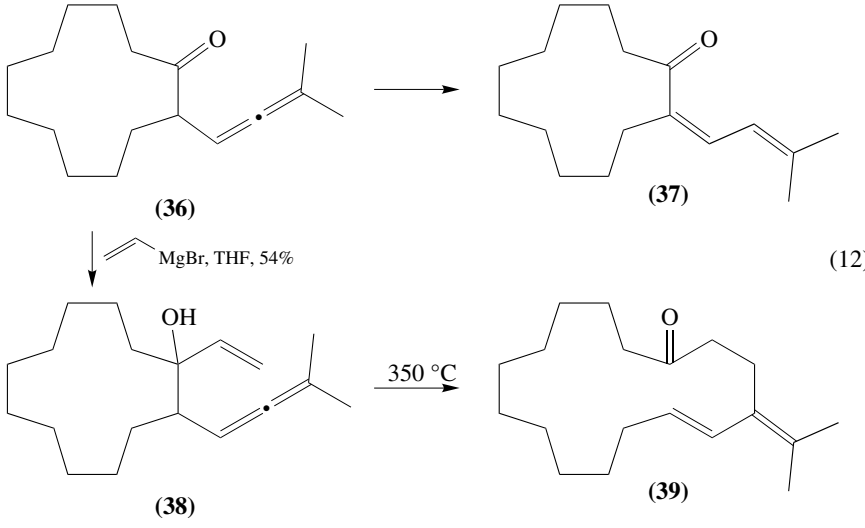
(10)

(a) R = CH_2OH, (b) R = CH_2OAc, (c) R = COOMe, (d) R = $CH(OMe)_2$



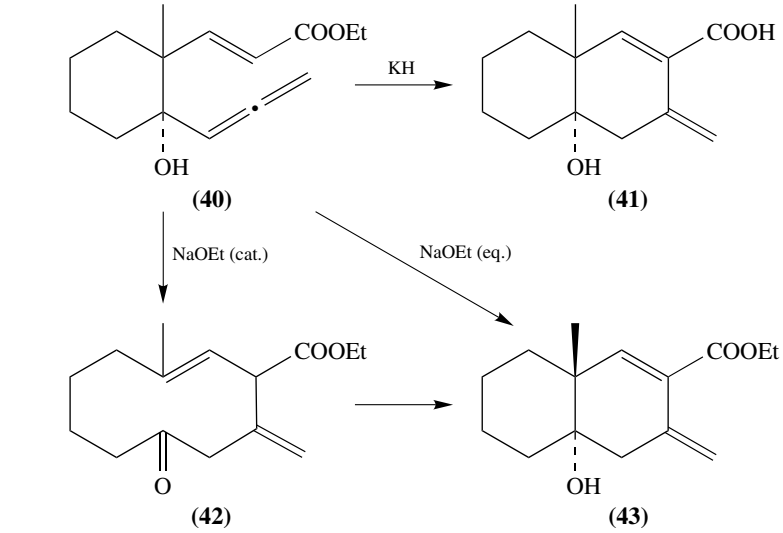
(11)

Similar to the typical Cope rearrangement for dienes (Section IV.C), the allene systems can also participate in oxy-Cope rearrangements (Section IV.D). Generally, it should be noted that only a few examples of both thermal and base-catalyzed oxy-Cope rearrangements are known in which one of the π-systems is replaced by an allenic fragment. Thus, alcohol **38** rearranges at 350 °C to ketone **39** in 80% yield (equation 12)[28]. It is interesting that triene **38** does not undergo a photochemical isomerizations, even during prolonged UV irradiation in ether in the presence of acetone as a photosensitizer. The starting allenic ketone **36** has been converted into conjugated dienone **37** by both acid and base catalysis[28].

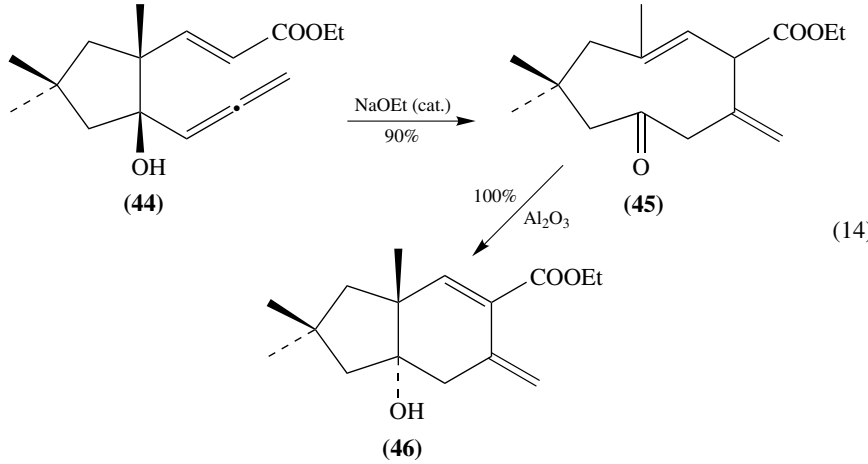


(12)

Anionic oxy-Cope rearrangement of allene alcohol **40** under standard conditions (KH, 18-crown-6, I_2, THF, 2 h at 20 °C, in 40% yield) gave rise to the carboxylic acid **41** (equation 13)[29]. Treatment of **40** with a catalytic amount of NaOEt (THF, 20 °C, 12 h) forms the cyclodecenone **42** in 80% yield while the bicyclic product **43** is formed in the presence of a stoichiometric amount of sodium ethoxide (THF, 20 °C, 12 h, 85%). Formation of **43** apparently proceeds via the initial oxy-Cope rearrangement of **40** to the ring enlargement product **42**, followed by a transannular reaction. A similar result was obtained when the oxy-Cope rearrangement of the cyclopentane derivative **44** gave the hydrindane **46** (equation 14)[29]. The isolated dienone **45** cyclizes to form the dienol **46** during purification with Al_2O_3. Compound **46** can serve as a potential synthon for the sesquiterpenoid candicansol[29].

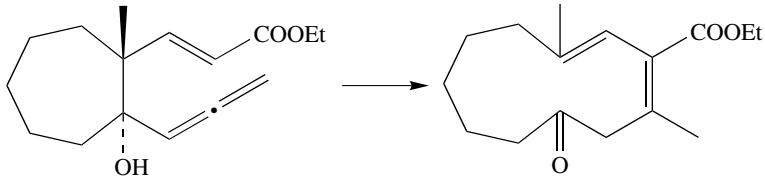


(13)



(14)

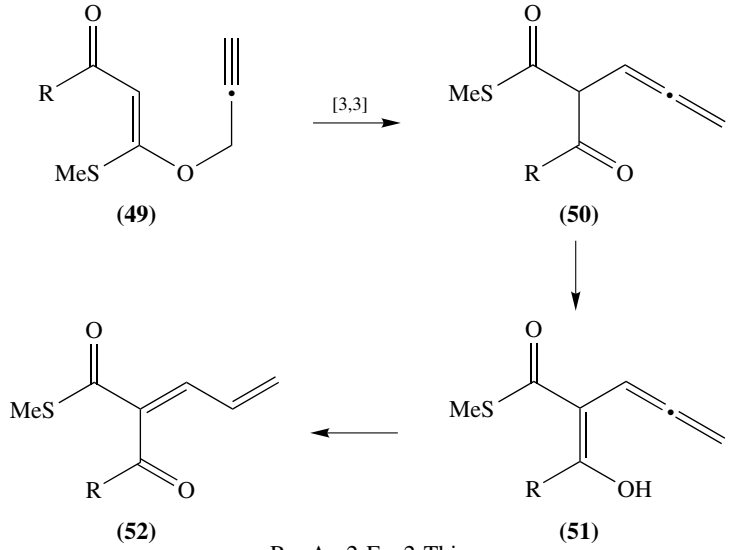
Furthermore, the oxy-Cope rearrangement of allenic cycloheptane alcohol **47** (NaOEt, THF, 20 °C, 12 h, 80%) gave rise only to ring-enlarged product **48** without transannular cyclization (equation 15)[29]. The above transformations can be rationalized either by the fragmentation–recombination mechanism or by a concerted oxy-Cope mechanism[29].



(15)

(47) **(48)**

The Claisen rearrangement of *O*,*S*-ketal **49** under neutral conditions (refluxing toluene or xylene) leads to the intermediate **50** which undergoes a rearrangement to the diene ester **52** through enolization and a subsequent 1,5-hydrogen shift within intermediate **51** that carries the hydroxy group at the double bond end (equation 16)[30].



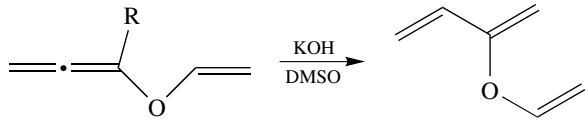
(16)

(49) **(50)** **(51)** **(52)**

R = Ar, 2-Fu, 2-Thi

Investigations of base-catalyzed isomerizations of allene derivatives have been recently continued. For instance, the rearrangement of allene ethers **53** under superbasic conditions (KOH-DMSO) is considered as one of the steps in hydration of acetylene derivatives (equation 17)[31,32].

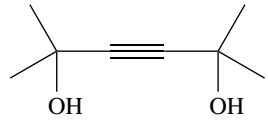
However, acid-catalyzed isomerization attracts more attention, probably due to its connection with the recent intensive development of carbenium ion chemistry. It is common knowledge that effective methods for stabilization of reactive carbocations have been known since 1962 while base-catalyzed processes with the participation of carbanions were developed more than 100 years ago.



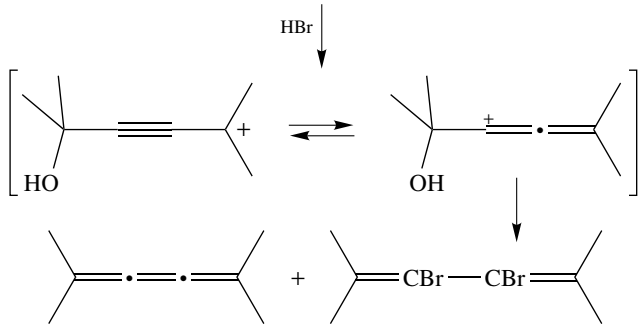
(53) (for R = Me) (17)

R = Me, Et, Pr, *i*-Pr, *n*-Bu, *t*-Bu

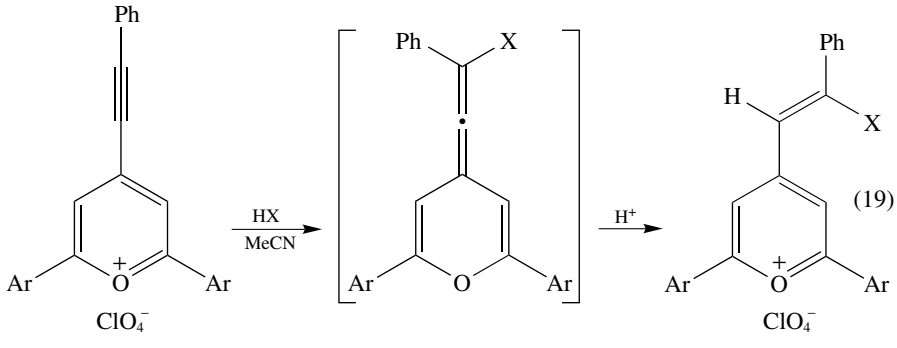
The various products obtained from acetylenic diols **54** in the presence of acids suggest the formation and interconversion of acetylene–allene–diene cationoid intermediates (equation 18)[33]. The allene intermediates can be sometimes isolated and they were reported as participants in the acid-catalyzed reactions of alkynylpyrylium salts **55**, a driving force of which is an aromatization of the pyrane ring (equations 19–21)[34,35].



(54)

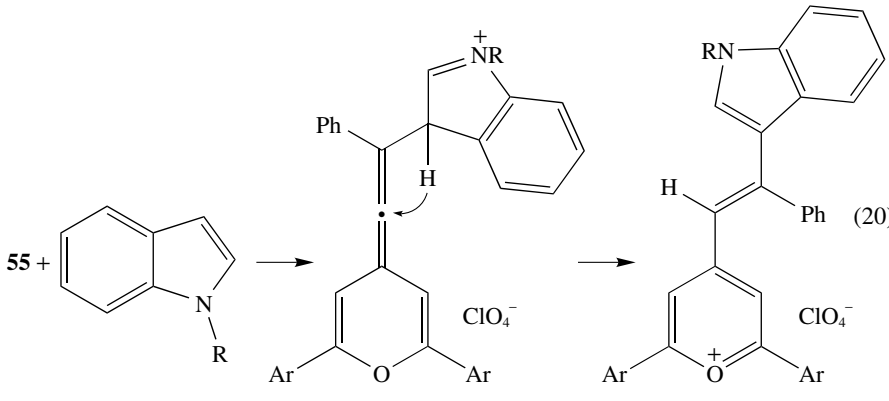


(18)



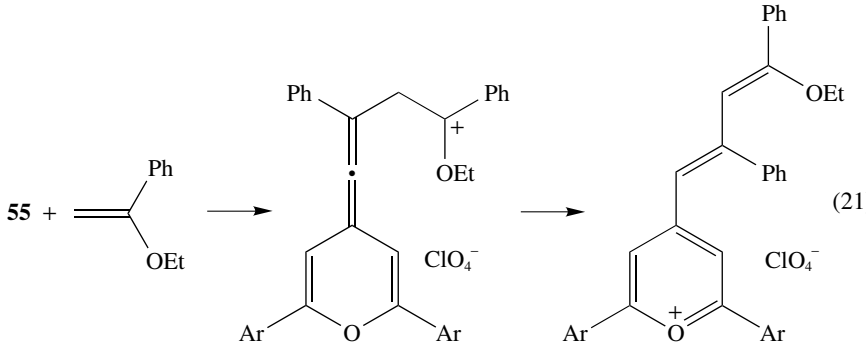
(55) (19)

X = Cl, Br; Ar = Ph , 4-$MeOC_6H_4$



(20)

Ar = Ph, *p*-$MeOC_6H_4$



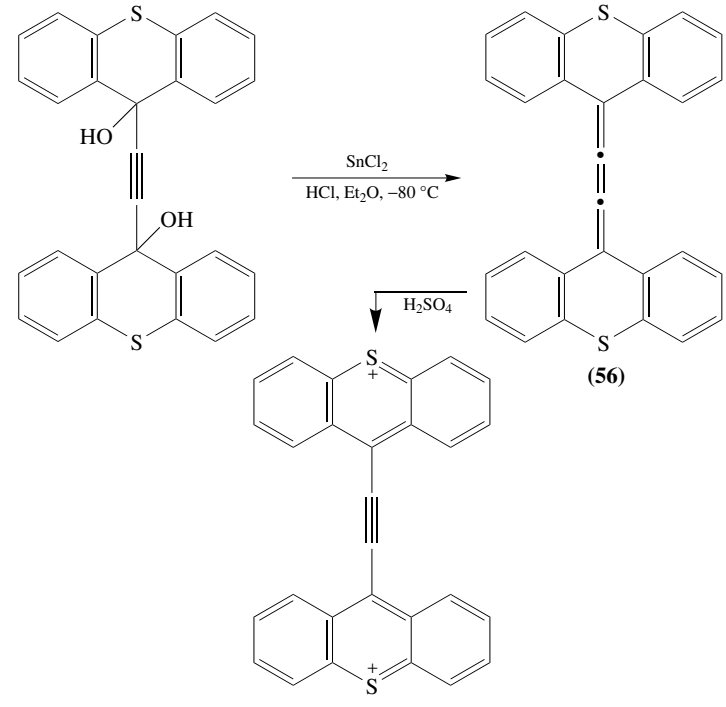
(21)

Ar = Ph, *p*-$MeOC_6H_4$

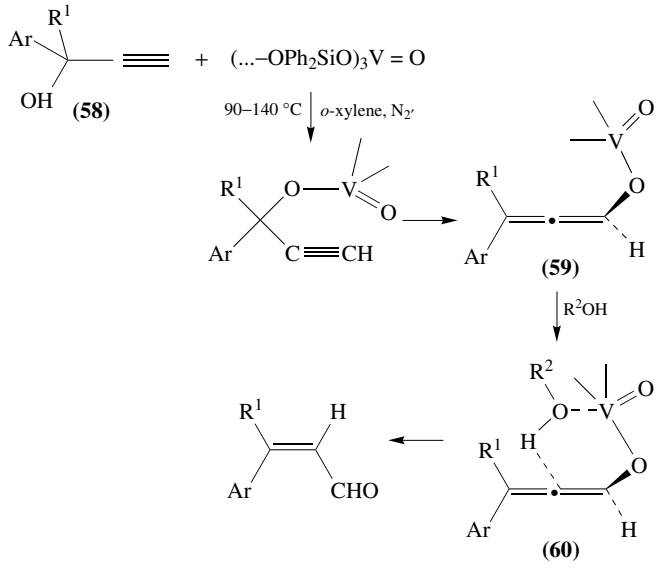
In a search of π-donor systems for the preparation of compounds having a metallic conductivity, the bis-thioxanthene cumulene **56** was obtained. It was oxidized by conc. H_2SO_4 to the acetylenic dication **57** rather than undergoing the expected protonation of the multiple bonds (equation 22)[36].

The rearrangement of arylethynyl carbinols **58** that occurs via allene intermediates **59** and **60** in the presence of a polymeric silylvanadate catalyst[37] (equation 23) is noteworthy.

In the 1980s an extensive investigation of allenyl cations **62**, which were generated from haloallenes **61** and reacted with various nucleophilic reagents, was carried out (for reviews of previous work, see References 16, 18, 38 and 39). The conditions under which stepwise and concerted cycloaddition reactions take place were studied. For example, a treatment of chlorotriphenylallene **61** with silver trifluoroacetate in the presence of cyclopentadiene in pentane and subsequent work up with KOH/EtOH gave a mixture of products **63–66**, **68–70** in 95% total yield (equations 24 and 25)[40]. An analysis of the reaction products has shown that the dienes **65** and **66** can be formed via a stepwise [2 + 2]-cycloaddition while compounds **68** and **69** were produced by a concerted [4 + 2]-cycloaddition through the intermediate allyl cation **67**[40,41]. A change of the reaction conditions resulted in the isolation of triphenylallenium hexachloroantimonate **71** which can be easily hydrated to the ethynyl carbinol **72** and the unsaturated ketone **70** in a ratio of



(22)

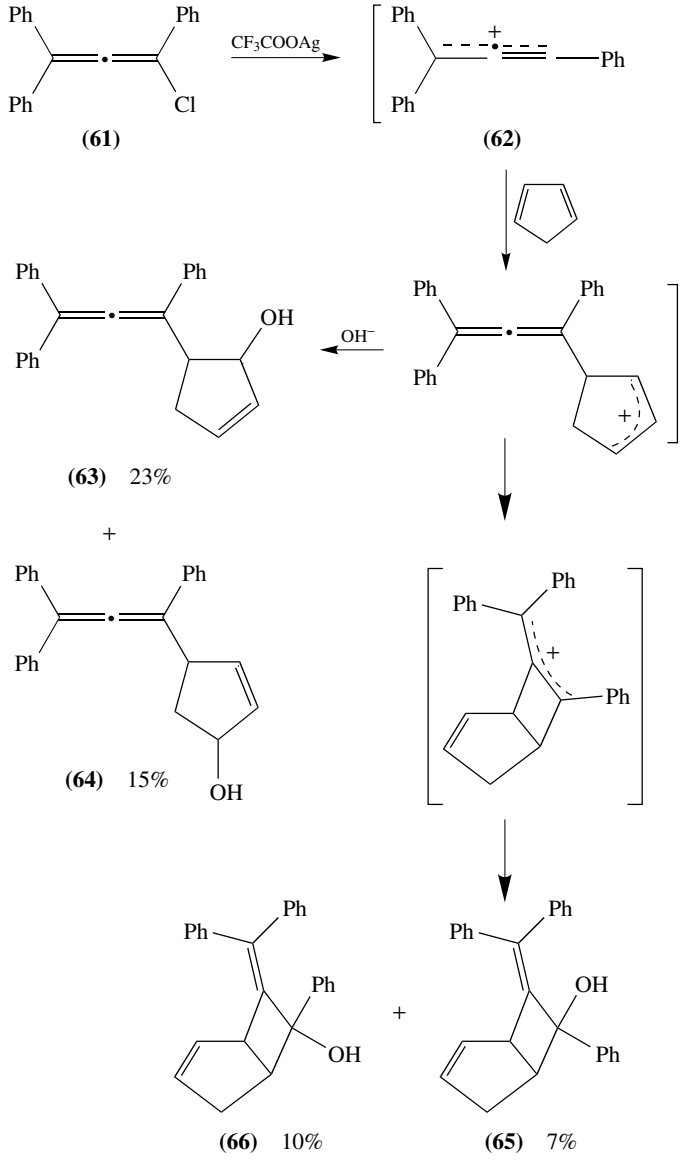


(23)

R = H, Me; Ar = Ph, 4-*i*-PrC_6H_4, 4-*t*-BuC_6H_4, 4-MeOC_6H_4, 4-MeC_6H_4, 2,4-$Me_2C_6H_3$

44 : 56 (equation 26)[42]. The reaction of the solution of the salt **71** in liquid SO_2 at $-30\,^{\circ}C$ with a solution of cyclopentadiene in dichloromethane, followed by an alkali hydrolysis of the reaction mixture obtained, gave rise to a mixture of the aforementioned bicyclic products **65** and **66** and the secondary alcohol **73** in a 39 : 50 : 11 ratio (equation 27)[42].

It is interesting to mention the cyclizations of allene systems which are accompanied by rearrangements. Protonation of the bis-cumulene **74** by 5% H_2SO_4 in aqueous acetone produces the adamantane derivative **75** in 95% yield (equation 28)[43].



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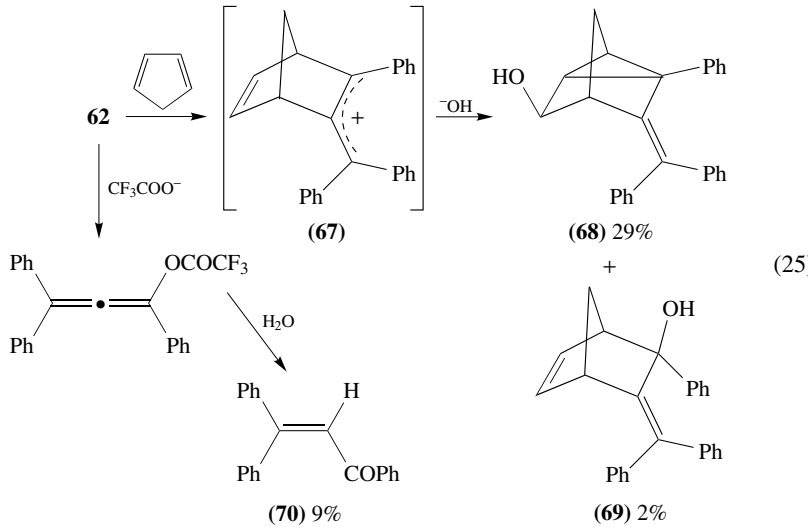
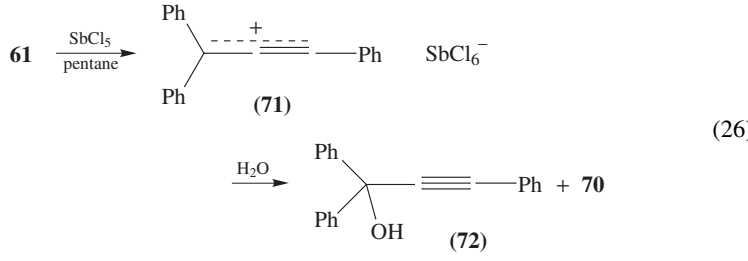
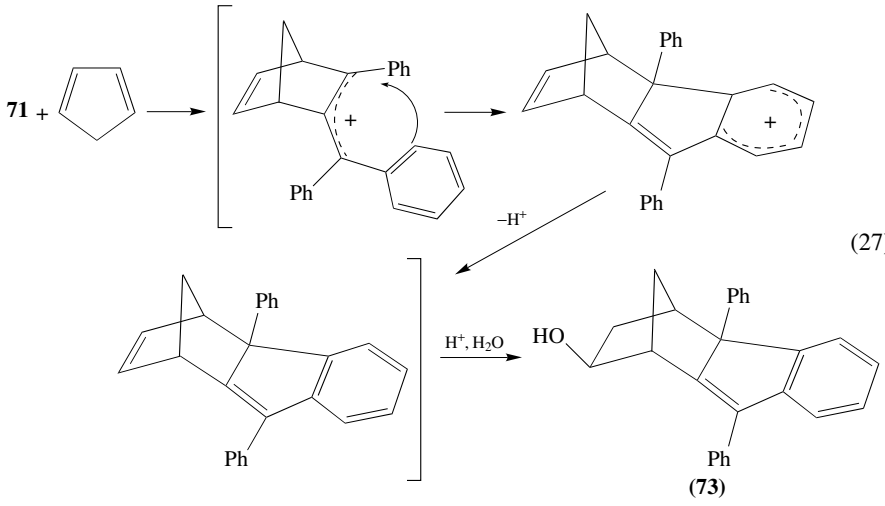
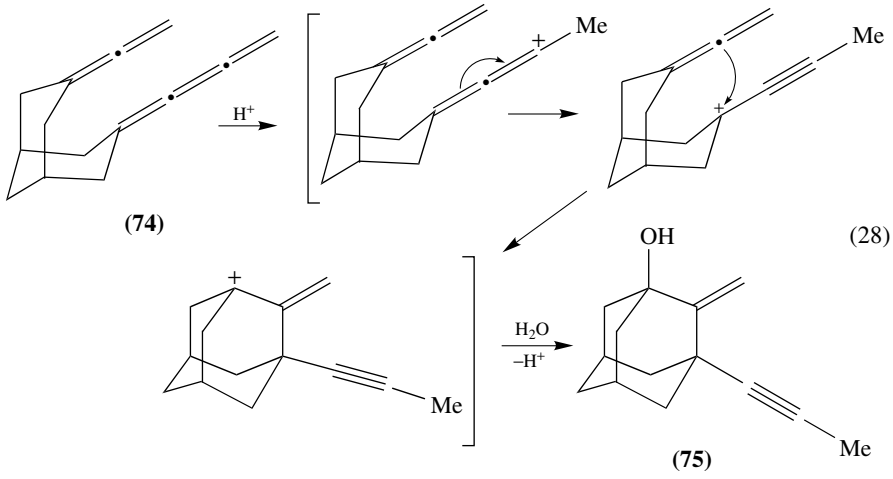

62
Ph
Ph
+
Ph
Ph
−OH
HO
Ph
Ph
Ph
CF3COO−
(67)
(68) 29%
+
(25)
Ph
OCOCF3
Ph
Ph
H2O
OH
Ph
Ph
Ph
H
Ph
COPh
Ph
(70) 9%
(69) 2%


61
SbCl5
pentane
Ph
+
Ph
Ph
SbCl6−
(71)
(26)
H2O
Ph
Ph
Ph
OH
+ 70
(72)


71 +
Ph
+
Ph
Ph
+
Ph
Ph
–H+
(27)
Ph
Ph
H+, H2O
HO
Ph
Ph
(73)



(28)

III. REARRANGEMENTS OF CONJUGATED DIENES AND POLYENES

A. Vinylcyclopropanes and Related Systems

This wide range of transformations includes many reactions which are one way or another connected with cyclopropane derivatives. The cyclopropane moieties can be part of the structure of both the linear dienes or of annulated polycyclic unsaturated systems as well as being part of a spiro compound.

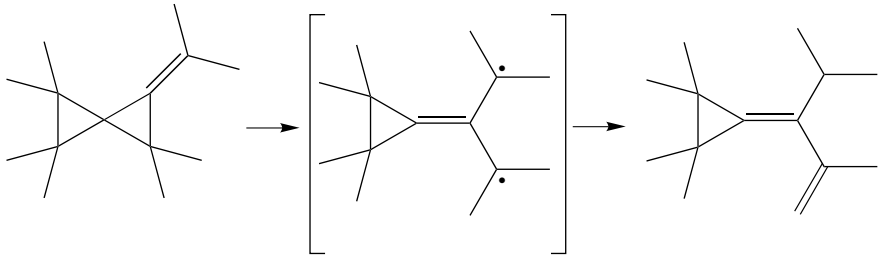
One such typical transformation is the thermal isomerization of the spiropentane derivative **76** into triene **80** which is assumed to occur via the diene intermediate **78** with the intermediate participation of the cyclopropyl–trimethylenemethane (TMM) **77** and the vinyl–TMM **79** diradicals (equation 29)[44]. It was shown by using deuterium labels that the diradical **79** forms the triene **80** by 1,6-hydrogen shift. The pathway **76** → **80** which occurs via tetramethylene–ethane diradical was recognized as a less probable route.

Tetramethylene–ethane (TME), or 2,2′-bis-allyl diradical **81**, was suggested as an intermediate in the thermal dimerization of allene, as well as in the interconversions of 1,2-dimethylenecyclobutane **82**, methylenespiropentane **83**, bis-cyclopropylidene **84** and other bicyclic systems (equation 30)[45]. The isolation of two different isomeric dimethylene cyclobutanes **87** and **88** (in a *ca* 2 : 1 ratio) after the thermal rearrangement of the deuteriated 1,2-dimethylene cyclobutane **85** suggests that the rearrangement proceeds via a 'perpendicular' tetramethyleneethane diradical (2,2′-bisallyl) **86** (equation 31)[45].

The participation of the above mentioned trimethylenemethane (TMM) diradicals in the thermal rearrangements of methylenecyclopropanes was also investigated by using systems containing an additional vinyl group which was part of rings fused with the cyclopropane (equations 32 and 33)[46,47]. The diene **91** was obtained from dichloride **89** (in 50% yield) via the diene intermediate **90** which undergoes the so-called methylenecyclopropane rearrangement to diene **91**.

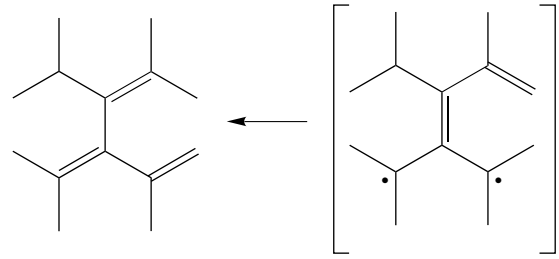
However, bicyclic dichloride **95** under the same conditions was converted into diene **96** and not to the rearrangement product **94** (equation 33). This result is explained by the larger size of the ring, which is far less strained than that in diene **90**[46]. The gas-phase thermolysis of diene **91** at 126–186 °C afforded an almost equimolar mixture of bicyclic diene **92** and triene **93** which are formed, presumably, via the TMM-diradicals

98a and **98b** (equation 34). Heating of diene **96** in DMF gave the triene **97** as a result of hydrogen shift (equation 33)[46]. The intermediate **99** was isolated by using flash pyrolysis of compound **91** at a temperature of 200 (±5) °C and a pressure of 10^{-3} Torr. As expected, this *cis*-2-vinyl-1,3,5-hexatriene **99** rearranges smoothly at 220 °C to yield only the triene **93**[48].

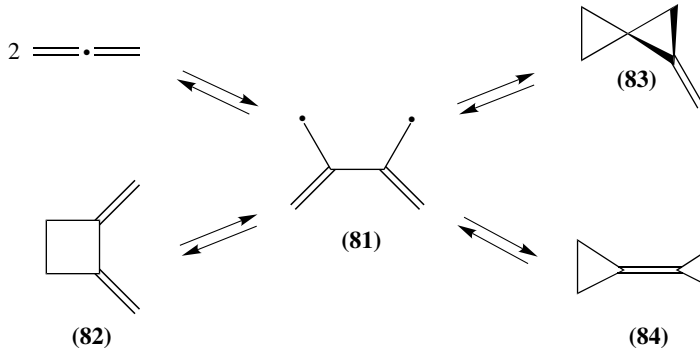


(76) **(77)** **(78)**

(29)

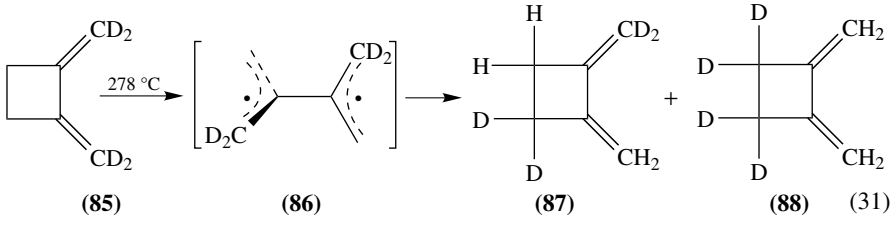


(80) **(79)**

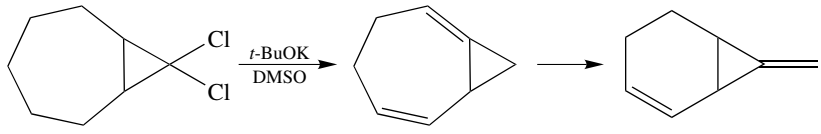


(83) **(81)** **(82)** **(84)**

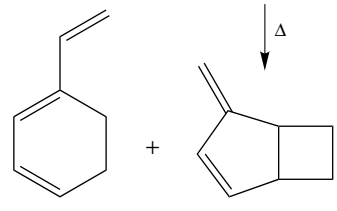
(30)



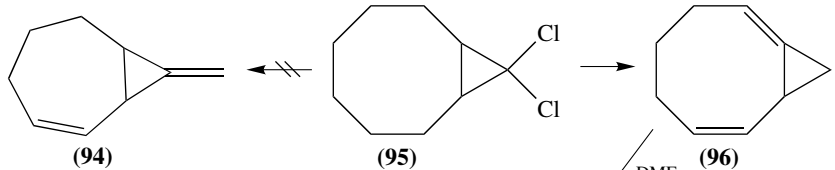
(85) **(86)** **(87)** **(88)** (31)



(89) **(90)** **(91)**

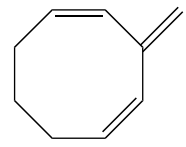


(93) **(92)** (32)

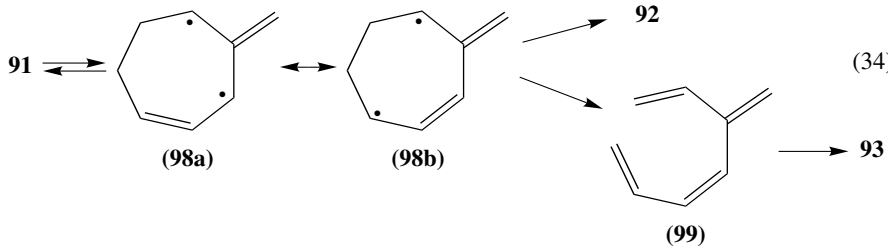


(94) **(95)** **(96)**

(33)



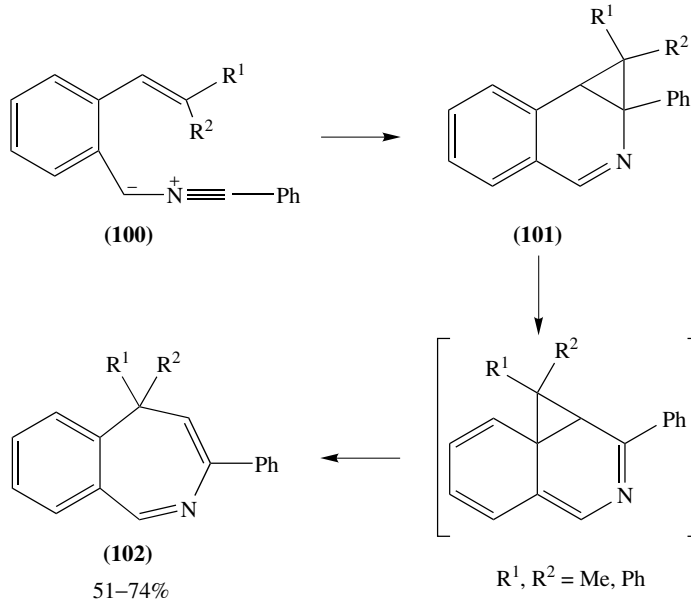
(97)



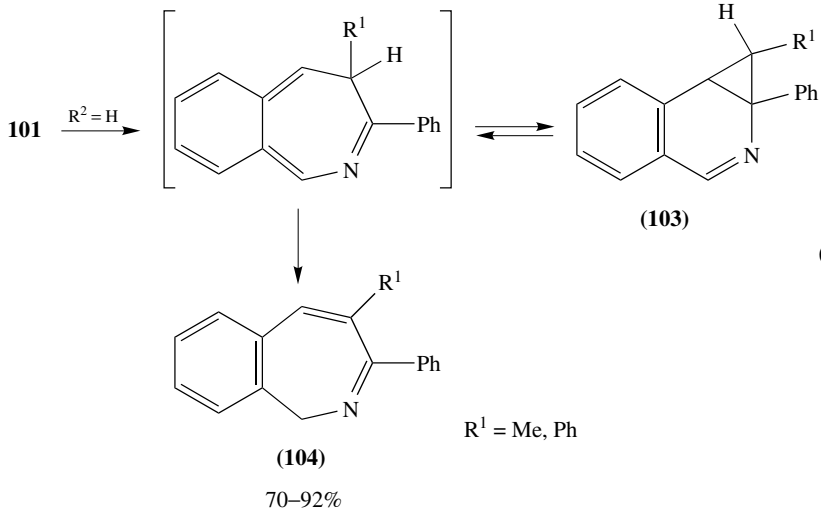
(98a) **(98b)** **(99)** (34)

The thermal rearrangements of vinylcyclopropanes to form cyclopentenes as well as 1,4-hexadienes by homodienyl [1,5]-shift are well-known[16,49–51] and even described in textbooks (see, e.g., Chapter 18 in Reference 4). However, the heteroanalogous transformations are less known.

Thus, cycloprop[*c*]isoquinolines **101** obtained by a stereospecific 1,1-cycloaddition of nitrile ylides **100** undergo two distinct thermal (80 °C) rearrangements depending on the substituents in the cyclopropane ring (equations 35 and 36)[52].



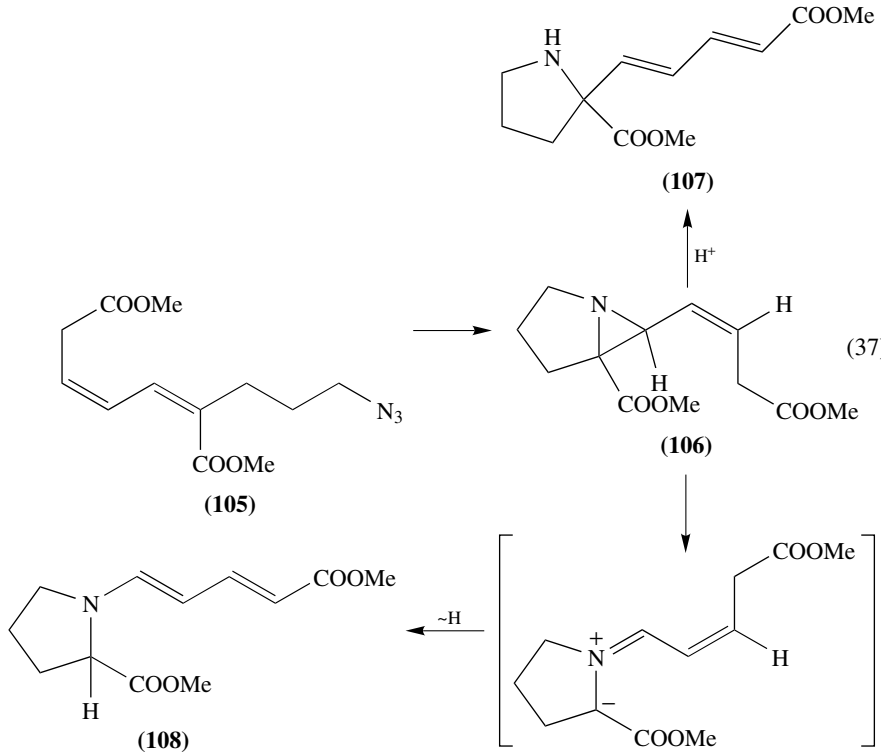
(35)



(36)

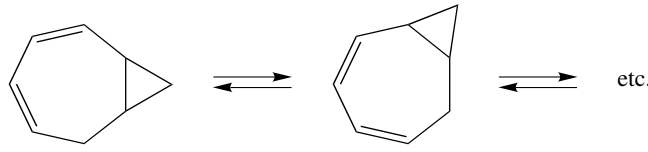
If one of the substituents R^1 or R^2 is hydrogen, then the interconversion of the *endo*- and *exo*-isomers (**101** and **103**) is accompanied by an irreversible transformation into 1*H*-2-benzazepines **104** (equation 36). Otherwise (i.e. when R^1, $R^2 \neq H$) the rearrangement of compounds **101** is slower and leads to formation of 5*H*-2-benzazepine system **102** (equation 35)[52].

Interesting rearrangements proceed upon refluxing the azido diene **105** in benzene solution and form 61% of the vinylaziridine **106** as a mixture of diastereoisomers and the vinylogous urethane **108** (28%) (equation 37)[53]. It was shown that the process **106** → **108** occurs entirely at elevated temperature (refluxing xylene, *ca* 140 °C). However, treatment of the aziridine **106** with *p*-toluenesulfonic acid in THF at room temperature gives rise to *trans,trans*-1,3-butadiene carboxylic ester **107** in 98%[53].

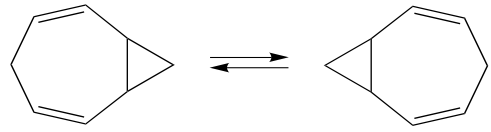


(37)

In bicyclo[5.1.0]octa-2,4-diene **109** which is quite stable at room temperature the so-called degenerate *butadienylcyclopropane rearrangement* takes place at elevated temperatures (above 110 °C), and it can be revealed by using the deuterium labels (equation 38)[54]. This transformation is interesting because the bicyclic diene **109** shows the invariable NMR spectra within the temperature range between −80 °C and +180 °C. Such unusual behavior differs from the rapid reversible Cope rearrangement of isomeric diene **110** which already proceeds at room temperature (so-called 'fluxional structure') (equation 39)[1,55]. The rearrangements of related divinylcyclopropanes as non-conjugated dienes will be considered in Section IV.C.2.d).

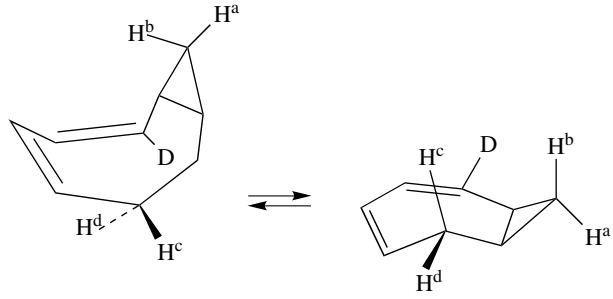


(109) (38)

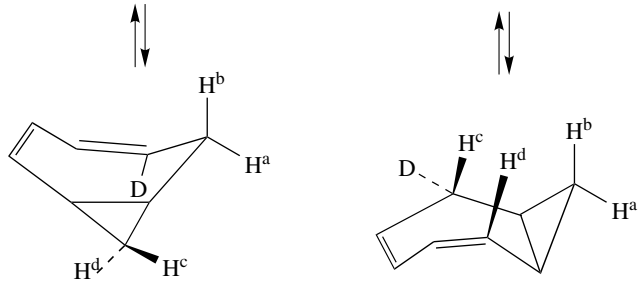


(110) (39)

It was found that heating of the deuteriated bicyclodiene **111** at 110 °C was accompanied by two competitive processes having comparable rates: (a) butadienylcyclopropane rearrangement via a transoid transition state (**111** ⇌ **113**) and (b) *endo,endo*-1,5-hydrogen shift (**112** ⇌ **114**) (equation 40)[54,56].



transoid **(111)** cisoid **(112)**

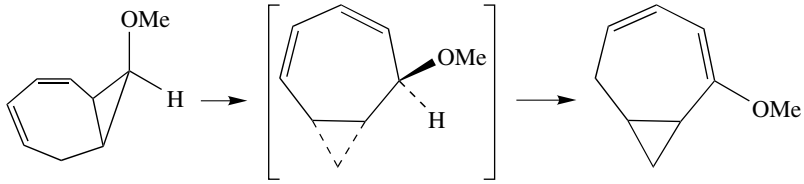


(113) **(114)** (40)

It was shown that [1,5]-hydrogen shift occurs in this case about 30 times more quickly than that in the cycloheptatriene, while the butadienylcyclopropane rearrangement proceeds 3×10^{-9} slower than the Cope rearrangement of the isomeric 2,5-diene **110**[54].

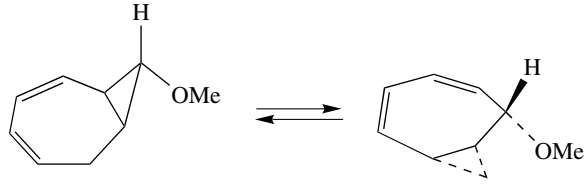
This difference in reaction rates can be attributed to different energies of corresponding transition states. According to the Woodward–Hoffmann rules[57], the Cope rearrangement is a sigmatropic [3,3]-shift (see Section IV.C.1) while the butadienylcyclopropane rearrangement can be considered as an sigmatropic antarafacial [1,5]-shift with inversion at the migrating carbon atom.

The thermolysis of the bicyclodiene **109** at 225 °C gives rise to equilibrium mixture of cyclooctatriene and its transformation products (see below)[54]. More recently the influence of a methoxy group on the thermal behavior of the bicyclo[5.1.0]octa-2,4-diene system was studied[56]. Heating of 8-*endo*-methoxydiene **115** in cyclooctane at 95 °C gaves rise to methoxy substituted diene **117** and not to the product **116** of butadienylcyclopropane rearrangement (equation 41). The thermolysis of the 8-*exo*-isomer **118** has taken place as an equilibrium reaction to give 6-*endo*-methoxy diene **119** (equation 42)[56]. These two reaction partners were separated by TLC.



(41)

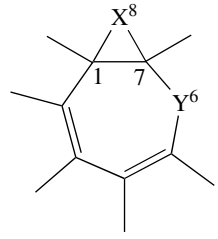
(115) **(116)** **(117)**



(42)

(118) **(119)**

Recently, molecular orbital calculations (MP2/6-31G*//RHF/6-31G* level) which cover a series of bicyclic systems from the stable bicyclic compound **109** to the unknown 6,8-dioxabicyclo[5.1.0]octa-2,4-diene (2,3-epoxyoxepin, **120**), as well as the two intermediate 8-oxa- **(121)** and 6-oxa- derivatives **(122)**, were carried out[58]. These structures are interesting because the bicycle **120** is suggested as a transient intermediate in the metabolic oxidation of benzene leading to the muconaldehyde, which is responsible for the hematotoxicity of benzene.

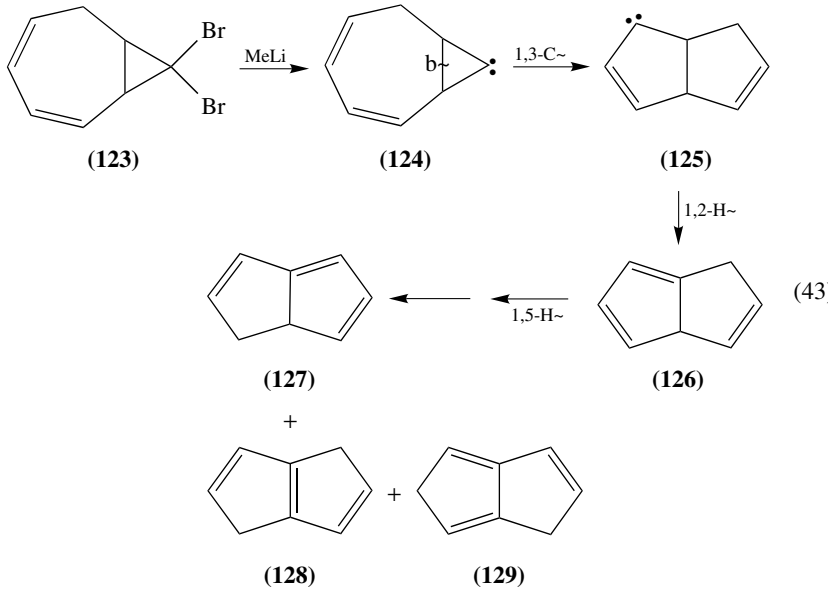


(109) $X^8 = Y^6 = CH_2$
(120) $X^8 = Y^6 = O$
(121) $X^8 = O$; $Y^6 = CH_2$
(122) $X^8 = CH_2$; $Y^6 = O$

From the calculations on **109**, **120**–**122**, as well as that of the corresponding ring fission products, the influence of oxygen substitution on some reactions such as the interconversion between cisoid and transoid bicyclic conformers, the degenerate Cope rearrangement and the 1,5-hydrogen shift, in which the overall structure is conserved, as well as the ring fission reactions in which both three-membered and the seven-membered rings are broken, was traced. It was shown that the oxygen substitution has little effect on the interconversion and the 1,5-hydrogen shift. However, the Cope rearrangement of structure **120** is much slower than that of compound **109**[58].

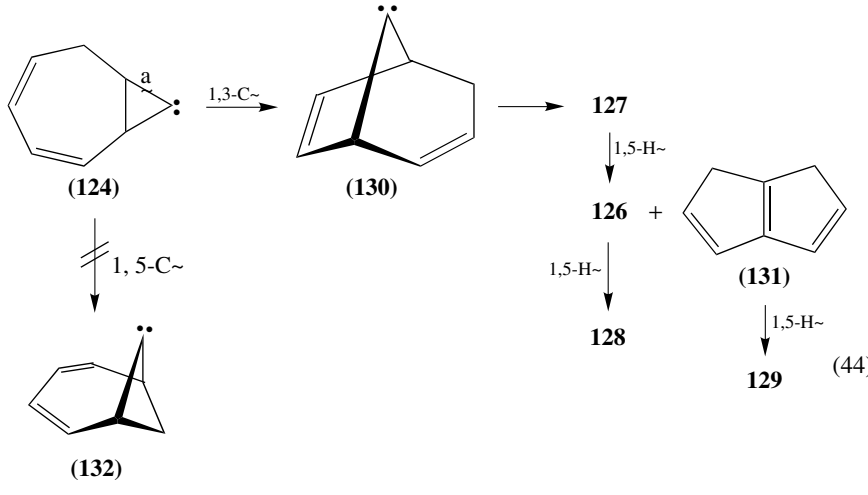
A cascade of rearrangements occurs upon interaction of methyllithium with 8,8-dibromodiene **123**. The carbenes **124** and **125** are intermediates of these reactions (so-called 'carbene–carbene rearrangements') which proceed via 1,3-C-migrations (Skattebøl rearrangement) followed by successive 1,2-H- and 1,5-H-shifts to yield dihydropentalenes **126**–**129** by cleavage of distal bond 'b' (equation 43)[59]. Another scheme suggests a different pathway for the transformation of carbene **124**, namely through a cleavage of the lateral bond 'a' and 1,3-carbon migration to furnish the 7-homonorbornadienylidene **130**. The subsequent 1,2-vinyl shift leads to the dihydropentalenes **127** which rearrange to compounds **128** and **129** via intermediates **126** and **131**, respectively (equation 44)[59]. Pathway **124** → **130** was supported by C-labelling of the starting material **123** as well as by the known reactivity of carbene **130**[59].

Since the reactive substructure of *cis*-2-(1,3-butadienyl)cyclopropylidene is contained in the bicyclic carbene **124**, there is a possibility that a carbene–carbene rearrangement occurs together with 1,5-carbon migration. Analysis of the probable reaction pathways allows one to conclude that 1,5-C-migration (**124** → **132**) in the fixed *cis*-1,3-butadienyl fragment of structure **124** is impossible. The 1,3-carbon migration (**124** → **130**) which takes place instead is mechanistically analogous to the vihylcyclopropylidene–cyclopentylidene



(123) **(124)** **(125)** **(126)** **(127)** **(128)** **(129)** (43)

rearrangement (Skattebøl reaction). Other carbene–carbene rearrangements including a participation of 'foiled methylenes'[60] are discussed elsewhere[48].



(44)

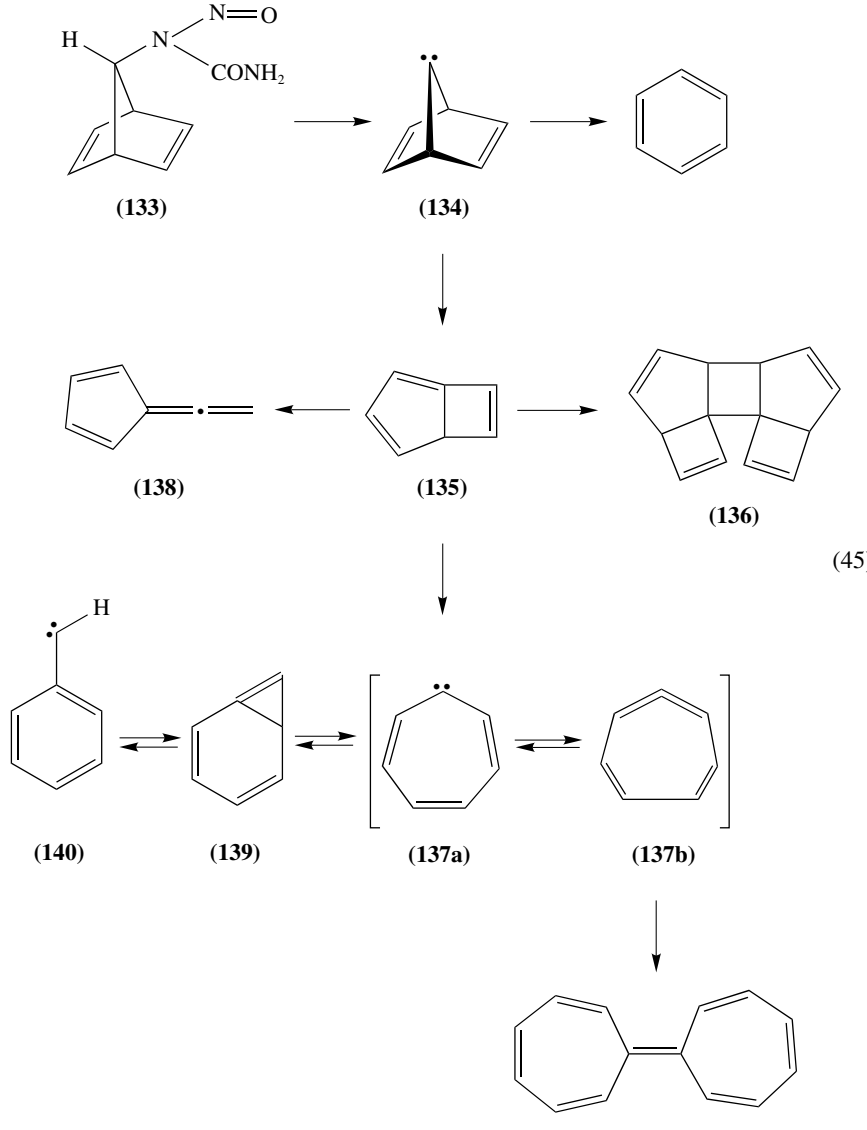
One of the principal 'foiled carbenes', i.e. 7-norbornadienylidene **134**, is described in the literature[61]. This dienyl carbene can be generated by pyrolysis (200–400 °C) of the corresponding N-nitrosourea **133** and it undergoes a series of transformations including a loss of carbon to produce benzene as well as rearrangements to bicyclo[3.2.0]heptatriene **135**. The latter either dimerizes to give the tetraene **136** or undergoes a ring opening to form cycloheptatrienylidene **(137a)** ⇌ cycloheptatetraene **137b**, or rearranges to fulvene-allene **138** (equation 45)[61].

The seven-membered ring system **137** can rearrange to bicyclo[4.1.0]heptatriene ('fused cyclopropene') **139** and benzylidene **(140)**. This rearrangement underlies the arylcarbene ring-expansion mechanism which was first proposed by Vander Stouw and colleagues in 1972 to explain the formation of styrene during thermolysis (150–350 °C) of various (2-methylphenyl)diazomethanes **141**[62]. According to this mechanism, the intermediate 2-methylbenzylidenes **142** can isomerize to give the fused cyclopropenes **143** and the corresponding 2-methylcycloheptatrienylidenes **144** which are capable of (1) undergoing a carbon–hydrogen insertion to provide fused alkylidenecyclopropanes **145** and then styrenes, and/or (2) rearranging to fused cyclopropenes **146** with subsequent isomerization into 1-phenyl-1-ethylidenes **147** and then to styrenes (equation 46). A possible alternative is a direct conversion of the cyclopropenes **143** to **146**, followed by styrene formation.

The above transformations are very important from the point of view of industrial technology for high temperature cracking of alkylaromatics and therefore are of great interest for basic science. Thus, the reported interconversion between benzylcarbenes (e.g. **142** and **147**) and cycloheptatrienylidenes (e.g. **144**)[63] can occur via the intermediate bicyclo[4.1.0]heptatrienes (**143** and **146**). This work[63] contains also a brief survey of related publications. It should be noted that its authors utilize a dehydrogenation method rather than thermolysis because the former is an attractive route due to the possibility of preparing the target bicycloheptatrienes as their ground states at or below room temperature in solution and without any excited states.

It was found that the treatment of compound **148** with *t*-BuOK in THF gave the starting material (39%) and *tert*-butyl ethers **149** and **150** (in 43% combined yield) in a ratio 3 : 2 (equation 47)[63].

Another paper[64], which also contains a literature survey about the problem discussed, describes the rearrangements of C_7H_6 systems which can be generated by thermolysis of phenyldiazomethane. By using spectral methods and chemical reactions, the formation of bicyclo[4.1.0]hepta-2,4,6-triene **(139)**, cycloheptatrienylidene **(137a)** and bicyclo[3.2.0] hepta-1,3,6-triene **(135)** was excluded, and evidence for the formation of intermediate cycloheptatetraene **(137b)** (see equation 45) was furnished.



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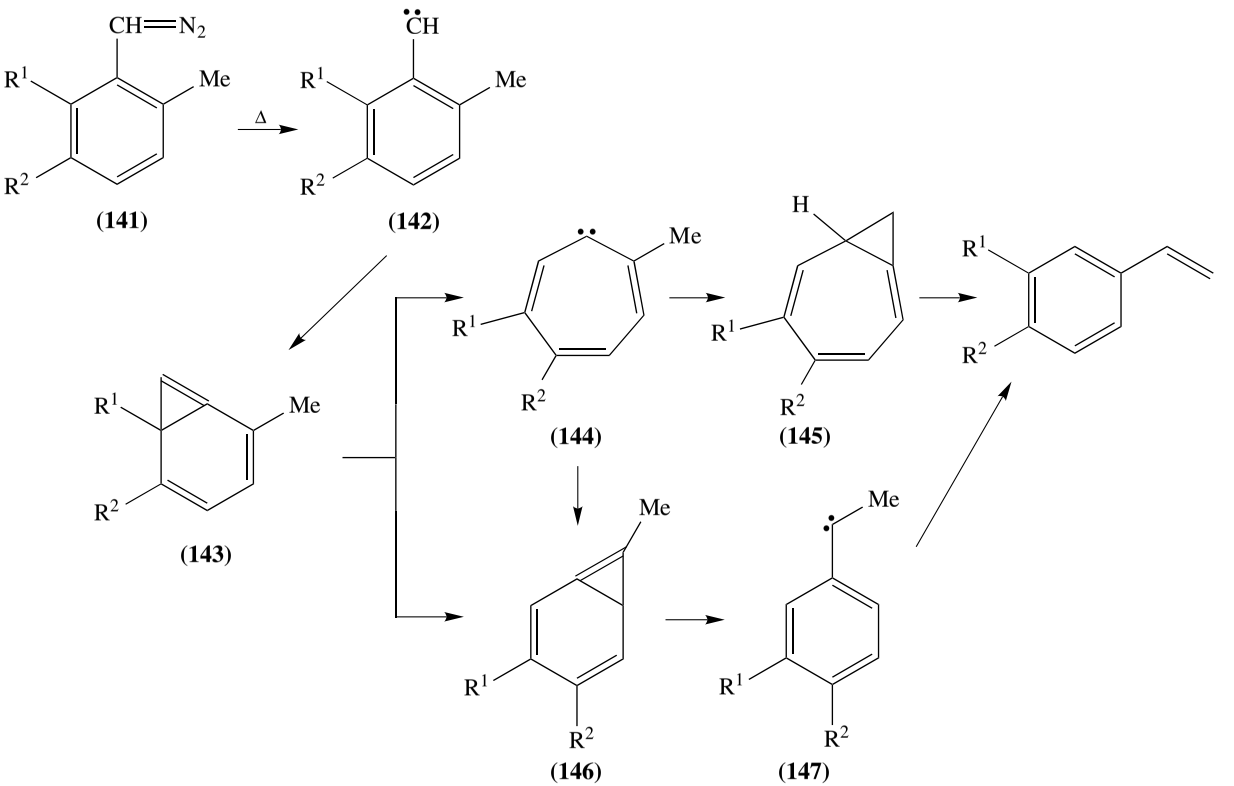

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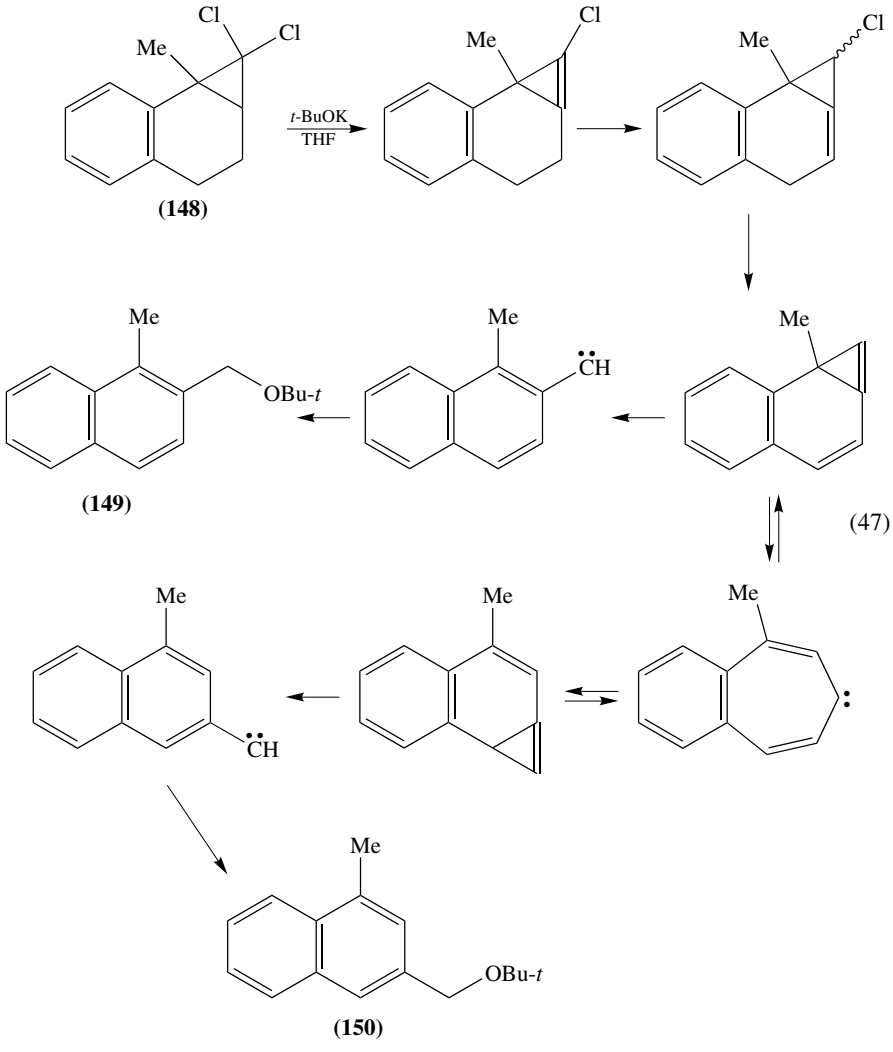


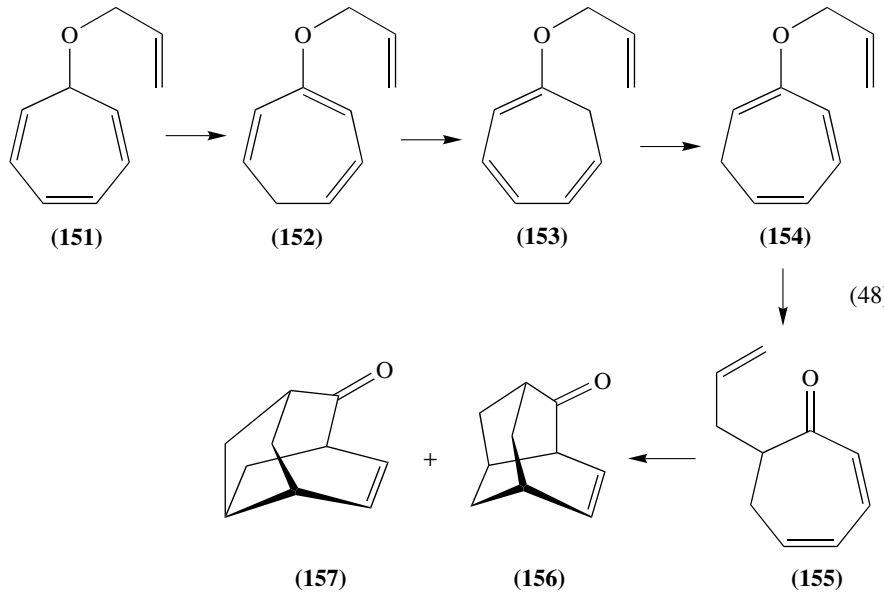
(47)

B. Cyclic Polyenes

1. Cycloheptatrienes

For cycloheptatriene and a series of its derivatives various thermal unimolecular processes, namely conformational ring inversions, valence tautomerism, [1,5]-hydrogen and [1,5]-carbon shifts, are known. An example of such multiple transformations was described[65] which can provide a facile approach to new polycyclic structures by a one-step effective synthesis (yields up to 83%) of the two unique ketones **156** and **157**. The thermolysis of the neat ether **151** at 200 °C for 24 h gives initially the isomeric allyl vinyl

ethers **152–154** by successive [1,5]-hydride shifts, and subsequent Claisen rearrangement (see Section IV.E.1) provides the allyl cycloheptadienone **155** which easily undergoes an intramolecular Diels–Alder reaction to afford a 50 : 50 mixture of the two isomeric ketones **156** and **157** (equation 48)[65].

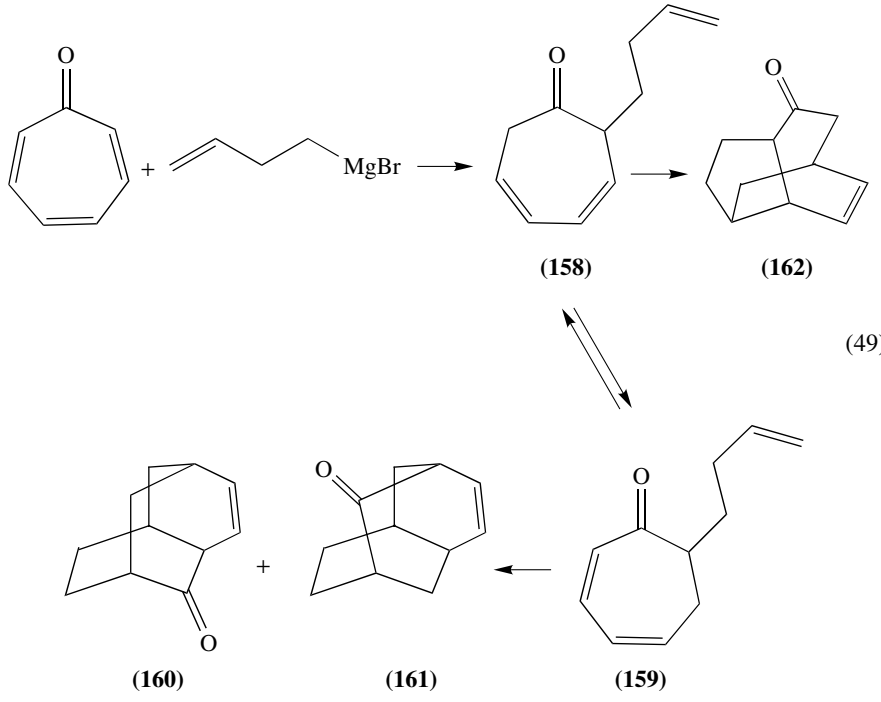


These transformations were applied to develop a new promising method for synthesis of various bridged polycyclic systems[66], viz. ketones **160** and **161.** Tropone reacts with butenyl magnesium bromide (−78 °C, 75%) to form a mixture of 2-(3-butenyl)dihydrotropones **158** and **159**, the pyrolysis of which (200–210 °C, neat or in heptane solution) leads to 60% total yield of the isomeric homoprotoadamantenones **160** and **161** and the tricyclic ketone **162** in a ratio of 58 : 18 : 24, respectively (equation 49)[66].

Similar results were obtained for the synthesis of azapolycycles having relatively rigid skeletal frameworks. Thus, refluxing of *N*-substituted *N*-allylamines **163** under conditions of high dilution in xylene gave the cycloadducts **164** in 67% yield along with the products of hydrogen shift **165** and **166** (equation 50)[67].

A novel thermal rearrangement with loss of sulfur dioxide leading to the stilbene or styrene derivatives **169** and **170** in highly stereospecific manner was carried out by heating (in dioxane, DMSO, dioxane–water or THF) the sulfene-tropone adducts (γ-sultones) **167** or **168** (equations 51 and 52)[68].

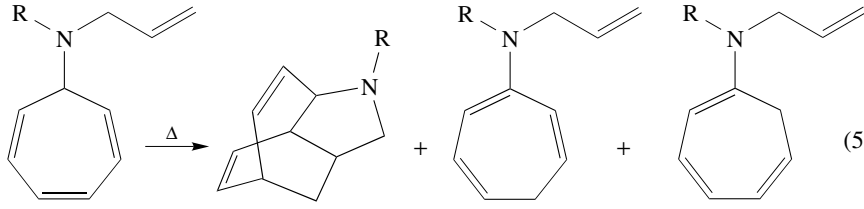
It is worthwhile mentioning here that the thermal hydrogen shifts can occur not only in the cyclic seven-membered substrates but also in open-chain systems. For example, the antarafacial thermal [1,7]-sigmatropic hydrogen shift in epimeric *cis*-isotachysterol analogues **171** and **172** which give **173** and **174** was reported (equations 53 and 54)[69]. This work was carried out in order to investigate the reactions of parent previtamin D_3 to afford vitamin D_3. However, it should be noted that an analogous example was already known for a long time (see e.g. Chapter 7 in Reference 5).



(49)

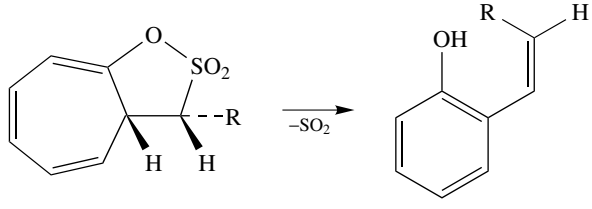
2. Cyclooctatrienes

The reversible rearrangement of 1,3,5-cyclooctatriene **175** into bicyclo[4.2.0]octa-2,4-diene **176** was first postulated[70] and then corroborated[71] by Cope and coworkers almost 50 years ago. These authors[71] and their followers[72] have shown that isomers **175** and **176** can be separated and both undergo interconversion to the same equilibrium mixture of 85% **175** and 15% **176** by a short-term heating at 80–100 °C (equation 55). This equilibrium system was later investigated intensively, including the finding of the conditions of the photochemical transformations[72]. However, from the synthetic standpoint the system consisting of the fused cyclooctatriene and cyclopropane rings is apparently the most interesting. An initial short communication about the behavior of such systems was published in 1961[73]. The norcaradiene vinylogue, *cis*-bicyclo[6.1.0]nona-2,4,6-triene **177**, as well as some of its derivatives were obtained by addition of carbenes to the cyclooctatetraene. It was shown that the bicyclic triene **177** is thermally labile and rearranges easily already at 90 °C without any catalyst to the indene derivative **178** (equation 56)[73]. The dihalocarbene adducts **179** in which the halogen atoms show no solvolytic activity rearrange almost quantitatively at 80–90 °C to afford the indene derivatives **181**. The location of the halogen atoms in the products **181** allows one to exclude the possibility that the bicyclic compounds **179** rearrange via the cyclononatetraene intermediate **182**. Instead, the tricyclic structures **180** are assumed to be the most probable intermediates in this process (equation 56)[73].

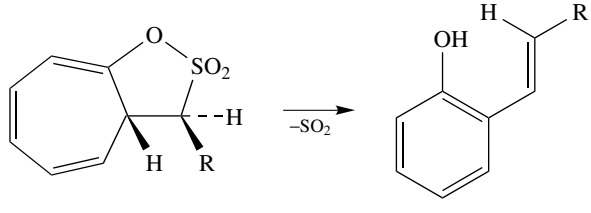


(163) (164) (165) (166) (50)

R = COOEt, COOBu, COMe, COPh

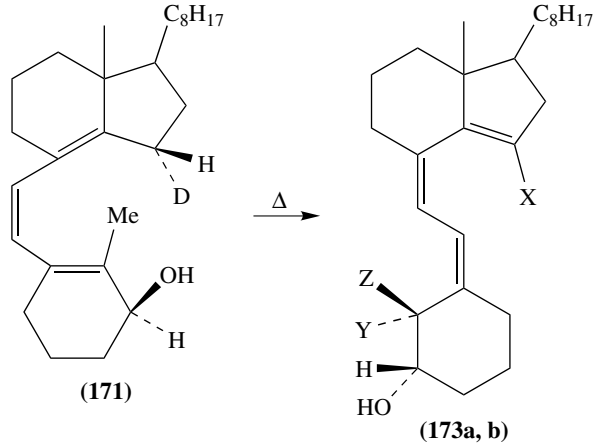


(167) (169) (51)

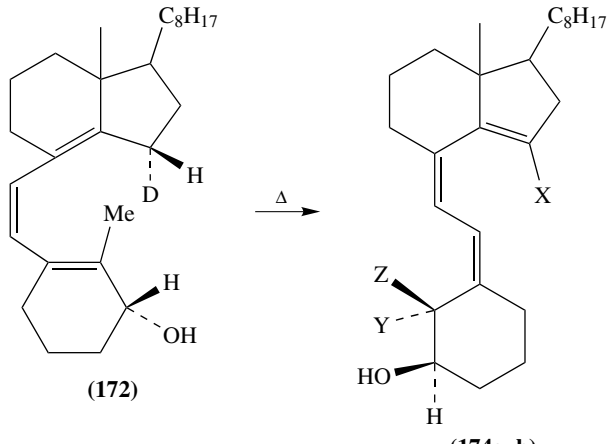


(168) (170) (52)

R = Ph, Ar, PhCO, CN, SO_2Me, $CH{=}CH_2$ (90 °C, 6–10 h, 40–95%)



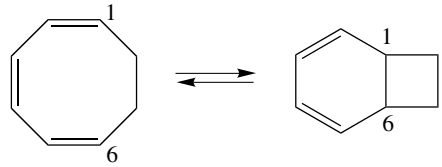
(171) (173a, b) (53)



(54)

(172) **(174a, b)**

(173a, 174a) X = D, Y = Me, Z = H
(173b, 174b) X = H, Y = D, Z = Me



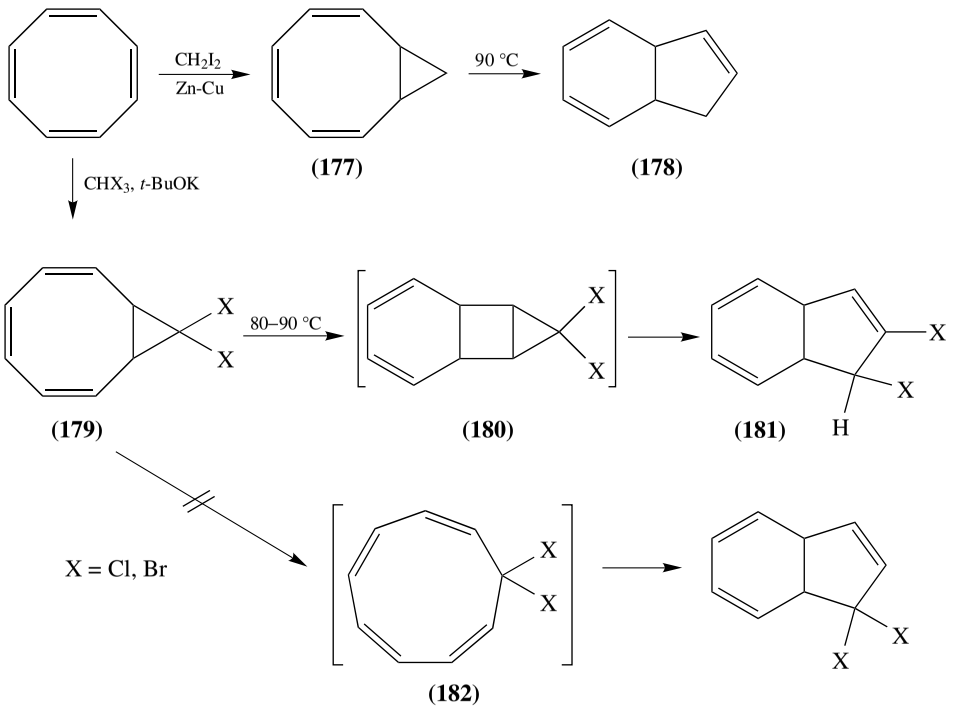
(55)

(175) **(176)**

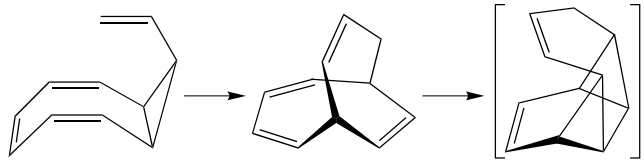
It was shown[74] that the folded conformation of bicyclic substrates is a prerequisite for isomerizations such as **177** → **178**. Thus, *syn*-9-vinyl triene **183**, being in the open conformation, undergoes an unusual Cope rearrangement to give the intermediate **184** which starts a cascade of thermal isomerizations at 60–65 °C (equation 57) whereas the *anti*-9-vinyl epimer **185** rearranges into the indene derivative **186** at 110 °C in benzene solution (equation 58)[74].

Further, the thermal decomposition of the dry sodium or lithium salt of the tosylhydrazone **187** gives a complex mixture of products **189**–**195**[75] (equation 59). The authors suggest that the cyclooctatetraene **189** can be formed via two-bond cleavage reaction of **188** typical for cyclopropylcarbenes. The *trans*-9,10-dihydronaphthalene **192** is most likely the rearrangement product of the intermediate **196** which occurs via cyclodecapentaene **197** (equation 60). The formation of *cis*-9,10-dihydronaphthalene **194** and *cis*-1-phenylbutadiene **190** provides mechanistic mysteries, although two-step reactions leading to them can be imagined (equation 61).

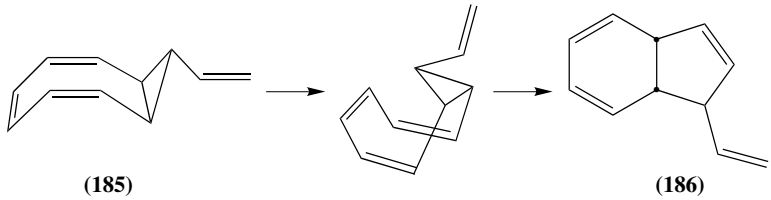
The formation of the bridged product **191** was investigated using the cyclopentadiene system as a model. Thus, the salt of the tosylhydrazone **198** was prepared and thermolyzed in order to examine three possible variants of rearrangements (equation 62)[75]. Analysis of the reaction products **200**–**202** and their transformations [e.g. the pyrolysis of bicyclic triene **202** to *cis*-8,9-dihydroindene **203** (equation 63) rather than to product **200** or **201**] allows one to conclude that the mechanism involves a transformation of carbene **188** into diradical **204** which can be the precursor of all the products observed (equation 64)[75]. An analogous conversion takes place via radical **205** in the case of carbene **199** (equation 65).


CH2I2
Zn-Cu
90 °C
CHX3, t-BuOK
(177)
(178)
X
X
80–90 °C
X
X
X
X
H
(179)
(180)
(181)
X = Cl, Br
X
X
X
X
(182)

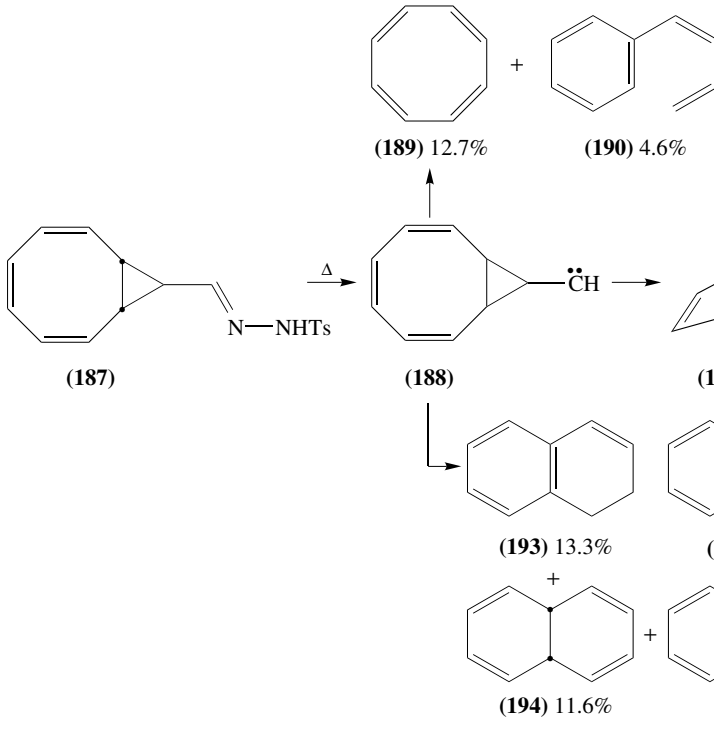
(56)



(183) **(184)** (57)



(185) **(186)** (58)

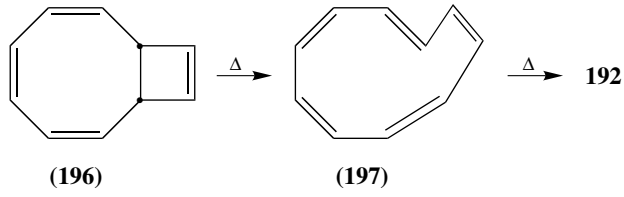


(189) 12.7% **(190)** 4.6%

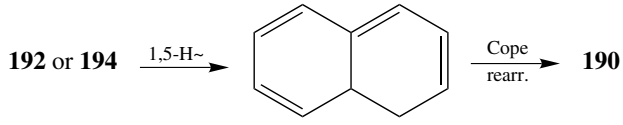
(187) **(188)** **(191)** 37.8% (59)

(193) 13.3% **(192)** 20%

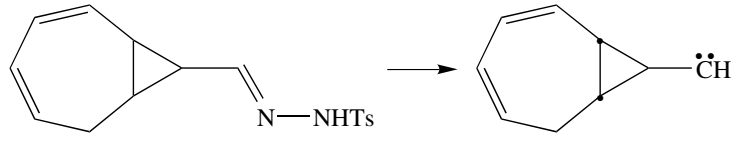
(194) 11.6% **(195)**



(196) (197) (60)

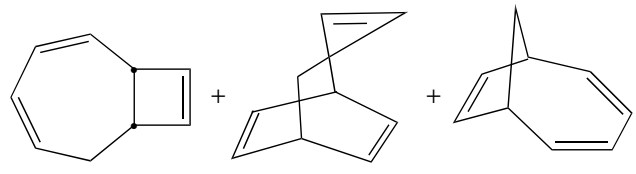


(61)

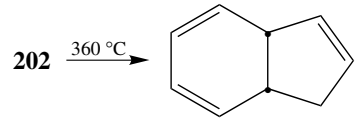


(198) (199)

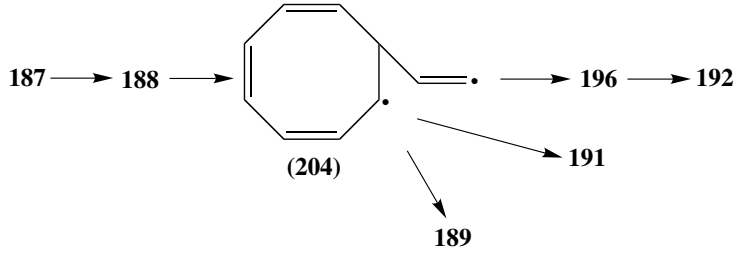
(62)



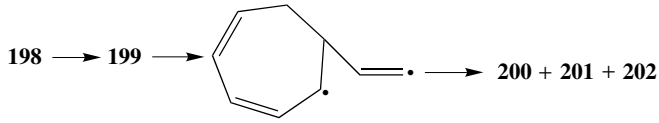
(202) 27% (201) 12% (200) 37%



(203) (63)

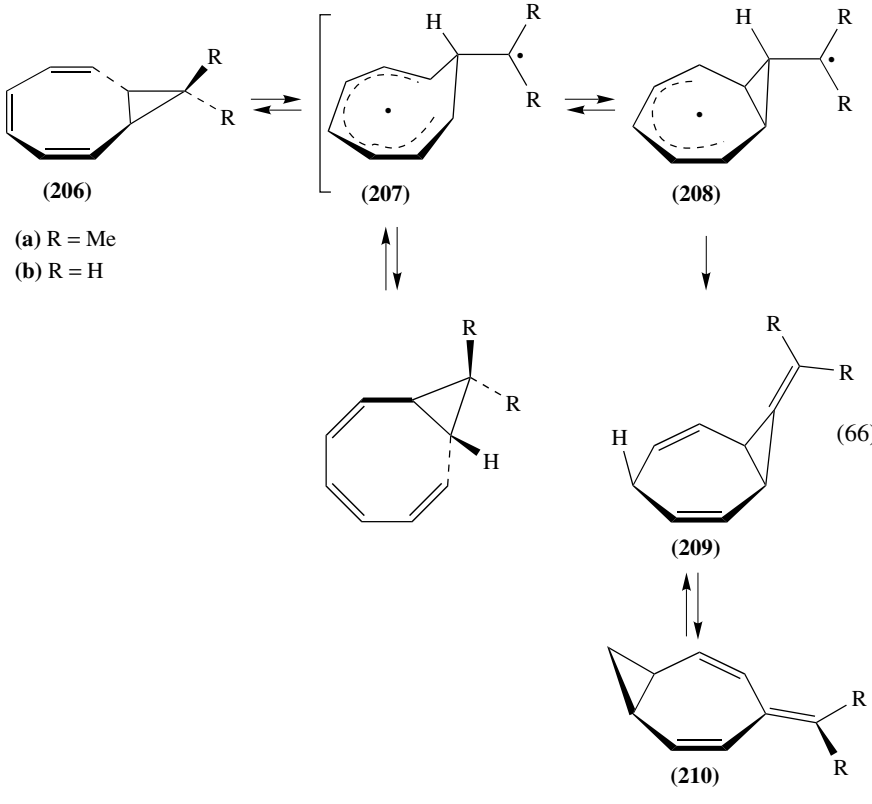


(204) (64)



(205) (65)

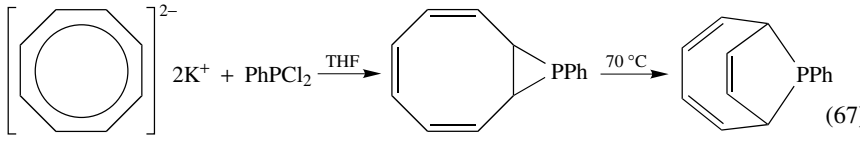
It should be noted that, in contrast to well-known *cis*-bicyclo[6.1.0]nonatrienes, the thermal behavior of *trans*-bicyclo[6.1.0]nonatrienes has been insufficiently explored[76–78]. It was found that the thermolysis of *trans*-nonatriene **206a** and the parent compound **206b** occurs surprisingly easily to form the previously unknown 3,4-homoheptafulvene system **210**. Using an optically active compound **206a**, a degenerate cyclopropane-walk-rearrangement which precedes the structural isomerization was detected. In both processess the diradical *exo*-**207** was considered to be a possible intermediate (equation 66)[77]. The thermolysis of triene **206a** (180 °C, degassed benzene, 3 h, conversion 100%) and **206b** (200 °C, degassed toluene, 10 min, 90% conversion) gives in every case only the sole product **210a** or **210b**. Compounds **210a** and **210b** are very sensitive to air and prone to undergo polymerization. The probable mechanism for process **206** → **210**



(66)

includes a cleavage of distal bond in cyclopropane ring of **206** to give the diradical intermediate **207**, which undergoes an electrocyclic ring closure to form the diradical **208**. A subsequent hydrogen shift leads to the homotropylidene **209** which relieves the excessive internal strain by a rapid Cope rearrangement into the homoheptafulvene **210**.

Interesting transformations in which the phosphorus analogues of bicyclo[6.1.0]nona-2,4,6-triene undergo various rearrangements were reported. Thus, dipotassium cyclooctatetraenide reacts with dichlorophenylphosphine in THF to give an adduct **211** which isomerizes upon heating to bicyclic triene **212** (equation 67)[79]. The same approach was utilized to prepare the bridged phosphonium barbaralanes **215a** ⇌ **215b** which are degenerate Cope systems (equation 68)[80] (see also Section IV.C.2.d). The alkylation of the 9-phospha derivatives **213** with trialkyloxonium salts leads to products **215**, presumably via the intermediate phosphonium salts **214** which undergo a disrotatory ring opening, followed by successive conversions of cationic bicyclic ylides. The P-barbaralane **215** demonstrates the rapid degenerate Cope rearrangement above 25 °C which can be frozen below −72 °C[80].



(67)

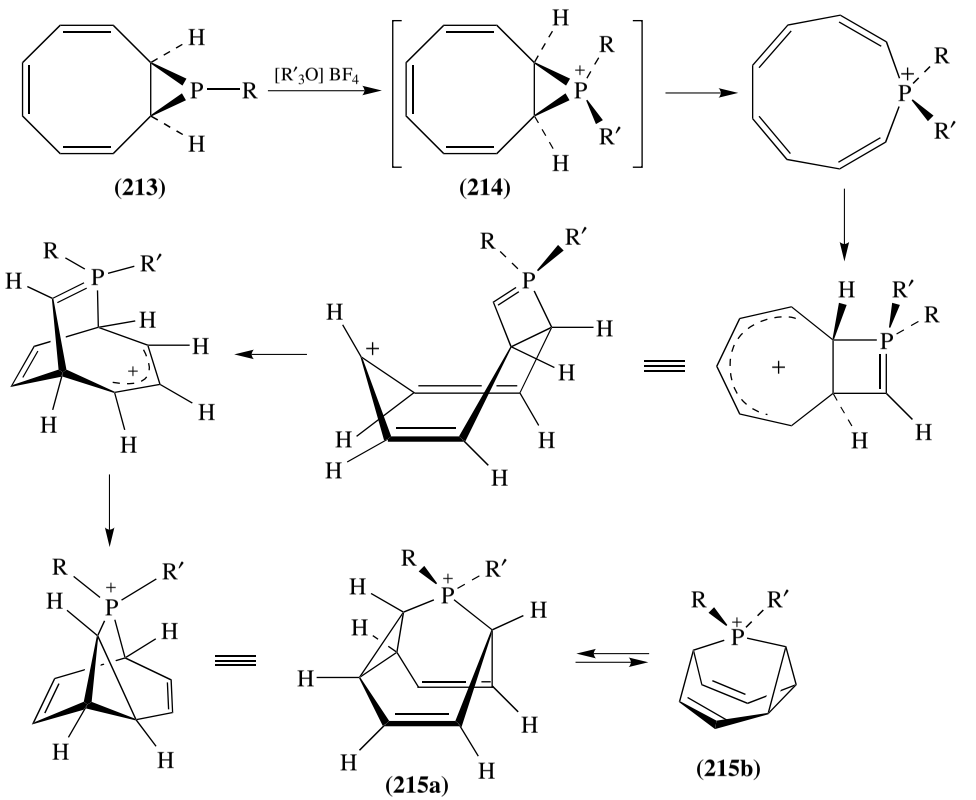
(211) **(212)**

The reaction of phenyllithium with the bridged phosphine oxide **216** gives the rearrangement product **217** in 60% yield (equation 69)[81]. The behavior of the heterocyclic system **218** toward oxidizing reagents and a new pathway for its skeletal rearrangement were described[82]. Treatment of compounds **218** with hydrogen peroxide or *tert*-butyl hydroperoxide at −15 °C leads to a cleavage of the C−C bond of the three-membered ring to form the relatively instable phosphonin ring system **219**. When the latter was warmed to 25 °C it was completely rearranged to dihydrophosphindole **220** (equation 70)[82].

3. Cyclooctatetraenes

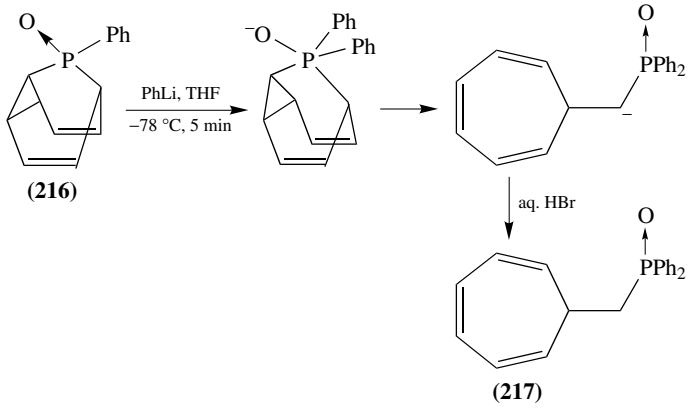
The numerous transformations of cyclooctatetraene **189** and its derivatives include three types of structural changes, viz. ring inversion, bond shift and valence isomerizations (for reviews, see References 83–85). One of the major transformations is the interconversion of the cyclooctatetraene and bicyclo[4.2.0]octa-2,4,7-triene. However, the rearrangement of cyclooctatetraene into the semibullvalene system is little known. For example, the thermolysis of 1,2,3,4-tetra(trifluoromethyl)cyclooctatetraene **221** in pentane solution at 170–180 °C for 6 days gave three isomers which were separated by preparative GLC. They were identified as 1,2,7,8-tetrakis(trifluoromethyl)bicyclo[4.2.0]octa-2,4,7-triene **222** and tetrakis(trifluoromethyl)semibullvalenes **223** and **224** (equation 71)[86]. It was shown that a thermal equilibrium exists between the precursor **221** and its bond-shift isomer **225** which undergoes a rapid cyclization to form the triene **222**. The cyclooctatetraenes **221** and **225** are in equilibrium with diene **223**, followed by irreversible rearrangement to the most stable isomer **224** (equation 72)[86].

The interaction of cyclooctatetraene as a dienophile with the diazadiene, 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **226**, is accompanied by nitrogen elimination and gives rise to the 1,1-adduct **227**. The latter displays interesting thermal rearrangements depending on the solvent polarity and temperature (equation 73)[87]. In toluene solution a [1,3]-carbon

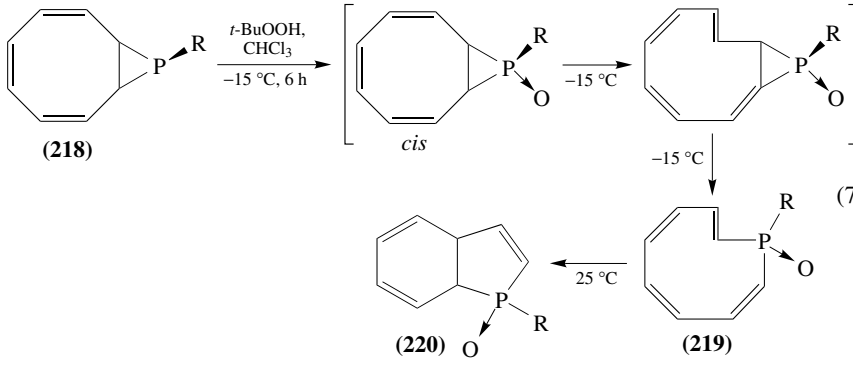


R = Me, *t*-Bu, CH_2Ph, Ph; R′ = Me, Et

(68)

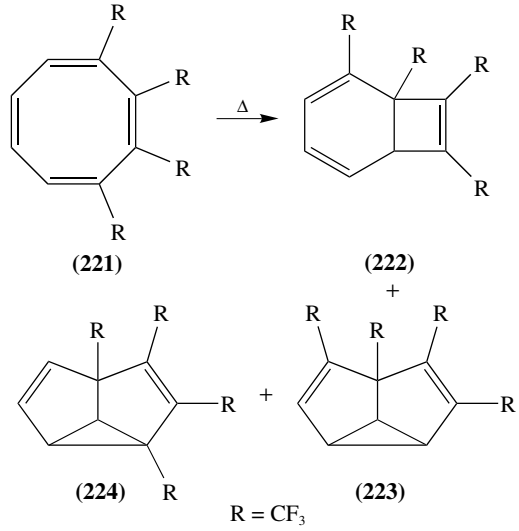


(216) **(217)** (69)



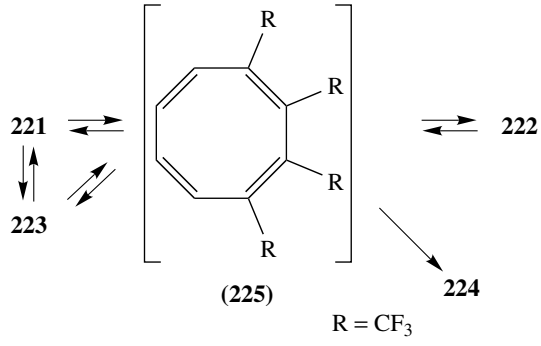
(218) **(220)** **(219)** (70)

R = *t*-Bu, Ph

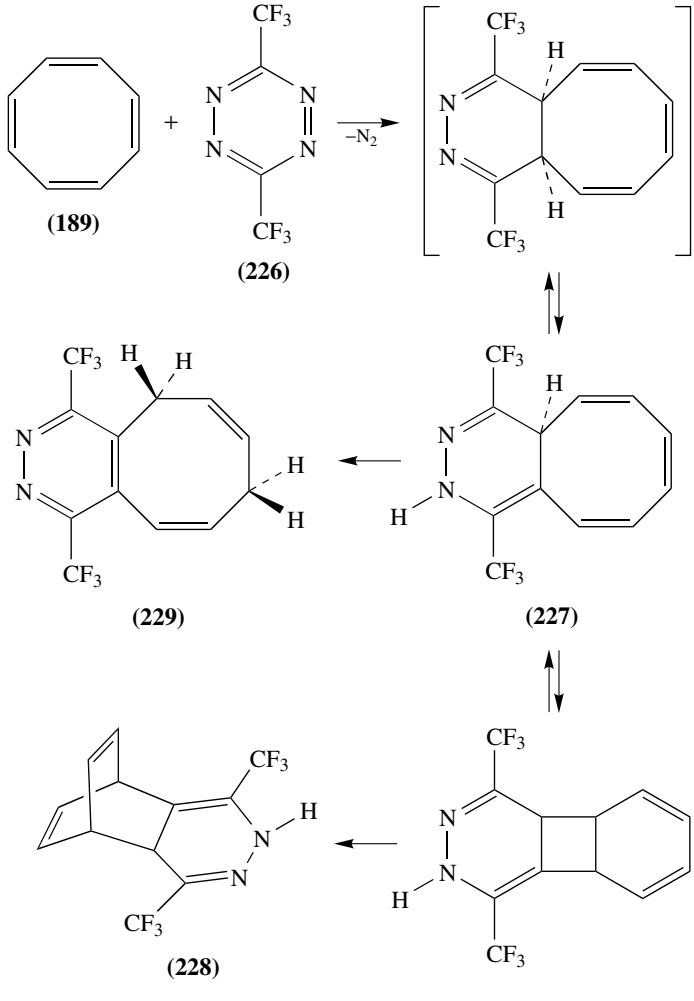


(221) **(222)** **(224)** **(223)** (71)

$R = CF_3$


R
R
R
R
221
222
223
(225)
224
R = CF3

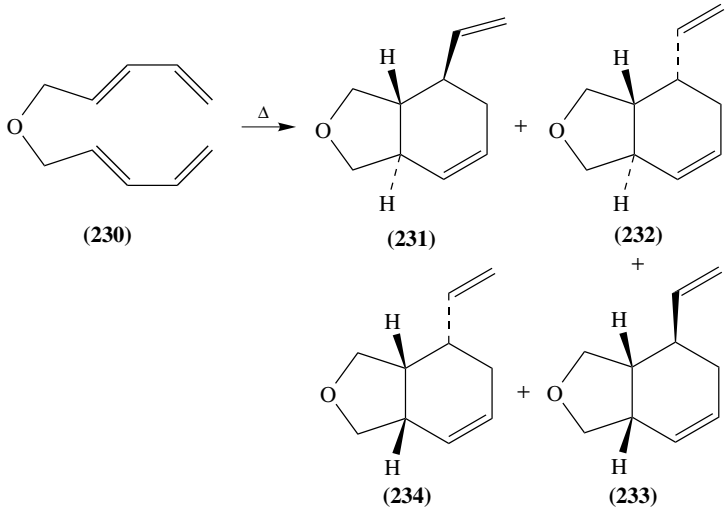
(72)


CF3
N
N
N
N
CF3
(189)
(226)
–N2
H
H
(227)
(229)
(228)

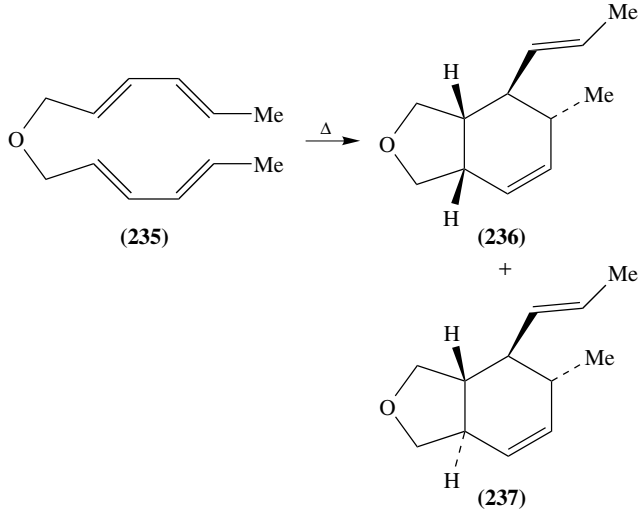
(73)

migration occurs at 111 °C (10 h) to afford the barreleno[*d*]pyridazine **228** while the isomer of **228**, i.e. the dihydrocyclooctapyridazine **229**, is formed in the more polar nitromethane (2 days at 90 ± 2 °C). Presumably, **229** is more stable than **228** and it originates from the adduct **227** via proton-shift tautomerism and [1,5]-sigmatropic hydrogen shift. No equilibrium between compounds **228** and **229** via intermediate **227** was observed[87].

In connection with the behavior of the eight-membered ring system, it is interesting to mention that the uncatalyzed thermolysis of the open-chain tetraene ether **230** in toluene at 150 °C (11 h) gives rise to a mixture of four intramolecular Diels–Alder products **231–234** in 80% total yield (equation 74)[88]. The thermolysis of dimethyl homologue **235** (toluene, 150 °C, 11 h, 81%) affords the *cis*-fused cyclohexene derivative **236** and

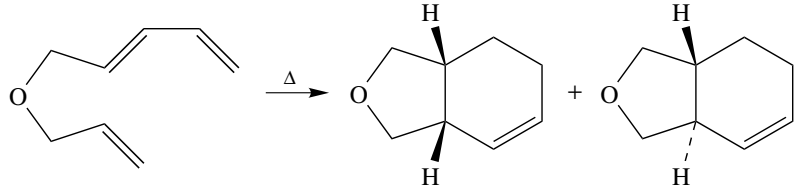


(74)



(75)

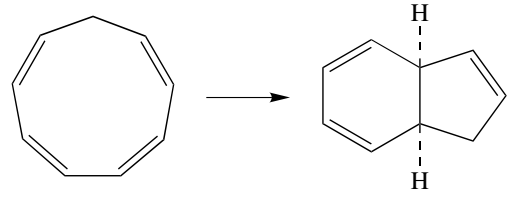
the *trans*-fused isomer **237** in a 1 : 4 ratio (equation 75)[88]. The thermolysis of the triene ether **238** (150 °C, 5 h, 45%) results in a mixture of *cis*- and *trans*-fused isomers **239** and **240** in a 3 : 1 ratio (equation 76)[88]. It should be noted that these cyclizations rank with the Cope rearrangements of divinylcyclobutanes (see Section IV.C.2.c).



(76)

(238) **(239)** **(240)**

The tetra-*cis*-cyclononatetraene **241** is unstable and easily rearranges at 23 °C ($t_{1/2}$ ~ 50 min) to the isomeric *cis*-8,9-dihydroindene **242** (equation 77)[89]. It is interesting, however, that the iron(III) tricarbonyl complex of tetraene **241** is stable for many days at room temperature and isomerizes to the Fe-complex of **242** only upon heating in octane at 101 °C[89]. The principle of stabilization of the reactive multiple bonds with metal carbonyl complexes is well-known in modern organic synthesis (e.g. see the acylation of enynes[90]).

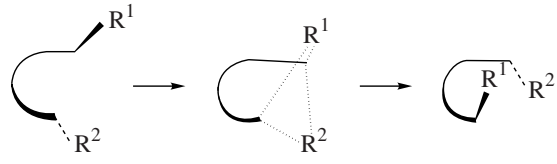


(77)

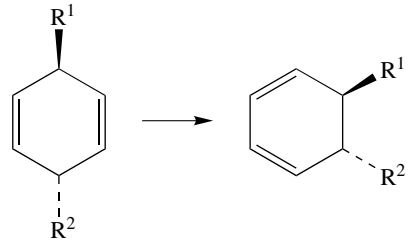
(241) **(242)**

4. Dyotropic rearrangements

Dyotropic rearrangements are uncatalyzed concerted dihydrogen exchange reactions, another class of orbital symmetry controlled processes, which involve the simultaneous migration of two σ-bonds. These conversions can be both thermal and photochemical. They can be subdivided into two types: (1) reactions in which two migrating σ-bonds interchange their positions (equation 78), and (2) reactions without such positional interchange (equation 79)[91,92].

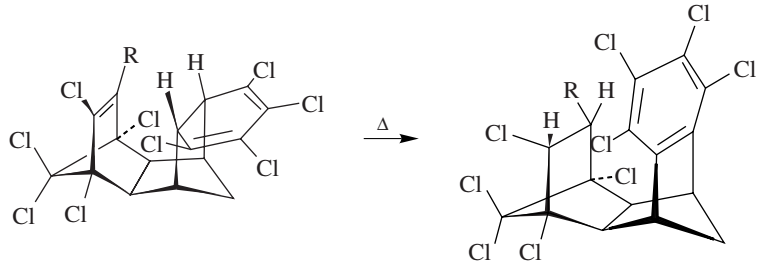


(78)



(79)

The discovery of a new reaction, the transannular dihydrogen transfer, was reported in 1965[93]. Mackenzie found that the polychloro-*endo,endo,exo*-1,4 : 5,8-dimethanooctahydroanthracenes **243**, having an isodrine carbon framework (isodrine is the *endo,endo*-isomer of aldrin, the known insecticide HHND), rearrange smoothly to form the isomers **244** (equation 80). This exothermic reaction proceeds when pure crystalline compounds **243** undergo heating and melting near 180 °C. The isomerization of **243** also occurs at much lower temperature (110 °C) in solution. No effect of catalysts such as boron trifluoride, palladium on carbon or chloranil was observed, i.e. this reaction is purely intramolecular. The author has already noted in this paper[93] that the reaction is probably assisted by the energy released on aromatization of the dienes-containing ring, together with some reduction in the overall steric strain in the system due to aromatization of the six-membered ring and saturation of the C1C=CR bridge.



(80)

(243) **(244)**

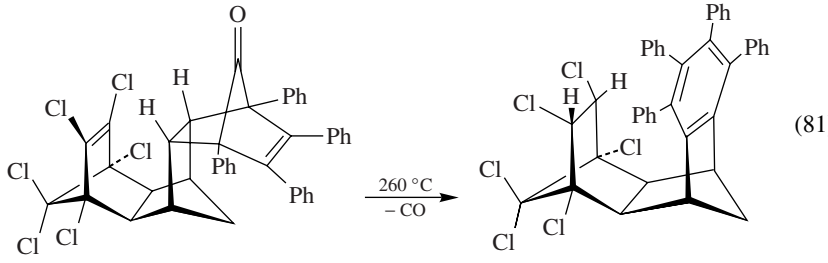
R = Cl, OEt, OMe

The reaction was investigated later in more detail[94–97]. It was suggested that these isomerizations are almost certainly concerted sigmatropic rearrangements. However, independent of their mechanism these reactions can be considered as disproportionations in which at least one fragment achieves a high degree of stabilization. Further examples of this rearrangement include polycarbocyclic as well as heterocyclic derivatives (equations 81–83)[95,96].

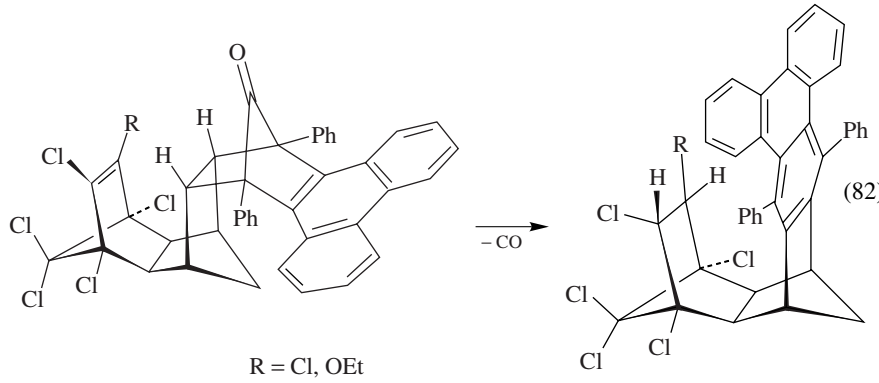
The methods for synthesis of starting cyclic dienes, the rearrangement conditions and kinetic characteristics of basic substrate reactions over a wide range of substitution variations were generalized in work[97] which included a quite detailed survey of related publications.

Furthermore, a brief review of dyotropic rearrangements starting with the hypothetical transformations of 1,2-disubstituted cyclobutenes was published[98] in which two types of these processes were described and a general theory covering such rearrangements was outlined. Quantum chemical calculations of the reaction barrier for the dihydrogen

exchange reaction between ethane and ethylene were discussed[99] (see also the diimide reduction of olefins[100]).

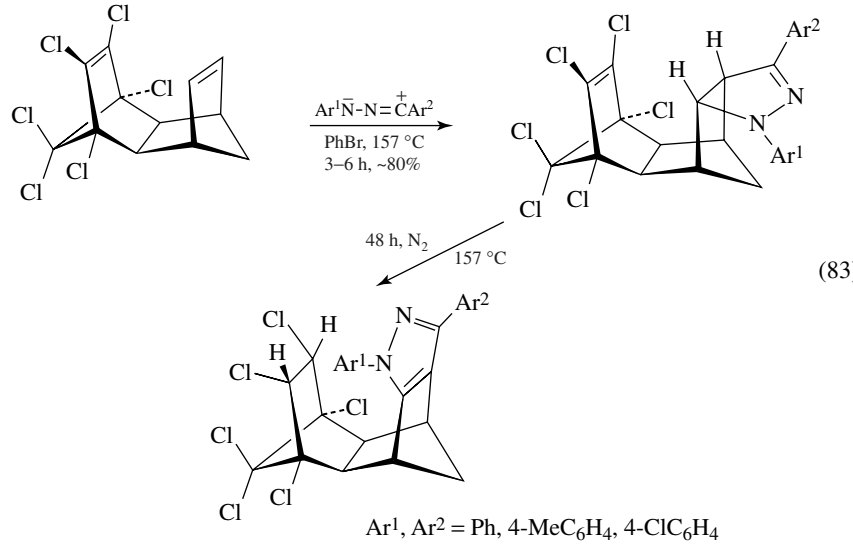


(81)



(82)

R = Cl, OEt

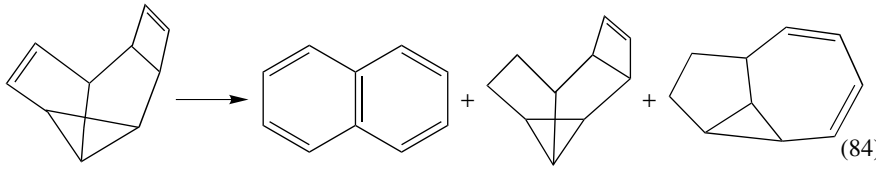


(83)

Ar[1], Ar[2] = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$

The isodrine framework was used for synthesis of 'pagodane' in which one of the key steps is Mackenzie's transannular dyotropic hydrogen transfer[101]. Also, a 'very intriguing'

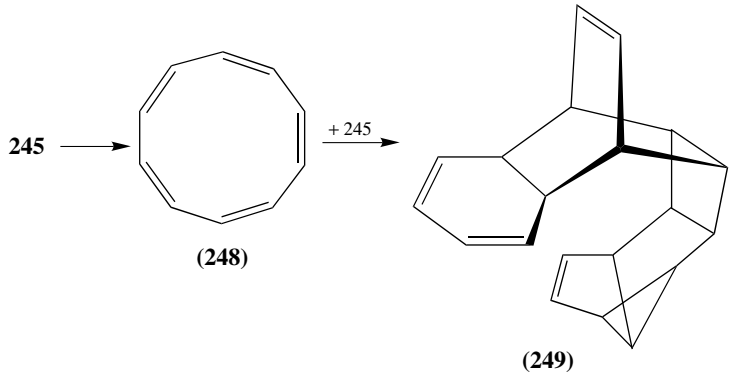
process was found upon thermal decomposition of the tetracyclic diene **245**[102]. When **245** is heated at 200 °C in cyclohexane solution, it undergoes a rapid ($t_{1/2} \sim 1$ h) thermal disproportionation to afford naphthalene (43%) and the two new hydrocarbons **246** and **247** whose ratio depends upon the extent of decomposition (equation 84). Rate studies indicated that compound **246** can be thermally rearranged into **247**. At 230 °C only the latter could be isolated.



(84)

(245) **(246)** **(247)**

Using deuterium labelling it was shown that the isotope atoms lost from precursor **245** in the formation of naphthalene are almost exactly those picked up by a second molecule **245** which gives the olefin **246**. No reorganization of the carbon framework takes place. The transfer of two hydrogen or deuterium atoms with high degree of specificity can include an initial addition of the presumable intermediate **248** to diene **245** to form a transient cage species such as **249**, which can subsequently split into $C_{10}H_8$ and $C_{10}H_{12}$ moieties (equation 85). This scheme can account for the preferential hydrogenation of the double bond in the cyclopentene ring rather than of the cyclobutene ring within structure **245**[102].



(85)

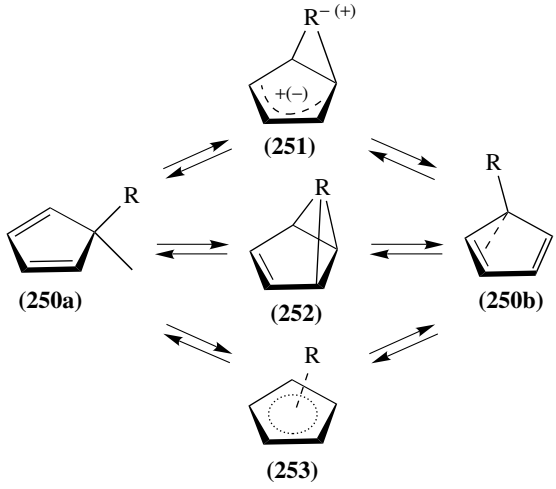
(248) **(249)**

C. Circumambulatory Rearrangements

The discovery in 1956 of the ability of certain organometallic groups to migrate along the cyclopentadiene ring perimeter[103] stimulated the development of the fundamental concept of fluctuating molecular systems (called also 'structurally non-rigid system')[3]. More recently it was shown that migrating moieties having a Main Group (III–VI) central atom are also capable of a fast, intramolecular sigmatropic shift around a cyclopentadiene ring which can be detected by using NMR spectroscopy[9,104,105]. At present the processes of dynamic sigmatropic rearrangements (named also 'circumambulatory' as well as 'merry-go-round', 'ring walk', 'ring runner' and 'ring whizzer', but more generally 'fluxional'

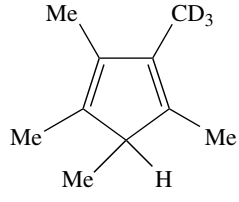
or 'degenerate' rearrangements) involve already the elements of all the groups (except Group VIII) of the periodic system.

The general picture of intramolecular migrations of substituents R in the cyclopentadiene ring (equation 86) covers the intermediates or transition states of η^2-type (1,2- or 1,5-shift) **(251)**, η^3-type (1,3-shift) **(252)** and η^5-type (randomization because of the formation of a π-complex or ion-pair structure) **(253)**. Furthermore, other possible routes are a randomization with formation of tight or solvent-separated ion pairs (e.g. in the case of arylazo groups) and radical pairs as well as intermolecular mechanisms. The experimental determination of the specific rearrangement mechanism is usually based on line-shape analysis of the temperature-dependent NMR spectra of the rearranging compound. Since a number of extensive reviews[106–109] about walk rearrangements are available, we will consider only briefly the information concerning walk rearrangements recently obtained.

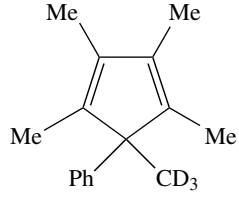


(86)

Degenerate sigmatropic rearrangement of 1,2,3,4,5-pentamethylcyclopentadiene (here and below designated as PMCPD) involving a migration of hydrogen was investigated using the dynamic NMR (DNMR) technique on system **254**[110]. The activation energy was estimated to be 106.8 ± 1.25 kJ mol^{-1} (for comparison, the activation energy for Si-migrants is 54.9 to 64 kJ mol^{-1}) (for reviews, see Reference 108).



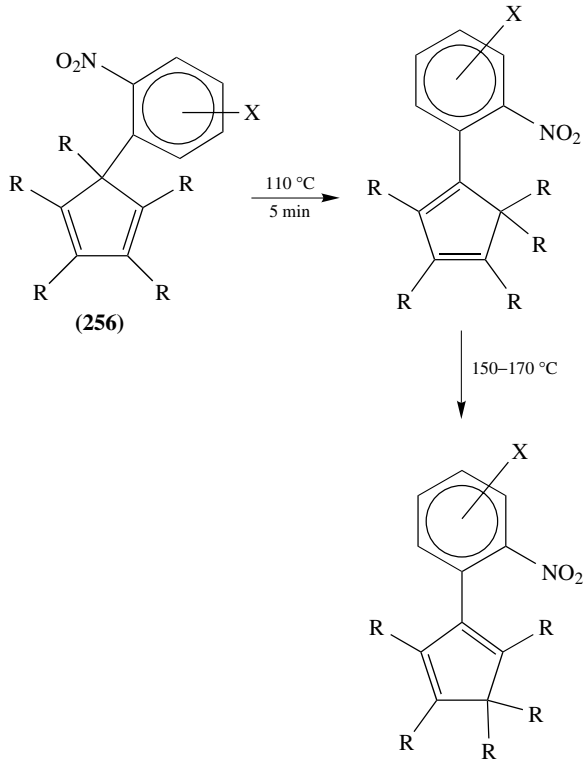
(254)



(255)

The carbonotropic migrations include a number of various migrants. A migration of phenyl group in system **255** was shown[111] to involve a [1,5] migration mechanism with an activation energy of 154.9 ± 1.25 kJ mol^{-1}. However, a migration of the

methoxycarbonyl group with $\Delta G^{\neq}_{298} \sim 109-126$ kJ mol^{-1} was observed in the system **256** (equation 87)[112,113]. The [1,5]-sigmatropic formyl migration in the 5-formyl-PMCPD system occurs rapidly at 25 °C with $\Delta G^{\neq}_{298} = 61.9$ kJ mol^{-1} [114].



(87)

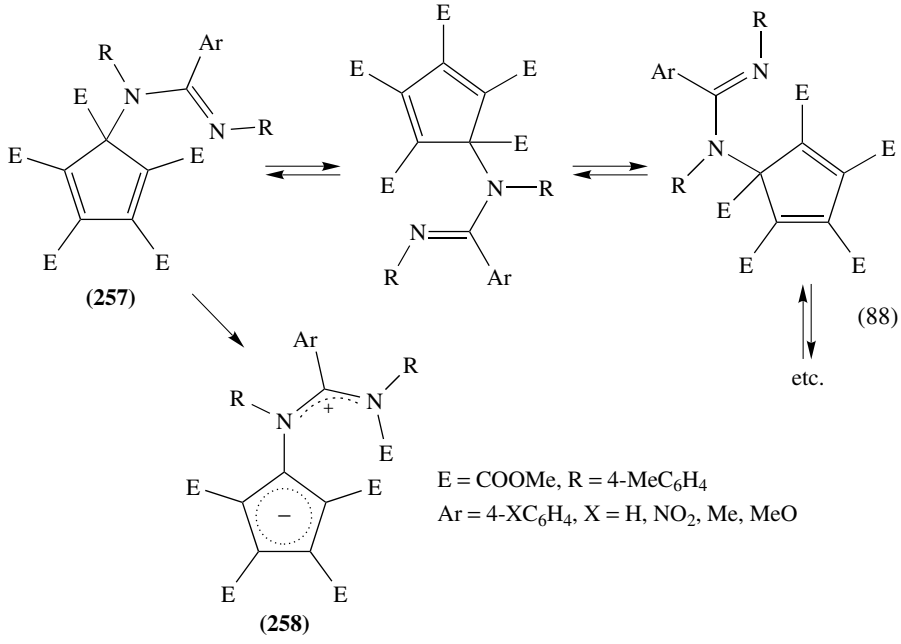
R = COOMe X = H, 4-NO_2, 6-NO_2

It is considered that [1,5] alkyl shifts usually require temperatures above 330 °C and proceed with free energies of activation greater than 180 kJ mol^{-1}. The 1,5-migratory aptitude of the formyl group is comparable with that of a trimethylsilyl group. However, 5-acetyl- and 5-ethoxycarbonyl-PMCPDs under the same conditions show a temperature-invariant ^{1}H NMR spectra, i.e. the migratory aptitude decreases in order CHO $\gg$ COMe $\sim$ COOMe[114].

It was found that the migratory aptitude of an acyl group can be increased by the introduction of strong σ-acceptor substituents. Fairly rapid [1,5]-sigmatropic migrations of trihaloacetyl groups (CF_3CO, $\Delta G^{\neq}_{298} = 86.1$ kJ mol^{-1}; CCl_3CO, $\Delta G^{\neq}_{298} = 103.3$ kJ mol^{-1}) were observed in systems 5-CX_3CO-PMCPD (X = F, Cl) using DNMR[115].

Fivefold degenerate reversible [3,3]-sigmatropic shifts were first reported in 1988[116,117] in the CPD-amidine system **257**, where $\Delta G^{\neq}_{298} = 117$ to 120 kJ mol^{-1} (equation 88) (for aza-Cope rearrangements see Section IV.E.2). In addition, a slow accumulation of a colored by-product was observed at elevated temperatures. This was identified as a product of a novel intramolecular carbon to nitrogen 1,4-shift of the methoxycarbonyl

group to give the N-ylides **258** (equation 88)[118]. The reaction proceeds upon heating *o*-dichlorobenzene solutions of benzamidines **257** at 120–140 °C for 0.5–1 h.

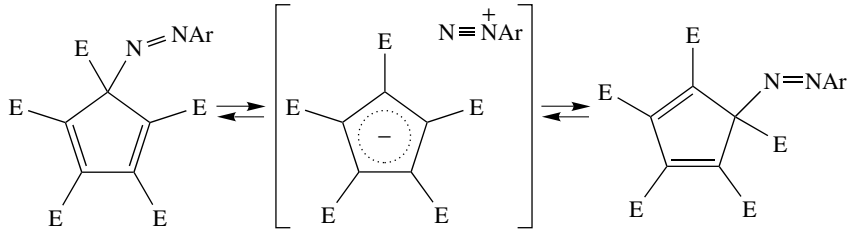


Migrations of arylazo groups were first detected in the 1,2,3,4,5-penta(methoxycarbonyl) cyclopentadiene **259** (equation 89)[119–122]. The randomization mechanism was considered as most probable because the reaction rate increases with increase in the solvent polarity ($\Delta G^{\neq}_{298} = 56.9$ to 69.1 kJ mol^{-1}).

The migrations of nitro group were ascribed to [1,5]-sigmatropic shifts [in Ph_2O or $(CD_3)_2SO$ solutions at 172 °C, $\Delta G^{\neq} = 105.6 \pm 0.4$ kJ mol^{-1}] in 5-nitro-PMCPD system **260** (degenerate rearrangement)[123] as well as in 5-nitro-5-methyl-1,2,3,4-tetra(methoxycarbonyl) CPD **261** (**261a** + **261b**)[124] and 5-nitro-5-alkyl-1,2,3,4-tetra(methoxycarbonyl) CPD **262** (**262a** + **262b**)[125]. A **261a** ⇌ **261b** equilibrium (in a ratio 0.85 : 0.15) is established within 20 min at 80 °C in chlorobenzene solution ($\Delta G^{\neq}_{298} \sim 109$ kJ mol^{-1}).

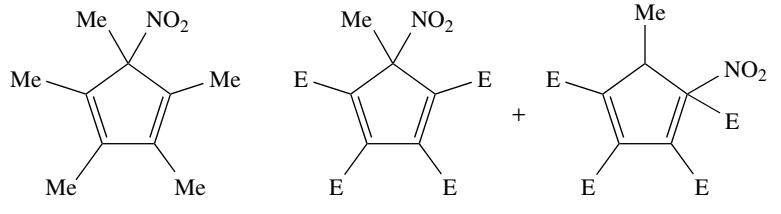
The reversible non-degenerate migrations of aryloxy and aroyloxy groups were studied by using pentaphenyl-substituted cyclopentadiene systems **263** and **265** (equations 90 and 91)[126,127]. The transition states **(264)** are assumed to be η^2-dipolar structures according to MINDO/3 calculations[126]. The conversion **265** ⇌ **266** most probably proceeds via a [3,3]-sigmatropic shift, i.e. via Cope rearrangement. Analogous [3,3]-sigmatropic shifts were found in the 5-(4-methylphenyl)-5-acyloxy-1,2,3,4-tetraphenyl CPD ($\Delta G^{\neq}_{298} = 109–146$ kJ mol^{-1}) (**265**, $R^2 = CF_3$, CCl_3, $CHCl_2$, CH_2Cl, CH_3)[128]. The above-mentioned migrations of amidinyl and acyloxy groups were generalized[129].

Degenerate migrations of PhSe and PhS groups ($\Delta G^{\neq} = 84.6 \pm 0.4$ and 102 ± 0.4 kJ mol^{-1}, respectively) were observed in PMCPD systems[130–135]. The authors suggest a mechanism of PhSe and PhS migrations similar to that for ArO migrations, i.e. via dipolar η^2-states, while the dithioacyloxy groups [−SC(S)R] are assumed to migrate analogously



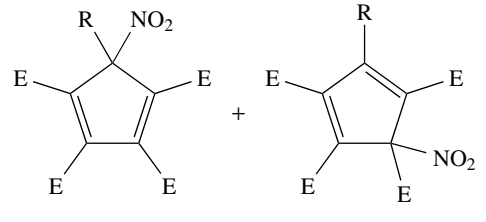
(259)

E = COOMe, Ar = 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$, 2,6-$(NO_2)_2C_6H_3$, 2,4,6-$(NO_2)_3C_6H_2$



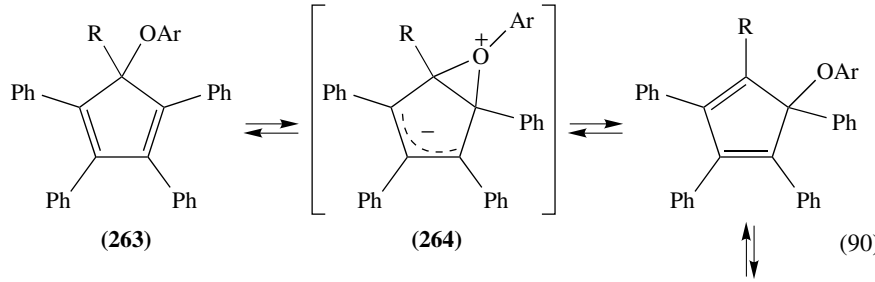
(89)

(260) **(261a)** **(261b)**



(262a) **(262b)**

E = COOMe; R = Me, *i*-Pr, CH_2COOMe, CH_2COMe



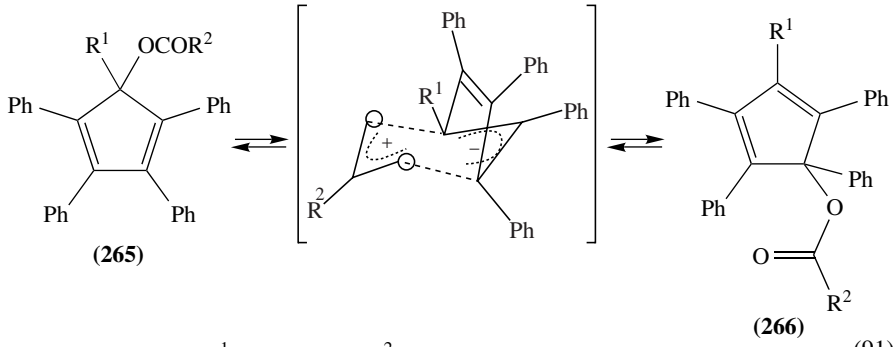
(263) **(264)**

(90)

R = XC_6H_4, X = H, Me, NH_2, MeO, Cl, NO_2

$\Delta G^{\neq}_{453}$ = 99–110 kJ mol^{-1}

to acyloxy groups (with an energy barrier of 100–125 kJ mol^{-1})[136]. The synthesis and rearrangements of 5-(1,2,3,4,5-pentaphenylcyclopentadienyl)isoselenocyanate were recently reported[137].



R^1 = 4-MeC_6H_4, R^2 = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

$\Delta G^{\neq}_{298}$ = 114–136 kJ mol^{-1} (91)

Using quantum-chemical calculations (MINDO/3, MNDO) the migrations of SH and OH groups in the cyclopentadiene system were discussed[138]. The calculations have confirmed a preference for 1,2-shift with η^2-structure of the transition state.

The [1,5]-sigmatropic shifts of chlorine and bromine atoms were investigated in the CPD system[109,139]. The comparison of migrations of N-centered (NCS) and S-centered [SPh, SC(OEt)=S] groups in the corresponding derivatives of cyclopentadiene, 1,2,3-triphenylcyclopropene and cycloheptatriene was carried out by using the dynamic ^{1}H and ^{13}C NMR spectroscopy[140]. The migrations of the phenylthio group around a perimeter of the cycloheptatriene ring proceed by a 1,2-shift mechanism (see also References 141 and 142). The 1,3-shift ([3,3]-sigmatropic migration) of azide group in the cycloheptatriene system was observed in liquid SO_2 solutions by using DNMR and is dependent on the solvent polarity[143].

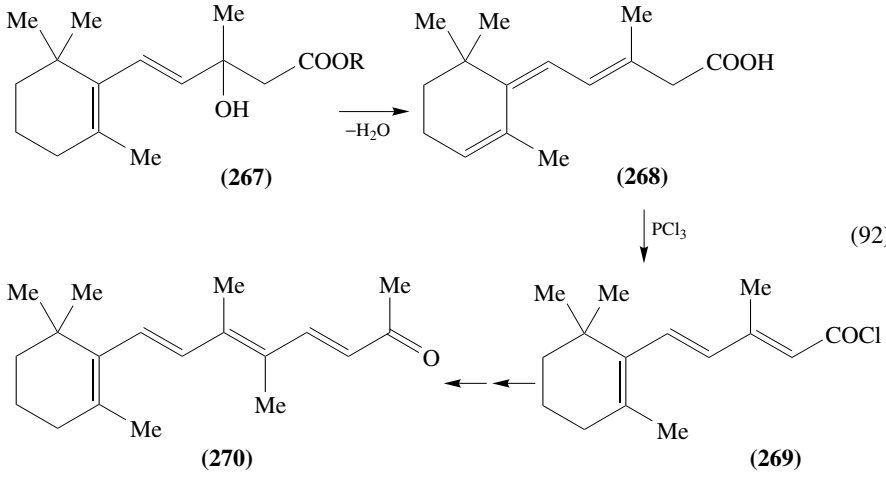
Finally, theoretical studies of haptotropic rearrangements of polyene-ML_n complexes were reported together with detailed literature surveys[144,145].

D. Retroionylidene Rearrangement

The transformations of compounds which are precursors for vitamin A and carotenoids have a special position among the rearrangements of the conjugated polyenes. Numerous isomerizations such as *cis–trans*-isomerization, the dehydration of polyunsaturated acetylenic carbinols etc. were utilized to prepare the various carotenoides (e.g. β-carotene, lycopene, cryptoxanthin, zeaxanthin) (for reviews, see References 146 and 147). However, one of these rearrangements turned out to be a considerable hindrance for the synthesis of target products.

It was found that the simultaneous dehydration and saponification of the hydroxy ester **267** used for synthesis of the β-carotene precursor, ketone C_{18} **(270)**, was accompanied by a very facile allylic rearrangement which gave rise to the C_{15} acid **(268)** having, however, a different arrangement of double bonds than that in β-ionone[146,148]. It was shown that treatment of acid **268** with the specially purified phosphorus trichloride results

in another isomerization (in 99% yield) which affords acid chloride **269** having a 'normal' arrangement of double bonds[148] (equation 92).



Oroshnik and coworkers have described the dehydration of the substituted β-ionol **271** which gave the retrovitamin A methyl ether **272** as a major product together with a very small amount of the target vitamin A methyl ether **273** (equation 93)[149,150]. They have discussed the possible mechanism of this reaction which was called the 'retroionylidene rearrangement'. It was proposed to call the products of this rearrangement 'retroionylidene compounds'.

It was shown by many examples[146] that the majority of methods used for synthesis of vitamin A gave rise to biologically inactive or little active products owing to this retroionylidene rearrangement. This reaction proceeds when the starting compound contains a side chain which is fully conjugated with a double bond in a six-membered ring (e.g. equations 92 and 93). Such reactions are usually the dehydrations of carbinols by using acids, iodine, phenyl isocyanate etc. Therefore, the first really successful industrial synthesis of vitamin A which was developed includes the intermediate **274** incapable of undergoing the retroionylidene rearrangement[146].

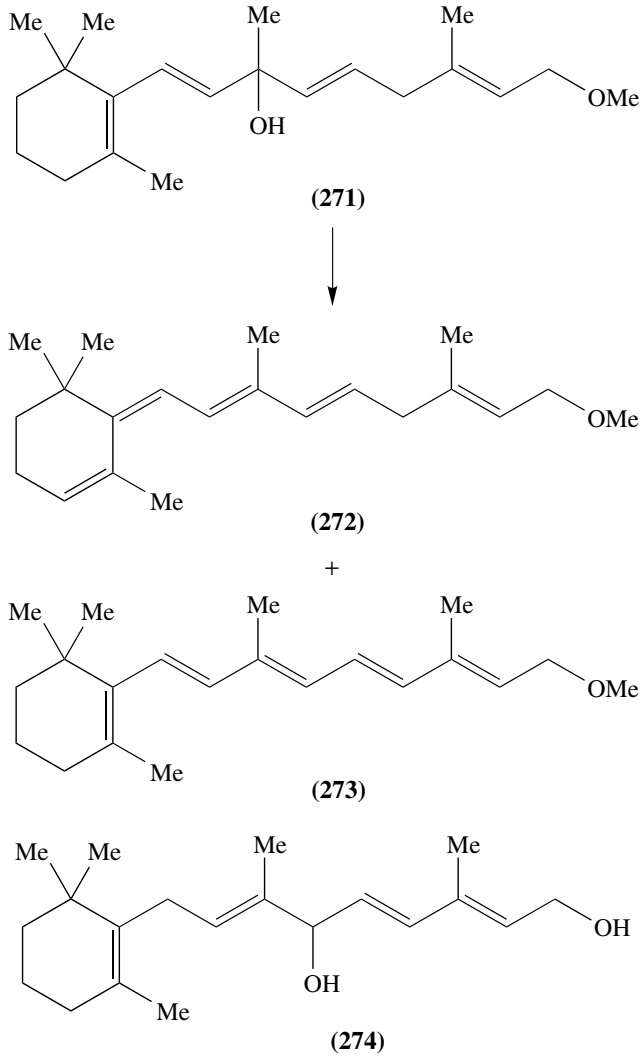
In that way, one of the principal approaches to the preparation of vitamin A derivatives consists of a selection of starting and/or intermediate structures which cannot be rearranged. In contrast, the object of another approach is to search the conditions of the reverse transformation, i.e. a rearrangement of retro-structures to the desirable ionylidene systems. Most frequently, basic reagents (e.g. NaOH, KOH, AcOK, pyridine, AlkONa etc.) are used for this purpose but an application of acid reagents is also known[146].

It is interesting that the retroionylidene rearrangement is suppressed when the compound to be dehydrated contains strong electron-withdrawing substituents (equations 94–96). Another method to prevent the retroionylidene rearrangement consists in the introduction of a carbon–carbon triple bond conjugated with the ring and retention of this bond up to the end step of synthesis[146] (e.g. equation 97).

E. Carbocation Rearrangements of Cyclodienes and Polyenes

Shubin and colleagues have described a series of rearrangements of unsaturated cyclic systems which occur via cationoid intermediates. Protonation of the triene **275** with

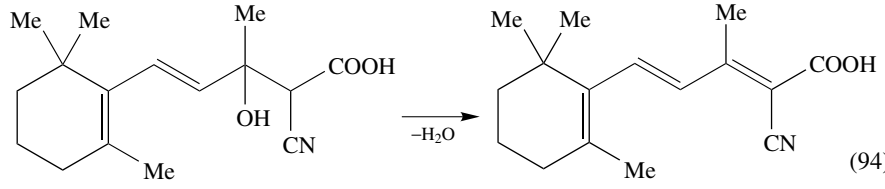
$HSO_3F–SO_2FCl$ at −120 °C proceeds to form the cycloheptatrienes **276** and **277** (equation 98)[151]. However, under the same conditions, as well as in the presence of H_3PO_4, the analogous propargyl substituted diene **278** affords the much more active vinyl cation **279**, thus changing the reaction pathway[152] (equation 99). The cyclic ketone **280** obtained was also obtained upon treatment of the tetraene **281** with H_3PO_4[152].



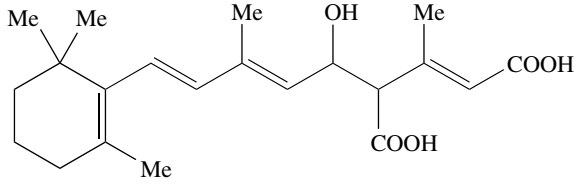
(93)

Introduction of methyl substituents into the propargyl fragment changes again the situation. The penta- and hexamethylated homologues **(282)** react with $FSO_3H–SO_2ClF–CD_2Cl_2$ (1 : 9 : 2, v/v) at −120 °C to form the vinyl cations **283** and then the allyl cations

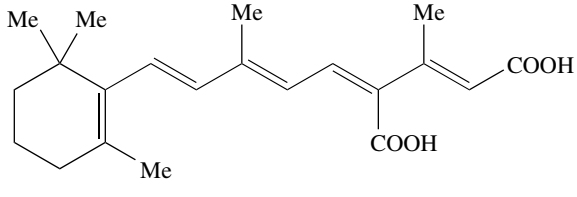
284 which transform to the cyclic cations **285** capable of a walk rearrangement. These cations, which can be produced also by action of H_3PO_4, undergo an electrocyclic ring opening to furnish the styrene derivatives **286** (equation 100)[153,154].

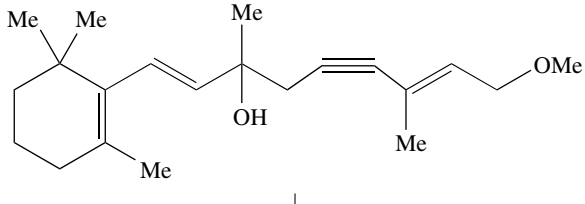


(94)

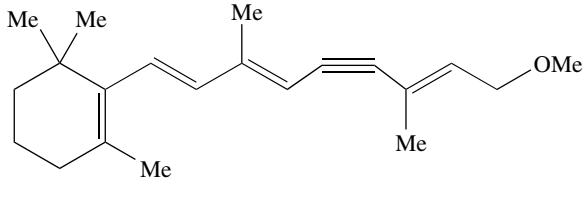


(95)



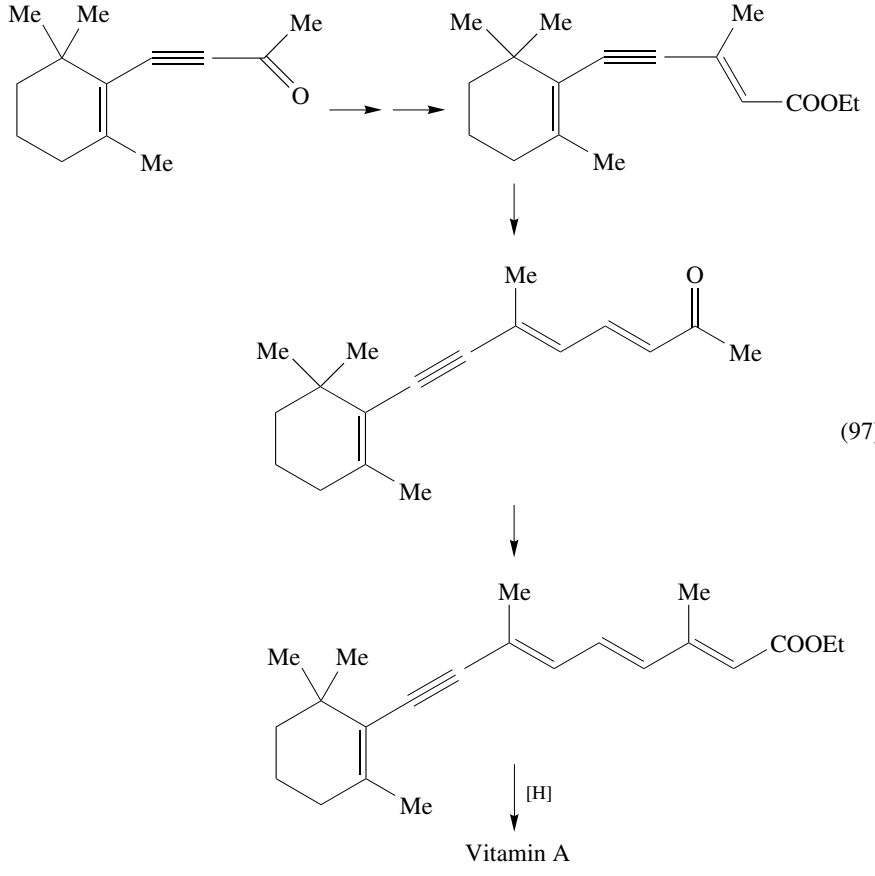


(96)



The polysubstituted benzenes **291** and **292** were also obtained by protonation of the cyclohexadiene derivatives **287**–**289** (equation 101)[155]. The migration of the propynyl

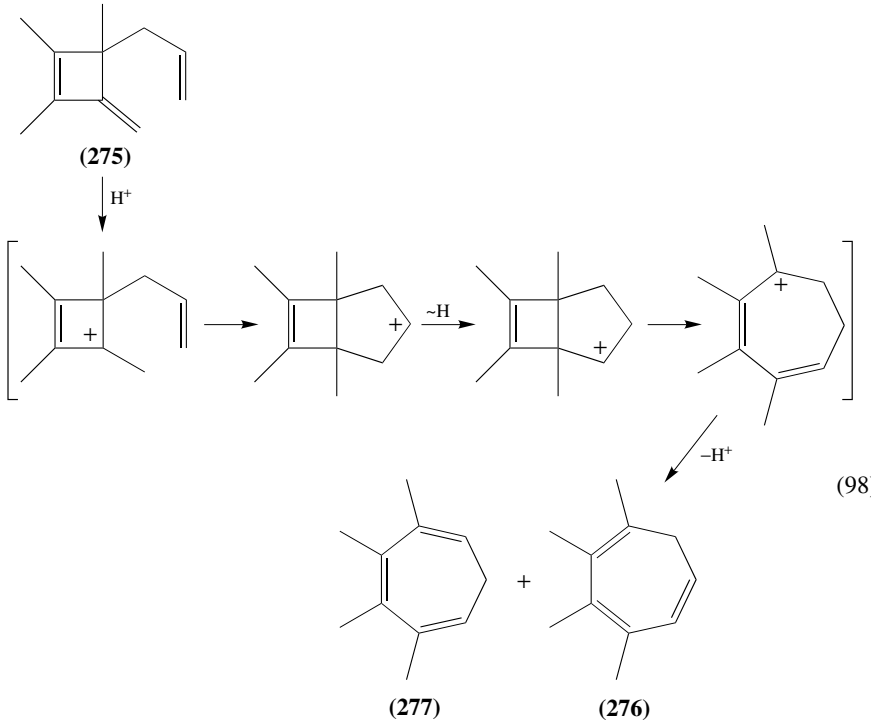
fragment in the cationoid intermediate **290** is assisted by subsequent aromatization. Analogous transformations take place during a dienone–phenol rearrangement including conjugated systems (see Section IV.A).



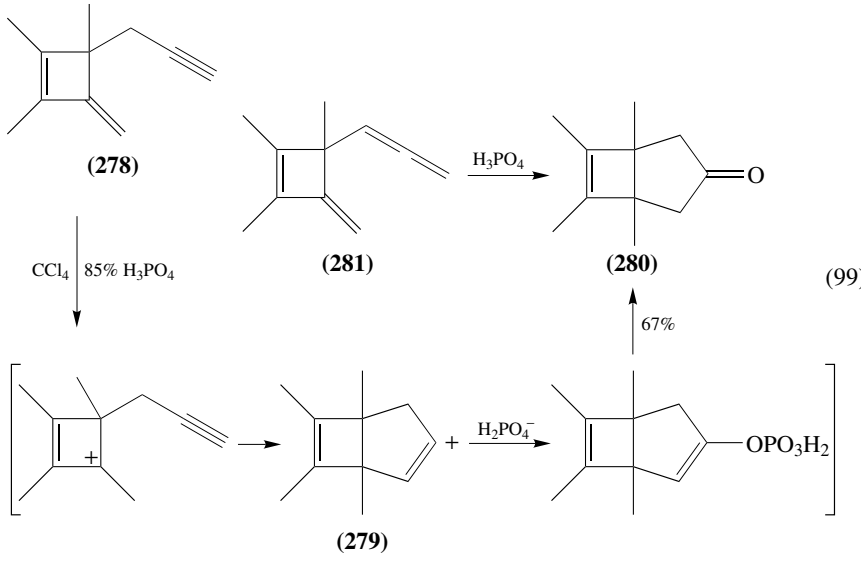
(97)

In the course of dolastane synthesis (the dolastanes are a group of marine diterpenes) interesting rearrangements catalyzed by Lewis acids were found. Treatment of the trienone **293** with excess (1.5 eq) ethylaluminum dichloride at low temperatures (−5 °C, 48 h) gave the tetracyclic enone **295** in 53% yield while the tricyclic dienone **296** (50%) was formed at room temperature (equation 102)[156]. It was assumed that both products can be derived from the common zwitterion **294** which undergoes intramolecular alkylation at low temperatures (path a) whereas an alkyl shift takes place at elevated temperatures (path b), followed by a 1,2-hydride shift (equation 102).

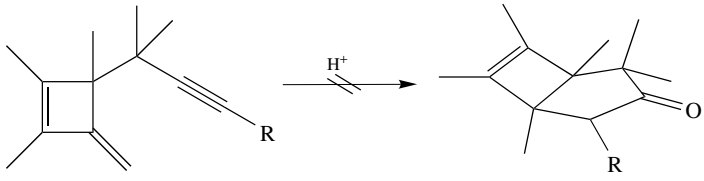
The rearrangement of the conjugated diene **298** to the non-conjugated one **299** was found in the course of the investigation of lauren-1-ene conversions in the presence of *p*-toluenesulfonic acid (equation 103)[157]. Tricyclic ketone **297** in cold benzene transforms slowly into diene **298**, but a further conversion to diene **299** occurs in refluxing benzene.


(275)
H+
~H
–H+
(277)
(276)

(98)

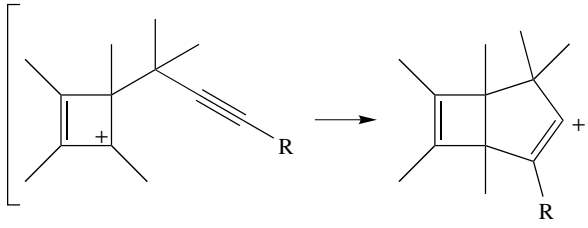

(278)
H3PO4
O
(281)
(280)
CCl4
85% H3PO4
67%
H2PO4–
OPO3H2
(279)

(99)



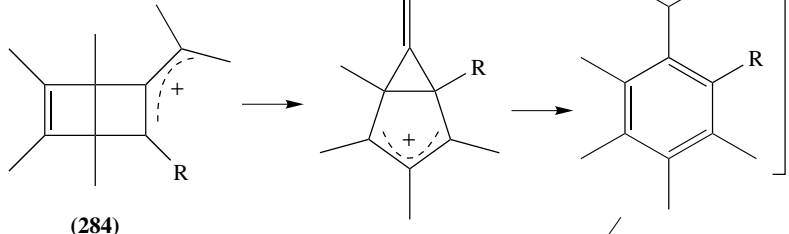
(282)

R = H, Me

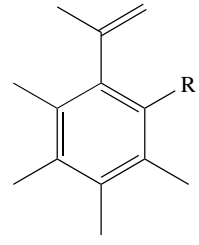


(283)

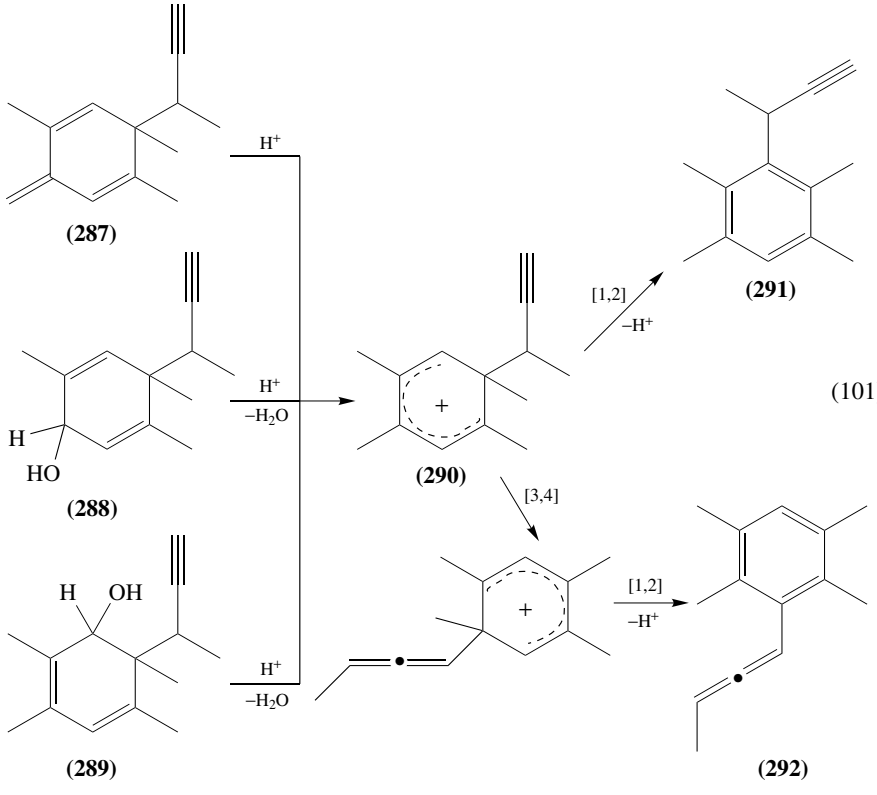
(100)



(284) **(285)**



(286)

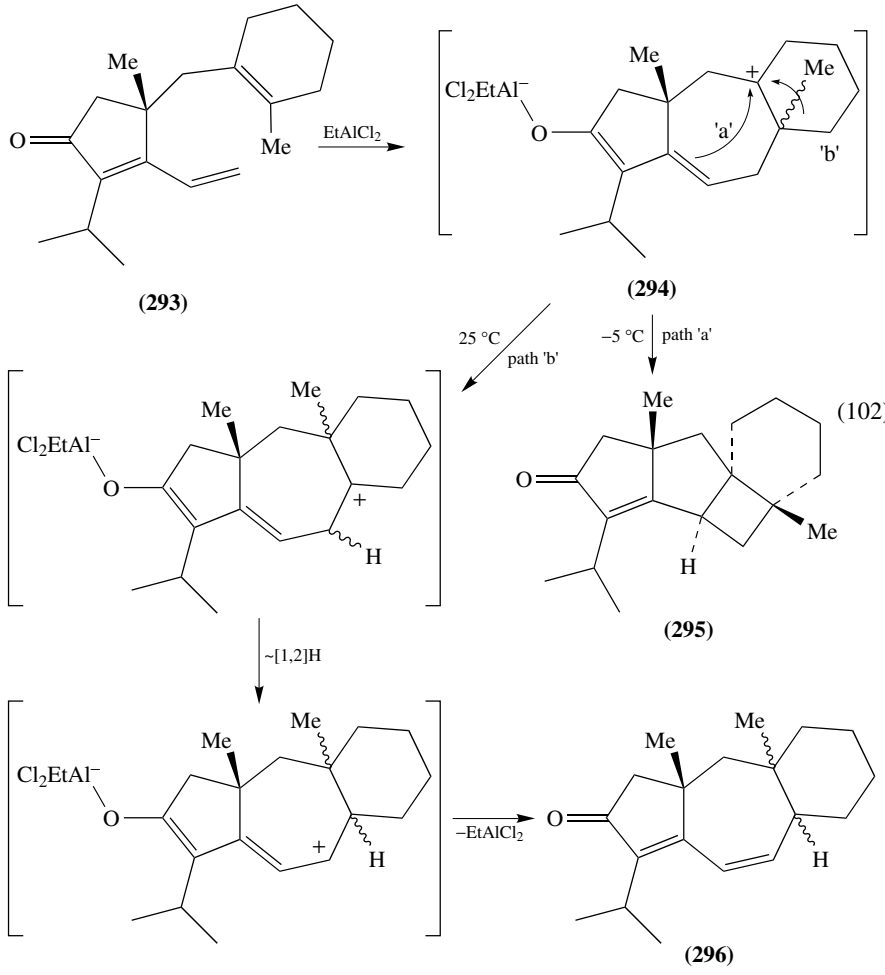


(101)

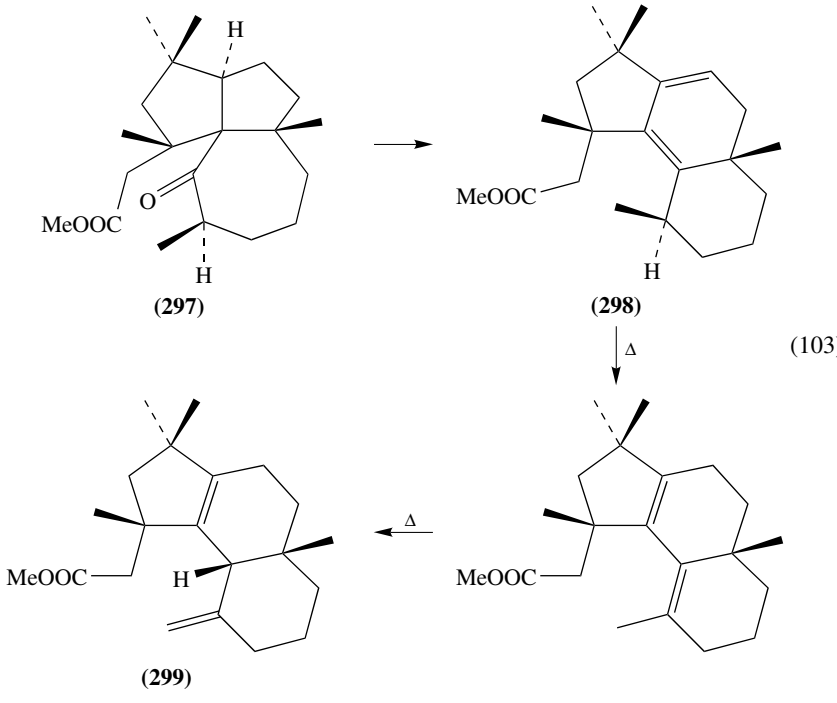
IV. REARRANGEMENTS OF NON-CONJUGATED DIENES AND POLYENES

A. Dienone–Phenol Rearrangements

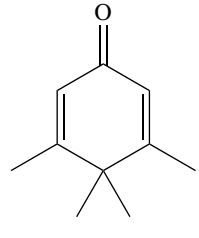
In general, the dienone–phenol rearrangements can be represented by acid-catalyzed transformation of the dienones **300** to phenols **301** which proceed with migration of group R and aromatization of the ring (equation 104). However, there are numerous variants of this reaction depending upon the structure of starting cyclic dienes and the nature of substituents as well as on the reaction conditions. These various pathways of the dienone–phenol rearrangement were already shown in one of the first reviews[158]. It is emphasized in Miller's very detailed survey[159] that both linearly-conjugated (*'ortho'*) 2,4-cyclohexadienones and cross-conjugated (*'para'*) 2,5-cyclohexadienones are incapable of undergoing the thermal rearrangements. In contrast, cyclohexadienones containing allyl substituents rearrange easily at relatively low temperatures (20–80 °C)[159]. It was shown that acid-catalyzed rearrangements of cyclohexadienones can occur, including [1,2]-, [1,3]-, [1,4]-, [1,5]-, [3,3]-, [3,4]- and [3,5]-migrations of carbon–carbon bonds[159].



The mechanism of dienone–phenol rearrangement was investigated very thoroughly in work of Vitullo and colleagues[160–164]. It was established that the first step is a protonation (or coordination with Lewis acid) of the carbonyl oxygen to form a cyclohexadienyl cation. The second step includes a migration of a group (aryl or alkyl) to the adjacent electron-deficient carbon atom. The subsequent elimination of proton leads to the stable phenol (equation 104). By using deuterium isotope effects it was shown[161,164] that the rate-determining step is unequivocally the migration, which occurs even in the presence of very high acid concentrations. The competitive migratory aptitudes established for various groups (e.g. Me, MeO) as well as the kinetic parameters of the dienone–phenol rearrangement depending on the acid concentration[162,163] confirm the reaction mechanism assumed.

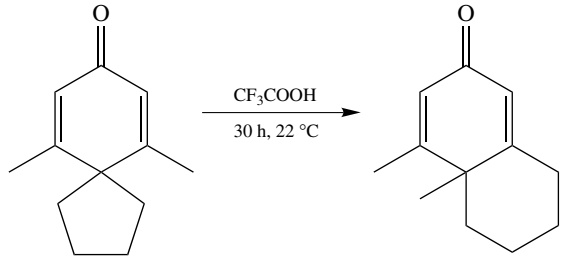


Besides aromatization, the energy resulting from relief of cyclic strain can be a driving force of the dienone–phenol rearrangement. Thus, it was reported that dienone **302** is



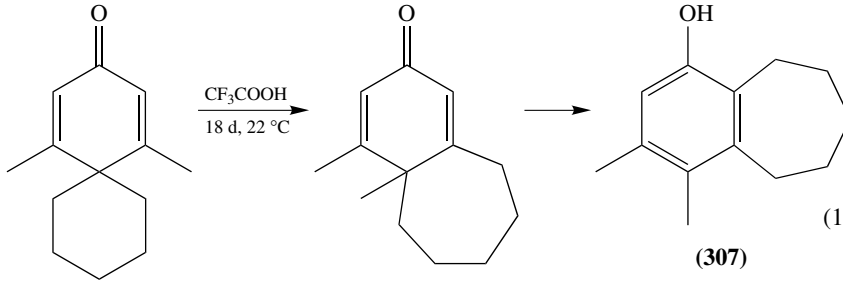
(302)

quite stable in trifluoroacetic acid, whereas the dienones **303** and **305** rearrange to give the ring-enlargened dienones **304** and **306** (equations 105 and 106). However, only product **306** is capable of undergoing a further transformation into the stable final phenol **307**[165].



(105)

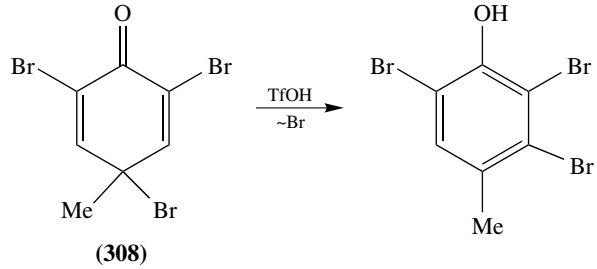
(303) **(304)**



(106)

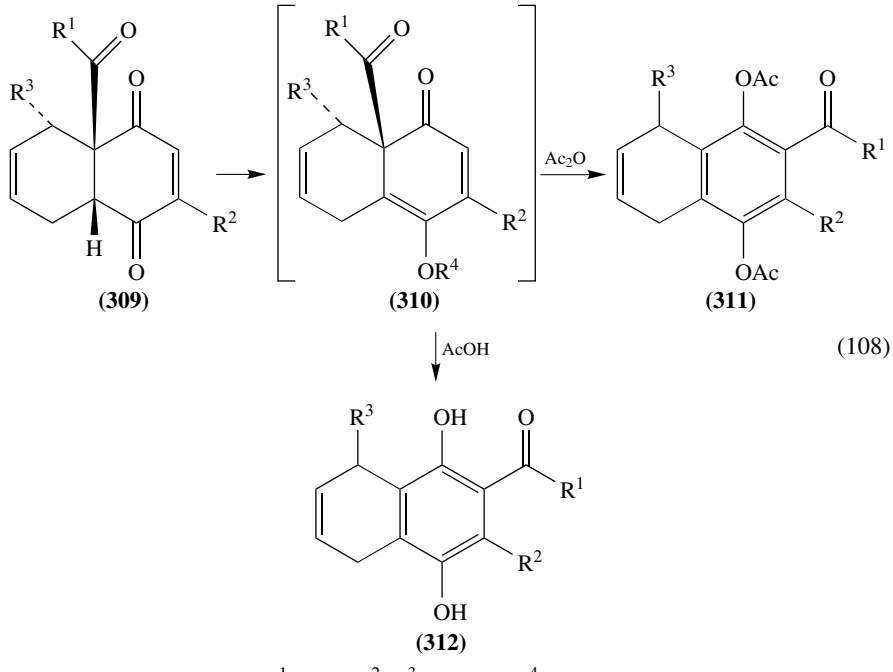
(305) **(306)** **(307)**

The dienone–phenol rearrangements can occur with transposition of other migrants. For example, the migration of a bromine atom rather than of a methyl group was observed upon treatment of the tribromodienone **308** with trifluoromethanesulfonic acid (equation 107)[166]. The migrations of angular acyl substituents were investigated by using the bicyclic Diels–Alder products **309** obtained from buta-1,3-diene and acetyl-1,4-benzoquinone[167–169]. In refluxing acetic anhydride adducts **309** gave 2-acetyl-5,8-dihydronaphthalenes **311**, whereas the corresponding 5,8-dihydro-1,4-dihydroxynaphthalenes **312** were formed upon refluxing in acetic acid (equation 108)[167]. It was shown that no 'retrodiene-recombination' pathway takes place during the isomerization, which is an intramolecular process with more than 90% regioselectivity. It corresponds to a [1,5]-acetyl shift in the enol **310** (R^4 = H) or in its acetate (**310**, R^4 = Ac).



(107)

(308)

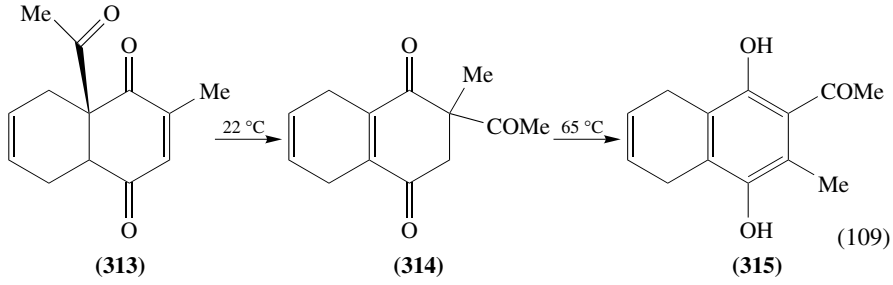


(108)

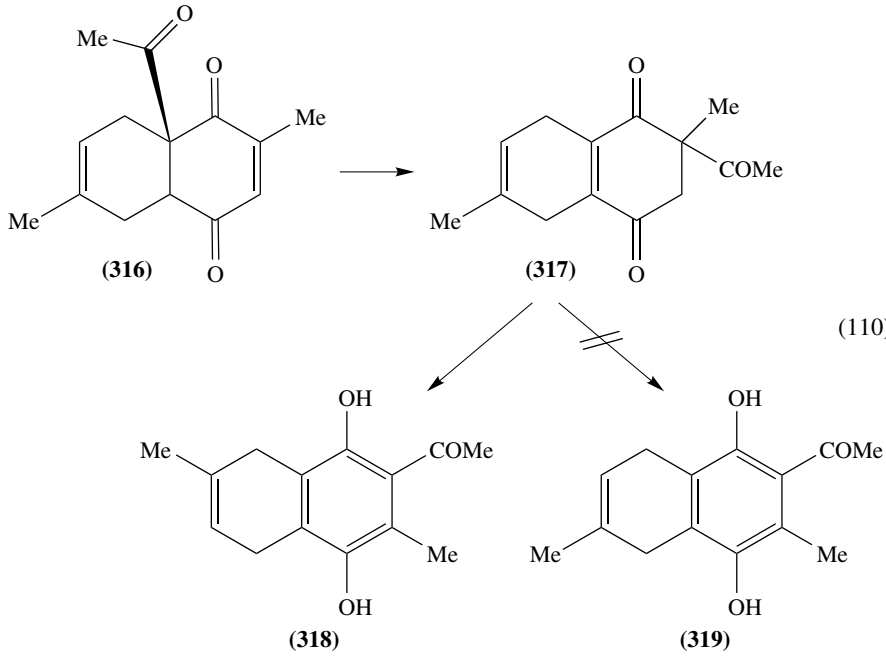
R^1 = Me; R^2, R^3 = H, Me; R^4 = H, Ac

The behavior of Diels–Alder adducts substituted at the C(3) position **(313)** is different because the substituent has to prevent an aromatization. Treatment of triketone **313** with pyridine–methanol (1 : 1, v/v) at 22 °C results in the expected [1,5]-acetyl shift and gives a good yield of the triketone **314**, which isomerizes smoothly when heated in the same medium at 65 °C to furnish dihydronaphthalene **315** (equation 109)[168]. Similar treatment of the triketone **316** affords the bicyclic product **318** rather than **319**, presumably via the intermediate **317** (equation 110)[168].

Acyl migrations in the acylbenzoquinone cycloadducts were also described elsewhere[170]. It was shown that the direction of acyl migrations in the cycloadducts obtained from dienes and 2-acetyl- as well as 2-benzoyl-1,4-benzoquinones depends on the substituents in diene fragment.

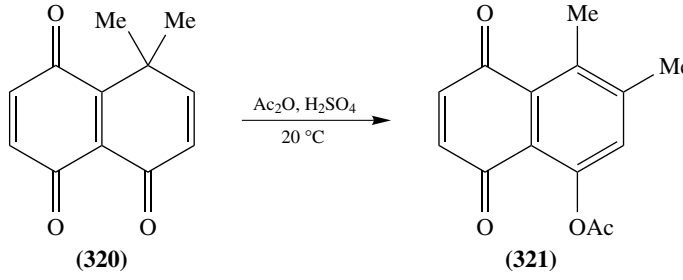


(109)



(110)

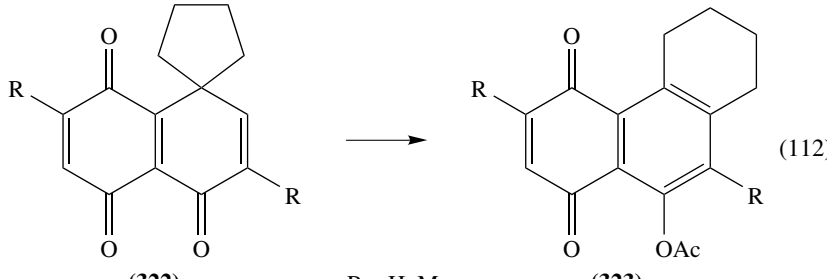
An attempt to carry out the Thiele–Winter acetoxylation of triketone **320** (Ac_2O, H_2SO_4, 20 °C) gave rise to the product of dienone–phenol rearrangement **321** in 83% yield (equation 111)[171]. This reaction was claimed to be a convenient entry into the tetrahydrophenanthrene-1,4-quinone **323**, starting from the spiro(cyclopentanonaphthalene) triones **322** (equation 112). The rearrangements of cyclohexadiene systems can also be catalyzed by Lewis acids; for example, under metalation conditions with $HgCl_2$ (HgO, $NaHCO_3$, THF, 20–45 °C) products **324** and **325** are formed in a 5 : 1 ratio (equation 113)[172].



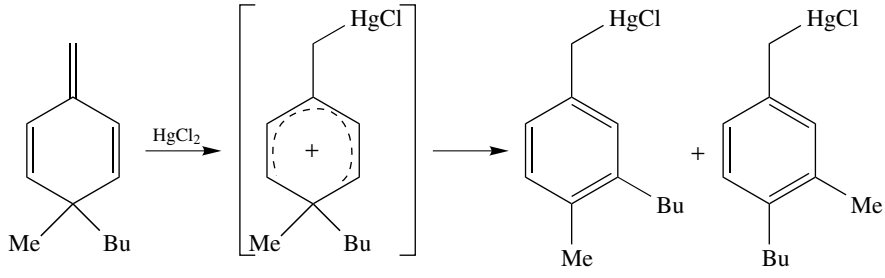
(111)

In contrast to well investigated acid-catalyzed rearrangements of the cross-conjugated cyclohexadienones mentioned above, the isomerizations of linearly-conjugated cyclohexadienones have not received much attention, except for special cases in which allyl groups migrate. Acid-catalyzed rearrangements of conjugated 2,4-cyclohexadienones can occur via [1,2]- and [1,5]-shifts depending on the nature of the migrant. Thus, dienone **326** isomerizes by a [1,2]-shift of a methyl group (equation 114) whereas the dienone **327**

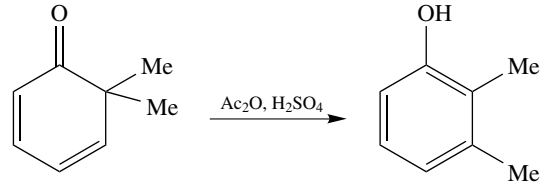
transforms into 2-benzyl-6-methylphenol **328** (AcOH + 1% H_2SO_4, or aqueous dioxane + HCl, 25 °C, 20 min) (equation 115)[173]. The migration of a benzyl group to the C(2) position can proceed even if the latter is occupied by a *tert*-butyl group. The rearrangement of the dienone **329** (in 2N HCl in 80% aqueous methanol) results in partial elimination of the *tert*-butyl group to provide 2-benzyl-6-methylphenol **328** and 5-benzyl-2-*tert*-butyl-6-methylphenol **330** in a 5 : 7 ratio (equation 116)[173].



(322) **(323)** (112)



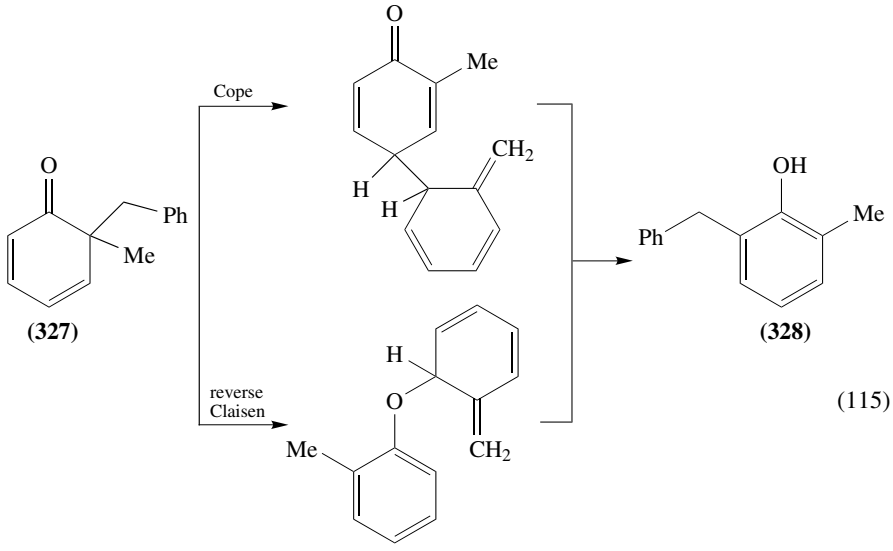
(324) **(325)** (113)



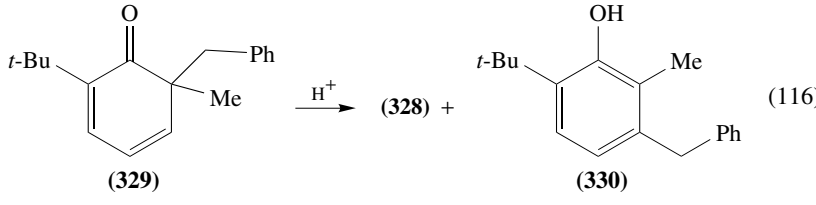
(326) (114)

Various mechanisms are discussed for the migration of a benzyl group including, e.g., a two-stage Cope or reverse Claisen rearrangement as well as a preference of direct [1,5]-shift over successive Wagner–Meerwein migrations (equation 115)[173].

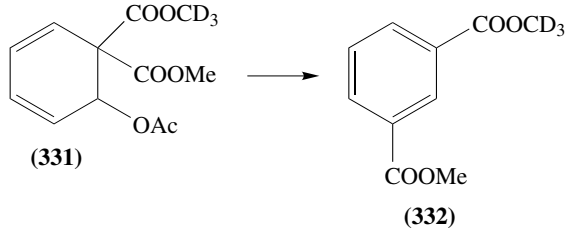
Besides catalyzed rearrangements, thermal isomerizations in a series of linearly-conjugated cyclohexadiene systems, which are accompanied by migrations of various groups having a complex structure, are also known. The thermal sigmatropic migrations of methoxycarbonyl groups proceed upon pyrolysis of the acetoxydiene **331** to give dimethyl isophthalate **332** without a change in the isotope distribution (equation 117)[174]. This excluded a radical-chain mechanism and confirms the complete intramolecularity of the rearrangement. By using NMR spectral analysis the behavior of the deuterium labeled



(115)



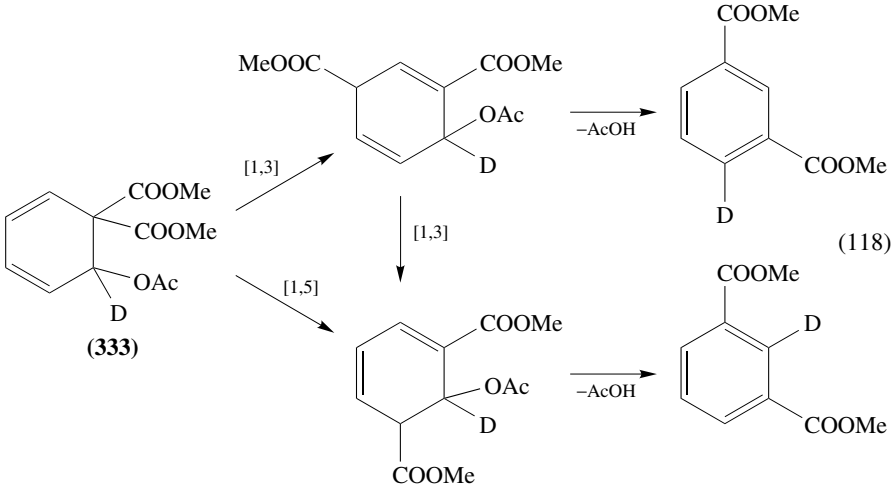
(116)

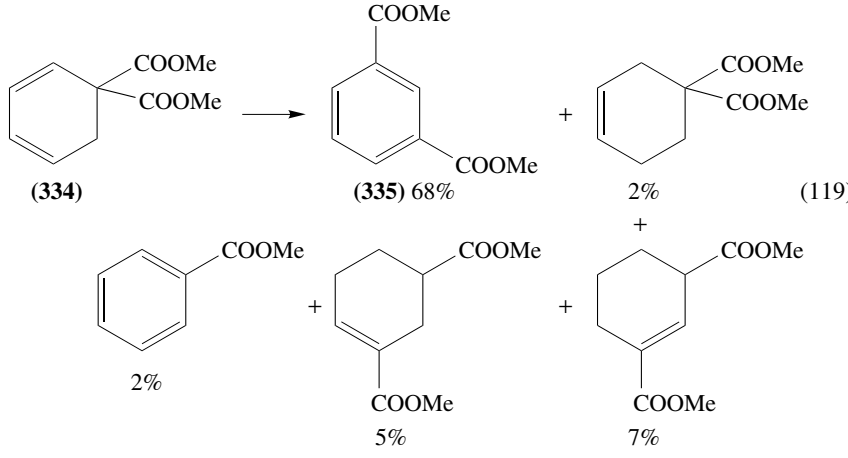


(117)

triester **333** was investigated in order to distinguish two possible pathways: (1) direct [1,3]-methoxycarbonyl migration, and (2) direct [1,5]- or two successive [1,3]-shifts. Path (1), which involves a single [1,3]-shift, was excluded in this way, whereas the [1,5]-shift mechanism was found to fit the observations without special assumptions (equation 118).

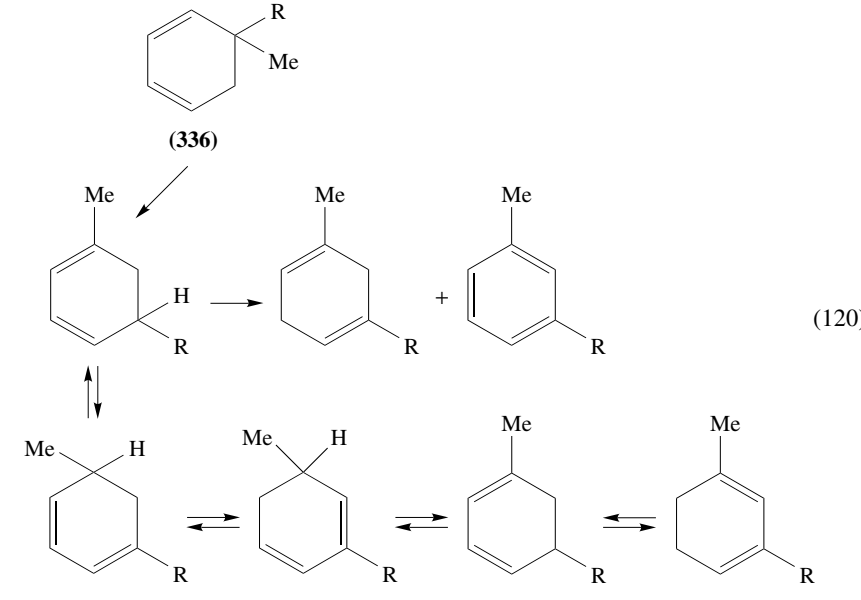
The presence of an acetoxy group is not a necessary condition for the methoxycarbonyl rearrangement. Thus, the pyrolysis of diene **334** (300–320 °C, 1 h, 97% conversion) gave the diester **335** as the major product (equation 119)[174]. Dicarboxylates like **334** were suggested to be the intermediates in pyrolysis (420 °C, flow system) of dimethyl and diethyl 2-acetoxycyclohex-3-ene 1,1-dicarboxylates[175].



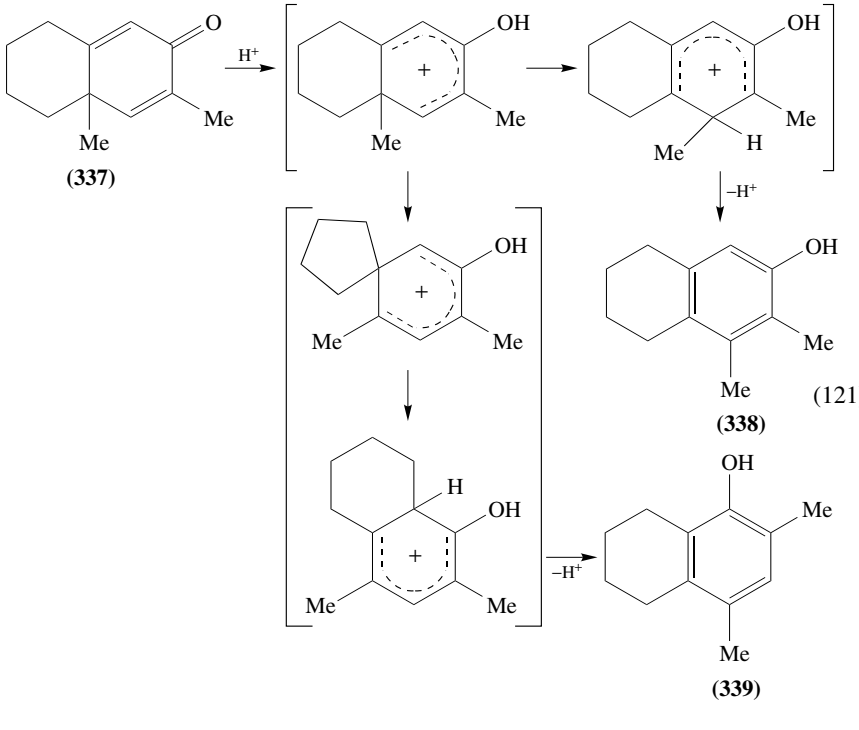


The comparative migratory aptitudes of formyl, acetyl and methoxycarbonyl groups relative to hydrogen atom in thermal [1,5]-sigmatropic shifts were studied by measuring the rearrangement rates of 1-R-1-methylcyclohexa-2,4-dienes **336**[176]. In comparison with 1-methylcyclohexa-2,4-diene (**336**, R = H) it was found that a formyl group migrates faster than hydrogen by more than two orders of magnitude, a methoxycarbonyl group is slower by a factor of about 70 and an acetyl group has a comparable migration aptitude to hydrogen (equation 120)[176].

Different directions in rearrangement of the same precursor were shown by using the bicyclic dienones **337** (equation 121)[177]. The formation of two different products, **338** by methyl migration and **339** by a stepwise cyclohexane ring migration, is considered confirmation of a multistage mechanism.

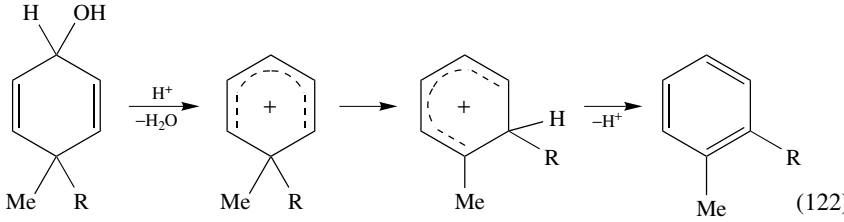


(120)



(121)

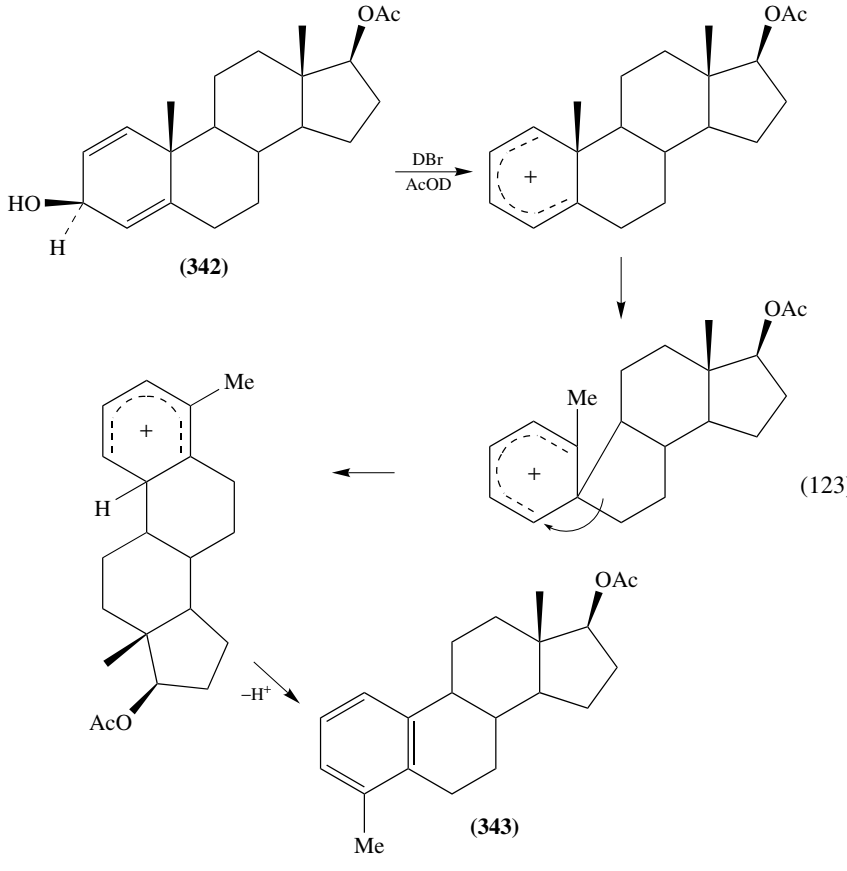
Besides the dienone–phenol rearrangement there are also several types of a related dienol–benzene rearrangement in which the intermediate cyclohexenyl cation **341** is generated from cyclohexadienols **340** by elimination of the appropriate nucleofuge, e.g. hydroxy group, rather than by addition of an electrophile as above (equation 122)[178]. Such nucleofuge can also be a chlorine atom (see also equation 101). The mechanism of the dienol–benzene rearrangement in a series of steroides was studied by using ^{2}H NMR spectroscopy during the transformations of the steroid alcohol **342** (equation 123)[179]. The



(122)

(340) **(341)**

R = Me, CCl_3

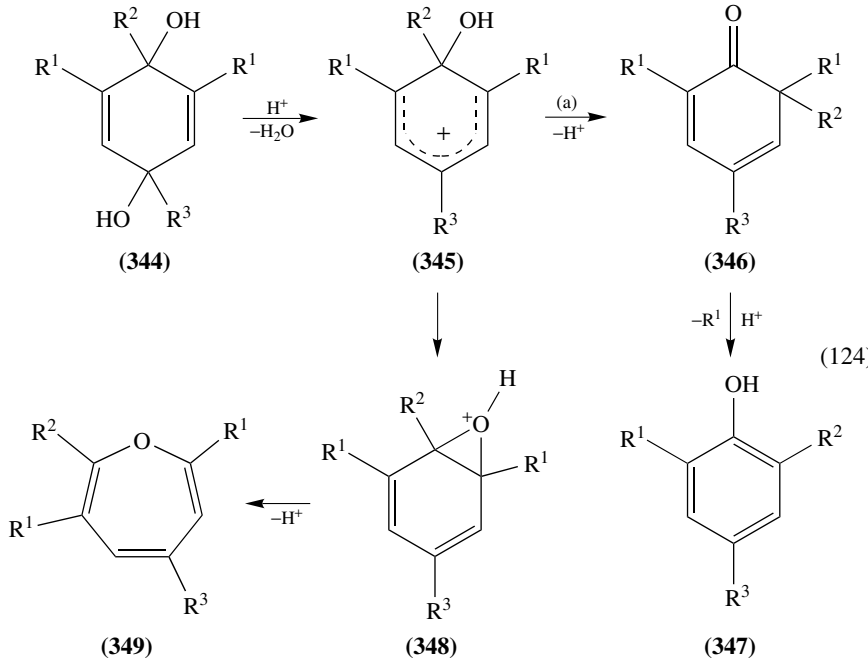


(123)

(342) **(343)**

absence of a deuterium label in the aliphatic fragment of the final structure **343** suggests that the rearrangement proceeds by a cleavage of the C(3)−O bond rather than through a prior dehydration to 1,3,5(6)-triene and subsequent reprotonation[179].

A related dienediol–phenol rearrangement which can occur by different pathways was reported as a new method for synthesis of the oxepine system[180]. Protonation of the starting diol **344** produces a cation **345** which can follow 'normal' dienone–phenol rearrangement (path a) when the substituents R^2 = Me, Ph and R^1 = *t*-Bu are eliminated in the step **346** → **347**. However, when R^1 = *t*-Bu and R^2 is a substituted phenyl which decreases the nucleophility, the cationoid intermediate **345** cyclizes to the oxonium ion **348** (path b) which then undergoes deprotonation to give the oxepine **349** (equation 124)[180].

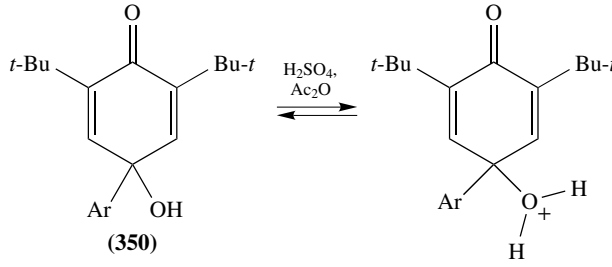


(124)

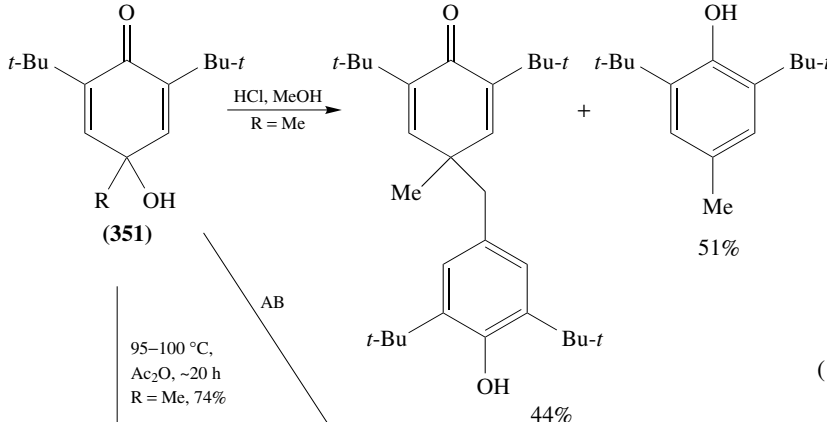
R^1 = Me, Ph, *t*-Bu; R^2 = Me, Ph, Ar; R^3 = *t*-Bu, Ph, Ar

Various transformations take place upon interaction of acid reagents with hydroxycyclohexadienones containing both hydroxy and carbonyl groups. Thus, treatment of compound **350** with an $Ac_2O + H_2SO_4$ mixture leads to elimination of the OH group and substitution of a *tert*-butyl moiety (equation 125)[181]. An analogous behavior of 4-alkyl-substituted dienones **351** in the presence of Ac_2O or other acidic reagents was described a few year later (equation 126)[182].

A two-step transformation of conjugated dienes into non-conjugated ones was proposed for the synthesis of the difficult to-obtain lapachol **(355)** (a member of a class of antimalarial agents having an activity against the Walker carcinosarcoma 256) from the more available isolapachol **352**[183]. This method consists in an oxidative cyclization of isolapachol **352** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to form a mixture of the products **353** and **354** (equation 127). Treatment of this mixture with dilute acid in

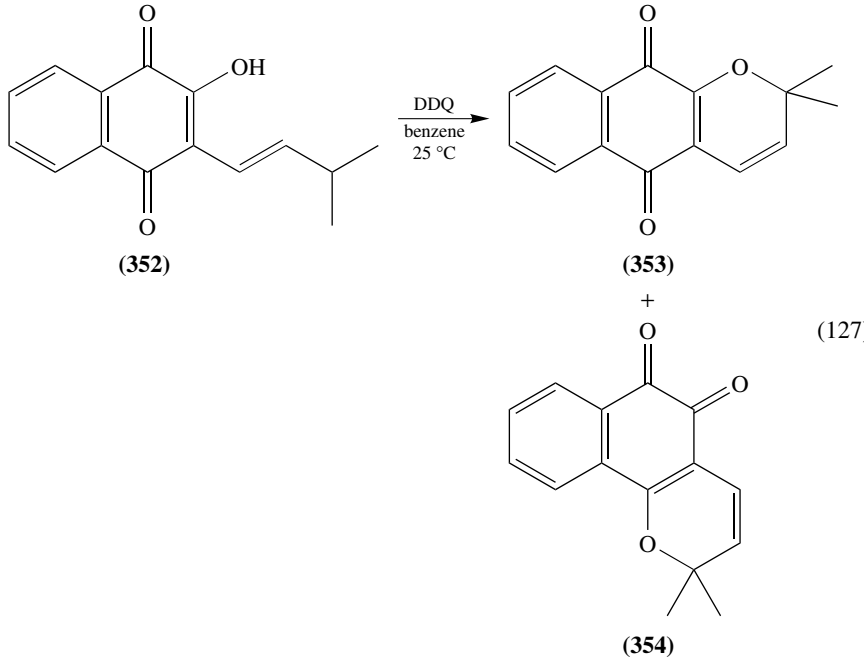


(125)



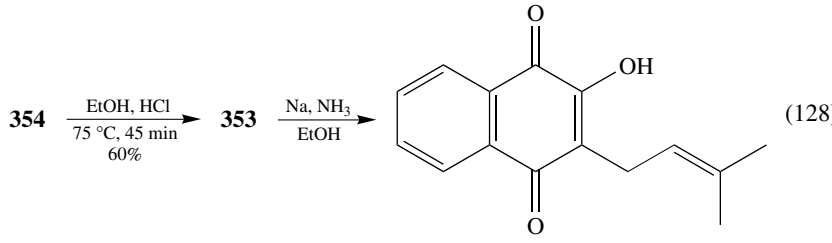
(126)

R = Me, Et, *i*-Pr, *t*-Bu, $(CH_2)_2CH_2OH$



(352) **(353)** **(354)** (127)

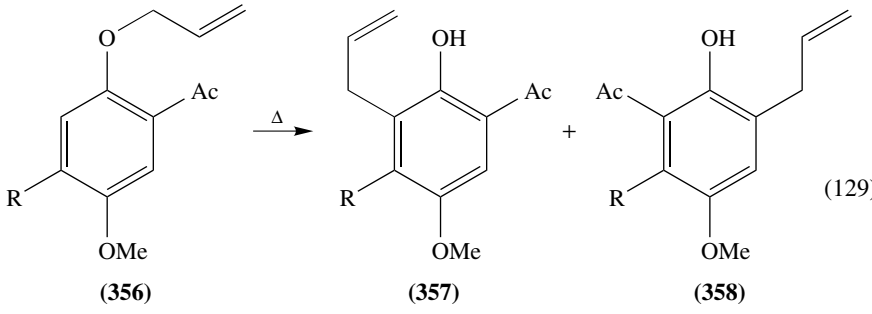
ethanol leads to '*ortho–para*'-rearrangement to afford 60% yield of the single product **353**. The ring opening of the α-pyrane fragment by Na in NH_3 gives the target lapachol in *ca* 20% yield (equation 128)[183].



(355) (128)

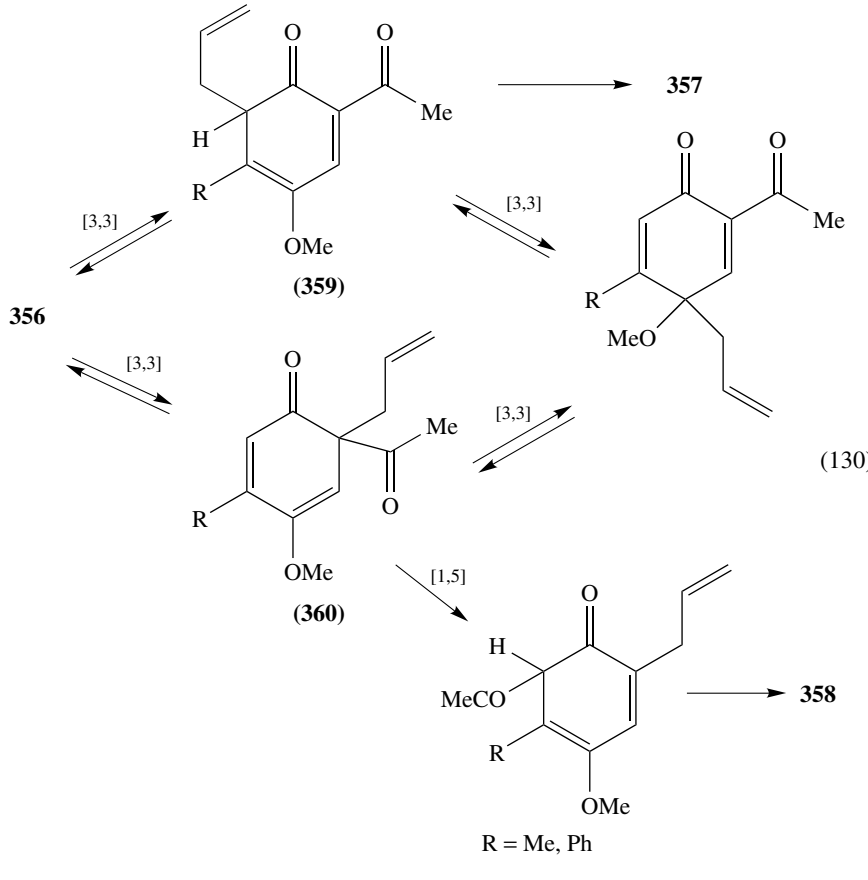
The competition of Claisen rearrangement and [1,5]-acetyl shift upon thermal treatment of allyl aryl ether **356** resulted in a mixture of the expected Claisen product **357** and its isomer **358** (equation 129)[184]. It was assumed that the usual Claisen rearrangement (Section IV.E.1) resulted in an equilibrium with the intermediates of successive [3,3]-sigmatropic shifts. The cyclohexa-2,4-dienones **359** and **360** formed leave this equilibrium cycle due to enolization to form the Claisen product **357** or because of [1,5]-shift followed by enolization give the unexpected product **358** (equation 130).

Unusual examples of the dienone–phenol rearrangement include the reactions of 1,4-dihydrosilabenzene **361** which rearranges in two directions upon treatment with BCl_3 or during purification on silica gel (equation 131)[185].



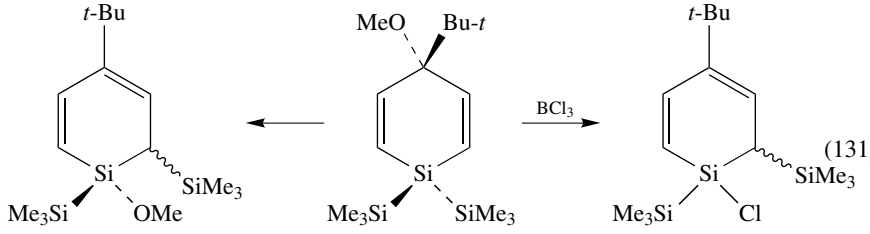
(356) (357) (358) (129)

(a) R = Ph
(b) R = Me



(130)

Finally, it should be noted that there are various reactions which can be called 'phenol–dienone' rearrangements. They proceed upon halogenation, nitration and alkylation of phenols as well as in the course of radical reactions of phenols[186].

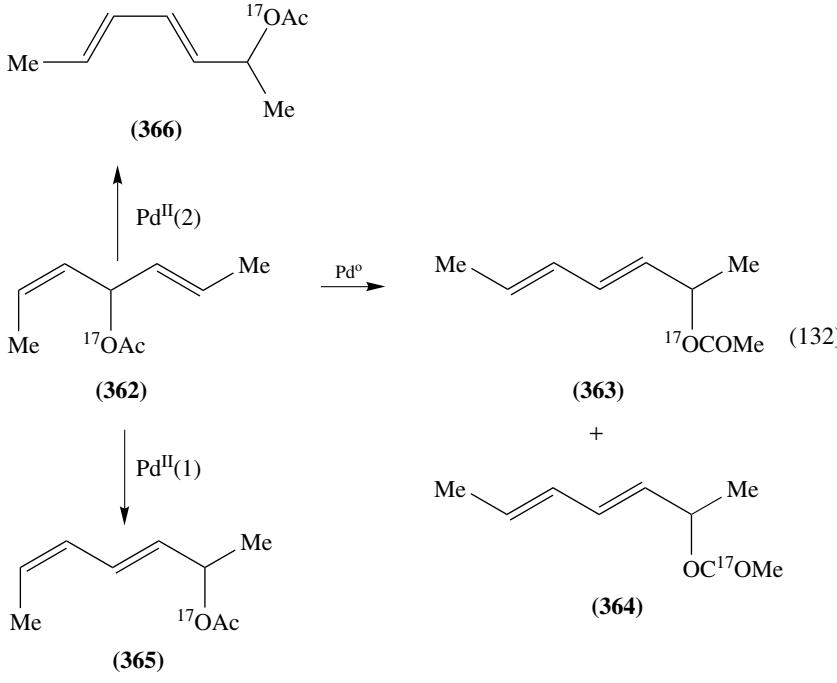


(131)

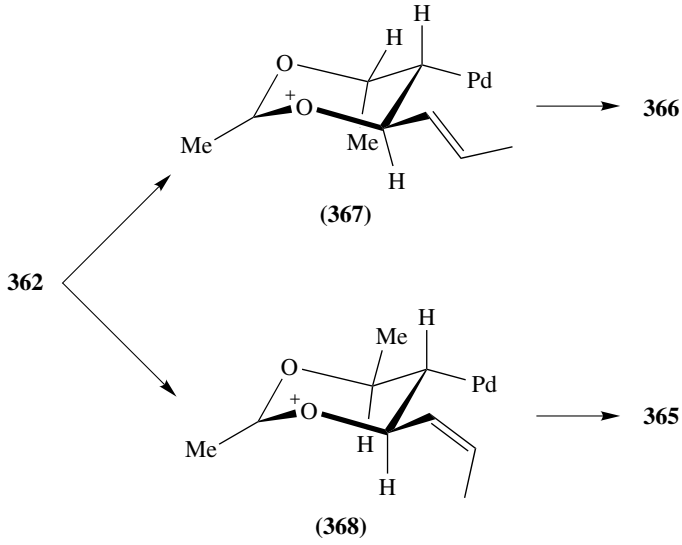
(361)

B. Carbocation Reactions of Non-conjugated Dienes

The mechanism of the catalysis in the rearrangements of 4-acetoxyhepta-2,5-dienes was investigated by using the ^{17}O-labeled acetate **362** in the presence of Pd^0 and Pd^{II} catalysts[187]. It was shown by ^{17}O NMR spectroscopy that the reaction catalyzed by Pd^0 affords a 1 : 1 mixture of the dienes **363** and **364** which results from the Pd-coordinated pentadienyl species intermediate and ^{17}O-acetate (equation 132). By using two Pd^{II}-catalysts, viz. $(RCN)_2PdCl_2$ (R = Me, Ph) [Pd^{II}(1)] and $(Ph_3P)_4Pd$ [i.e. Pd^{II}(2)], two rearrangement products **365** and **366**, respectively, were obtained. The heterocyclic 1,3-dioxanium cations **367** and **368** were assumed to be intermediates of these isomerizations (equation 133).



(132)



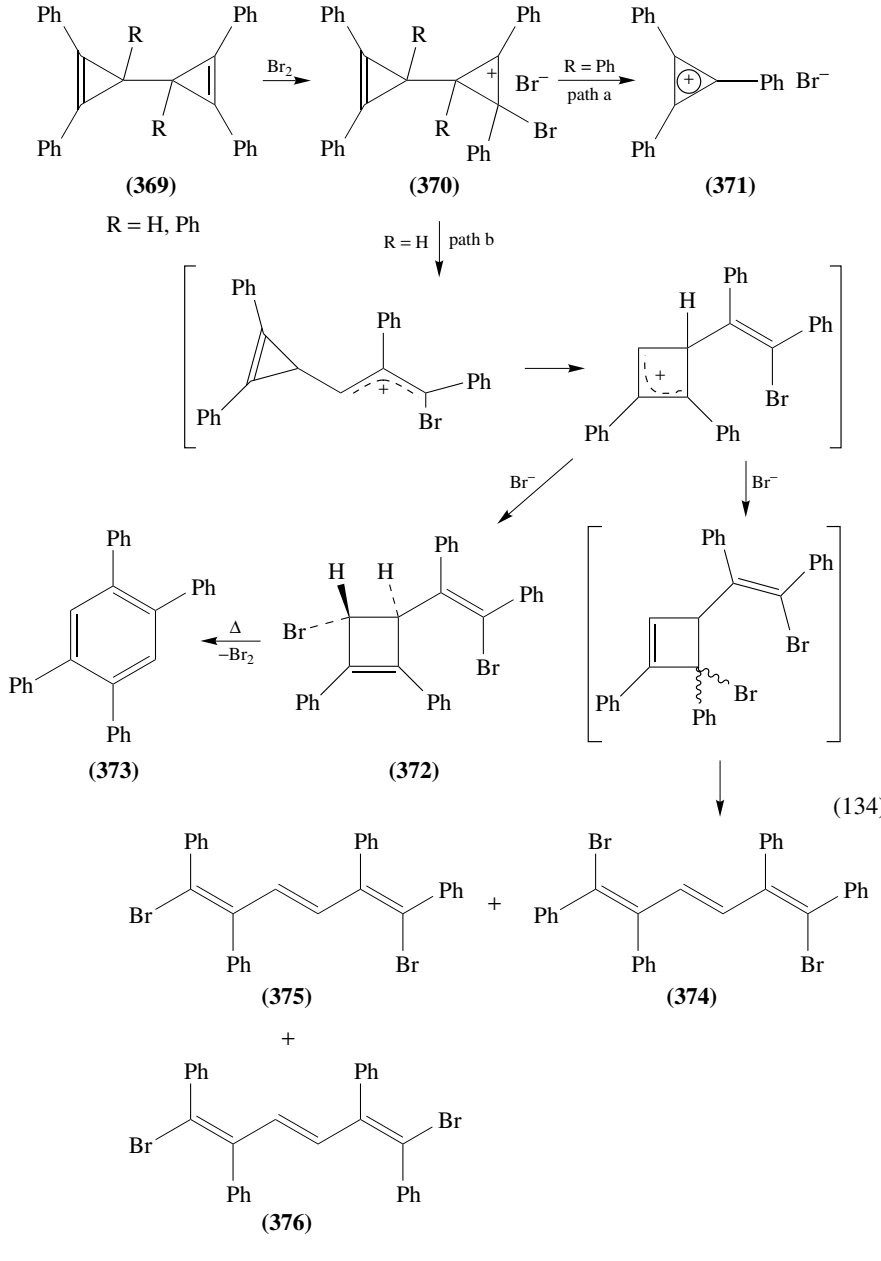
(133)

Bromination of bicyclopropenyl system **369** at ambient temperature in absolute $CHCl_3$ leads either to diene **372** (15%) and trienes **374–376** (15%, 35% and 10%, respectively) when R = H, or to the stable cyclopropenium salt **371** (95%) when R = Ph (equation 134)[188]. The electrophilic attack of bromine on compounds **369** creates the cationoid intermediates **370** which undergo either fragmentation to salt **371** (path a) or an electrocyclic ring opening (path b). When diene **372** is heated at about 150 °C in the solid state it rearranges to 1,2,3,5-tetraphenylbenzene **373** with concomitant loss of bromine.

Similarly, the bromination of 2-bromobenzobarrelene **377** gives a mixture of tribromo products which were separated by column chromatography (equation 135)[189]. The major product **378** was isolated in 58% yield (whereas the combined yield of the rest of products was 37%). By using ^1H and ^{13}C NMR it was shown that bromine was added to the unsubstituted double bond only.

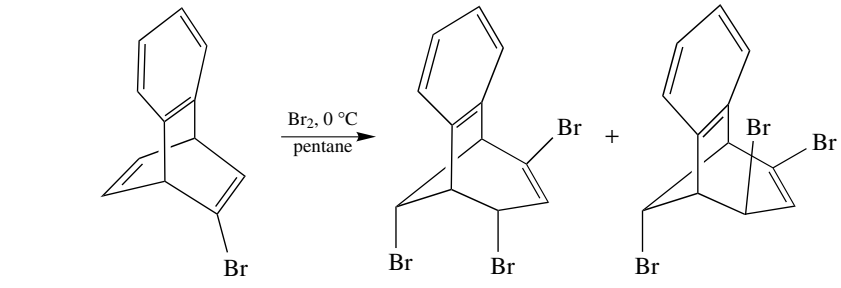
The iodination of *cis*-bicyclo[4.3.0]nona-3,7-diene **379** in CCl_4 is accompanied by a regio- and stereospecific transannular cyclization (see below) to form 40% of the diiodobrexane **380** which can be transformed into brexa-4,8-diene **381** (*t*-BuOK, DMSO, 120 °C, 12 h, 70%) (equation 136)[190]. The mechanism of this rearrangement was studied by reacting diene **382** with the deuteriated superacid $DSO_3F–SO_2FCl$ (−115 °C) to afford the brendane derivatives[191]. According to the ^1H NMR data the protonation of **382** gives a mixture of ions **383** and **384** (equation 137). The quenching of the acidic mixture with a $MeOH–Et_2O$ (2.5 : 1, v/v) mixture affords a mixture of diene **385** and methyl ether **386** in a 1 : 10 ratio (equation 138)[191].

Ionic hydrogenation of the same bicyclic diene **382** by Et_3SiH in the presence of CF_3COOH at room temperature or at 80 °C via ions **387** and **388** is accompanied by transannular cyclizations (equation 139)[192]. The behavior of diene **382** under Ritter reaction conditions (MeCN, H_2SO_4) reveals new possibilities to control the transannular cyclizations (equation 140)[193]. Depending on the sulfuric acid concentration, the reaction temperature and the presence of a nucleophilic solvent, these transformations can be directed to the formation of either the bicyclic amides **389** and **390** having the precursor structure or the tricyclic products **391**[193].

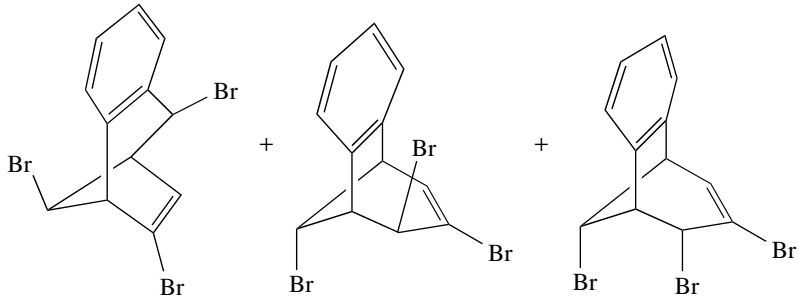


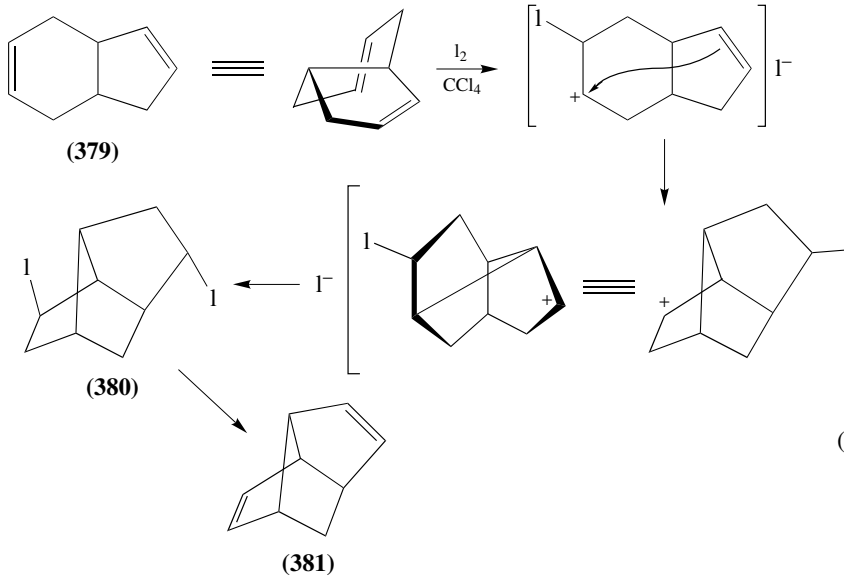
Under Ritter reaction conditions the cycloocta-1,5-diene **392** is prone to undergo transannular cyclization into *cis*-bicyclo[3.3.0]octane derivatives (equation 141)[194]. Norbornadiene **393** and 5-ethylidenenorbornene **394** rearrange under the same conditions to

afford the polycyclic amides (equations 142 and 143)[194]. Brexadiene **381** undergoes Wagner–Meerwein rearrangement under Ritter reaction conditions (MeCN, 20 °C, 1.5 h, 50–60%) (equation 144)[195].

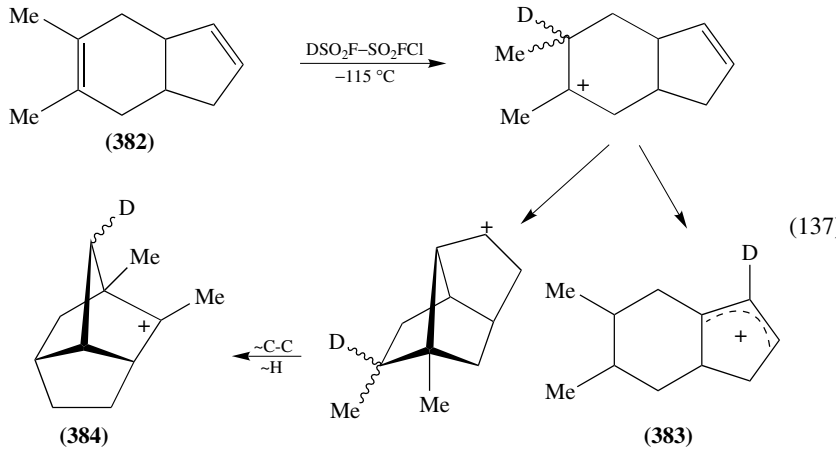


(377) **(378)** (135)

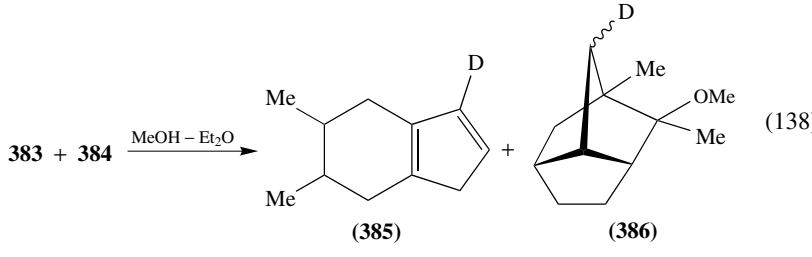




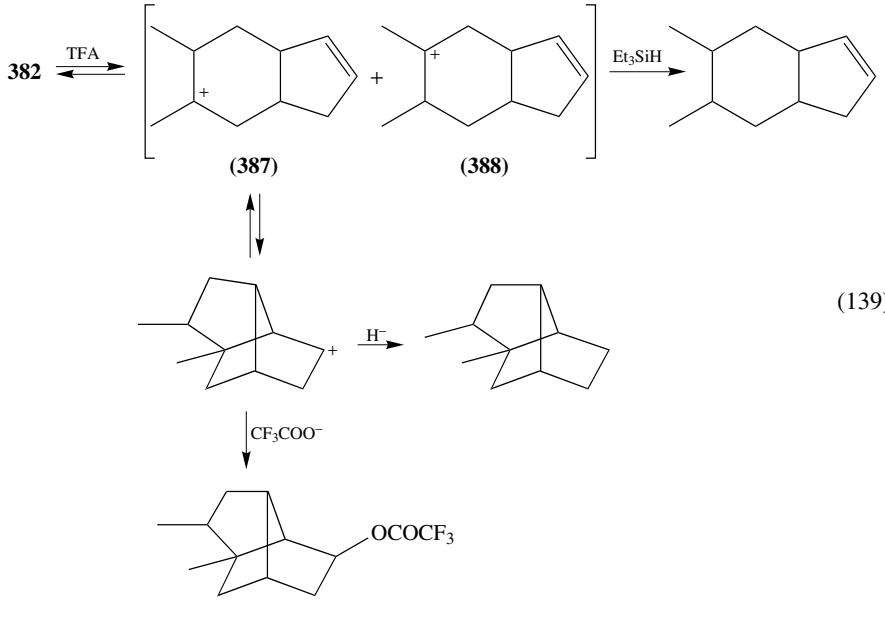
(379) **(380)** **(381)** (136)


Me
Me
(382)
DSO2F–SO2FCl
–115 °C
D
Me
Me
~C-C
~H
(384)
(383)

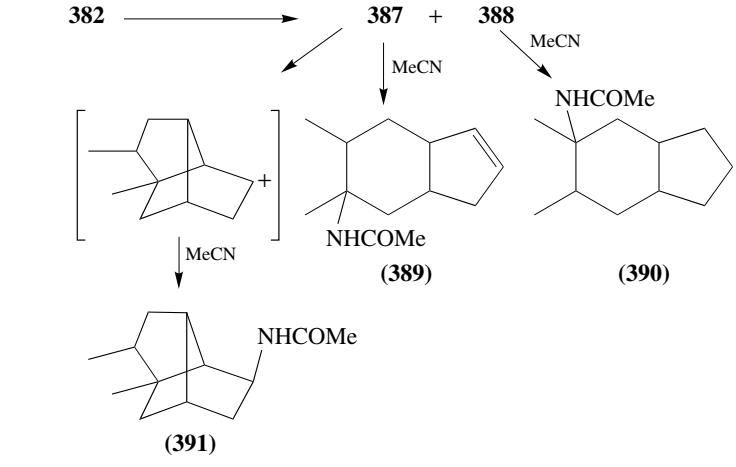
(137)


383 + 384
MeOH – Et2O
(385)
(386)

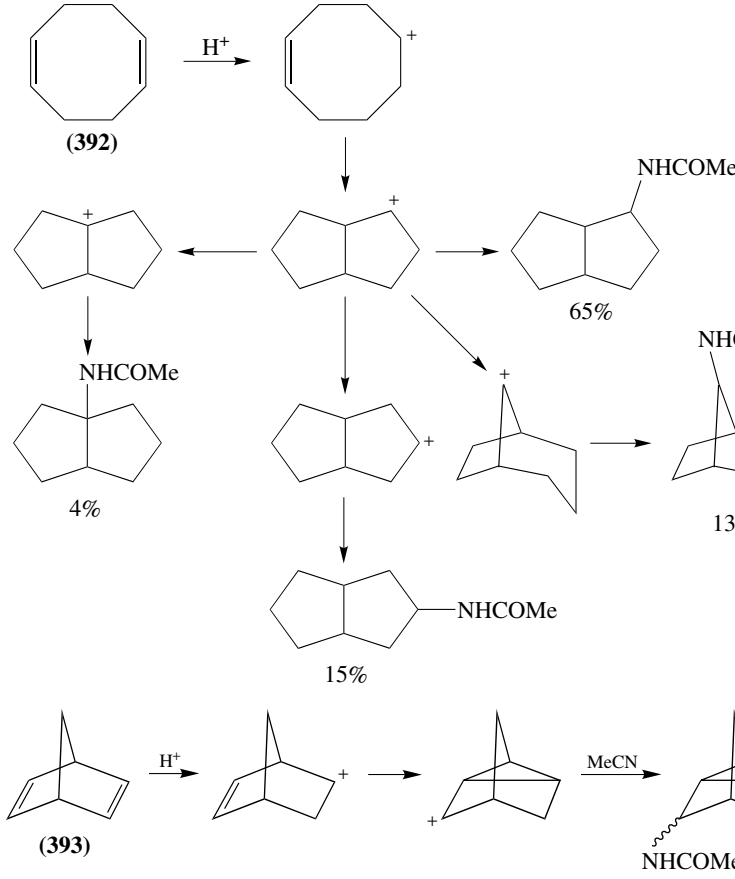
(138)


382
TFA
(387)
(388)
Et3SiH
H–
CF3COO–
OCOCF3

(139)


382
387
+
388
MeCN
MeCN
NHCOMe
NHCOMe
(389)
(390)
MeCN
NHCOMe
(391)

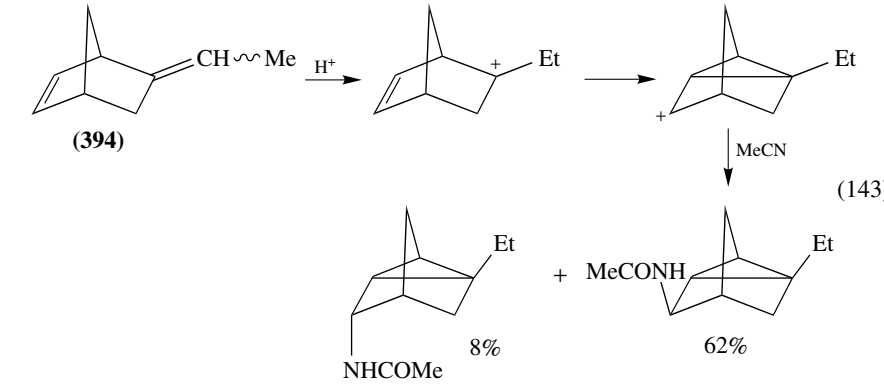
(140)


H+
(392)
NHCOMe
65%
NHCOMe
4%
NHCOMe
13%
NHCOMe
15%

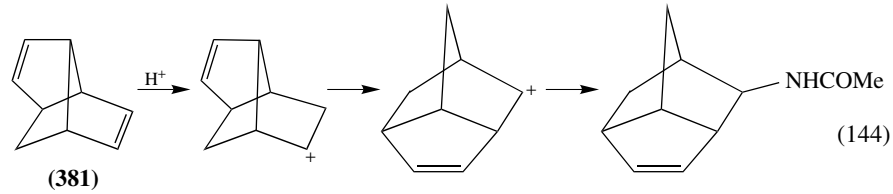
(141)

H+
MeCN
(393)
NHCOMe

(142)

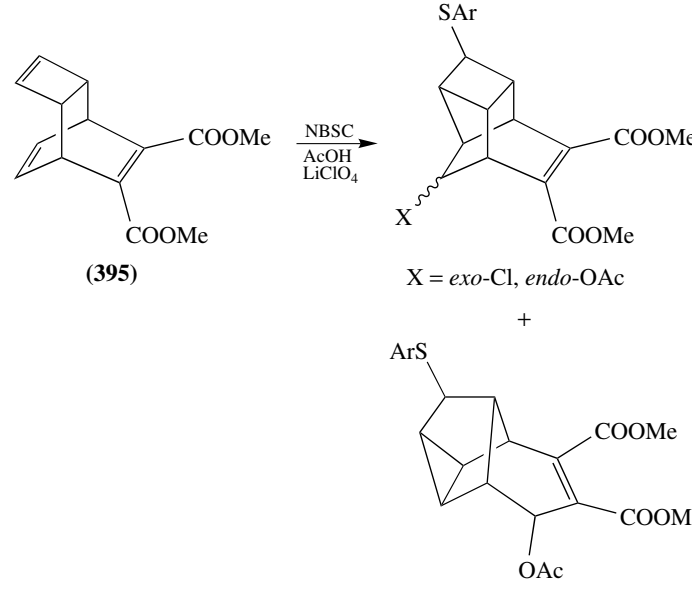


(394) (143)



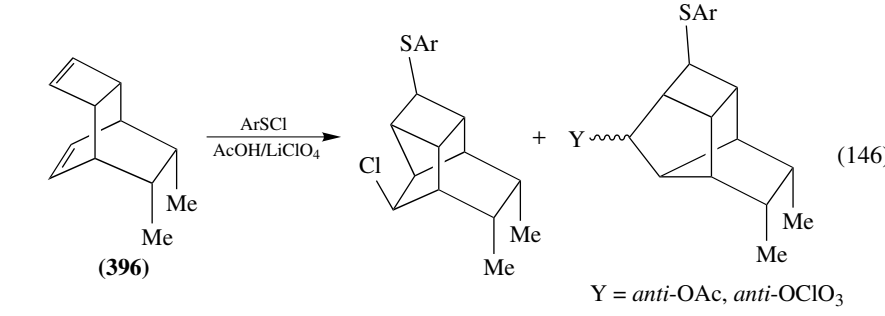
(381) (144)

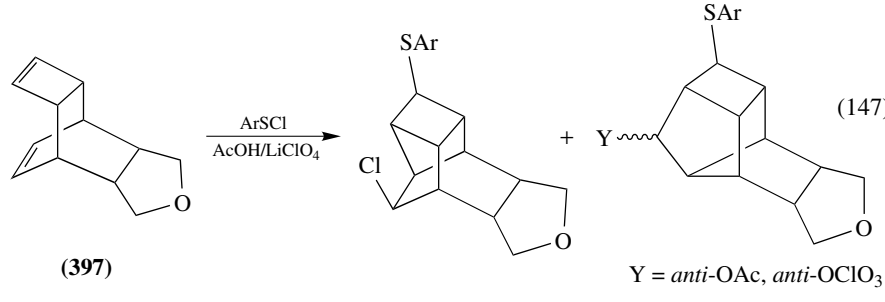
Wagner–Meerwein rearrangements occur also when arylsulfenyl chlorides or the mixtures $R_2NCl + SO_3$ (R = piperidino, morpholino) add to norbornadiene **393**[196,197]. An addition of 2-nitro- (NBSC) or 2,4-dinitrobenzenesulfenyl chloride to the polyenes **395**–**397** in AcOH and under 'doping conditions' (AcOH, with $LiClO_4$) is accompanied by Wagner–Meerwein rearrangements (equations 145–147)[198]. Thus, new types of struc-

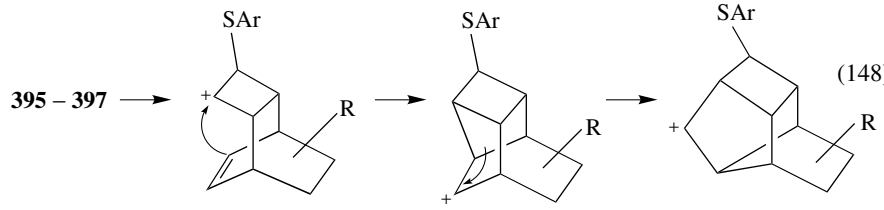


(395) (145)

tural Wagner–Meerwein rearrangements leading to the unusual cage structures, following the general mechanism, were discovered (equation 148).

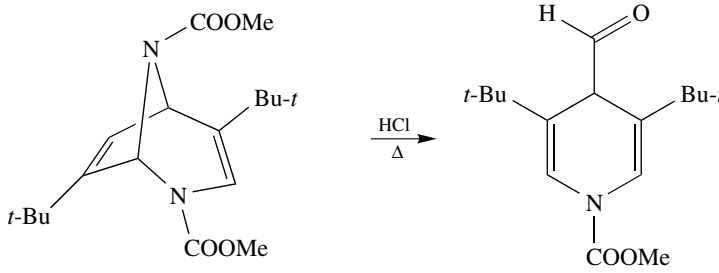






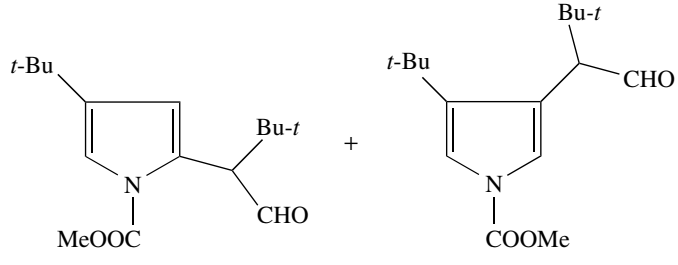
An interesting rearrangement of a bridged heterocyclic system proceeds under conditions of acid catalysis. The pyridine and pyrrole derivatives **(399–401)** were obtained in 31%, 14% and 10% yields, respectively, upon heating the diazabicyclic diene **398** in refluxing methanol for 12 h in the presence of 2M HCl (equation 149)[199]. The transannular cyclizations which were repeatedly mentioned above are typical transformations also for dimethylcyclooctadiene **402**[200,201]. It was shown that diene **402** in the presence of *p*-toluenesulfonic acid or $BF_3 \cdot Et_2O$ forms the bicyclic olefin **403** rather than its bicyclic isomer **404**[200]. When this reaction was carried out in aqueous medium containing an equivalent amount of *p*-TsOH, the isomeric bicyclooctane system **405** was obtained (equations 150 and 151).

A quite detailed review of transannular cyclizations was published[201] wherein their important role in biomimetic syntheses of sesquiterpenes as well as explanation of the biogenetic formation of the polycyclic natural compounds from their monocyclic precursors is discussed. The great significance of these transformations for the synthesis of natural products is also emphasized in a series of reviews which describe the cyclizations to form terpene derivatives, e.g., of the germacrane and humulene systems[202–206].

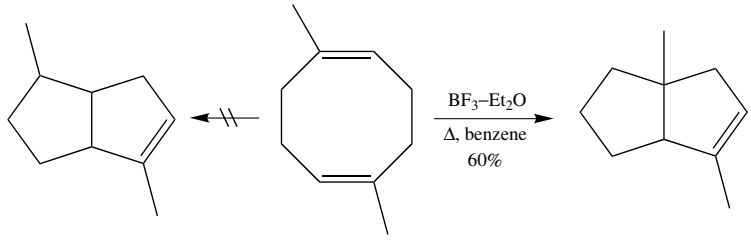


(398) **(399)**

(149)

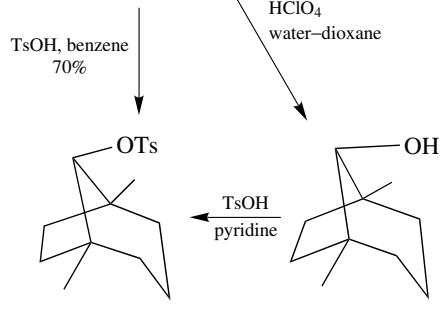


(401) **(400)**



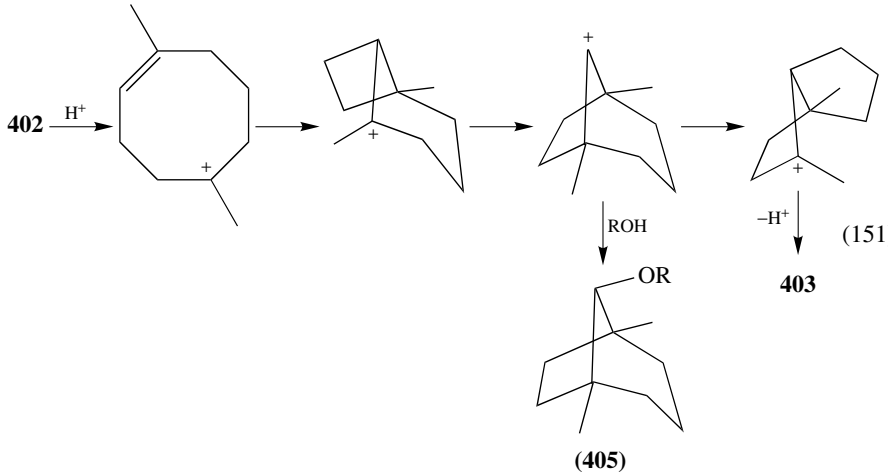
(404) **(402)** **(403)**

(150)



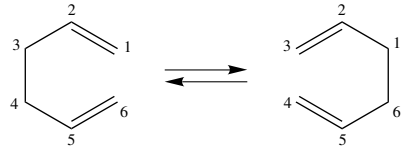
C. Cope Rearrangement

The main information available on the rearrangement of dienes and polyenes probably relates to the Cope rearrangement and its modifications. To our knowledge, more than 550 papers published since 1980 are devoted to this field, not counting the numerous descriptions in textbooks, monographs and the patent literature. Since there is no possibility to cover here all the voluminous information, we will consider, therefore, only the principal recent trends.



(151)

The Cope rearrangement and its variants are described very thoroughly in numerous reviews (see, e.g., References 11, 207 and 208). In general, these reactions can be represented by an extremely laconic scheme (equation 152). This system can also include cumulenes[24,25] and acetylene fragments[209] as well as various substituents and heteroatoms (see Sections IV.D and E).



(152)

1. Mechanistic considerations

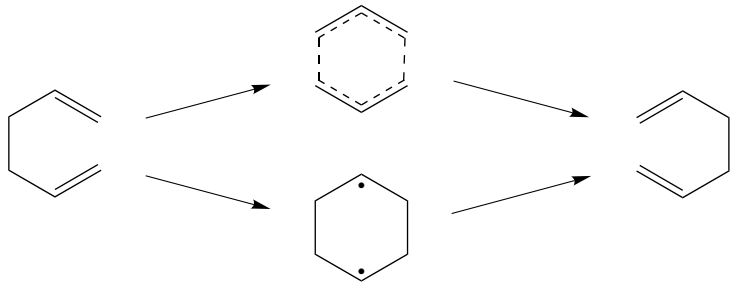
Along with a very wide synthetic application the Cope rearrangement continues to be a subject of intense debates. The key mechanistic question is whether the rearrangement of 1,5-hexadiene derivatives is concerted and passes via a six-electron 'aromatic' transition state, or whether it involves the formation of a diradical intermediate, i.e. a 'cyclization-cleavage' mechanism. In the former case, bond making and bond breaking occur synchronously (a survey of this question has been published[210]).

Cope himself formulated this transformation as what would now be called 'a synchronous pericyclic reaction'. This interpretation was supported by Woodward–Hoffmann's analysis of pericyclic processes. The Cope rearrangement of 1,5-hexadiene derivatives was regarded therefore for a long time as a classical example of an 'allowed' pericyclic reaction

which takes place via an aromatic transition state having a chair geometry. However, in 1971 Doering and coworkers[211] suggested an alternative non-synchronous mechanism in which formation of the new [C(1)−C(6)] bond precedes the rupture of the old [C(3)−C(4)] bond, and where the transition state can be formally represented as a diradical-like species derived from the 1,4-cyclohexylene diradical (so-called 'biradicaloid') (see Section II).

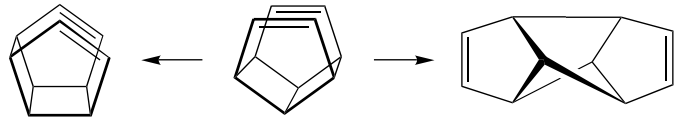
This problem was intensively studied both experimentally and theoretically. The quantum chemical calculations were carried out using various methods at different levels. The earlier calculations for the Cope rearrangement based on a CASSCF wave function for six electrons in the bonds rearranged were found to overestimate the diradical character of the wave function[212,213]. More recently, MP2 methods for the multireference wave function have been developed whose application to an estimate of the energy of the chair transition state has been described[214]. AM1 calculations of alternative transition states for the Cope rearrangement of 1,5-hexadiene derivatives have been discussed by Dewar and colleagues[215−217].

Using a valence bond scheme parametrized with an effective Hamiltonian technique, it was shown that the mechanistic preference for a synchronous pathway with an aromatic transition state versus a non-synchronous mechanism via biradicaloid intermediate can be controlled by two factors: (1) the stability of the long bond in the Dewar valence bond structure, and (2) the softness of the Coulomb interaction between the end methylene groups in the 1,5-diene chain. This means that the mechanism of rearrangement (equation 153) can strongly depend on substituents[218].



(153)

An AM1 study of the structure and mechanism of a degenerate Cope rearrangement, as well as a comparison with bullvalene and other $C_{10}H_{10}$ isomers, have been described[219] for hypostrophene **406** which was first obtained in 1971 by Pettit and coworkers[220]. Hydrocarbon **406** is capable of undergoing a degenerate isomerization and, at 80 °C, it can rearrange into another $(CH)_{10}$ isomer **407** (equation 154)[219]. The semiempirical AM1 SCF (self-consistent field) MO calculations for the degenerate Cope rearrangement of **406** show that the activation energy is greater than that for the comparable rearrangement of bullvalene, barbaralane and semibullvalene (see also Section IV.C.2.d).

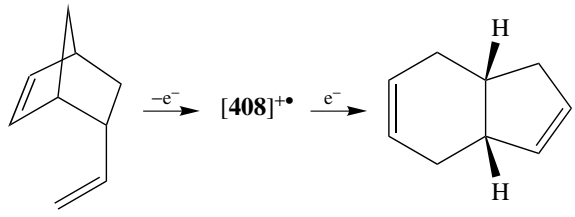


(154)

(406) **(407)**

The first evidence that the radical cation generated by a single-electron transfer (SET) of an unsymmetrical 1,5-diene **408** can undergo a [3,3]-sigmatropic shift (Cope reaction)

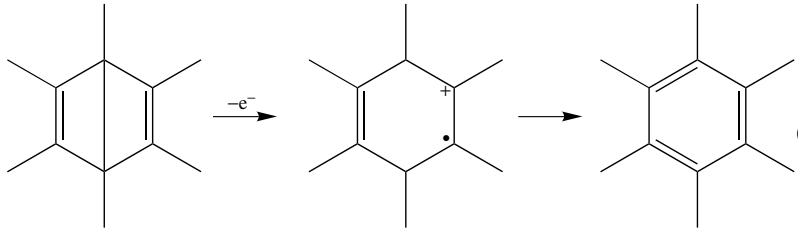
at 100–150 K to form diene **409** whereas the neutral Cope rearrangement **408** → **409** occurs at 400–440 K only (equation 155) (see also Section IV.C.1.b) was reported in 1992[221]. This demonstration of a normal Cope rearrangement at the radical cation stage involved ESR measurements. The very detailed magnetic resonance studies (CIDNP and ESR) as well as *ab initio* calculations of the radical derived from various hexadiene systems (dicyclopentadiene, semibullvalene, barbaralane) have established three distinct structural types for such radical cations, namely a 'dissociative' species containing two separate allylic fragments, cyclohexane-1,4-diyl radical cations in a chair conformation and bridged cyclooctadiene-diyl structures (boat conformers)[222]. This work states that the radical cations derived from 1,5-hexadiene systems are related to the putative mechanistic extremes of the Cope rearrangement. However, most generally this reaction can be formulated via three mechanistic extremes: (1) an associative mechanism when addition precedes cleavage, (2) a dissociative mechanism when cleavage precedes addition (*vide infra*) and (3) a concerted mechanism via synchronous addition and cleavage. The extensive experimental and theoretical investigations have established that the thermal Cope rearrangements proceed via the concerted mechanism[222]. The chair-like and boat-like conformations of the transition state in Cope rearrangement involving diradical intermediates were discussed in the publications mentioned above[24,25].



(155)

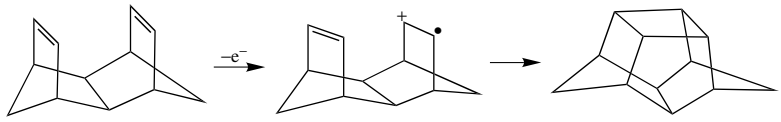
(408) **(409)**

A radical-cation Cope rearrangement of 2,5-diphenylhexa-1,5-dienes under electron ionization conditions (by mass spectrometry at 70 eV) has been described to occur in the gas phase. The reaction directionality differs from that in a thermal transformation[223]. The rearrangement of hexamethyl-Dewar-benzene **410** into hexamethylbenzene (equation 156) as well as the closure of the bridged hexahydrodiene **411** into the so-called 'birdcage hydrocarbon' **412** proceed during hemin-catalyzed epoxidation via a radical cation intermediate (equation 157)[224]. These processes are Cope-like rearrangement because two double bonds are separated by one CH_2 group in **410** and by three sp^3-hybridized C-atoms in **411**.



(156)

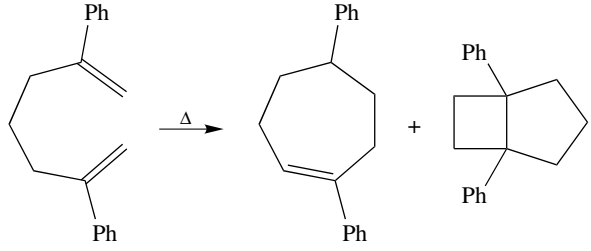
(410)



(157)

(411) **(412)**

Numerous attempts to experimentally confirm the possibility of the diradical mechanism of the Cope rearrangement were conducted for example, by the introduction of substituents which are capable of stabilizing the radicals (e.g., the cyano or phenyl group) (for a review, see Reference 225). A peculiar approach to develop a reliable model of a non-concerted, diradical mechanism closely related to the Cope rearrangement was described[225]. It involves the insertion of a seventh carbon atom between positions C(3) and C(4) in 1,5-hexadiene, and was called a 'frustrated' Cope rearrangement. The authors believe[225] that the resulting system would still be able to undergo the first step of the rearrangement, i.e. the formation of a single C−C bond between the terminal atoms of the 1,5-diene, but it would be unable to complete the second step, i.e. the cleavage of the C(3)−C(4) bond (equation 158). Heating of 1,6-heptadiene **413** in *o*-dichlorobenzene at 220 °C for 401 h gave the cyclic olefin **414** (49%) along with the saturated bicycle **415** (19%) and the unconverted precursor **413** (32%). It was concluded that when the lifetimes of the conjectured diradicals become longer due to unavoidable conformational barriers which protect them from instantaneous collapse, the diradicals become the intermediates and can be more or less easily detectable[225].

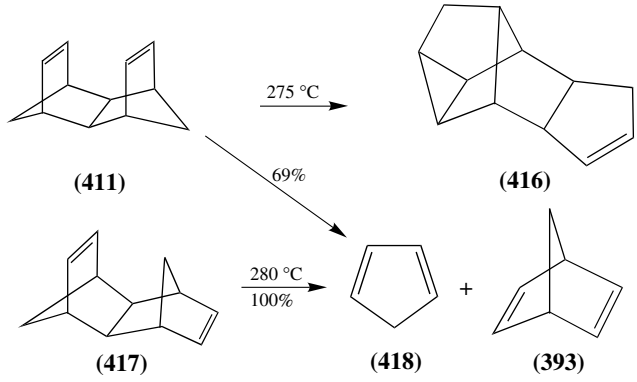


(158)

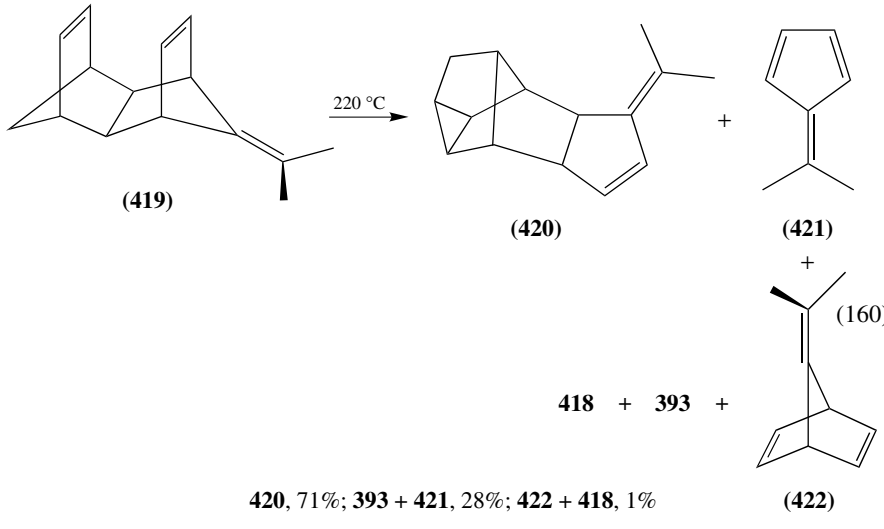
(413) **(414)** **(415)**

Another example of a similar approach for a novel type of homo-Cope rearrangement by thermolysis of the sterically rigid 1,5-heptadiene derivative *endo,endo*-dimethanenaphthalene **411** was described[226]. Relatively small structural variations in this system seem to bring about a change from a pericyclic to a stepwise mechanism. Gas-phase thermolysis of **411** at 275 °C under carefully controlled conditions (primarily in order to exclude an acid catalysis) leads to isomerization to the polycyclic olefin **416** (31%) besides the expected retro-Diels–Alder products, cyclopentadiene **418** and norbornadiene **393** (formed in 69% combined yield) (equation 159)[226]. The *endo,exo*-isomer **417** forms under the same conditions only the latter two products (**418**, **393**) without rearrangement. Thus, one of the possible mechanisms, i.e., via a retro-Diels–Alder step, can be excluded. These results confirm a pericyclic *homo*-Cope rearrangement of *endo,endo*-**411** to **416**. This novel rearrangement was further studied by using structurally related *exo*-isopropylidene-substituted systems (**419**, *endo,endo*-; **423**, *exo,endo*-; and **424**, *endo,exo*-) (equations 160–162)[226]. Similarly to compound **411** the asymmetrical isomer **419** having face-to-face arrangement of the two *endo*-cyclic π-bonds was transformed on thermolysis at 220 °C to the rearrangement product **420** and the retro-Diels–Alder products **393**, **418**, **421** and **422**

(equation 160), whereas only dimethylfulvene **421** and norbornadiene **393** resulted from thermolysis of the *exo,endo*-triene **423** (equation 161). However, the *endo,exo*-isomer **424** undergoes predominant rearrangement to form the polycyclic diene **425** (equation 162). It was concluded from these findings, as well as from the activation entropy values, that the rearrangements of compounds **419** and **424** are stepwise processes, in contrast to the pericyclic *homo*-Cope mechanism of the parent system **411**. The change in the mechanism may be explained by a different stabilization of the potential diradical intermediates.

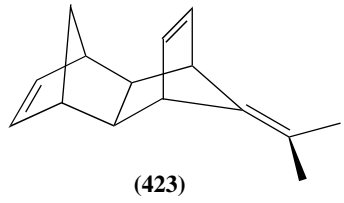


(159)

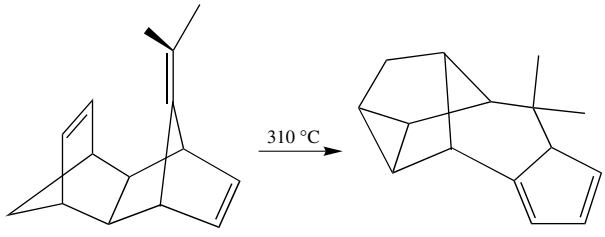


(160)

420, 71%; **393** + **421**, 28%; **422** + **418**, 1%



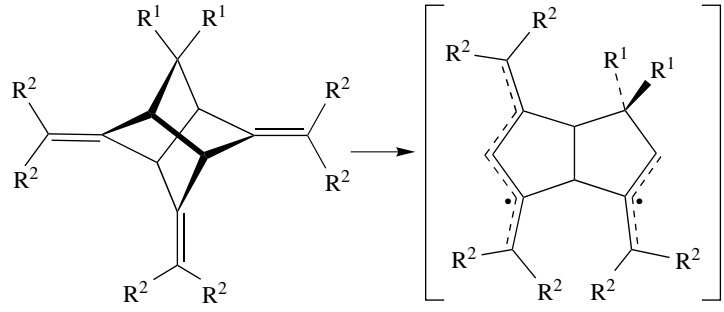
(161)



(424) **(425)** 63%

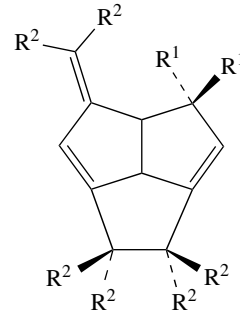
(162)

Gleiter and colleagues have described very interesting candidates for a two-step Cope rearrangement, namely the stellatriene **426a**, its hexamethyl derivative **426b** and the spirocyclic derivatives **426c** and **426d**[227,228]. These trienes and the corresponding dienones rearrange to form triquinane derivatives **427** at temperatures between 25 °C and 50 °C (equation 163). These reactions can be formulated as a stepwise Cope rearrangement involving a diradical mechanism. The thermal lability of the stellatriene derivatives [$t_{1/2}$ (30 °C) for **426a**, **426b** and **426d** equals 30, 75 and 300 min, respectively] can be attributed to the very easy cleavage of one of the long central bonds. The introduction of an alkyl group is one of the two general approaches to increase the stability of this strained structure.



(426a–d)

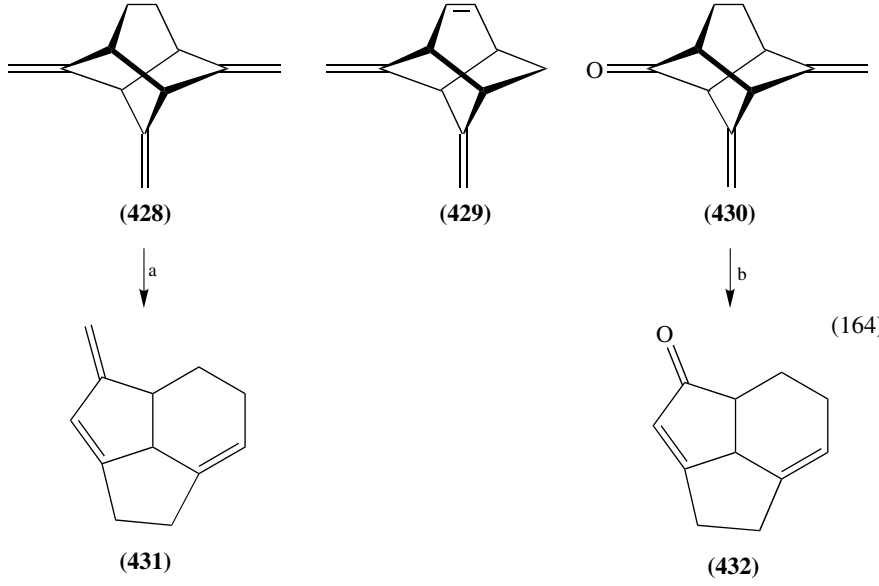
(163)



(427a–d)

(**a**) $R^1 = R^2 = H$
(**b**) $R^1 = H$; $R^2 = Me$
(**c**) $R^1R^1 = (CH_2)_4$; $R^2 = H$
(**d**) $R^1R^1 = (CH_2)_4$; $R^2 = Me$

Another possibility to overcome this lability consists in a release of strain by elongation of the 2,7-bridge, for example, by using compounds **428** and **429** and also dienone **430** (equation 164)[228]. Triene **429** is almost as labile as compound **426b** whereas the halflives of the stellatriene **428** and the dienone **430**, both having the two-carbon bridges and forming the polycycles **431** and **432**, are 560 h and 102 h at 80 °C, respectively.



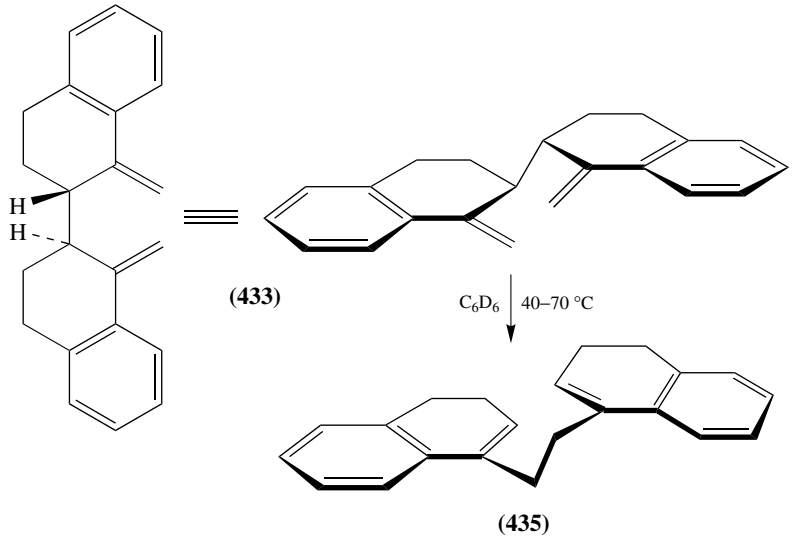
(428) **(429)** **(430)** (164)

(431) **(432)**

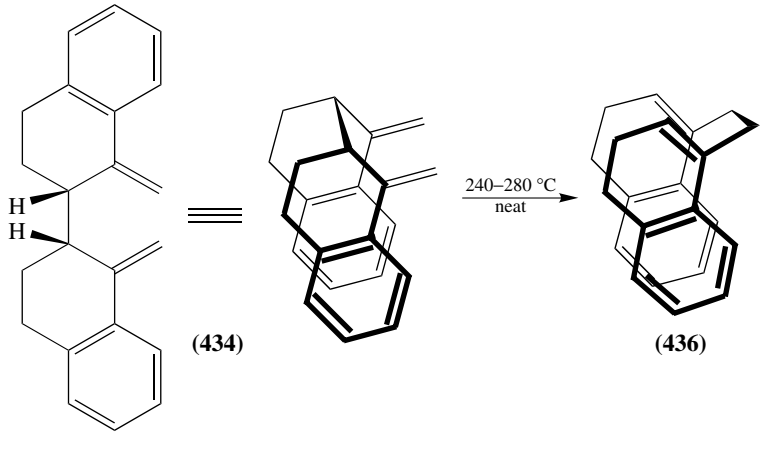
(**a**) 100 °C, toluene, 7 days
(**b**) 80 °C, benzene, 15 days

An influence of phenyl substituents on the geometry of the transition state was studied by using the *d*,*l*- and *meso*-isomers **433** and **434** of a polycyclic diene[229]. The *d*,*l*-diastereoisomer **433** is constrained to undergo Cope rearrangement in the chair conformation whereas the *meso*-diastereoisomer **434** is constrained to have a boat transition state: The activation free energies for their unimolecular [3,3]-sigmatropic rearrangement to give products **435** and **436** are 25.2 ± 2.9 (for **433**) and 38.1 ± 3.7 (for **434**) kcal mol^{-1} and from them a $k_{d,l}/k_{meso}$ ratio of 7×10^6 at 150 °C was determined (equations 165 and 166)[229].

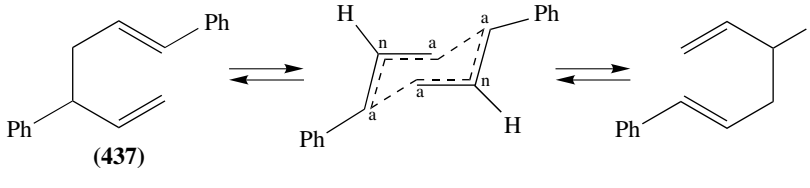
Doering and coworkers[230] have suggested distinguishing two types of positions in the hypothetical 'aromatic' transition state of the thermal Cope rearrangement, designated as 'a' ('active') and 'n' ("nodal") (equation 167). Previous examinations of radical-stabilizing substituents have concentrated on their influence in the 'n' positions. In order to obtain a quantitatively reliable estimate for the effect on the 'a' positions, the activation parameters of the degenerate rearrangement of 1,4-diphenyl-1,5-diene **(437)** ^{13}C-labeled in the C(6) position were evaluated. It was concluded that two phenyl groups in the 'a' positions have lowered the activation enthalpy by 32.2 kJ mol^{-1} relative to the parent 1,5-hexadiene while two phenyl groups in the 'n' positions of 3,5-diphenyl-1,5-hexadiene have lowered the activation enthalpy by 71.2 kJ mol^{-1}. These results explain an advantage of using phenyl substituents in order to construct systems which enable one to change the concerted mechanism of the Cope rearrangement toward the two-step, so-called 'diyl' mechanism[230].



(165)



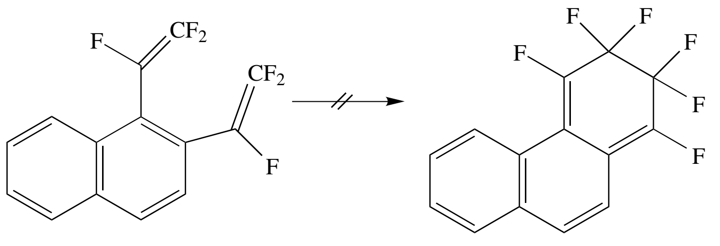
(166)



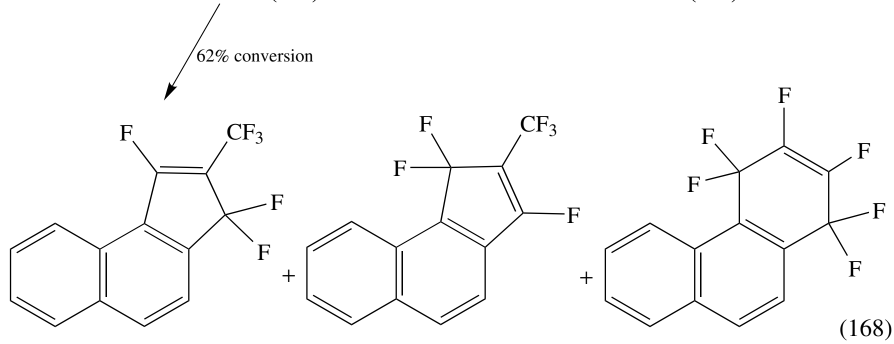
(167)

The Cope rearrangement mechanism can be also strongly affected by other substituents. Thus, the 'normal' electrocyclic process in the thermal isomerization of divinyl aromatics has been suppressed relative to the thermolysis of 1,2-bis(trifluorovinyl)naphthalene **438** (in benzene, at 193 °C, 24 h)[231]. Three major products **440**–**442** were isolated from the reaction mixture, but none of them was the expected product **439**. Also formed in low

yields were **443** and **444** (equation 168). The thermolysis of the more thermodynamically favorable phenanthrene derivative **445** has provided a greater insight into the chemistry of this process[231]. A small amount of the electrocyclic product **446** was obtained, but again the main products were **447**–**449**, i.e, the major reaction observed was similar to that for compound **438** (equation 169).



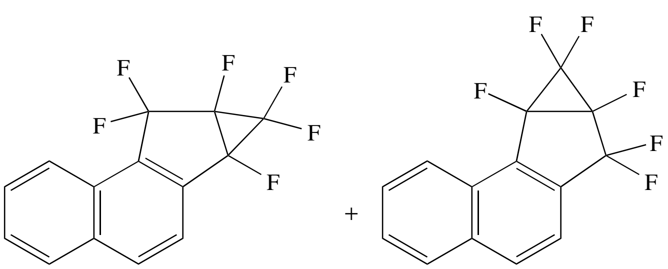
(438) **(439)**



(168)

(440) 43% **(441)** 32% **(442)** 15%

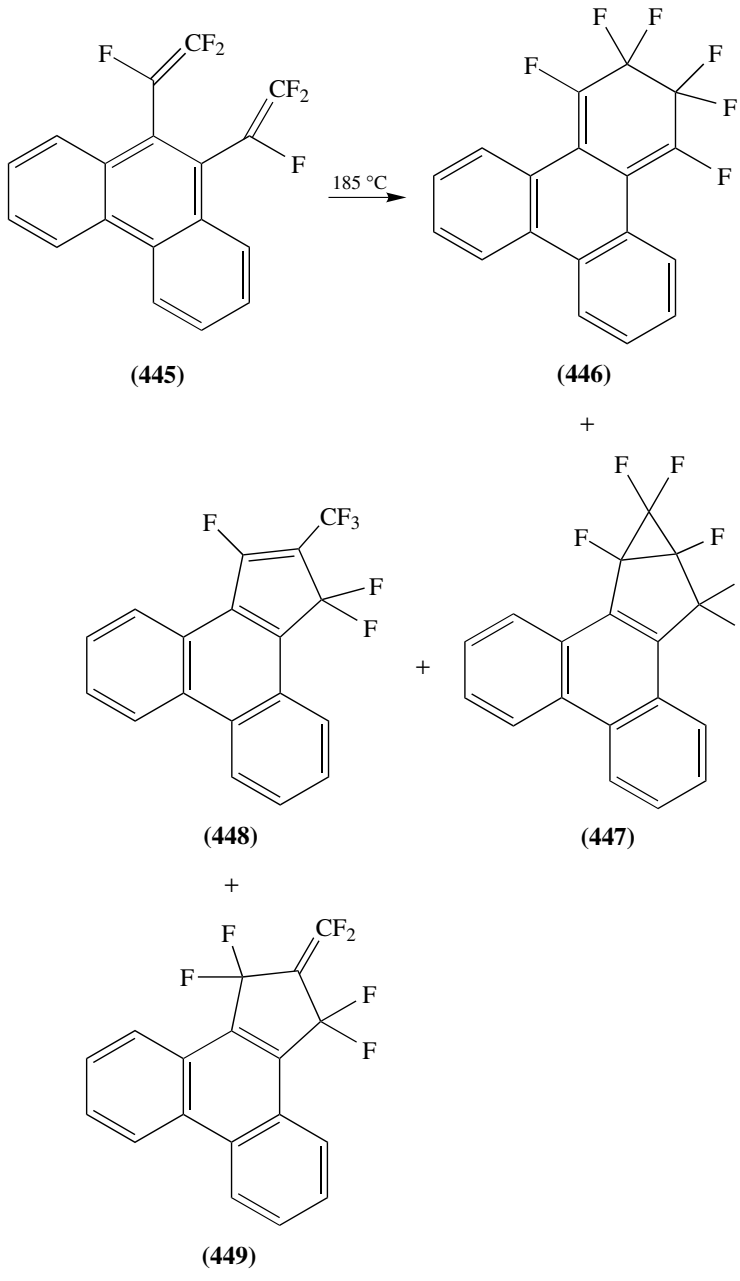
+



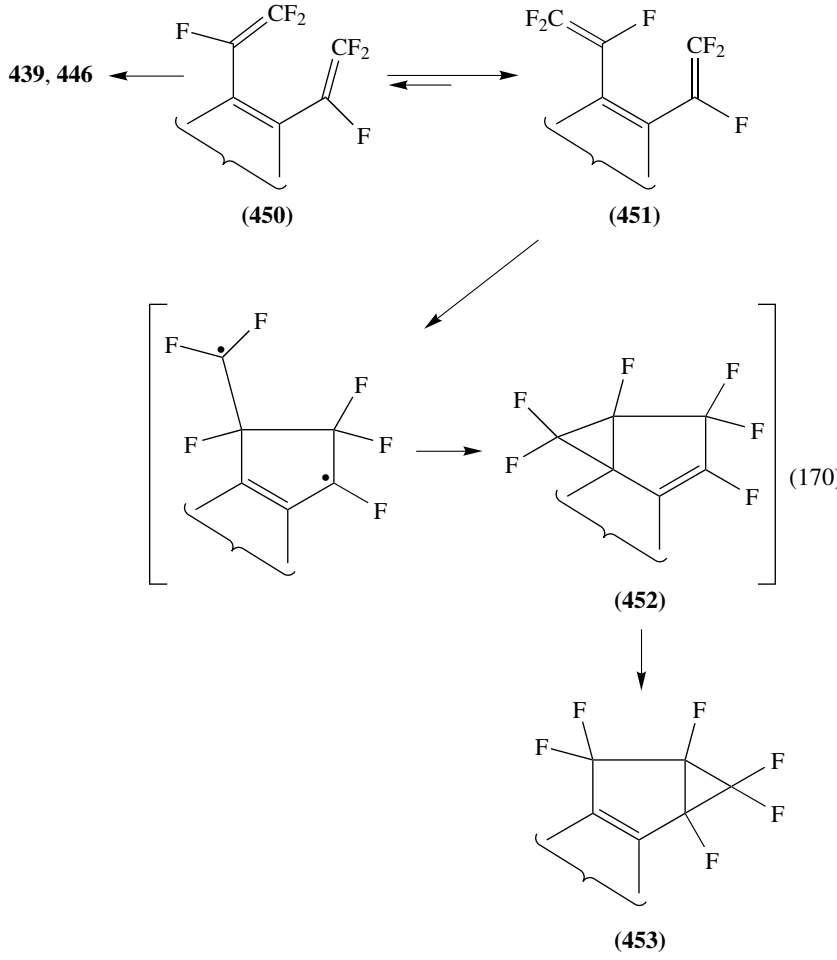
(444) 3.2% **(443)** 6.6%

It should be noted that products like **443** and **447** are the normal products of photochemical reactions of acyclic 1,3,5-hexatrienes, as well as of divinyl aromatics, but are quite unusual for thermal transformations of such substrates. Presumably, the electrostatic repulsion between CF_2 groups prevents the formation of conformation **450** which is necessary for the electrocyclic ring closure (i.e. **438** → **439** and **445** → **446**). Instead, it leads to conformation **451** which is favorable to generate the diradical and then the fused vinylcyclopropane intermediates **452** (equation 170). Note that the rearrangement **452** → **453**

(corresponding to formation of products **443**, **444** and **447**) is essentially a 'vinylcyclopropane rearrangement' (Section III.A), whose driving force is an aromatization of an annulated system.



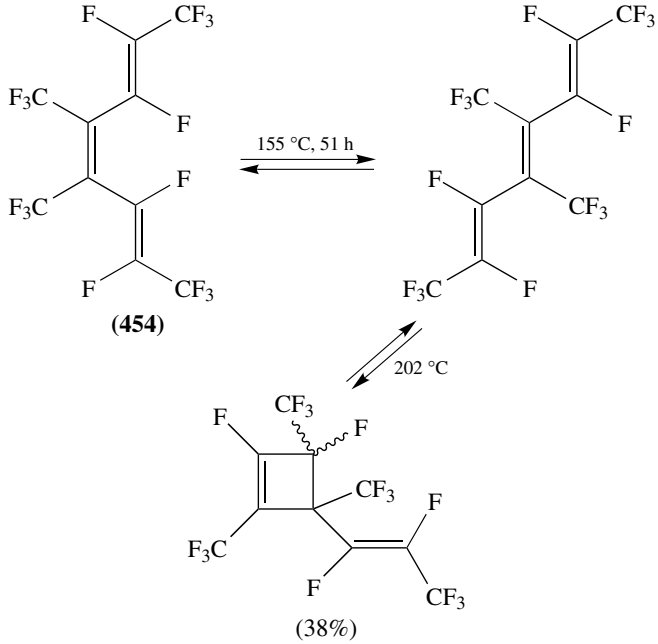
(169)



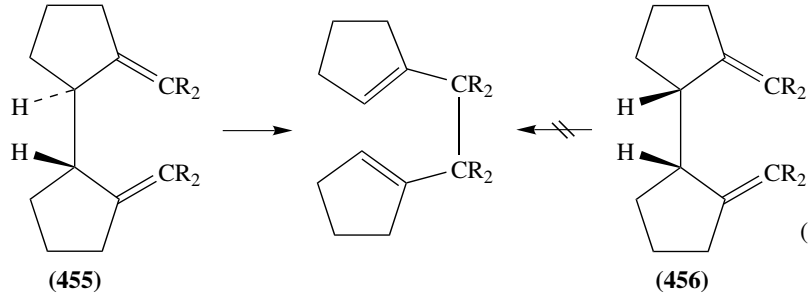
The acyclic fluorinated 1,3,5-hexatriene system **454** is also resistant to 6π-electron electrocyclic ring closure at temperatures up to 200 °C while the analogous hydrocarbons cyclize easily at 160 °C (equation 171)[232].

The rearrangements of the diastereoisomeric dienes **455** and **456** are compared in the same work[232]. In accordance with the results of a similar investigation[229] (equations 165 and 166) the isomer **455** (R = F) undergoes a Cope rearrangement more easily than its hydrocarbon counterpart (**455**, R = H) while the Cope rearrangement of isomers **456** (R = H, F) is strongly inhibited (equation 172). The contrasting behavior of compounds **455** and **456**, as well as of **433** and **434**, is ascribed to steric repulsions of the *cis*-fluorine C(1) and C(6) substituents in the former pair as well as to the presence of bulky phenyl groups in the latter pair of compounds.

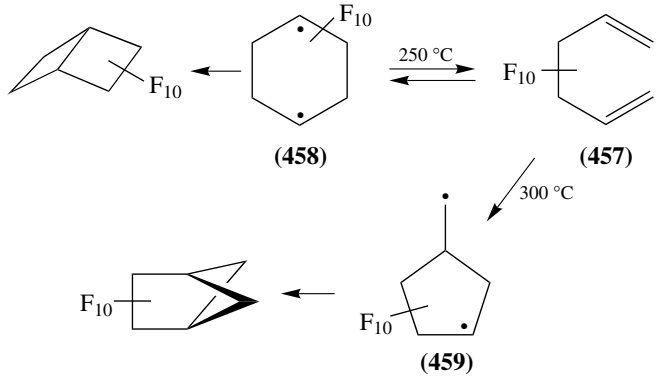
The competition of the Cope rearrangement with cyclization processes was reported for perfluoro-1,5-hexadiene **457**[233]. The cyclizations proceed undoubtedly via the corresponding diradicals **458** and **459** (equation 173). This course of events was revealed by using a


F
CF3
F3C
F
F3C
F
F
CF3
155 °C, 51 h
202 °C
(454)
(38%)

(171)

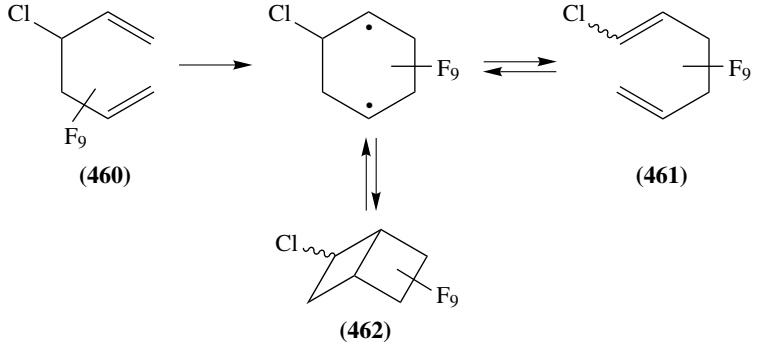

H
H
CR2
CR2
CR2
CR2
CR2
CR2
(455)
(456)

(172)


F10
F10
F10
250 °C
300 °C
(458)
(457)
(459)

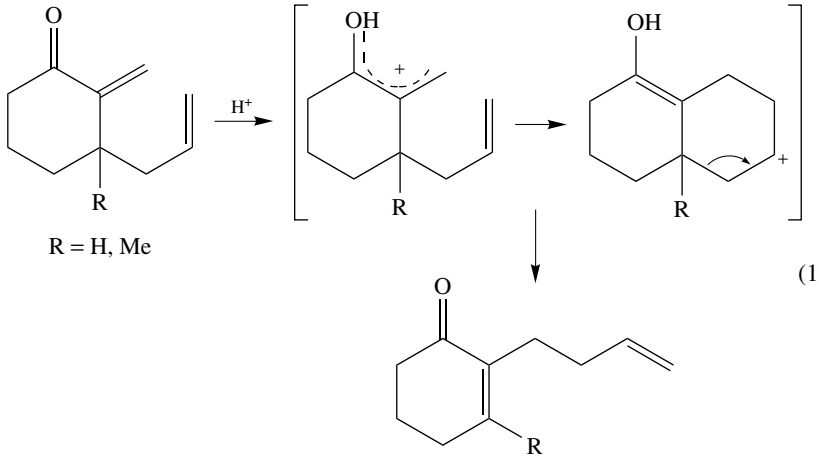
(173)

Cl-labeled fluorinated 1,5-hexadiene **460** (equation 174). The rearrangement occurs slowly above 210 °C to furnish compound **462** but without formation of Cope product **461**. The latter was detected only when the reaction was conducted for 2.5 days at 210 °C, when the **461** : **462** ratio was still only 1 : 10.



(174)

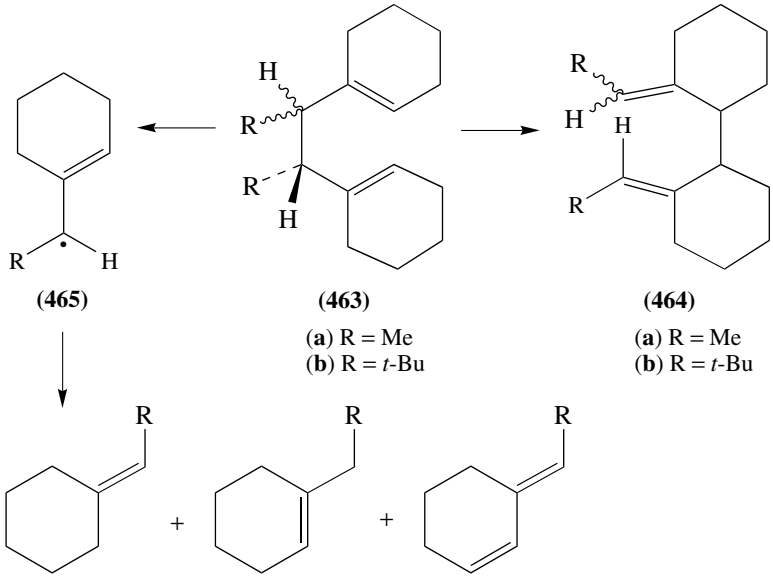
The influence of substituents on the Cope rearrangement can also originate from acid catalysis conditions. For instance, the rearrangement of 1,5-dienes having an acyl substituent at the C(2) position is strongly accelerated by both protic and Lewis acids (equation 175)[234]. The bulky substituents can also lead to a competition with the Cope rearrangement, with homolytic bond cleavage. For example, diene **463a**, which is less sterically hindered than diene **463b**, undergoes preferably a thermal Cope rearrangement to give diene **464a**. However, the thermolysis of the more strained **463b** affords the products of both Cope rearrangement **464b** and homolysis via radical **465** (equation 176)[235].



(175)

The dissociative mechanism of the Cope rearrangement casually mentioned above[222] can be illustrated by two examples of Pd-catalyzed reactions. The migration of an allyl group from carbon to carbon in the pyridine system **466** occurs in the presence of a Pd^0 catalyst[236]. Refluxing dilute solutions of precursors **466** (R^1, R^2 = H, Me) in toluene for 7 h or in *n*-heptane for 24 h gave derivatives **468**. The pyridine allyl ether **469** was also

converted to **468** by reflux for 24 h in dibutyl ether. However, all attempts to effect the thermal rearrangement of **466** ($R^1 = R^2 = Me$) failed. It was found that addition of a catalytic amount (4 mol%) of $(Ph_3P)Pd$ to solutions of various compounds **466** at room temperature catalyzed the allyl migration in both ether **469** (from O to C) and **466** (from C to C) in nearly 100% yields (equation 177). The authors[236] believe that this rearrangement of compounds **466** does not proceed via a 'cyclization-induced rearrangement'[237]. It seems more likely that ion pairs such as **467** having an extensively delocalized negative charge, can be formed. A similar explanation for the Pd^{II} catalyzed Cope rearrangement of 1,5-dienes was reported because the 1,5-dienes could generate acetone in the presence of oxygen and $(PhCN)_2PdCl_2$[238]. The general problems of catalysis in Cope and Claisen rearrangements were summarized in a survey[11].

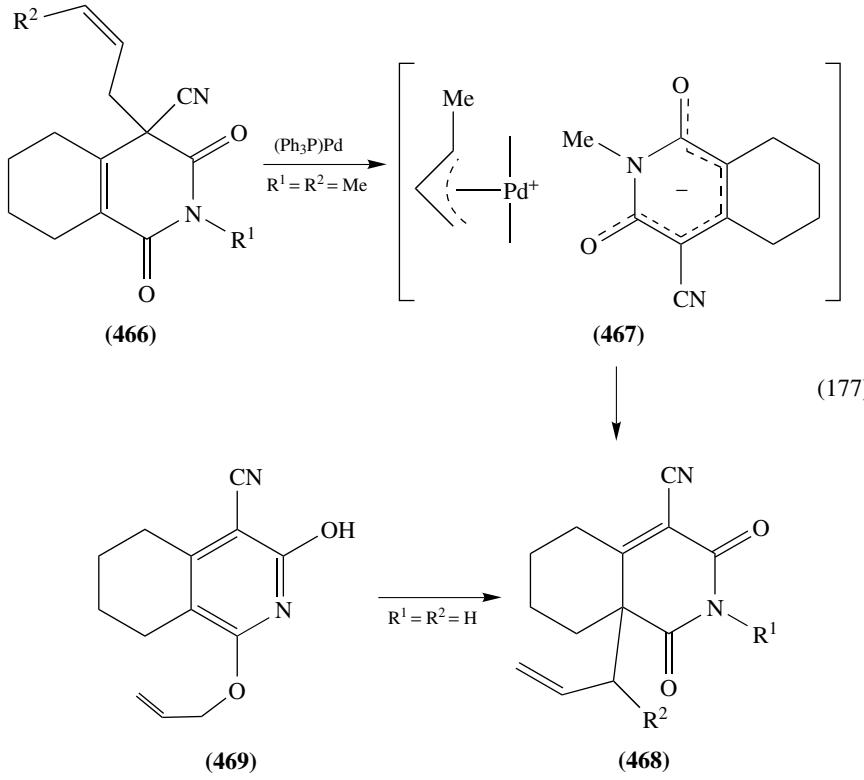


(176)

To shift an equilibrium Cope rearrangement in the desired direction, different driving forces such as aromatization, conjugation, strain or irreversible consecutive reaction of one of the dienes can be exploited. For example, the method for synthesis of the biologically active 3-indoleacetic acid derivatives is based on tandem Wittig olefination and Cope rearrangement induced by aromatization[239]. Treatment of indolin-3-ones **470** with phosphonium ylides **471** (R^3 = COOMe, COOBu-*t*, CN, COMe, COPh; R^4 = H, Me) affords dienes **472** which undergo the Cope rearrangement (refluxing toluene, 5–72 h, 32–87%) to give the indole derivatives **473** (equation 178)[239]. The first example of the transformation of polyolefinic hydrocarbons to their aromatic isomers as a result of Cope rearrangement was reported recently[240].

As appropriate model compounds for these reactions[240] the bridgehead substituted dihydro-4-methyleneazulenes **474** were employed. Allyl-, crotyl- and propargyl-substituted dihydroazulenes **474** and **476** can be easily rearranged to the 4-substituted azulenes **475** and **477** (equations 179 and 180) whereas all attempts to obtain 4-benzylazulene **479** by rearrangement of precursor **478** gave only polymeric products (equation 181). Undoubtedly, this failure can be explained by the fact that the Cope rearrangement becomes very

difficult or even impossible if one of the unsaturated fragments in the diene is part of an aromatic structure. However, it was shown that systems **480** derived from 2- or 3-benzo[*b*]thiophene are capable of undergoing the Cope rearrangement (equation 182)[241].

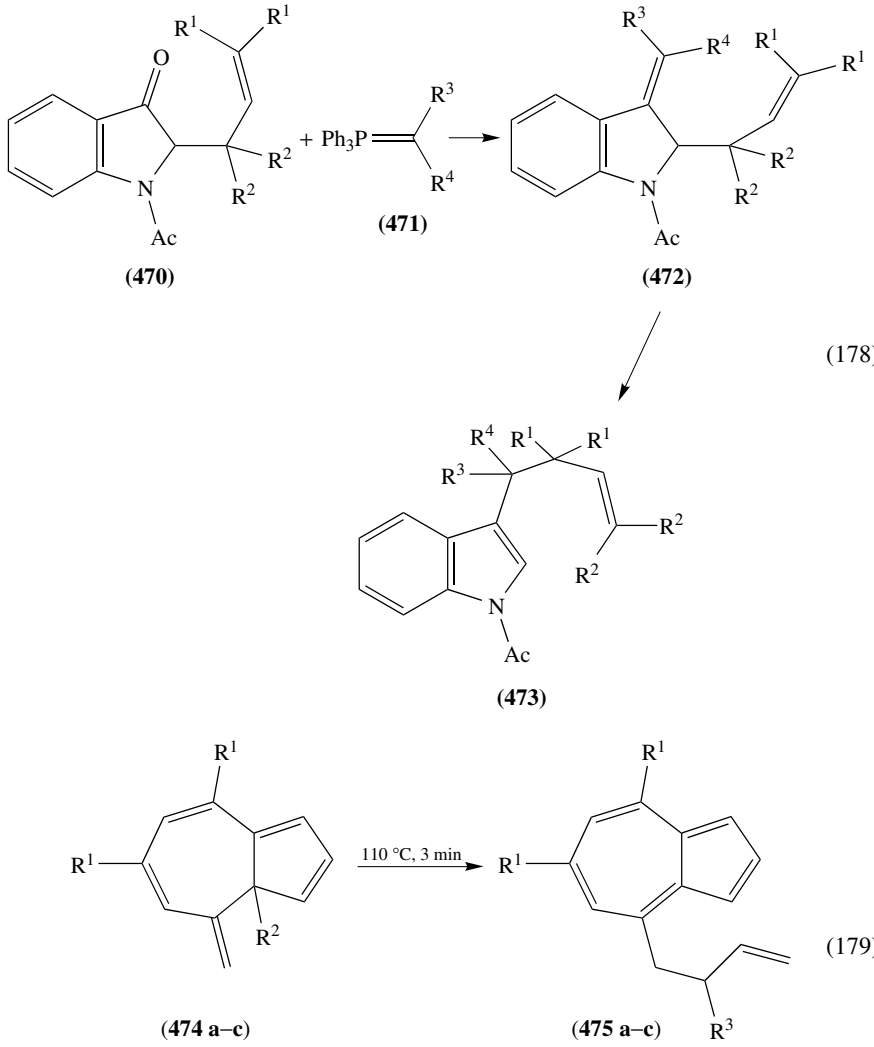


(177)

Apparently, the aromatization of the heterocyclic cation serves as a driving force of the Cope rearrangement in the transformation of the 3-formyl-4-allyl-4*H*-pyrane **(481)** into poly-substituted pyrylium salt **483** which presumably proceeds via **482** (equation 183)[242].

An irreversible consecutive reaction as a driving force to shift an unfavorable Cope rearrangement equilibria in the needed direction can be illustrated by the Cope–Claisen tandem process used for the synthesis of chiral natural compounds[243]. It was found that thermolysis of *trans*-isomeric allyl ethers **484** or **485** at 255 °C leads to an equilibrium mixture of the two isomers in a 55 : 45 ratio without conversion into any other products (equation 184). Under the same conditions the isomer **487** rearranges to give the Cope–Claisen aldehyde **491** (equation 185). Presumably, the interconversion **484** ⇌ **485** proceeds via intermediate **486** whose structure is not favorable for Claisen rearrangement. In contrast, one of the two cyclodiene intermediates of process **487** ⇌ **488** (viz. **490** rather than **489**) has a conformation appropriate for irreversible Claisen rearrangement[243].

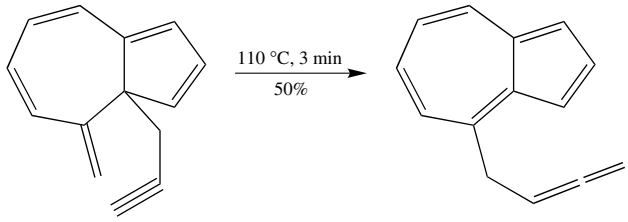
It should be noted that the stereochemical aspects of the Cope rearrangement are widely used for synthesis of various natural products, e.g. of the elemene-type derivatives **493**–**496** starting from germacrene-type sesquiterpenes **492** having cyclodeca-1,5-diene structure with stable conformations (equation 186)[244].



2. Reactions of divinylcycloalkanes

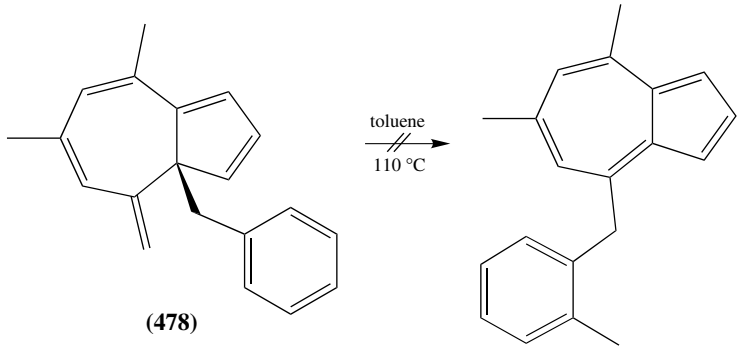
A large group of the peculiar 1,5-diene derivatives includes 1,2-divinylcycloalkanes in which one of the vinyl groups or even both can be part(s) of a carbo- or a heterocycle. Such structures were already mentioned above (e.g. **110**, **381**, **406**, **408**, **420**, **484**), and we will consider here their synthetic utility.

a. Divinylcyclohexanes. A key step in the synthesis of tricyclic ring systems containing the stereogenic centers of the morphine structure is a Cope rearrangement of ketone **497** to dienone **498** (xylenes, 250 °C, 22 h, 88%) (equation 187)[245].



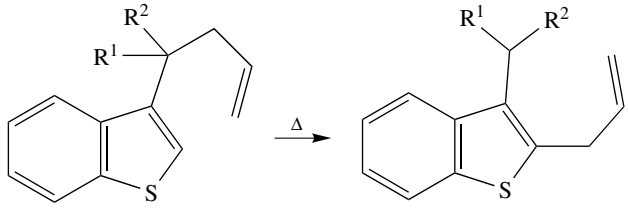
(180)

(476) **(477)**



(181)

(478) **(479)**

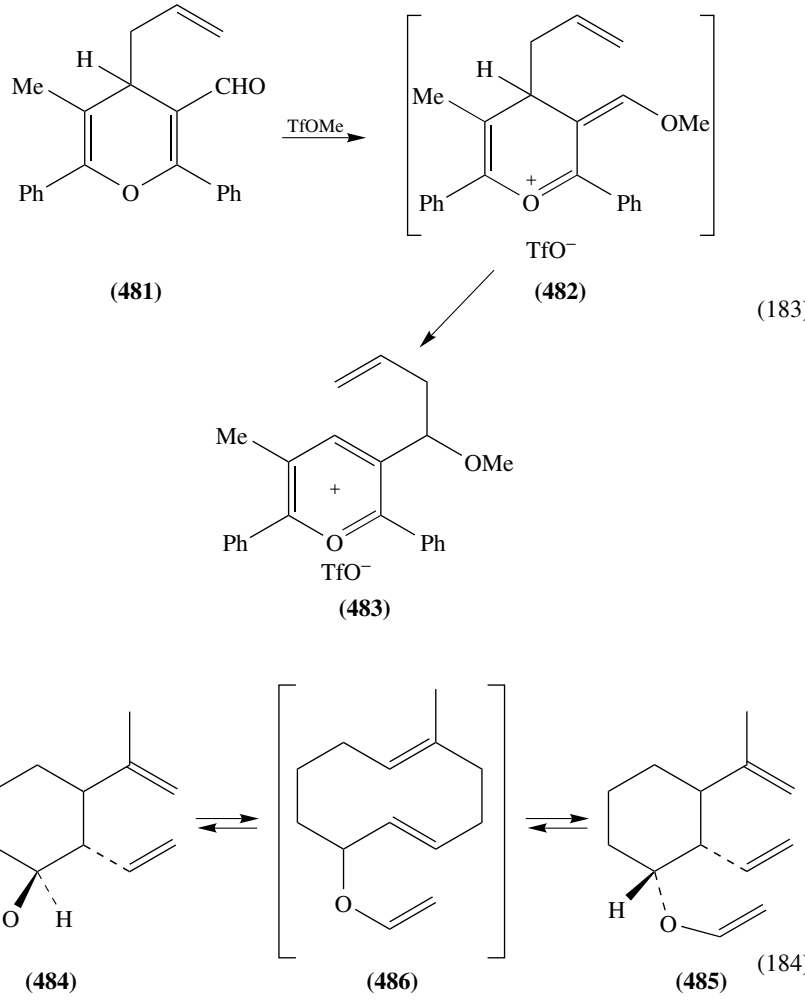


(182)

(480)

(**a**) $R^1 = R^2 = COOEt$ (215–225 °C, 11 h, 8%)
(**b**) $R^1 = CN$, $R^2 = COOEt$ (205–215 °C, 7 h, 6%)

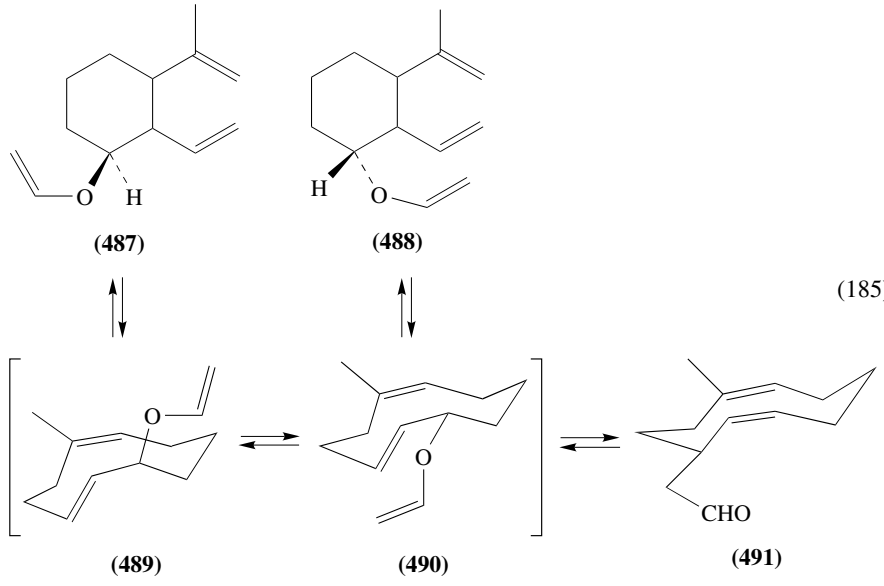
Interesting examples of a tandem Cope–Cope rearrangement are represented by the transformation of Cookson's diester **499**, which proceeds thermally to afford its ring-degenerate isomer **500** (330–350 °C, as a melt) (equation 188)[246], and by thermal isomerization of bicyclic triene **501** into hexahydro-1-vinylnaphthalene **502** upon heating in chlorobenzene at 220 °C for 20 h (equation 189)[247].



b. Divinylcyclopentanes. A peculiar cycle of two photochemical and one thermal isomerization was reported for 1,3-bis(α-naphthyl)propane **503**. The thermal rearrangement of the divinylcyclopentane **504** is presumably assisted by the conjugation created in the dihydronaphthalene fragments of product **505** (equation 190)[248].

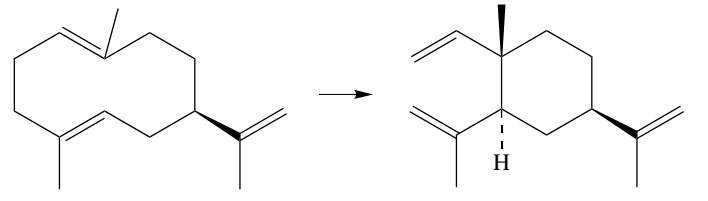
It was found that Cope rearrangement of the structurally rigid tetracyclic molecule **506** is remarkably accelerated by creating a remote (i.e. non-conjugated) carbenium ion center by an ionization of a ketal group (equation 191)[249]. The possibility of both classical and non-classical ion participation in this Cope rearrangement was revealed by using MNDO calculations.

The brief survey of various catalysts for the isomerization of vinylnorbornene **408** into ethylidenenorbornene **394** as well as the effectiveness of potassium amide in liquid ammonia for this purpose were described (equation 192)[250]. One step in the synthesis

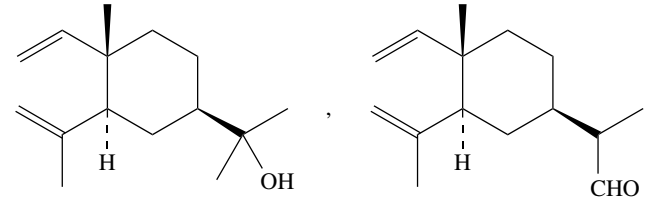


(487) **(488)** (185)

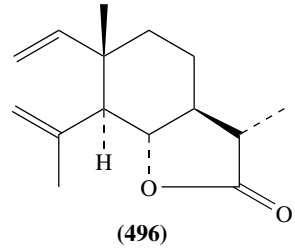
(489) **(490)** **(491)**



(492) **(493)** ;

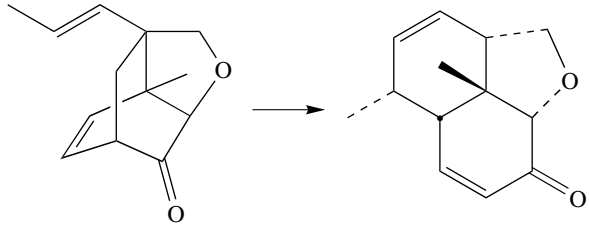


(494) , **(495)** , (186)

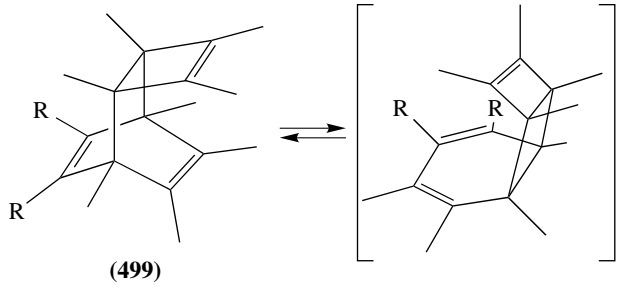


(496)

of 12-oxophytodienoic acid related to prostaglandines includes a Cope rearrangement of 5-vinylnorborn-2-ene **507** into the bicyclic diene **508** (equation 193)[251]. Similar rearrangements were also used for the preparation of prostaglandines (equations 194 and 195)[252,253]. The rearrangements of the tetracyclic systems **509** and **510** containing the vinylnorbornene fragment were employed to obtain the spiroepoxy cyclohexadienones **511** and **512** (equations 196 and 197)[254]. The angularly alkylated tricyclic esters **513** are very unstable and rapidly undergo an unusual Cope rearrangement to form the bridged ketones **514** even at an ambient temperature (equation 198)[255].



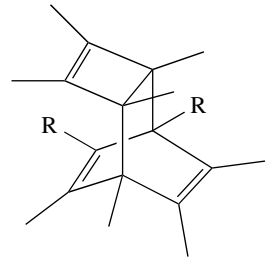
(497) **(498)** (187)



(499)

R = COOMe

(188)

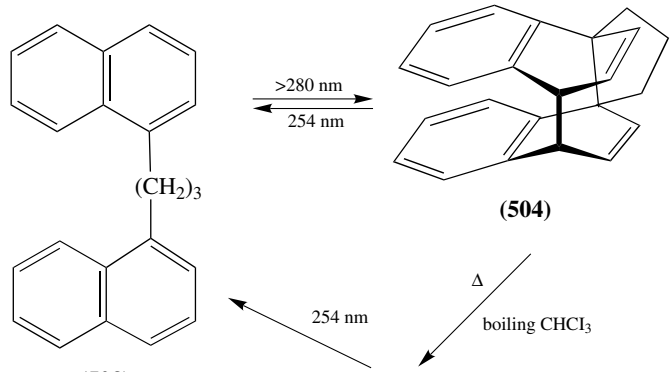


(500)

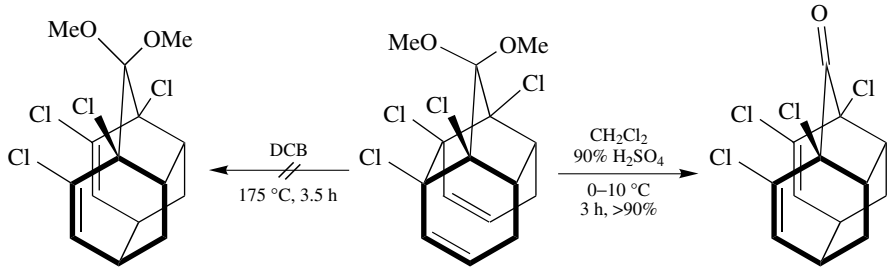
Rigid polycarbocyclic isomeric ketals **515** and **516** undergo a Cope rearrangement to afford the diketones **517** and **518** on heating in a H_2O–THF mixture at 55 °C in the presence of *p*-TsOH (equations 199 and 200)[256]. The rearrangements of bridged ketones

519 to α,β-unsaturated ketones **520** were reported to be greatly accelerated by both sulfuric acid and Lewis acids (equation 201)[234]. A very similar rapid Cope rearrangement was described for the SO_2-bridged polycyclic triene **521** (equation 202)[257].

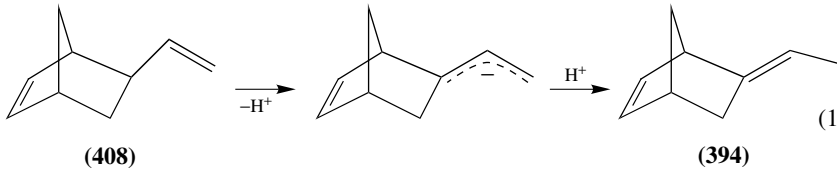
(501) **(502)** (189)



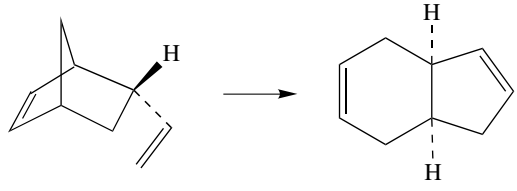
(503) **(504)** **(505)** (190)



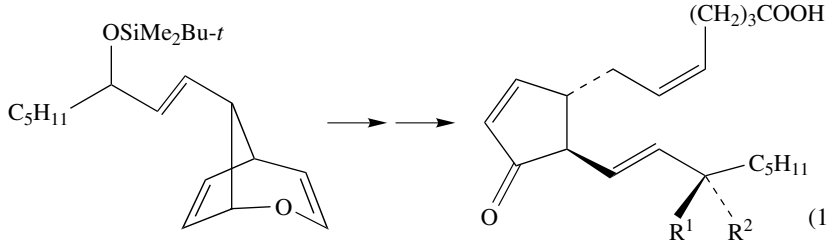
DCB = *o*-dichlorobenzene **(506)** (191)



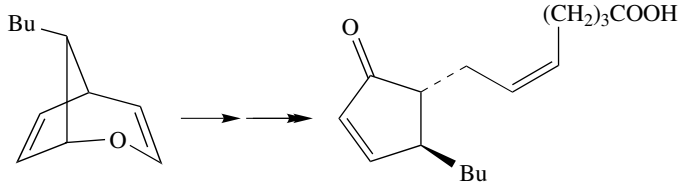
(408) (394) (192)



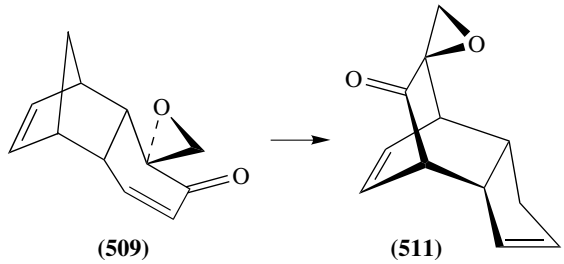
(507) (508) (193)



R^1, R^2 = H, OH (194)

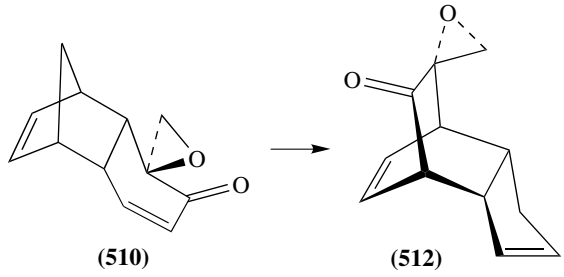


(195)

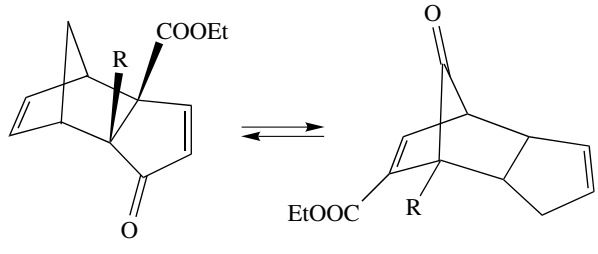


(509) (511) (196)

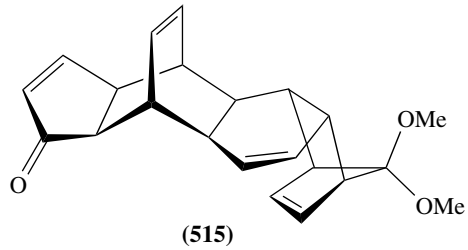
c. Divinylcyclobutanes. Thermal rearrangements of divinylcyclobutanes to form *cis*,*cis*-1,5-cyclooctadienes and 4-vinylcyclohexenes are well-known[88,230] and were already mentioned (see Section III.B.2, References 71 and 72). For example, thermolysis of the



(510) (512) (197)

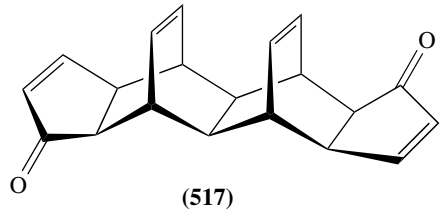


(513) (514) (198)



(515)

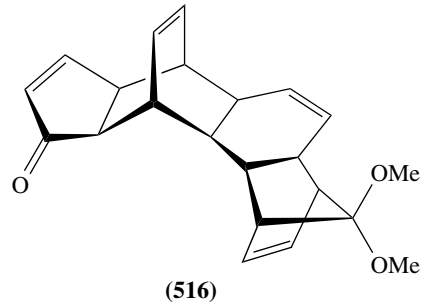
70% H^+ (199)



(517)

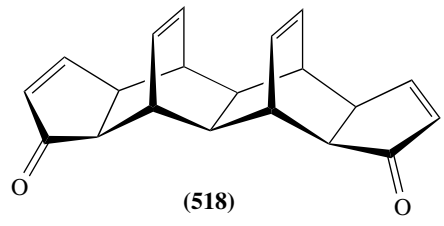
cycloadduct **522** obtained by photocyclization of the corresponding open-chain diethoxycarbonyl-substituted tetraene gives only *cis*-fused cyclooctadiene **523** (benzene, 130 °C, 4 h, *ca* 100%) (equation 203)[258]. However, more vigorous conditions (200 °C, 24 h) are required for the rearrangement of the isomeric cycloadduct **524** in which the cyclooctadiene **523** is again the major product (50%) together with the bicyclic diene **525**. Similarly, the heteroanalogues **526** and **527** undergo thermolysis at 200 °C for 22 h to yield *cis*-fused heterobicyclic product **528** (75%) (equation 204)[258]. Substrates **529** containing a

four-carbon chain between diene fragments are capable of cyclizing photochemically to afford the cycloadducts which undergo thermolysis to the cyclooctadienes **530**–**532** (in a ratio 5 : 1 : 2) in 42% total yield (equation 205)[258].

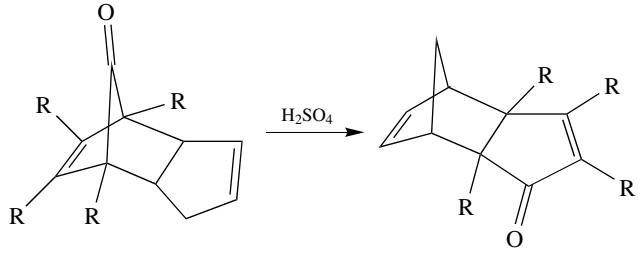


(516)

(200)

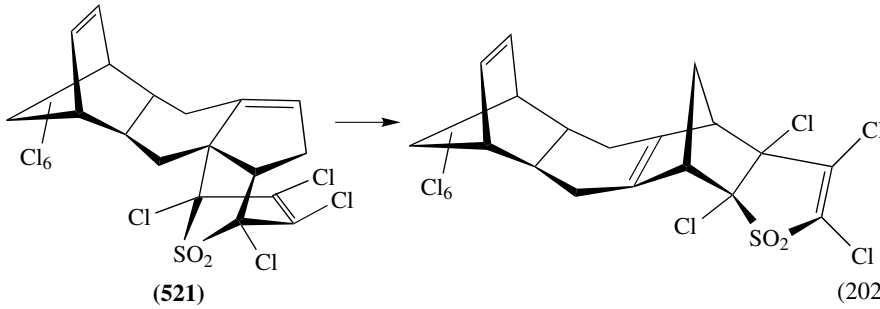


(518)



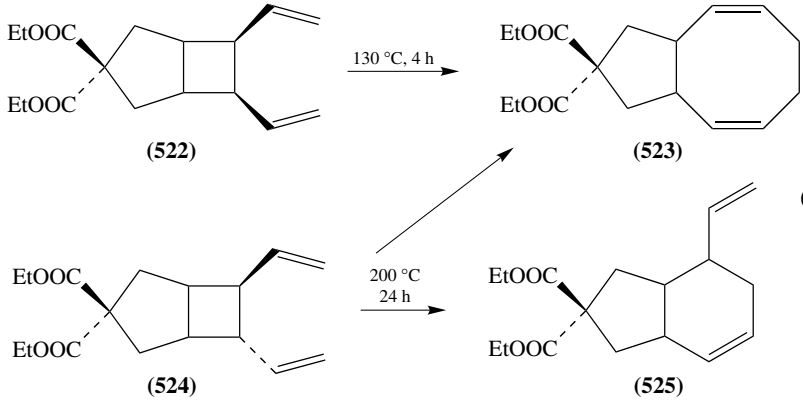
(519) R = H, Cl **(520)**

(201)

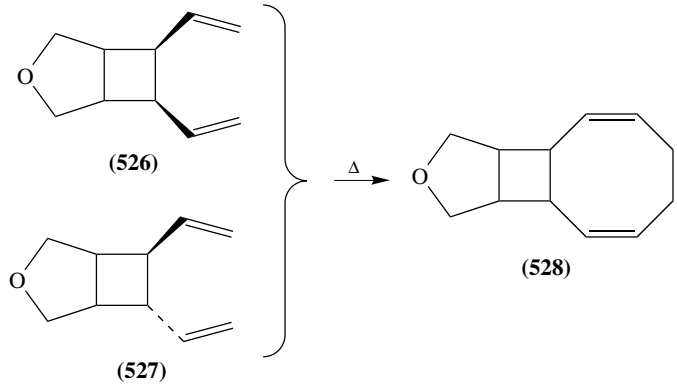


(521)

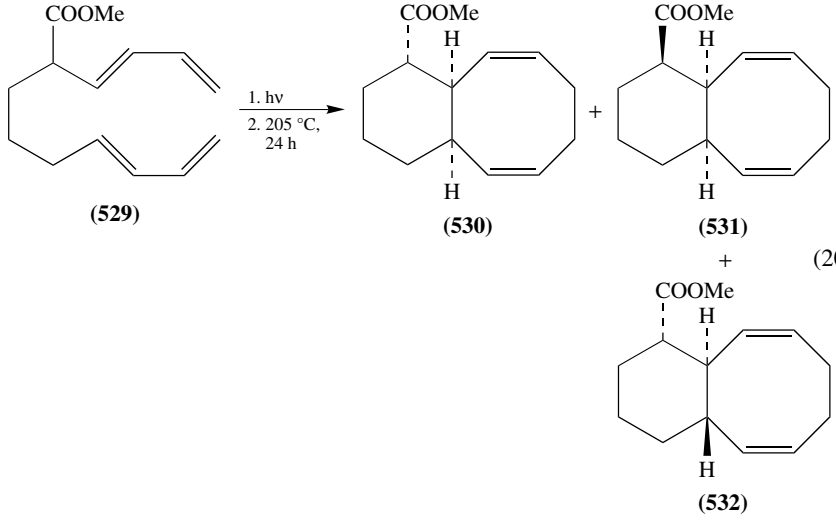
(202)



(522) **(523)** **(524)** **(525)** (203)

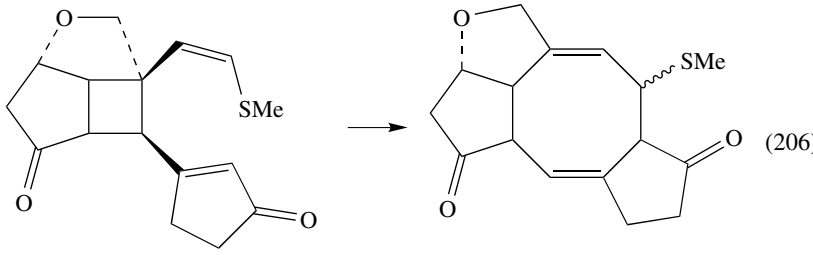


(526) **(527)** **(528)** (204)



(529) **(530)** **(531)** **(532)** (205)

The dicyclopenta[*a*,*d*]cyclooctane structure **534** which constitutes a characteristic element of some terpenoids was obtained in 100% yield by a very facile Cope rearrangement of the highly functionalized divinylcyclobutane derivative **533** on heating in benzene at 55 °C for 4 h. The mild conditions can be due to participation of the lone pair of the sulfur atom or to the strain energy of the divinylcyclobutane fragment (equation 206)[259].

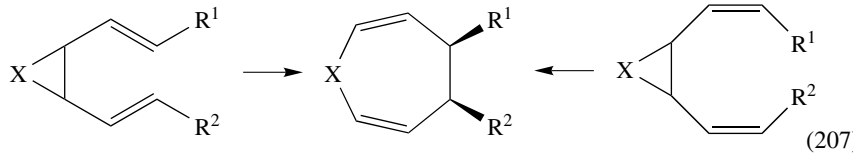


(206)

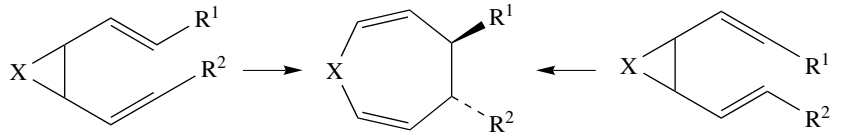
(533) **(534)**

d. Divinylcyclopropanes. Among the reactions discussed, the rearrangements of divinylcyclopropanes are of most importance. For instance, in the synthesis of various natural products containing densely functionalized seven-membered rings, the Cope rearrangement of *cis*-divinylcyclopropanes turned out as a most effective method with respect to stereocontrol, as it proceeds under mild conditions with very predictable stereochemistry. Therefore, a general approach which is based on a tandem 'cyclopropanation–Cope rearrangement' reaction is widely practiced. It is summarized in a recent survey[260].

In general, this approach can be represented by equations 207 and 208 wherein the formation of *cis*- and *trans*-substituted seven-membered rings (e.g. tropones or oxepines) is controlled by selection of appropriate isomeric divinylcyclopropanes or divinylepoxides as precursors. We will discuss here a series of examples which are not covered by a recent review[260].

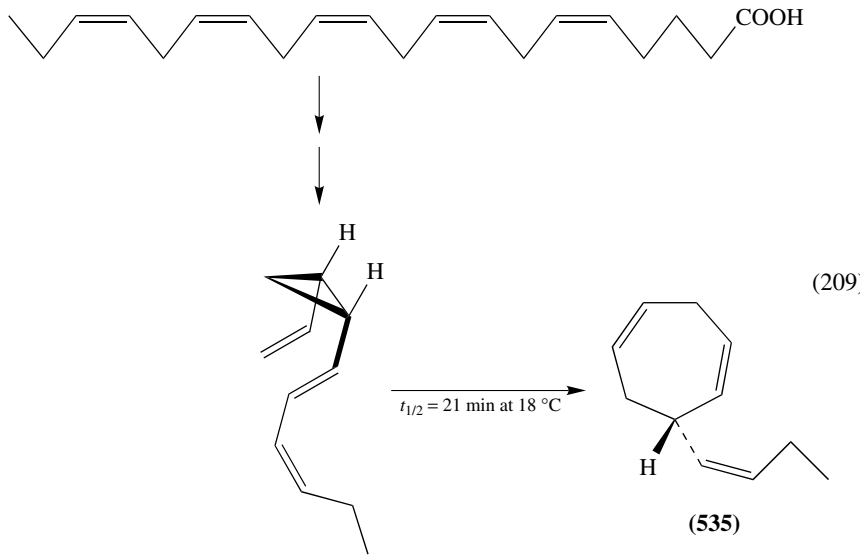


(207)



$X = CH_2, O$ (208)

To prepare ectocarpene **535** and desmarestene **536** which are examples of plant chemoattractants, synthetic approaches which can be named 'cyclopropanation–Cope rearrangement' (equation 209) and 'Wittig reaction–Cope rearrangement' (equation 210), respectively, were employed[261]. It suffices to say that the end products **536** and **537** were isolated in high enantiomeric purity (⩾94% ee).



(209)

(535)

A stereoselective convergent synthesis of hydroazulenes **538** was also based on a tandem intermolecular cyclopropanation–Cope rearrangement sequence with predictable stereocontrol (equation 211)[262].

It was emphasized that a particular advantage of this approach over other synthetic strategies based on Cope rearrangement consists in the facile way of selectively preparing *cis*-divinylcyclopropane intermediates[262].

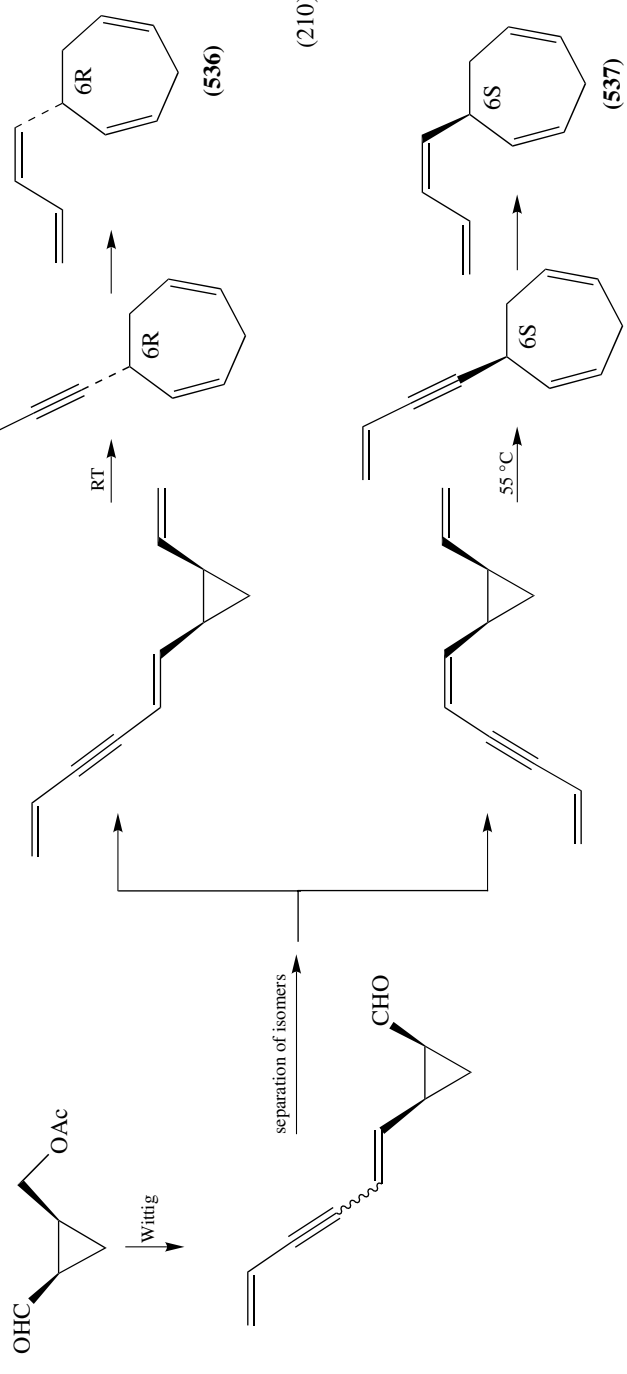
A method for highly efficient asymmetric cyclopropanation with control of both relative and absolute stereochemistry uses vinyldiazomethanes and inexpensive α-hydroxy esters as chiral auxiliaries[263]. This method was also applied for stereoselective preparation of dihydroazulenes. A further improvement of this approach involves an enantioselective construction of seven-membered carbocycles **(540)** by incorporating an initial asymmetric cyclopropanation step into the tandem cyclopropanation–Cope rearrangement process using rhodium(II)-(*S*)-N-[*p*-(*tert*-butyl)phenylsulfonyl]prolinate [$Rh_2(S-TBSP)_4$] **539** as a chiral catalyst (equation 212)[264].

An interesting approach to form a divinylcyclopropane structure capable of rearranging into seven-membered functionalized derivatives consists of the silyloxylation of cyclic ketones **541** followed by a spontaneous Cope rearrangement to produce the cyclic enol esters **542** which then hydrolyzed to ketones **543** (equation 213)[265].

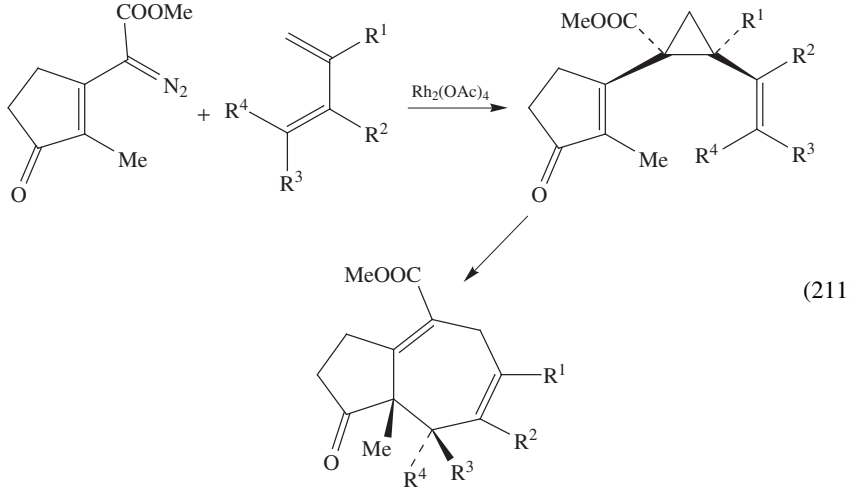
Flash vacuum pyrolysis of tricyclo[7.1.0.$0^{4,6}$]deca-2,7-diene **544** is accompanied by a long cascade of rearrangements leading to various azulenes (equation 214)[266]. The structures of these products were determined by using the chlorine atoms as labels for the ^{13}C NMR measurements.

The dihydroxyoxepine moiety is a part of a fungal metabolite such as aranotin acetate exhibiting an antiviral activity. To prepare the 4,5-dihydroxyoxepines **546**, the Cope rearrangement of the corresponding divinylepoxides **545** was used (equation 215)[267–269].

In principle, the divinylcyclopropane structure discussed here is incorporated into very well known systems such as bullvalene **547**, barbaralane **548** and semibullvalene **549**, which very easily undergo a Cope rearrangement.


OHC
OAc
Wittig
separation of isomers
CHO
RT
55 °C
6R
6R
6S
6S
(536)
(537)

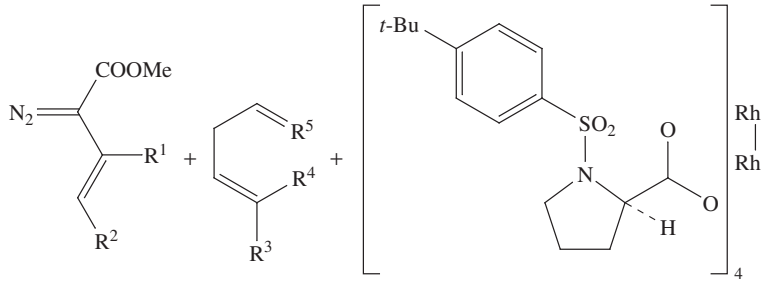
(210)



(211)

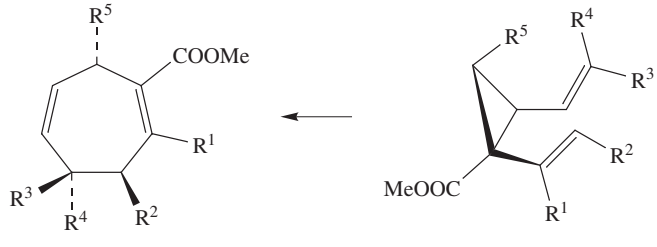
(538)

R^1, R^2 = H, Me; R^3, R^4 = H, OAc



(539)

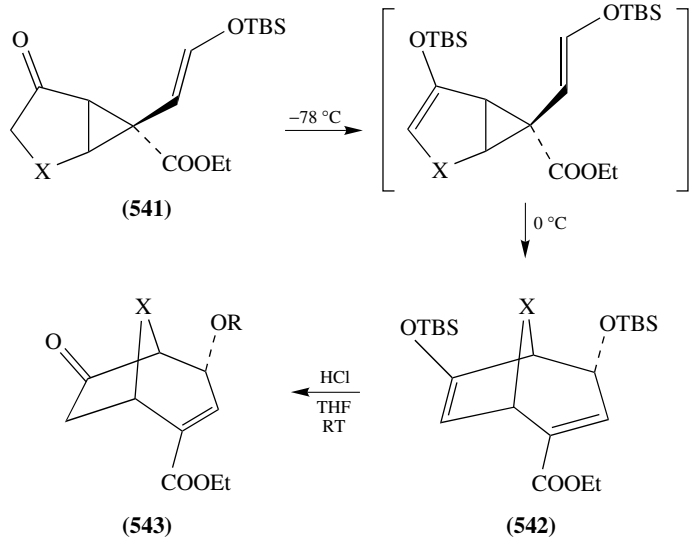
(212)



(540)

R^1 = H, Me; R^2 = H, Me, Ph, $CH=CH_2$, COOEt

R^1–R^2 = cyclo$(CH_2)_3$, cyclo$(CH_2)_4$

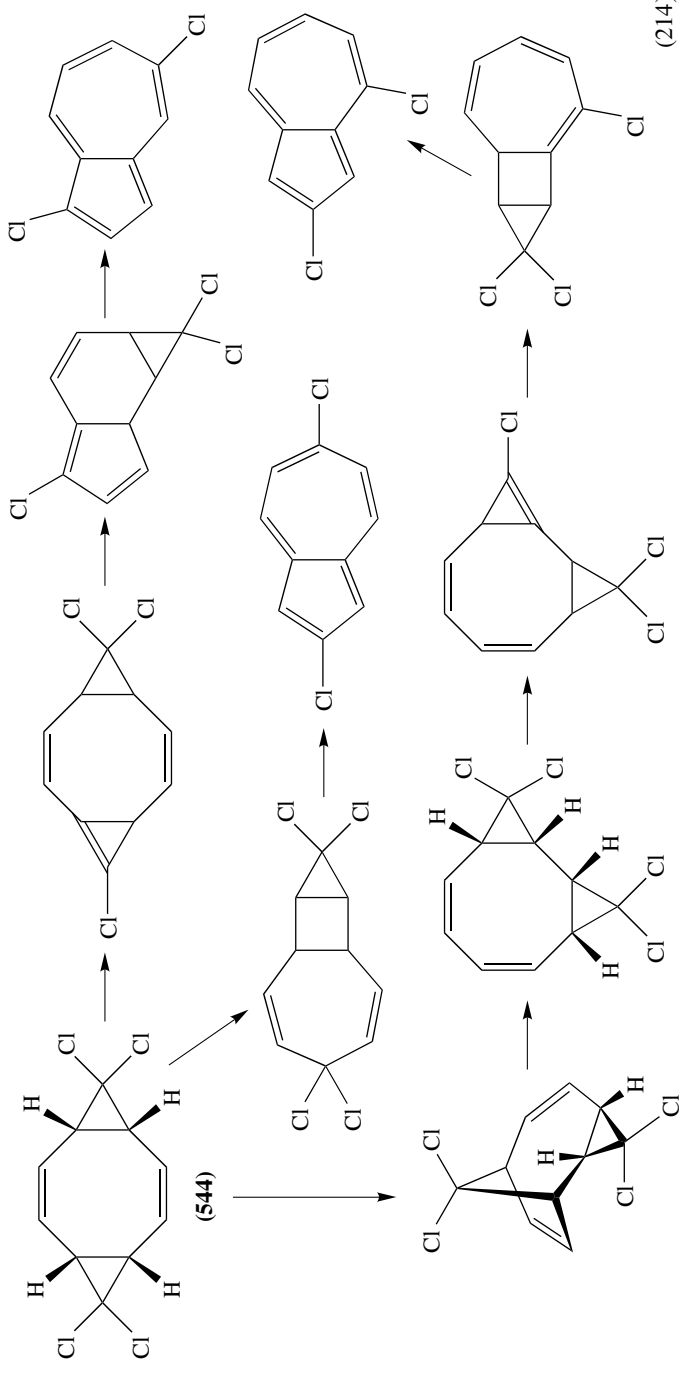


(213)

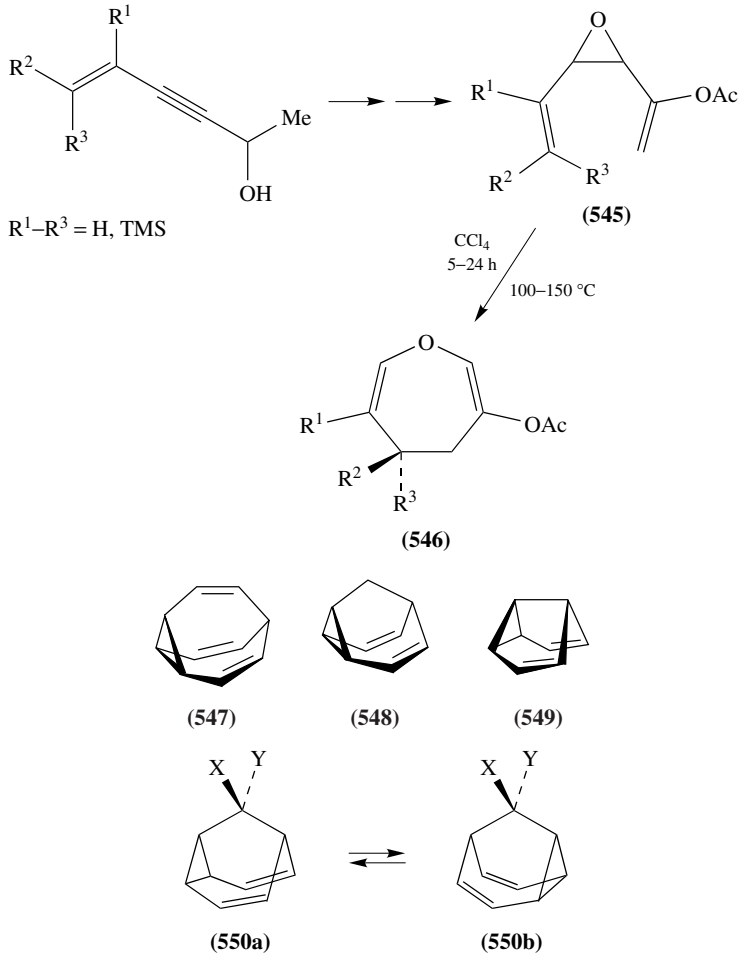
In spite of a very voluminous literature about bullvalene **547**, investigations in this field are still in progress. The solid state isomerizations of bullvalene in the temperature range between $-40\,^{\circ}C$ and $+85\,^{\circ}C$ were studied by using the carbon-13 magic angle spinning method (MAS NMR)[270]. These measurements have allowed to trace the separate steps of multiple Cope rearrangements as well as to estimate the activation energies of approximately 62.8 kJ mol^{-1} for the concerted Cope rearrangement/reorientation. The Cope rearrangement and the molecular reorientation in solid bullvalene have also been investigated by deuterium NMR spectroscopy in the temperature range $-13\,^{\circ}C$ to $+80\,^{\circ}C$[271].

Substituted bullvalenes no longer have the freely fluctuating structure. The preferable isomers are accompanied by others and equilibrium can be studied by means of low-temperature NMR spectroscopy. Since the bullvalene itself has four different positions in a rapid and reversible interconversion, some isomers of the substituted bullvalenes can possess a higher stability depending on the nature of substituents. Schröder and coworkers have investigated trimethyl- and tetramethylbullvalenes, hexamethylbibullvalenyl, penta- and hexabromobullvalenes as well as bullvalenes having one to six phenyl substituents[272−274]. The 4-, 6- and 10-positions in methyl-substituted bullvalenes are slightly preferable in respect to the 3-, 7- and 9-positions. No structure with a vicinal arrangement of two methyl groups was observed[272]. In contrast, pentabromobullvalenes constitute an equilibrium mixture of four isomers which can be separated by column chromatography. Two isomeric hexabromobullvalenes have virtually lost the ability for interconversion and they can be isolated as stable compounds[273]. Concerning the phenyl-substituted derivatives, some isomers starting with triphenylbullvalenes have exhibited a relatively high kinetic stability. This stability culminates for two isomers of hexaphenylbullvalenes which behave similarly to the hexabromo derivatives[274].

Barbaralane **548** (tricyclo[3.3.1.0^{4,6}]nona-2,7-diene) was first described in 1967 (see Reference 80 and literature cited therein). Barbaralane and its derivatives functionalized in the C(9) position **(550a,b)** are degenerate Cope systems whose equilibrium can be frozen


(544)
(214)

only at about −100 °C (equation 216). The activation energy for the interconversion of barbaralanes is about 36 kJ mol^{-1} and that for barbaralone is 49.4 kJ mol^{-1} [80].



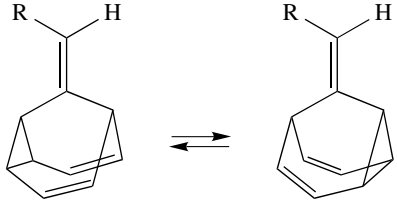
(215)

(216)

X = Y = H; X, Y = O (barbaralone); X = H, Y = OH; X = H, Y = Cl

The behavior of methylenebarbaralanes **551** monosubstituted in the methylene group is of great interest in respect to two problems: (1) the preference of either the *cis*-**(551a)** or *trans*-configuration **(551b)**, and (2) the possibility to determine the dependence of Cope rearrangement rate on the substituents (equation 217). According to ^{1}H NMR data obtained for these molecules having the fluctuating bonds and to temperature-dependent NMR spectra, structure **551a** is the more stable one[275]. It was found that 2,4,6,8-tetraphenyl- **(552)** and 2,6-dicyano-4,8-diphenylbarbaralane **(553)** in solution are capable of extremely rapid Cope rearrangement[276]. Compound **553** exists in solution as

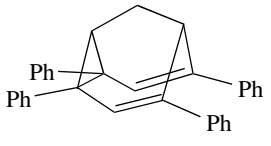
a pair of very quickly rearranging degenerate valence tautomers while the degeneracy is lifted in the solid state. As a result, the crystal consists of two rapidly rearranging but non-equivalent valence tautomers[276].



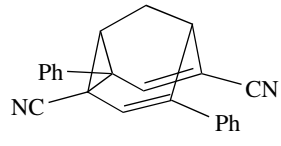
(217)

(551a) **(551b)**

R = H, F, Me, Ph, COOEt

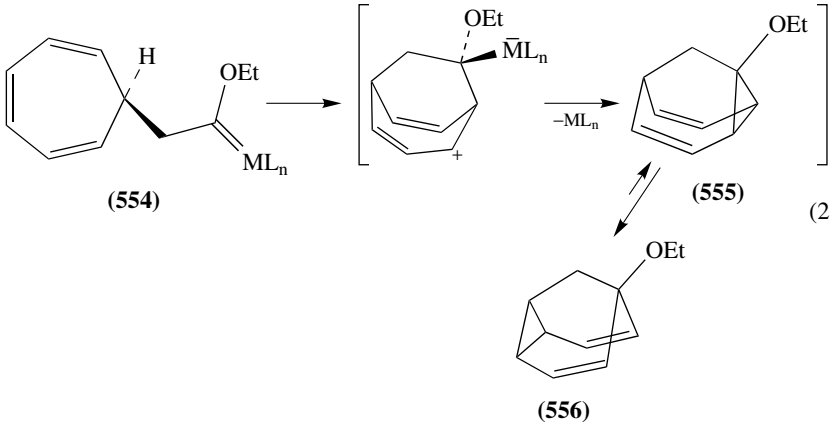


(552)



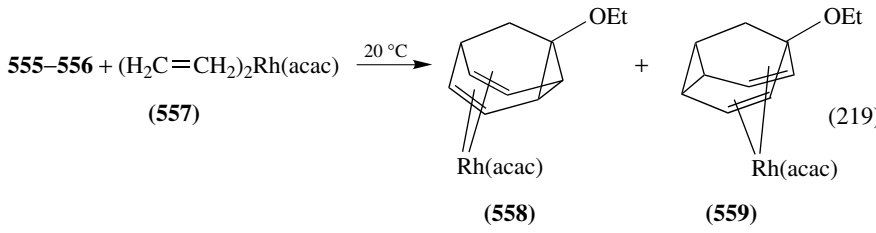
(553)

Thermolysis of (cycloheptatrienylmethyl)carbene complexes **554** [toluene, 1–2 h, 80–100 °C; $ML_n = Cr(CO)_5, W(CO)_5$] affords an equilibrium mixture of 4,5-homotropilidenes **555** and **556**. According to the NMR data and the results of AM1 calculations, the formation of isomer **556** (equation 218) is strongly favored[277]. This course of events was called 'intramolecular cyclopropanation', and it was shown that the equilibrium between the 4,5-homotropilidene complexes is significantly different from that of the metal-free ligands. By reaction of the latter (**555** and **556**) with bis(ethylene)rhodium 1,3-pentanedionate **557**, the complexes **558** and **559** of both 4,5-homotropilidenes were obtained in a 1 : 3 ratio. These complexes are non-fluxional and are configurationally stable at room temperature (equation 219)[277].



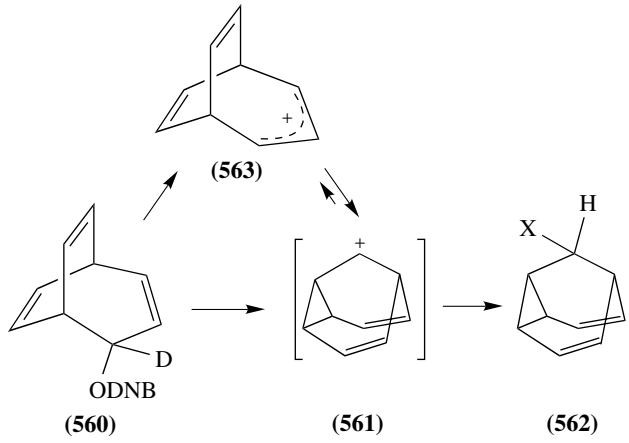
(554) **(555)** **(556)**

(218)

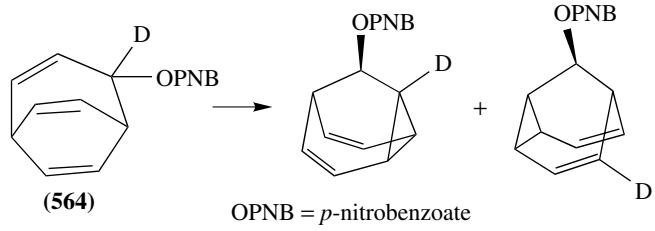


(219)

By means of deuterium labeling, the degree of degeneracy achieved during interconversions of bicyclic triene **560** and barbaralol **562** was studied[278]. Solvolysis of triene **560** (75 °C, 60% aqueous acetone with 10% excess lutidine) gave two products in a 1 : 1 ratio, namely 9-barbaralyl dinitrobenzoate **(562a)** and 9-barbaralol **(562b)**. The deuterium distribution in these products was determined by NMR. It was suggested that the 9-barbaralyl cation **561** is more stable than the bicyclononatrienyl cation **563** (equation 220)[278]. An analogous independent comparison of cations **561** and **563** was made at the same time by using the solvolysis (80% aqueous acetone, 100–125 °C) of bicyclotriene *p*-nitrobenzoate **(564)** (equation 221)[279].



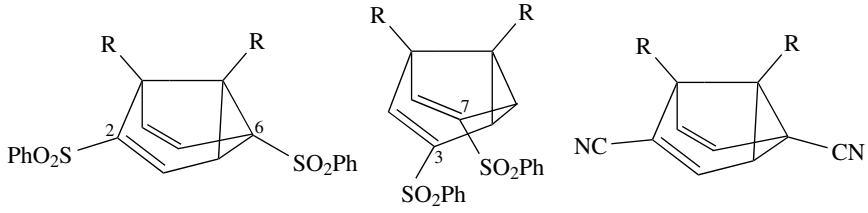
(220)



(221)

The various derivatives of another fluxional system, i.e. semibullvalene **549**, have been described in a series of publications[280–283]. To estimate the influence of substituents at

the bridgehead position as well as the effect of the size of 1,5-fused rings, the functionalized semibullvalenes **565** and **566** were studied by using X-ray diffraction analysis and ^{13}C NMR spectroscopy[280]. It is interesting that cyano groups in the 2,6-positions **(567)** impart unusual properties to semibullvalenes, for instance a color in the absence of any chromophor and a reversible thermochromism, while no such influence is observed in the case of the 3,7-dicyano derivatives.

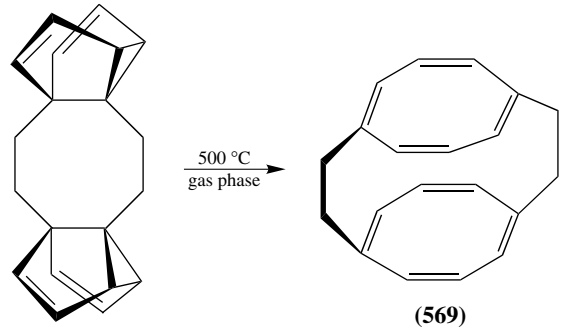


(565) **(566)** **(567)**

R = H, Me

(a) R = H, **(b)** R = Me,
(c) RR = $(CH_2)_3$, **(d)** RR = $(CH_2)_4$,
(e) RR = $(CH_2)_6$, **(f)** RR = $(CH_2)_{10}$

The synthetic application of semibullvalenes can be illustrated by the preparation of the double-decked [8]-annulene **569** from the thermal rearrangement of bis(semibullvalene) **568** (equation 222)[284].



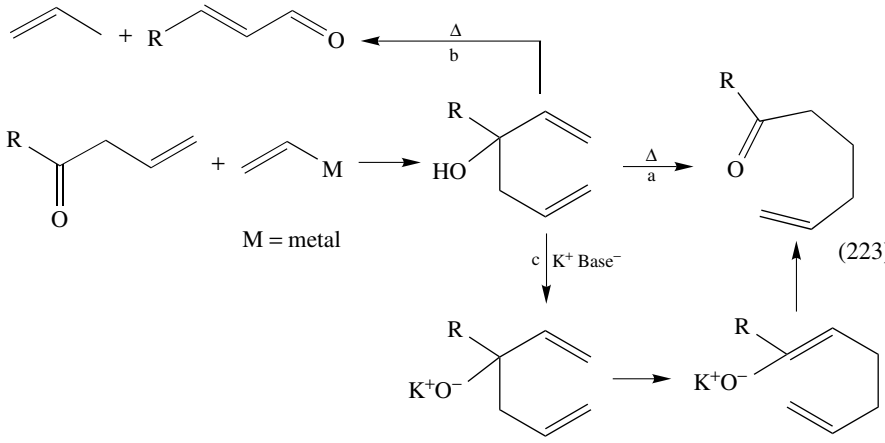
(222)

(568) **(569)**

D. Oxy-Cope Rearrangement

As mentioned above, the introduction of functional substituents into diene systems can change the conditions and sometimes even the direction of their rearrangements. In other words, the functionalization extends very considerably the synthetic potential of the rearrangement. The most obvious case is the oxy-Cope rearrangement, which is widely adopted now in organic synthesis since the preparative value of this reaction stems from the following important factors: (1) readily available starting materials; (2) high potential of efficient chirality transfer; (3) ample possibilities to control the reaction rate using, e.g., an anionic variant, and (4) the readiness of the resulting unsaturated carbonyl compounds to participate in further transformations. In addition, the oxy-Cope rearrangement can be

virtually made irreversible. Consequently, the oxy-Cope rearrangement can be represented by a general scheme (equation 223).



(223)

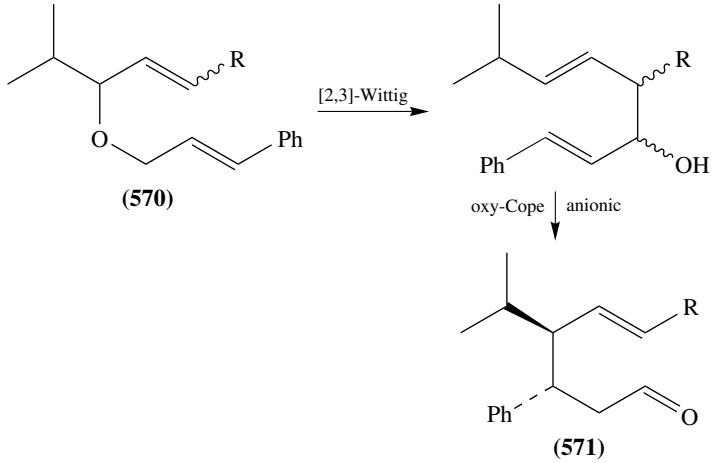
The oxy-Cope rearrangement can be thermally induced (equation 223, path a) but this process competes with an other well-established, concerted pericyclic reaction, i.e. the β-hydroxyolefin retro-ene cleavage (path b)[209]. However, it was found that the oxy-Cope rearrangement can be accelerated under base-catalysis conditions (e.g. in the presence of potassium alkoxides) by a factor of 10^{12} (the so-called 'anionic oxy-Cope rearrangement', path c)[285,286]. This base-induced acceleration is attributable to a dramatic decrease in the strength of the carbon–carbon bond adjacent to the OX-group in the sequence (OX = OH, ONa, OR, O^-) from about 384.3 ± 5 kJ mol^{-1} to 310.7 kJ mol^{-1}, according to *ab initio* calculations[287]. It is noteworthy that the rate of oxy-Cope rearrangement can be also affected by high pressure in the range 0.1–10 kbar. From experimental data for a family of [3,3]-sigmatropic rearrangements including the oxy-Cope process, an equation was derived which correlates the reaction rate and the pressure applied. The results corroborate the concerted mechanism of oxy-Cope rearrangement[288].

The synthetic aspects of the oxy-Cope rearrangement have been throughly summarized in a comprehensive review[289]. From the recent literature data, it is concluded that the anionic oxy-Cope process is most frequently used owing to a combination of low reaction temperature, a favorable thermodynamic driving force and high stereoselectivity. When the precursors are properly designated stereochemically, the oxy-Cope rearrangement provides a high level of diastereoselection and asymmetric transmission[290,291].

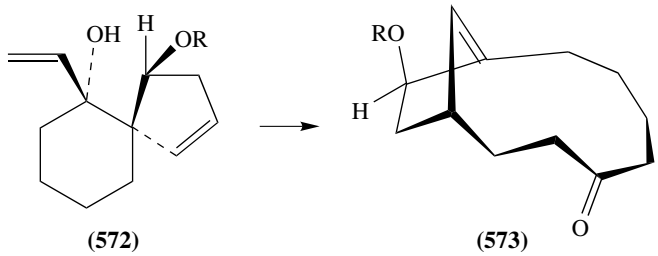
For instance, the one-pot tandem reaction '[2,3]-Wittig–anionic oxy-Cope rearrangement' affords the unsaturated aldehydes **571** starting from the bis-allylic ethers **570** at a high level of stereocontrol[291–294] (equation 224). It was shown that the efficiency of chirality transfer in anionic oxy-Cope rearrangements is determined only by the orientational preference of the oxyanionic bond in the precursors having a single carbinol carbon chiral center[295].

However, the resulting carbonyl products of the oxy-Cope rearrangement are sometimes very sensitive to strong bases. In certain cases this complication can be overcome by simply heating the starting carbinols which have a protective group at the oxygen atom. The rearrangement of spirobicycle **572** to bridged ketone **573** failed upon treatment with KH, $KN(SiMe_3)_2$ and other potassium bases, but it was carried out in 92% yield by

heating diene **572** in decalin at 190 °C for 9 h (equation 225)[296]. A similar, purely thermal oxy-Cope rearrangement was described using the siloxy-substituted polyfunctionalized 1,5-dienes **574** (equation 226)[297,298].

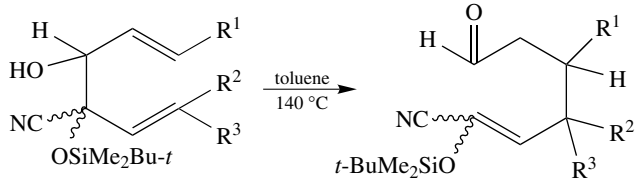


(570) **(571)** (224)



(572) **(573)** (225)

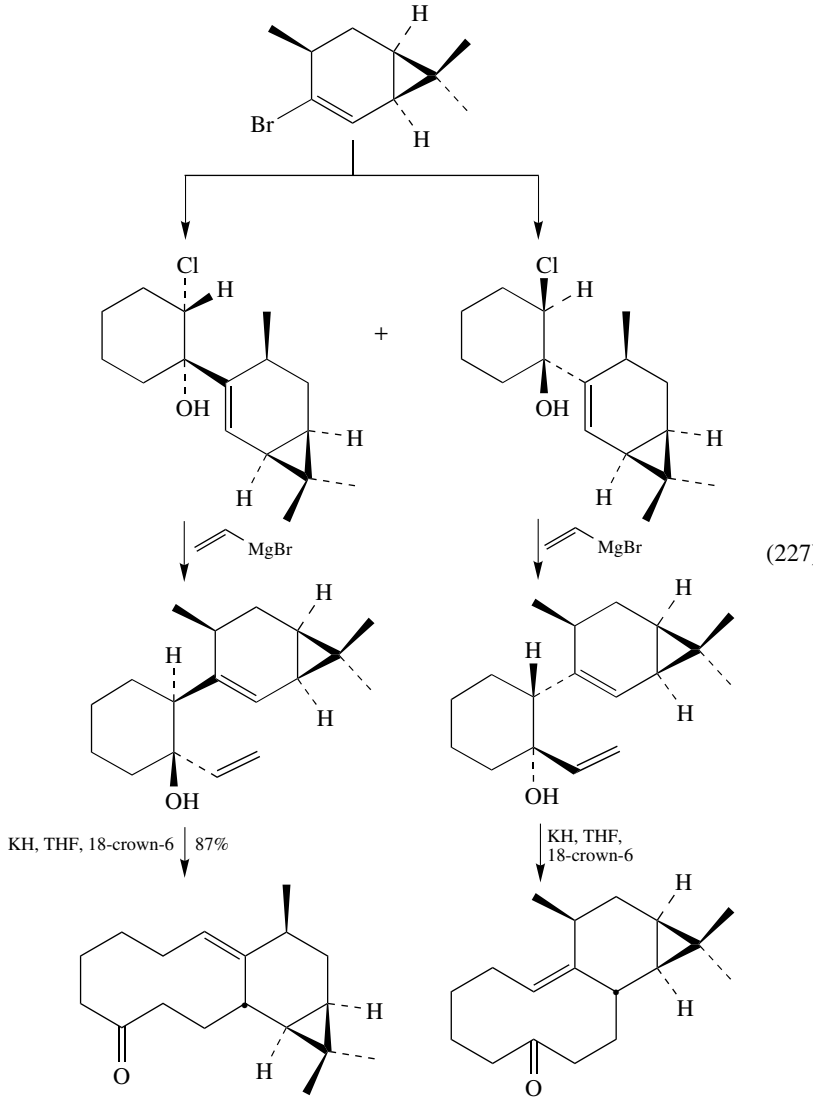
R = *t*-BuMe$_2$Si (TBDMS)



(574) (226)

An example of an intramolecularly competitive anionic oxy-Cope rearrangement was reported for synthesis of a carbon framework closely related to phorbol, a tetracyclic azulene derivative (cyclopropanebenzazulene) (equation 227)[299]. The synthetic approaches to potential precursors of taxane diterpenes and their structural analogues **577** were based on an anionic oxy-Cope rearrangement of bridged dienol **575** to form the tricyclic ketones **576** (equation 228)[300–303]. In the course of this investigation the first example of a thermally-induced retro-oxy-Cope rearrangement was found. In general, the oxy-Cope rearrangement is reputed to be an irreversible transformation (*vide supra*); however, when a solution of

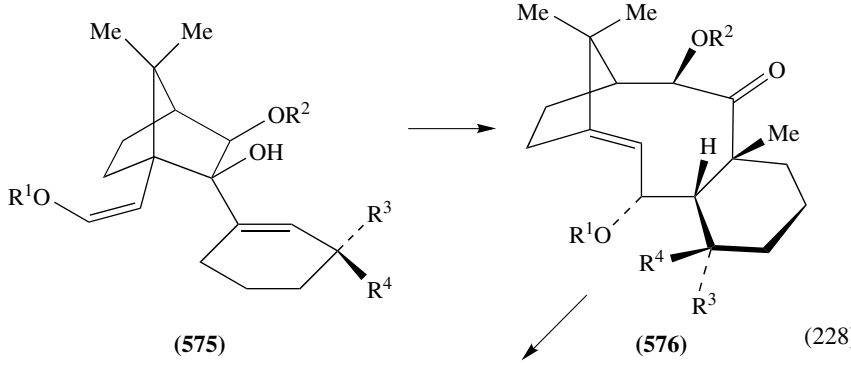
the unsaturated ketone **578** in toluene was refluxed under nitrogen for 5 days, two components of the reaction mixture were separated by chromatography (equation 229)[304]. A comparable heating of carbinol **579** for 3 days gave a mixture of 62% product **578** and 27% of the starting material **579**.



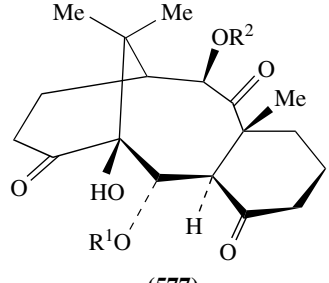
(227)

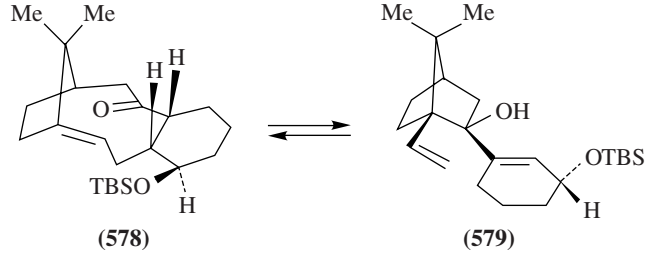
Anionic oxy-Cope rearrangement was also employed for the enantioselective total synthesis of compounds related to marine metabolites (equation 230)[305–307], as well as for the preparation of diterpenoide vinigrol (equation 231)[308] and cerorubenic acid-III

(equation 232)[309,310]. The anionic oxy-Cope rearrangement of bicyclo[2.2.2]octadienols **580** serves as a key step for the construction of substituted bicyclo[5.3.1]undecenones **581** and provides a convenient entry to the AB ring system of the taxane diterpenes (equation 233)[311]. Another approach to taxane derivatives is based on oxy-Cope rearrangement of 1,2-divinylcyclobutane alkoxides (see Section IV.C.2.c) (equation 234)[312]. Total synthesis of natural (−)-vulgarolide **584** from bicyclo[2.2.2]octadienol **583** uses also the anionic oxy-Cope rearrangement (equation 235)[313].



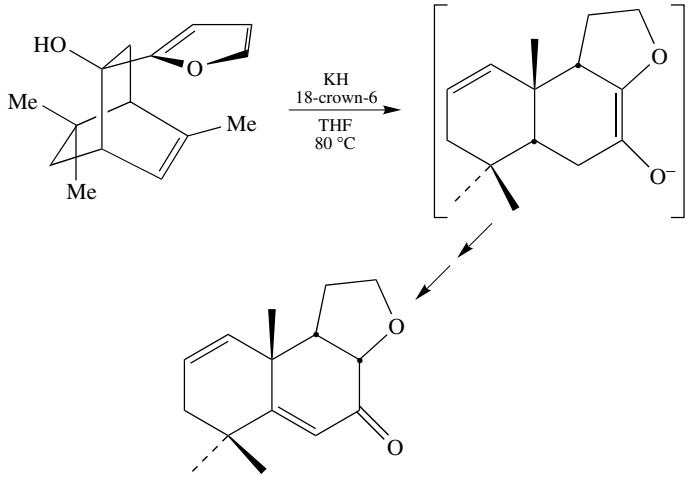
(228)



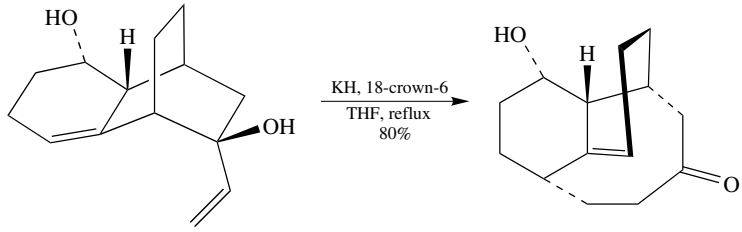


(229)

Anionic[29,314] and thermal[315] oxy-Cope rearrangements were reported as steps in the syntheses of various bicyclic systems **586** from divinylcycloalkanes **585** (see Section IV.C.2) (equation 236). The same anionic scheme was applied to prepare (±)-africanol and (±)-isoafricanol (hydroazulene systems)[316] as well as ajmaline-related alkaloids (equation 237)[317].



(230)



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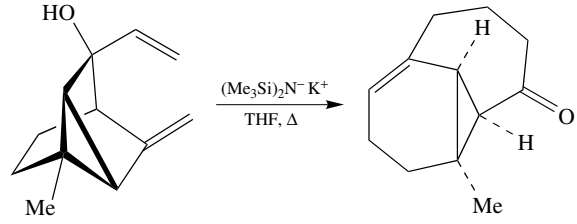
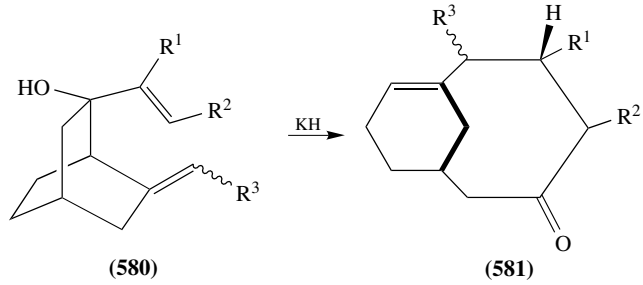


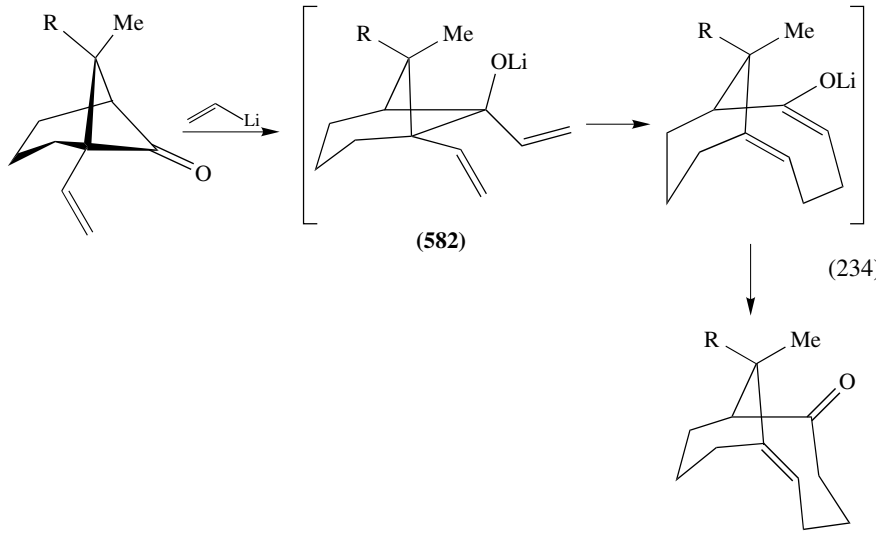
(232)



(580) **(581)**

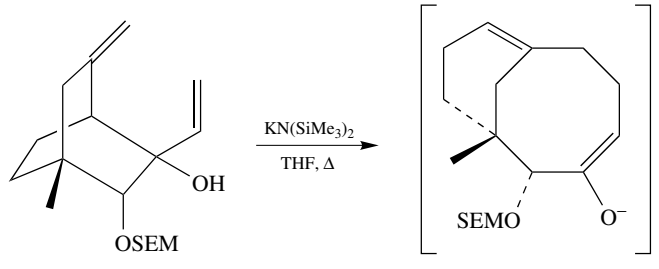
(233)

$R^1 = H$, $R^2 = H$, Me, $R^1R^2 = (CH_2)_4$; $R^3 = H$, Me, MeO



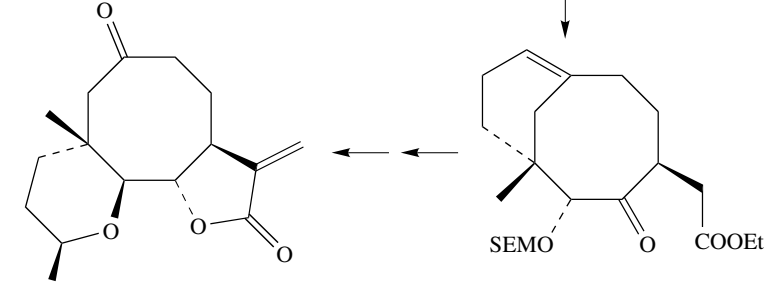
(582)

(234)



(583)

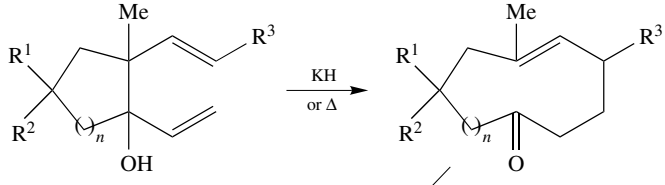
(235)



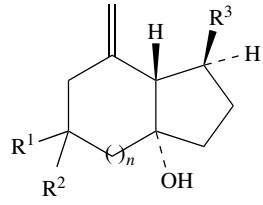
(584)

SEM = $Me_3Si(CH_2)_2OCH_2$

The estradiol derivative **588** was obtained in 91% yield via oxy-Cope rearrangement, which proceeded smoothly when the tertiary alcohol **587** was exposed to potassium hydride/18-crown-6 in THF at ambient temperature under an inert atmosphere

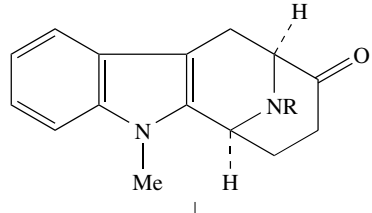


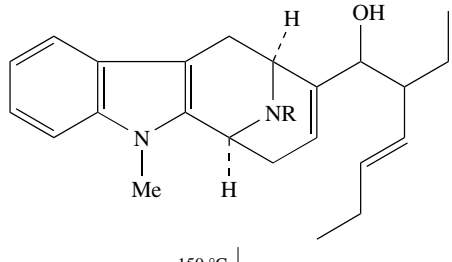
(585)



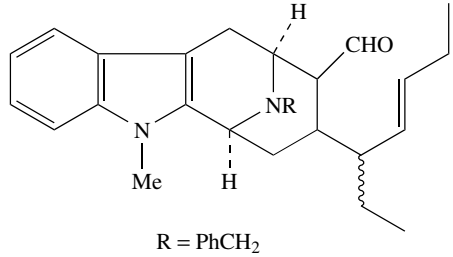
(586)

(236)



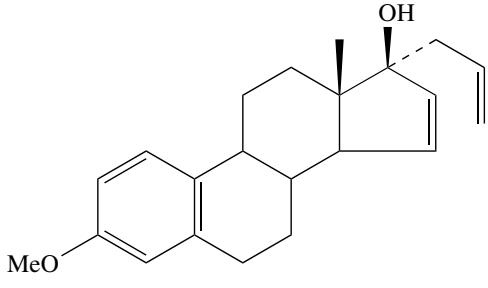


(237)



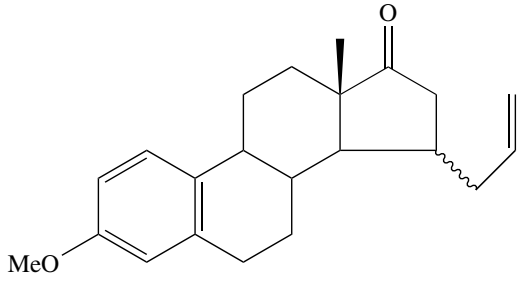
R = $PhCH_2$

(equation 238)[318]. Thermal oxy-Cope rearrangements were used to form the diterpene (equation 239)[319] and oxygen-bridged sesquiterpene (equation 240)[320] frameworks.

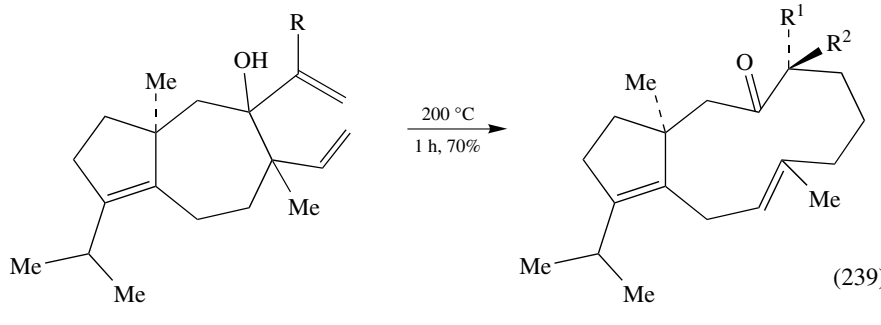


(587)

(238)



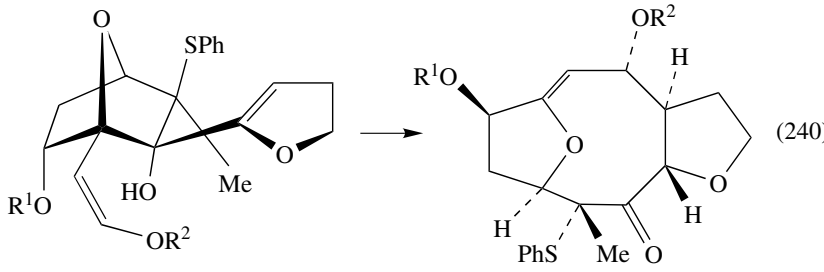
(588)



(239)

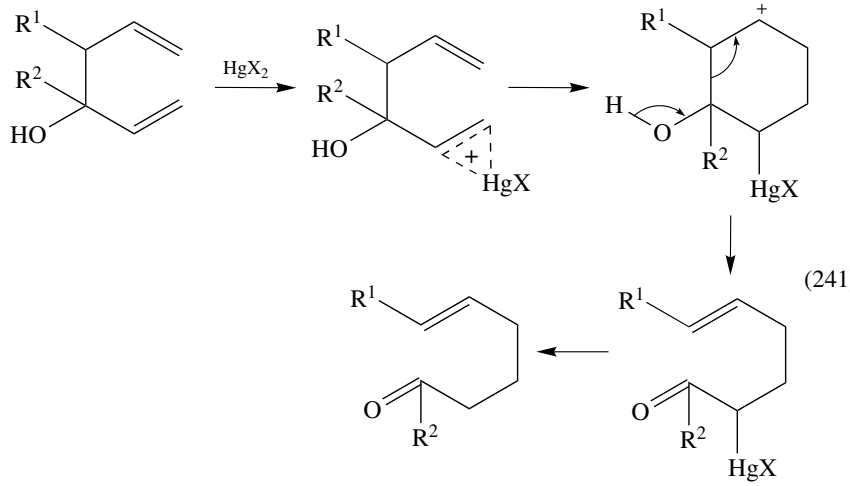
R = H, Me

$R^1 = R^2 = H$
$R^1 = H, R^2 = Me$
$R^1 = Me, R^2 = H$



(240)

The oxy-Cope rearrangement can be carried out using catalysis by mercury trifluoroacetate (equation 241)[321] as well as an antibody catalysis[322]. Reaction of two equivalents of 1-lithio-3,4-dihydronaphthalene with acenaphthenequinone at 0–20 °C affords a derivative of tricyclo[4.3.0.0^{5,9}]nonane **589** by double oxy-Cope rearrangement (equation 242)[323]. Another example of a little known double oxy-Cope rearrangement is the reaction of tricarbonyl chromium complex **590**, which undergoes a sequential transformation consisting of the double addition of vinyl lithium derivatives to the keto groups and subsequent double oxy-Cope rearrangement under very mild conditions (−78 °C) (equation 243)[324].



(241)

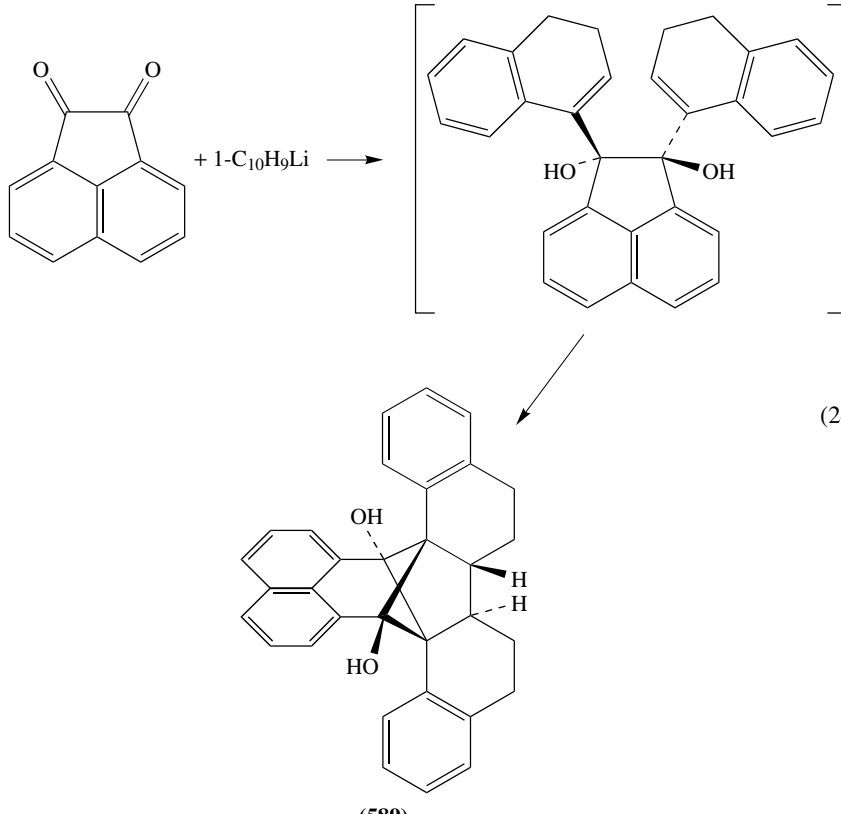
R^1, R^2 = Me, R^1R^2 = $(CH_2)_4$, $(CH_2)_{10}$ (35–75%)

X = $OCOCF_3$

E. Hetero-Cope Rearrangements

In principle, Cope-type rearrangements can occur in any 1,5-diene system consisting of six carbon and/or heteroatoms (equation 244). However, despite the apparent variety of potential possibilities, few examples of hetero-Cope rearrangements are known up to now. It should be noted that the structures depicted in equation 244 which can generally contain up to six heteroatoms are no longer real dienes. Nevertheless, we will briefly

consider the principal types of such systems as well as their transformations (for reviews, see Reference 325).

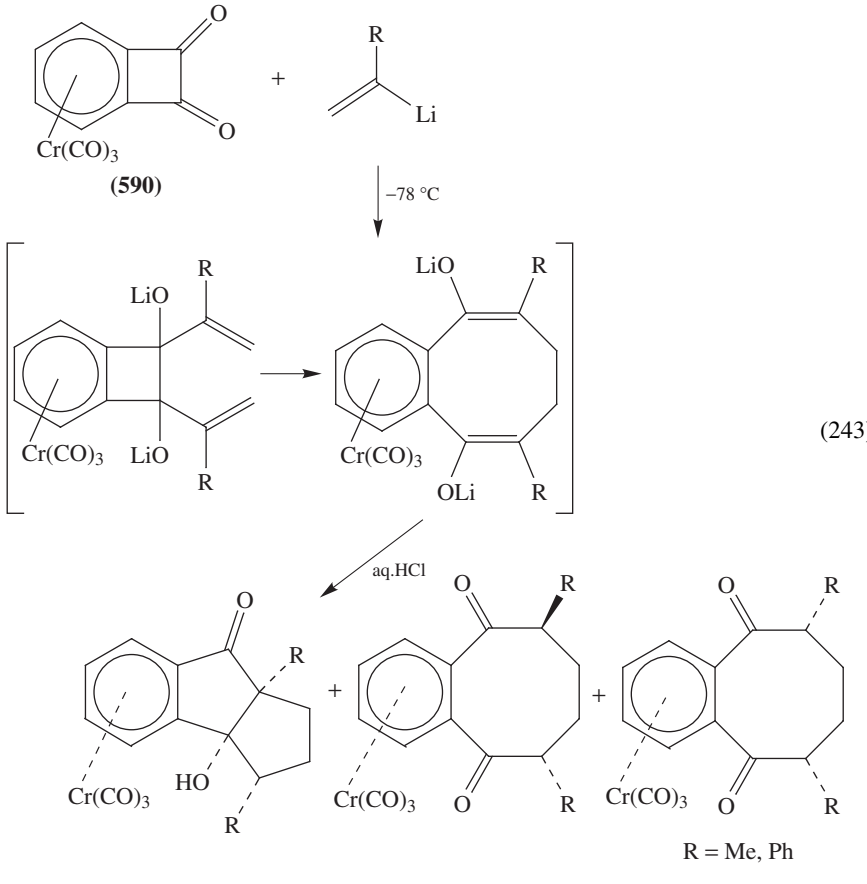


(242)

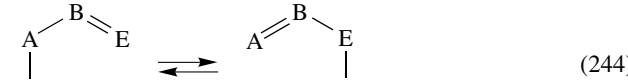
(589)

1. Claisen and related rearrangements

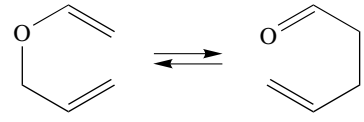
Among the hetero-Cope processes the Claisen rearrangement is the most known. It was discovered in 1912[326] as the first in a series of related [3,3]-sigmatropic isomerizations such as the Cope rearrangement. The synthetic significance of this reaction is obvious even by the numerous reviews about Claisen rearrangement (a list of 25 surveys since 1940 till 1979 is given in Reference 327; see also reviews 208 and 326). In principle, the Claisen rearrangement can be generalized by equation 245, i.e. it is a rearrangement of aliphatic allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds. It has been well established that a Claisen rearrangement proceeds through a cyclic chair transition state as an intramolecular concerted [3,3]-sigmatropic isomerization. The influence of substituents on the Claisen rearrangement[328,329] as well as some stereochemical aspects such as face selection have been studied recently[330]. Various synthetic methods such as tandem thermal Claisen–Cope rearrangements of coumarate derivatives **591** (equation 246)[331,332] were developed on the basis of Claisen rearrangement.



(243)

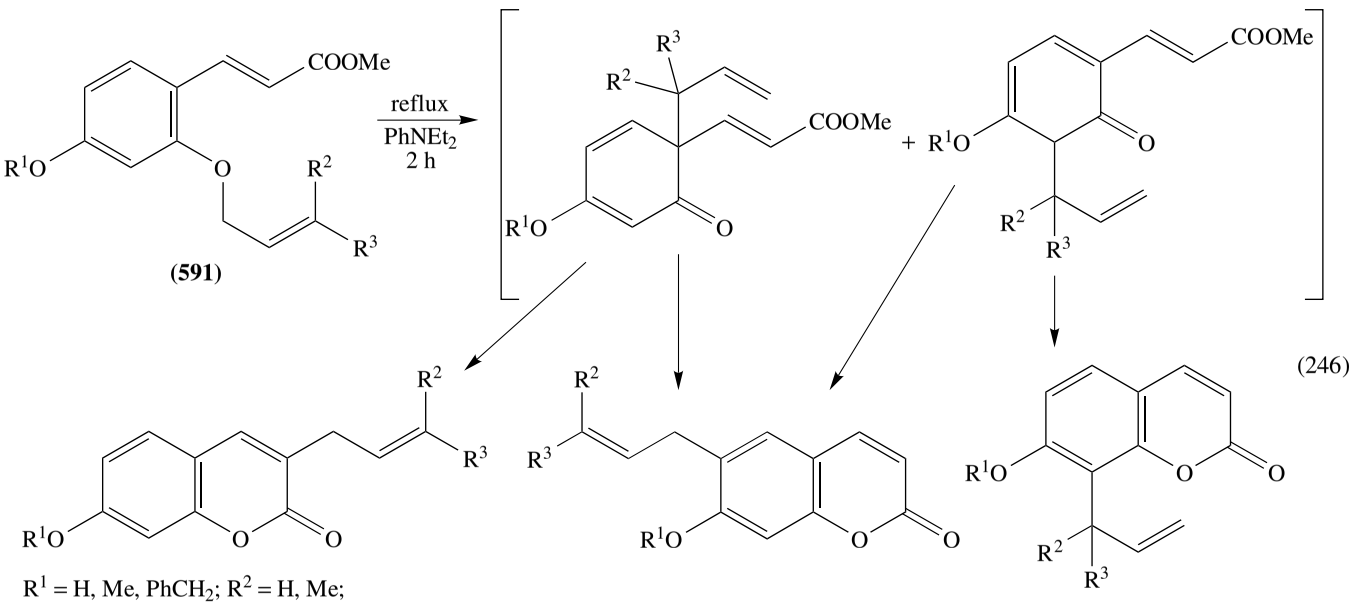


(244)



(245)

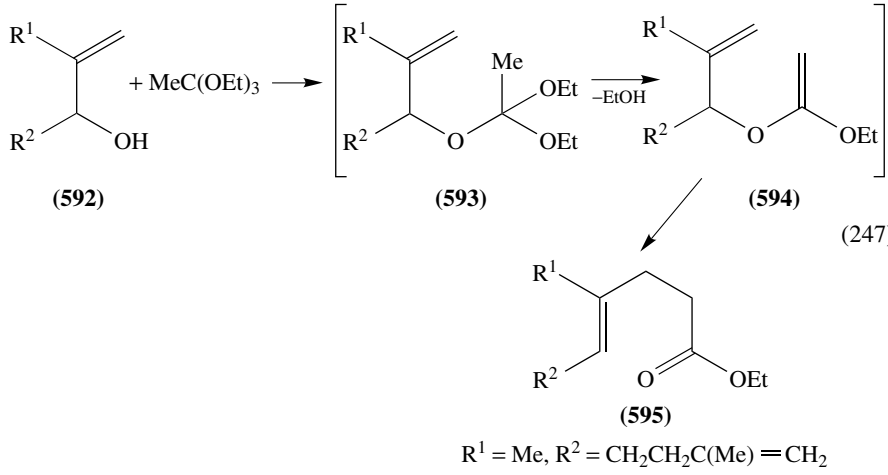
Further, the elegant biogenetic-like method for constructing steroid systems by a cascade of cyclizations deserves special attention. A simple, highly stereoselective version of the Claisen rearrangement leading to *trans*-trisubstituted olefinic bonds was discovered in 1970 by Johnson and colleagues[333]. This method is based on heating an allylic alcohol **592** with excess ethyl orthoacetate in the presence of a trace of weak acid (e.g. propionic acid). The dialkoxycarbenium cations evidently formed under such conditions react with the hydroxy group of alcohol **592** to give the mixed orthoesters **593** and then ketene



R^1 = H, Me, $PhCH_2$; R^2 = H, Me;

R^3 = H, Me, $(CH_2)_2CH{=}CMe_2$, $(CH_2)_2CH{=}C(Me)\text{-}(CH_2)_2CH{=}CMe_2$, etc.

acetals **594**, which undergo rearrangement to form the olefinic esters **595** in good yields (*ca* 90%) (equation 247). This general approach was later used for a series of biomimetic syntheses of various polycycles. For instance, the total synthesis of all-*trans*-squalene **597** from succinic dialdehyde **596**, which is about 98% stereoselective for each double bond, is exemplified by the synthetic sequence of equation 248[333]. Further examples of this fruitful approach to the synthesis of steroid systems (equations 249 and 250) were described in numerous papers[334–343] and reviews[344,345].

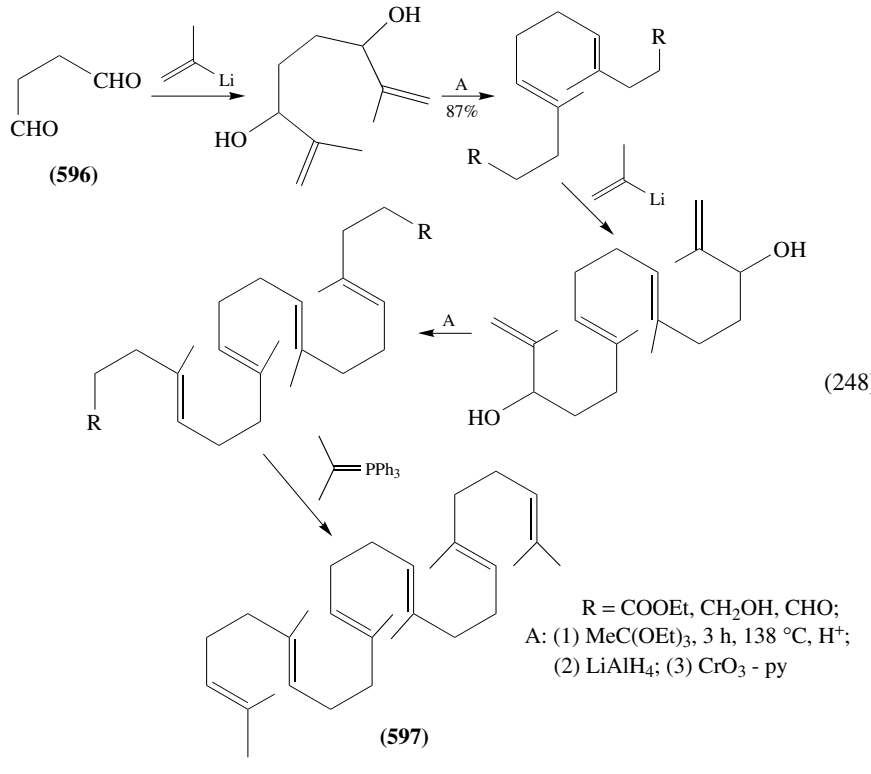


(247)

An analogous method based on treatment of the carbohydrate allyl alcohol **598** with an orthoester followed by Claisen rearrangement (called here the 'oxa-Cope rearrangement') was employed for the preparation of sphingosines (equation 251)[346]. An interesting example of a tandem reaction consisting of Claisen rearrangement and a subsequent shift of a carbon–carbon double bond was described as 'a silicon mediated homo-Claisen rearrangement' (equation 252)[326].

Along with the Claisen rearrangement, other related reactions are applicable for the preparation of natural products. For instance a [2,3]-Wittig rearrangement is one step in the stereospecific synthesis of HMG-CoA reductase inhibitor pravastatin[347] and in the total synthesis of the HMG-CoA synthase inhibitor 1233A[348] according to the general scheme (equation 253).

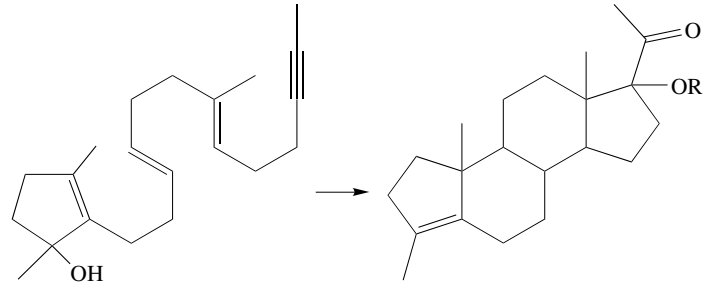
In order to prepare *cis*-jasmone, a route to γ-ketoaldehydes was developed by using a thio-Claisen rearrangement (equation 254)[349]. The same rearrangement is the basis of a methodology for the diastereoselective synthesis of some branched homoallylic amine derivatives[350]. The rearrangement occurs at room temperature (equation 255). Schroth and coworkers have investigated[351,352] the stereochemistry and reaction conditions for the chemical transformations of 3-*exo*-3′-*exo*-(1*R*, 1′*R*)-bis-thiocamphor **601** as a versatile source of functionally different 3,3′-bibornane derivatives. Compound **601** was obtained from (1*R*)-thiocamphor **599** with sodium hydride in benzene and subsequent oxidation with iodine in benzene. The intermediate disulfide **600** undergoes a spontaneous 'dithio-Cope' rearrangement to form **601** (equation 256). A similar thermal **602** → **603** rearrangement was assumed to be one step in the preparation of heterocyclic 1,2-dithiine precursors for the synthesis of 'dithioxothioindigo' (equation 257)[353].



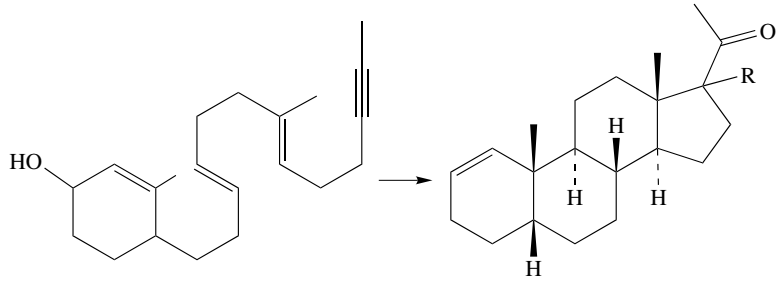
(596)

(597)

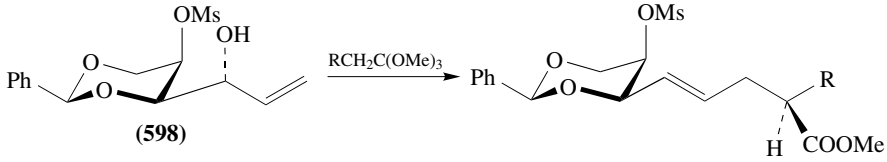
(248)



(249)

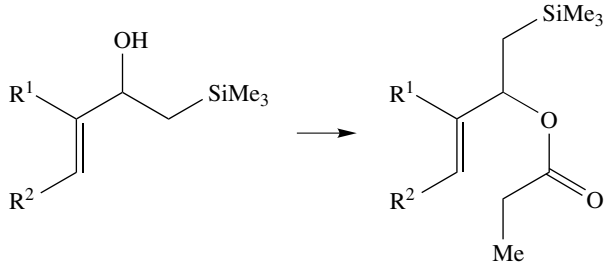


(250)

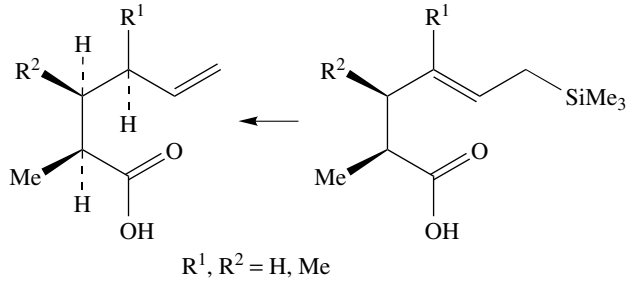


(598)

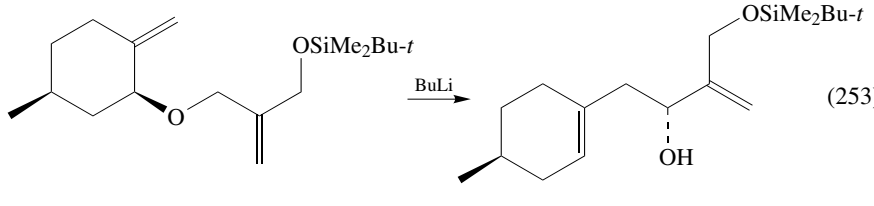
R = H, Me, Pr (251)



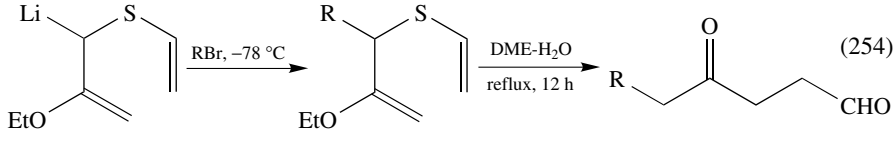
(252)



R^1, R^2 = H, Me



(253)

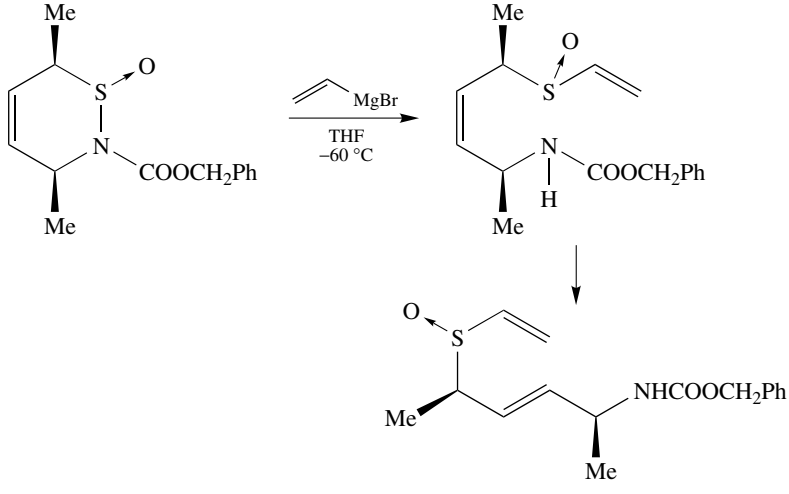


(254)

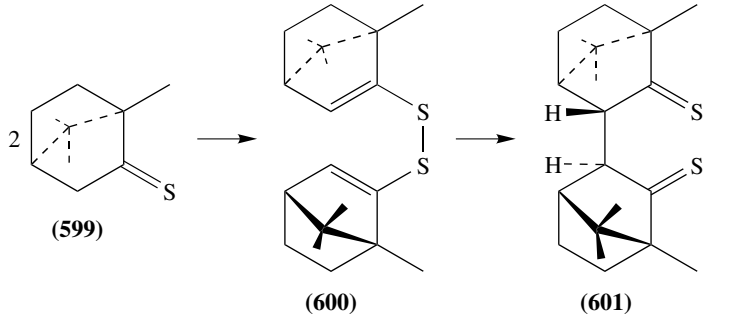
R = *n*-C_5H_{11}(66%), allyl (70%), $CH_2CH{=}CHEt$ (56%)

A disputable problem of the cationic 'oxa-Cope' rearrangement (equation 258) is whether open-chain oxonium ions are formed during transformations of 4-vinyl-1,3-dioxolanes **604** into acyltetrahydrofurans **605** (equation 259) as well as of methyl

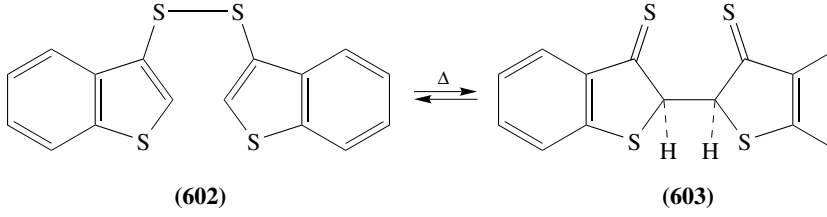
2-acetoxy-2-alkenoxyacetates **606** into tetrahydropyran derivatives **607** (equation 260)[354–356]. It is well known that the introduction of a charged atom causes a large increase in the [3,3]-sigmatropic rearrangement rate[11,325]. Typical examples are the anionic oxy-Cope rearrangement (*vide supra*) and the 2-azonia-Cope rearrangement



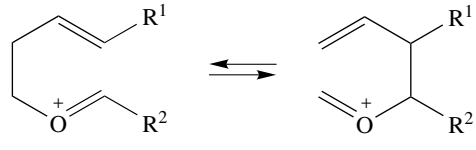
(255)



(256)

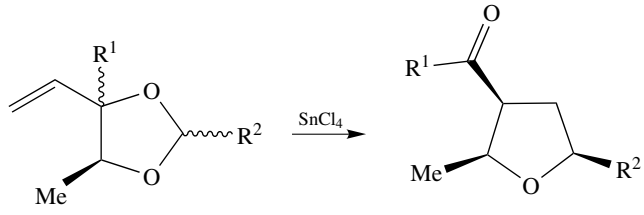


(257)



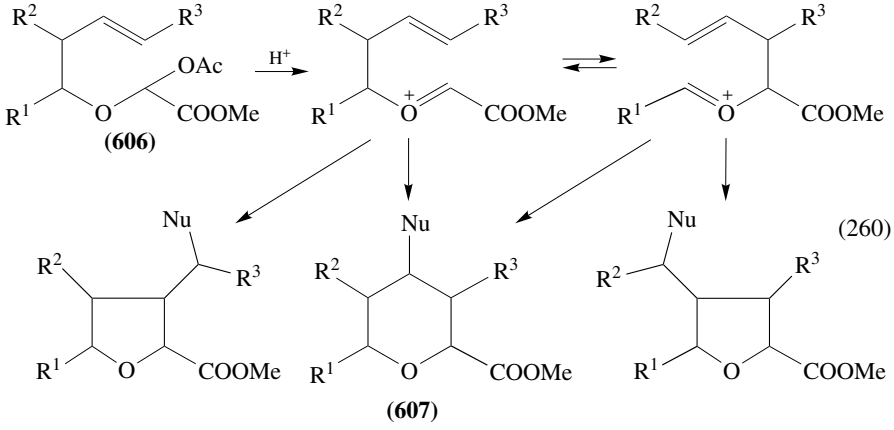
(258)

(*vide infra*). The so-called aza-Cope–Mannich reaction (**608** → **609**) constitutes an elegant entry to 3-acyl-pyrrolidines **609** which can be very useful in alkaloid total syntheses (equation 261)[356]. In a recent paper[356] clear evidence is presented that 2-oxonia-Cope rearrangement does proceed via intermediates **608** (X = O) in certain cases.



(604) **(605)** (259)

R^1 = Me, Bu; R^2 = Me, Ph, (*E*)-CH═CHMe



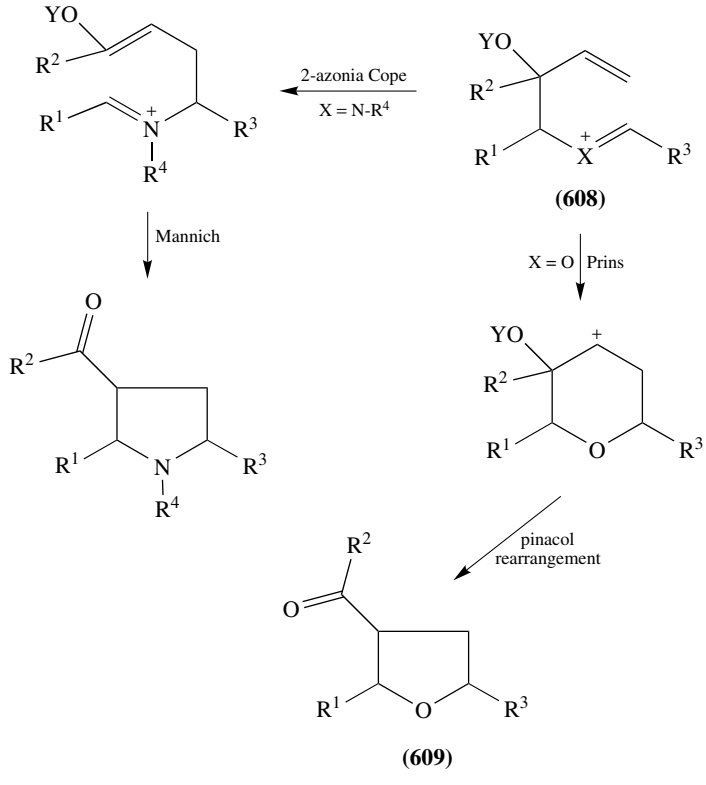
(260)

R^1 = H, Me, CO_2Me, CO_2Et, *c*-C_6H_{11}; R^2 = H, Me;
R^3 = H, Pr, $SiMe_3$; Nu = Cl (from $SnCl_4$)

2. Aza-Cope rearrangements

There is no unity of opinion in the literature concerning a classification, i.e, whether to call these transformations aza-Claisen or aza-Cope rearrangements. It is accepted that the term 'aza-Claisen' should be reserved only for those processes in which a carbon atom in the allyl vinyl ether system has been replaced by nitrogen[357]. Three different types of aliphatic 3-aza-Cope reactions which were studied theoretically are the rearrangements of 3-aza-1,5-hexadienes (**610**, equation 262), 3-azonia-1,5-hexadienes (**611**, equation 263) and 3-aza-1,2,5-hexatrienes (**612**, equation 264) (the latter is a 'ketenimine rearrangement')[357].

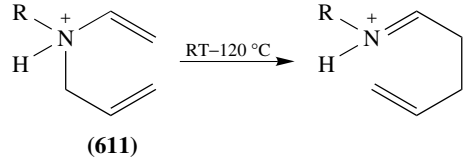
Examples of synthetic applications of these three principal reaction types can be illustrated by the $TiCl_4$-catalyzed interaction of the allylamine **613** with 2-phenylpropanal **614** in refluxing toluene (equation 265)[358] as well as by the $ZnCl_2$ promoted rearrangement of N-allylated benzoyl substituted heterocyclic keteneaminals **615** (equation 266)[359].



(261)

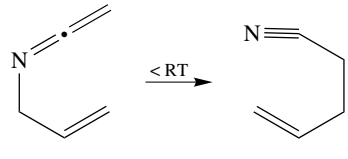
(610)

(262)



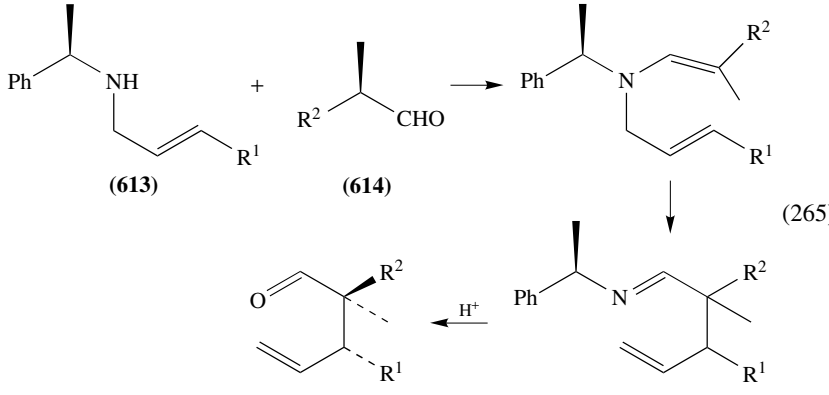
(611)

(263)



(612)

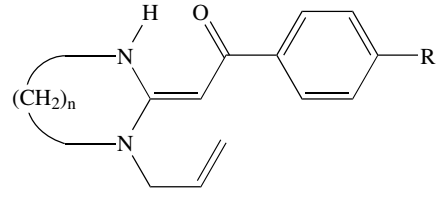
(264)



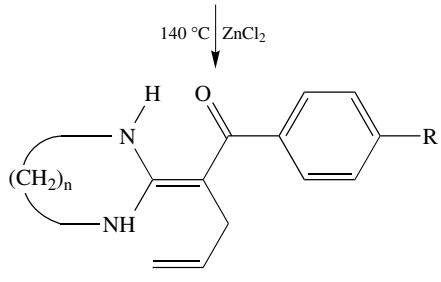
(613) (614)

(265)

R^1 = H, Me; R^2 = Me, Ph



(615)

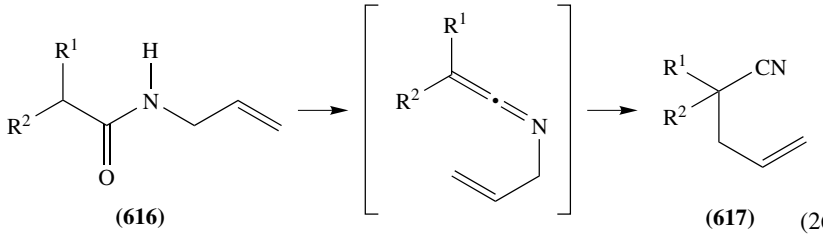


(266)

R = H, OMe

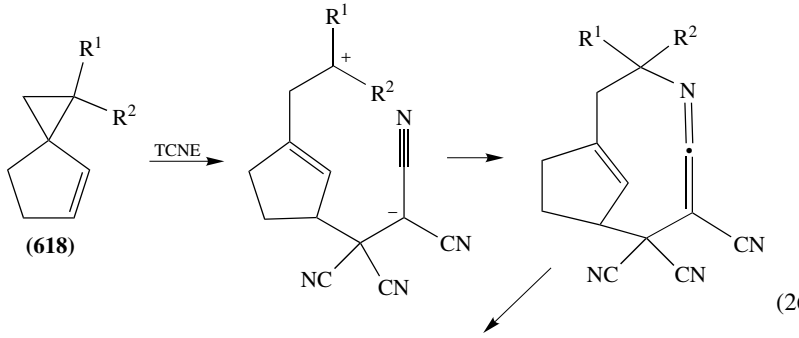
The stereochemical aspects of the 3-aza-Cope rearrangement of acyclic N-alkyl-N-allylenamines were compared with those of the O-analogues in Claisen rearrangement[360,361]. The transformation of the readily available N-allylamides **616** into nitriles **617** occurs via ketenimine rearrangement at room temperature ($Ph_3PBr_2/Et_3N/CH_2Cl_2$, 5–10 h, 30–89%) (equation 267)[362]. Ketenimine rearrangement also takes place during the interesting transformation of spiro[2,4]hept-4-ene derivatives **618** in the presence of tetracyanoethylene (TCNE) (equation 268)[363,364].

However, a better known version of the 2-aza-Cope rearrangement is that carried out by using 2-aza-1,5-hexadienes **619** (equation 269) and particularly their iminium ion counterparts, usually N-acyliminium cations **620** (equation 270)[365,366] (for reviews, see also Reference 367). Aza-Cope rearrangement of the norbornene ester **621** leads to tetrahydropyridine ester **622** when allowed to stand in solution at room temperature for

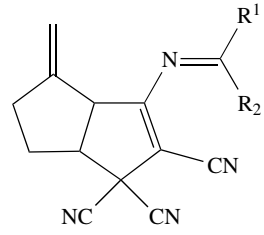


(616) **(617)** (267)

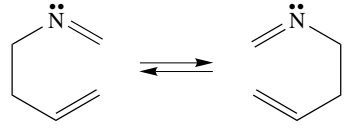
R^1 = Me, H; R^2 = Ph, CO_2Me, $(CH_2)_2CH_2Br$



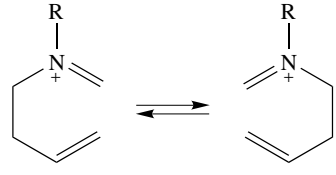
(618) (268)



R^1 = Pr, R^2 = Me; R^1 = R^2 = Pr



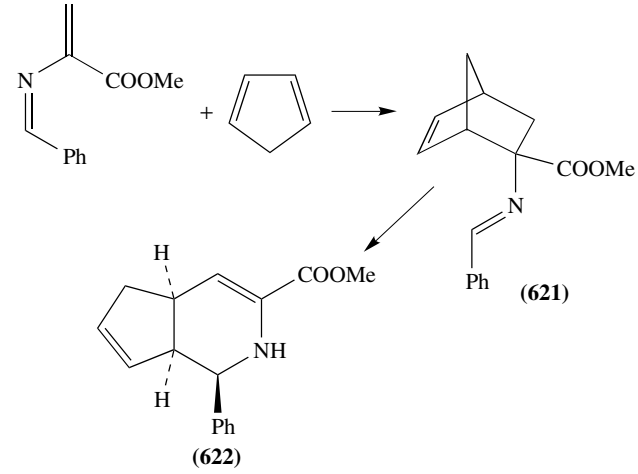
(619) (269)



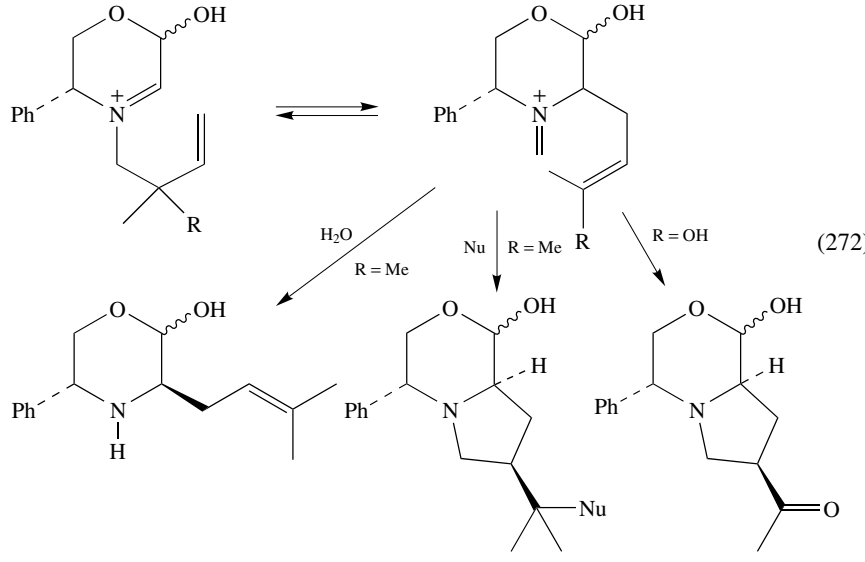
(620) (270)

R = H, Alk, Ac

10 days (equation 271)[368]. The tandem 'aza-Cope rearrangement–Mannich cyclization' (see the general scheme in equation 261) was successfully used to form the pyrrolidine ring in the course of synthesis of many natural compounds such as the antifungal antibiotic preussin[369] and strychnine[370,371]. The scope and mechanism of these useful reactions were investigated[372]. Various syntheses of natural products were carried out using tandem reactions in which the first step was a cationic aza-Cope rearrangement and the second step was either an iminium ion hydrolysis, a nucleophile-induced ene-iminium cyclization or a Mannich reaction (equation 272)[373].



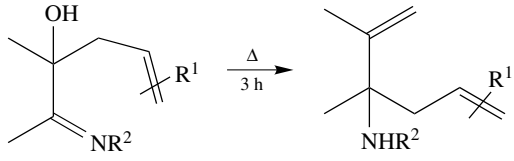
(271)



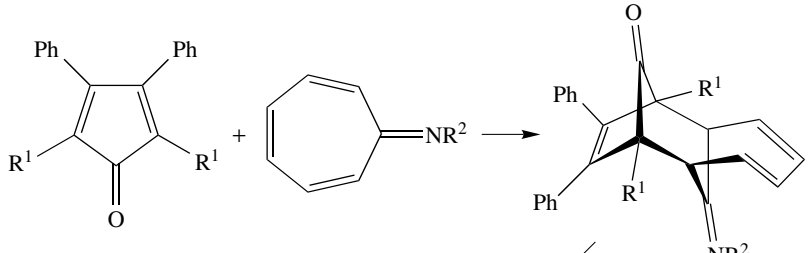
(272)

There are few examples of 1-aza-Cope rearrangements, e.g. the transformation of α-hydroxyimines **623** to aminoketones **624** in refluxing diglyme (equation 273)[374]. Diels–

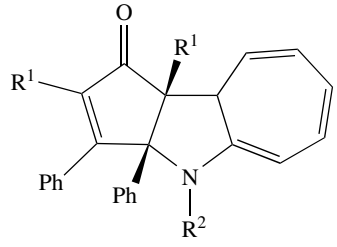
Alder adducts of cyclopentadienones with azaheptafulvenes **(625)** gave the tricyclic products **626** upon heating (refluxing benzene, 96 h, argon, in the dark) (equation 274)[375].



(623) **(624)** (273)



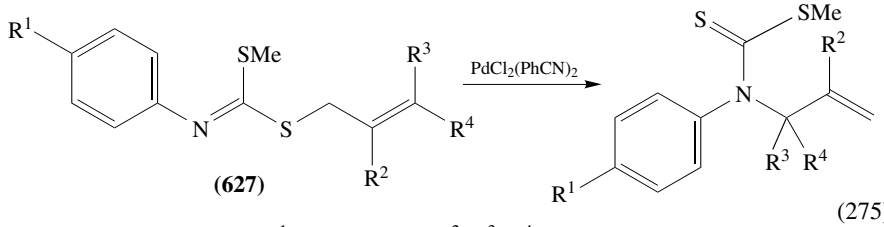
(625) (274)



(626)

3. Multihetero-Cope rearrangements

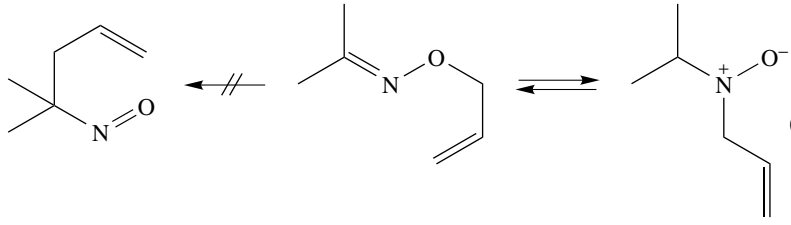
This series of rearrangements includes the dithia-Claisen rearrangement mentioned above (Section IV.E.1) as well as the palladium-catalyzed [3,3]-sigmatropic isomerizations of allyl methyl N-aryldithiocarbonimidates **627** (refluxing dioxane, 20 h, 62–90%) (equation 275)[376] and a Pd^{II}-catalyzed tandem [2,3]-sigmatropic shift, followed by 1,3-dipolar cycloaddition which takes place at equilibrium between O-allyl ethers of oximes **628** and the corresponding N-allyl nitrones **629** (equation 276)[377].



(627) (275)

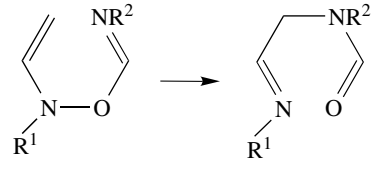
R^1 = H, Cl, OMe; R^2, R^3, R^4 = H, Me

Multihetero-Cope rearrangements were used for the preparation of heterocycles containing an imidazole ring (equations 277 and 278)[378] and α-amidoketones

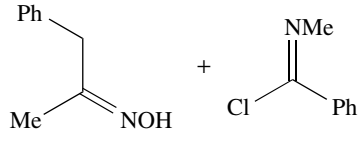


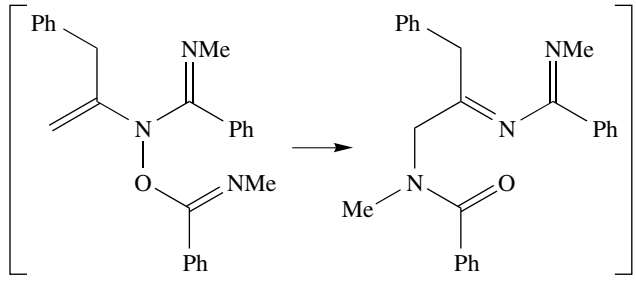
(276)

(628) **(629)**

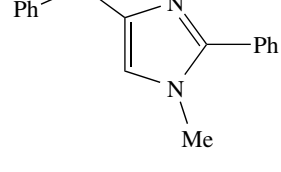


(277)

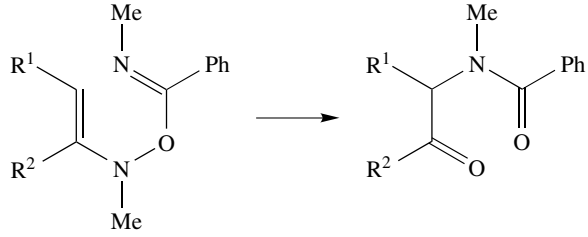




(278)

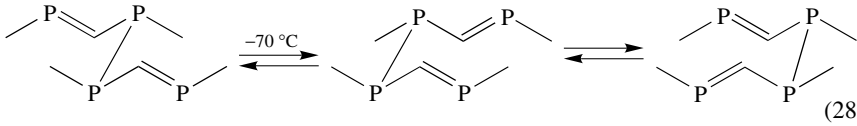


(equation 279)[379]. Finally, it should be noted that *ab initio* calculations as well as a brief literature survey were published about phospha-Cope rearrangements (equations 280 and 281)[380].

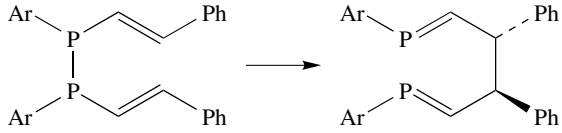


(279)

$R^1 = H, R^2 = Me; R^1 = Me, R^2 = Ph; R^1R^2 = (CH_2)_4$



(280)



(281)

Ar = 2,4,6-(*t*-Bu)$_3$C$_6$H$_2$

V. REFERENCES

1. C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, 1969.
2. M. J. S. Dewar and R. C. Dougherty, *The PMO Theory of Organic Chemistry*, Plenum Press, New York, 1975.
3. V. I. Minkin, L. P. Olekhnovich and Yu. A. Zhdanov, *Molecular Design of Tautomeric Compounds*, Reidel, Dordrecht, 1988.
4. J. March, *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, Wiley, New York, 1985.
5. T. L. Gilchrist and R. C. Storr, *Organic Reaction and Orbital Symmetry*, Cambridge University Press, Cambridge, 1972.
6. R. E. Lehr and A. P. Marchand, *Orbital Symmetry. A Problem-Solving Approach*, Academic Press, New York, 1972.
7. J. M. Tedder and A. Nechvatal, *Pictorial Orbital Theory*, Pitman, London, 1985.
8. L. T. Scott and M. Jones, Jr., *Chem. Rev.*, **72**, 181 (1972).
9. C. W. Spangler, *Chem. Rev.*, **76**, 187 (1976).
10. J. J. Gajewski, *Hydrocarbon Thermal Isomerizations*, Academic Press, New York, 1981.
11. R. P. Lutz, *Chem. Rev.*, **84**, 205 (1984).
12. A. T. Balaban and D. Fârcasiu, *J. Am. Chem. Soc.*, **89**, 1958 (1967).
13. M. V. Mavrov and V. F. Kucherov, *Usp. Khim.*, **36**, 553 (1967); *Chem. Abstr.*, **67**, 116478z (1967).
14. Sh. O. Badanyan, G. G. Khudoyan, M. G. Voskanyan and S. K. Vardapetyan, *Arm. Khim. Zh.*, **33**, 478 (1980); *Chem. Abstr.*, **93**, 149158k (1980).
15. Sh. O. Badanyan, G. R. Mkhitaryan, F. S. Kinoyan and S. K. Vardapetyan, *Arm. Khim. Zh.*, **33**, 899 (1980); *Chem. Abstr.*, **94**, 120327z (1981).

16. W. D. Huntsman, in *The Chemistry of Functional Groups, The Chemistry of Ketenes, Allenes and Related Compounds* (Ed. S. Patai), Part 2, Chap. 15, Wiley, Chichester, 1980, pp. 521–667.
17. W. Smadja, *Chem. Rev.*, **83**, 263 (1983).
18. Z. Rappoport, *Vinyl cations*, in *Reactive Intermediates*, Vol. 3 (Ed. R. A. Abramovitch), Plenum Press, New York, 1983, p. 427.
19. H. Hopf, G. Wachholz and R. Walsh, *Chem. Ber.*, **125**, 711 (1992).
20. K. A. Owens and J. A. Berson, *J. Am. Chem. Soc.*, **112**, 5973 (1990).
21. R. W. Thies, J. L. Boop, M. Schielder, D. C. Zimmerman and T. H. LaPage, *J. Org. Chem.*, **48**, 2021 (1983).
22. W. R. Roth, R. Langer, T. Ebbrecht, A. Beitat and H.-W. Lennartz, *Chem. Ber.*, **124**, 2751 (1991).
23. W. R. Roth, D. Wollweber, R. Offerhaus, V. Rekowski, H.-W. Lennartz, R. Sustmann and W. Müller, *Chem. Ber.*, **126**, 2701 (1993).
24. T. E. Wessel and J. A. Berson, *J. Am. Chem. Soc.*, **116**, 495 (1994).
25. W. R. Roth, T. Schaffers and M. Heiber, *Chem. Ber.*, **125**, 739 (1992).
26. M. B. Erman, I. M. Pribytkova, G. V. Cherkaev, I. S. Aul'chenko and S. A. Voitkevich, *Zh. Org. Khim.*, **26**, 1869 (1990); *Chem. Abstr.*, **115**, 48879p (1991).
27. G. V. Cherkaev and A. A. Kron, *Zh. Org. Khim.*, **32**, 1111 (1996); *Chem. Abstr.*, **126**, 185847t (1997).
28. R. C. Cookson and P. Singh, *J. Chem. Soc. (C)*, 1477 (1971).
29. A. Balakumar, S. Janardhanam and K. Rajagopalan, *J. Org. Chem.*, **58**, 5482 (1993).
30. L. Bhat, H. Ila and H. Junjappa, *J. Chem. Soc., Perkin Trans. 1*, 1749 (1994).
31. O. A. Tarasova, B. A. Trofimov, A. V. Afonin, L. M. Sinegovskaya, N. A. Kalinina and S. V. Amosova, *Zh. Org. Khim.*, **27**, 1172 (1991); *Chem. Abstr.*, **116**, 58693h (1992).
32. O. A. Tarasova, B. A. Trofimov, V. V. Kejko and S. V. Amosova, *Zh. Org. Khim.*, **27**, 1180 (1991); *Chem. Abstr.*, **116**, 58694j (1992).
33. W. Jasiobedzki, J. Wozniak-Kornacka and T. Mizerski, *Polish J. Chem.*, **56**, 1245 (1982); *Chem. Abstr.*, **101**, 6745x (1984).
34. A. V. Koblik and L. A. Muradyan, *Zh. Org. Khim.*, **31**, 276 (1995); *Chem. Abstr.*, **124**, 145820f (1996).
35. A. V. Koblik, L. A. Muradyan, G. V. Gridunova, D. S. Yufit, Yu. T. Struchkov and G. P. Zolotovskova, *Khim. Geterocycl. Soedin.*, 1316 (1992); *Chem. Abstr.*, **119**, 95275f (1993).
36. K. Nakasuji, K. Takatoh, M. Nakatsuka and I. Murata, *J. Chem. Soc., Chem. Commun.*, 717 (1981).
37. S. E. Gulyi, M. B. Erman, N. A. Novikov, I. S. Aul'chenko and M. E. Vol'pin, *Zh. Org. Khim.*, **19**, 808 (1983); *Chem. Abstr.*, **99**, 69934u (1983).
38. M. D. Schiavelli, T. C. Germroth and J. W. Stubbs, *J. Org. Chem.*, **41**, 681 (1976).
39. M. Hanack, *Acc. Chem. Res.*, **9**, 364 (1976).
40. H. Mayr and E. Bäuml, *Tetrahedron Lett.*, **24**, 357 (1983).
41. E. Bäuml and H. Mayr, *Chem. Ber.*, **118**, 683 (1985).
42. E. Bäuml and H. Mayr, *Chem. Ber.*, **118**, 694 (1985).
43. P. A. Krasutskii, A. A. Fokin and A. G. Yurchenko, *Zh. Org. Khim.*, **22**, 459 (1986); *Chem. Abstr.*, **106**, 17950q (1987).
44. R. J. Bushby and S. Mann, *J. Chem. Soc., Perkin Trans. 1*, 2497 (1987).
45. J. J. Gajewski and C. N. Shin, *J. Am. Chem. Soc.*, **94**, 1675 (1972).
46. W. E. Billups, K. H. Leavell, W. Y. Chow and E. S. Lewis, *J. Am. Chem. Soc.*, **94**, 1770 (1972).
47. W. E. Billups, B. A. Baker, W. Y. Chow, K. H. Leavell and E. S. Lewis, *J. Org. Chem.*, **40**, 1702 (1975).
48. U. H. Brinker and L. König, *Chem. Ber.*, **116**, 894 (1983).
49. J. M. Simpson and H. G. Richey, *Tetrahedron Lett.*, 2545 (1973).
50. T. Hudlicky, T. M. Kutchan and S. M. Naqvi, *Org. React.*, **33**, 247 (1989).
51. T. Hudlicky and J. W. Reed, in *Comprehensive Organic Chemistry* (Eds. B. M. Trost and I. Fleming), Vol. 5, Pergamon, Oxford, 1991, p. 899.
52. K. R. Motion, I. R. Robertson and J. T. Sharp, *J. Chem. Soc., Chem. Commun.*, 1531 (1984).
53. A. G. Schultz, R. R. Staib and K. K. Eng, *J. Org. Chem.*, **52**, 2968 (1987).
54. W. Grimme and W. v. E. Doering, *Chem. Ber.*, **106**, 1765 (1973).

55. W. v. E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).
56. W. Kirmse, R. Kühr, H.-R. Murawski, F. Scheidt and V. Ullrich, *Chem. Ber.*, **113**, 1272 (1980).
57. R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969); *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
58. P. George, C. W. Bock, J. P. Glusker, A. Greenberg and J. D. Gallagher, *J. Org. Chem.*, **60**, 4385 (1995).
59. I. Fleischhauer and U. H. Brinker, *Chem. Ber.*, **120**, 501 (1987).
60. R. Gleiter and R. Hoffmann, *J. Am. Chem. Soc.*, **90**, 5457 (1968).
61. W. T. Brown and W. M. Jones, *J. Org. Chem.*, **44**, 3090 (1979).
62. G. G. Vander Stouw, A. R. Kraska and H. Shechter, *J. Am. Chem. Soc.*, **94**, 1655 (1972).
63. W. E. Billups, L. E. Reed, E. W. Casserly and L. P. Lin, *J. Org. Chem.*, **46**, 1326 (1981).
64. R. J. McMahon, C. J. Abelt, O. L. Chapman, J. W. Johnson, C. L. Kreil, J.-P. LeRoux, A. M. Mooring and P. R. West, *J. Am. Chem. Soc.*, **109**, 2456 (1987).
65. C. A. Cupas, W. Schumann and W. E. Heyd, *J. Am. Chem. Soc.*, **92**, 3237 (1970).
66. C. A. Cupas, W. E. Heyd and M.-S. Kong, *J. Am. Chem. Soc.*, **93**, 4623 (1971).
67. G. R. Krow, K. C. Cannon, J. T. Carey, H. Ma, R. Raghavachari and S. W. Szczepanski, *J. Org. Chem.*, **53**, 2665 (1988).
68. W. E. Truce and C.-I. M. Lin, *J. Am. Chem. Soc.*, **95**, 4426 (1973).
69. C. A. Hoeger, A. D. Johnston and W. H. Okamura, *J. Am. Chem. Soc.*, **109**, 4690 (1987).
70. A. C. Cope and F. A. Hochstein, *J. Am. Chem. Soc.*, **72**, 2515 (1950).
71. A. C. Cope, A. C. Haven, F. L. Ramp and E. R. Trumbull, *J. Am. Chem. Soc.*, **74**, 4867 (1952).
72. T. Bally, K. Roth and R. Straub, *Helv. Chim. Acta*, **72**, 73 (1989).
73. E. Vogel, *Angew. Chem.*, **73**, 548 (1961).
74. W. Grimme and G. Wiechers, *Tetrahedron Lett.*, **29**, 5249 (1988).
75. M. Jones, S. D. Reich and L. T. Scott, *J. Am. Chem. Soc.*, **92**, 3118 (1970).
76. F.-G. Klärner and V. Glock, *Angew. Chem.*, **96**, 78 (1984); *Angew. Chem., Int. Ed. Engl.*, **23**, 73 (1984).
77. V. Glock, M. Wette and F.-G. Klärner, *Tetrahedron Lett.*, **26**, 1441 (1985).
78. H.-G. Korth, R. Sustmann, W. Sicking, F.-G. Klärner and H. I. Tashtoush, *Chem. Ber.*, **126**, 1917 (1993).
79. T. J. Katz, C. R. Nicholson and C. A. Reilly, *J. Am. Chem. Soc.*, **88**, 3832 (1966).
80. G. Märkl and B. Alig, *Tetrahedron Lett.*, **24**, 3981 (1983).
81. E. W. Turnblom and T. J. Katz, *J. Am. Chem. Soc.*, **95**, 4292 (1973).
82. L. D. Quin, N. S. Rao, R. J. Topping and A. T. McPhail, *J. Am. Chem. Soc.*, **108**, 4519 (1986).
83. R. A. Raphael, in *Non-Benzenoid Aromatic Compounds* (Ed. D. Ginsburg), Chapter VIII, Interscience Publishers, New York, 1958.
84. L. A. Paquette, *Tetrahedron*, **31**, 2855 (1975).
85. G. I. Fray and G. R. Saxton, *The Chemistry of Cyclooctatetraene and Its Derivatives*, Cambridge University Press, New York, 1978.
86. Y. Kobayashi, A. Ando, K. Kawada and I. Kumadaki, *J. Am. Chem. Soc.*, **103**, 3958 (1981).
87. L. Baumann, A. Folkerts, P. Imming, T. Klindert, W. Massa, G. Seitz and S. Wocadlo, *Justus Liebigs Ann. Chem.*, 661 (1995).
88. R. Hertel, J. Mattay and J. Runsink, *J. Am. Chem. Soc.*, **113**, 657 (1991).
89. E. J. Reardon and M. Brookhart, *J. Am. Chem. Soc.*, **95**, 4311 (1973).
90. A. A. Schegolev, W. A. Smit, Y. B. Kalyan, M. Z. Krimer and R. Caple, *Tetrahedron Lett.*, **23**, 4419 (1982).
91. M. T. Reetz, *Angew. Chem.*, **84**, 161 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 129 (1972).
92. M. T. Reetz, *Angew. Chem.*, **84**, 163 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 130 (1972).
93. K. Mackenzie, *J. Chem. Soc.*, 4646 (1965).
94. C. H. M. Adams and K. Mackenzie, *J. Chem. Soc. (C)*, 480 (1969).
95. K. Mackenzie, *J. Chem. Soc. (C)*, 1784 (1969).
96. K. Mackenzie, G. J. Proctor and D. J. Woodnutt, *Tetrahedron Lett.*, **25**, 977 (1984).
97. K. Mackenzie, G. J. Proctor and D. J. Woodnutt, *Tetrahedron*, **43**, 5981 (1987).
98. M. T. Reetz, *Tetrahedron*, **29**, 2189 (1973).
99. D. F. Feller, M. W. Schmidt and K. Ruedenberg, *J. Am. Chem. Soc.*, **104**, 960 (1982).

100. J.-P. Hagenbuch, B. Stampfli and P. Vogel, *J. Am. Chem. Soc.*, **103**, 3934 (1981).
101. W.-D. Fessner, G. Sedelmeier, P. R. Spurr, G. Rihs and H. Prinzbach, *J. Am. Chem. Soc.*, **109**, 4626 (1987).
102. R. Srinivasan, *Tetrahedron Lett.*, 4029 (1973).
103. T. S. Piper and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **2**, 32 (1956).
104. R. F. Childs, *Tetrahedron*, **38**, 567 (1982).
105. P. Jutzi, *Chem. Rev.*, **86**, 983 (1986).
106. H. Kessler and M. Feigel, *Acc. Chem. Res.*, **15**, 2 (1982).
107. L. A. Fedorov, D. N. Kravtsov and A. S. Peregudov, *Usp. Khim.*, **50**, 1304 (1981); *Chem. Abstr.*, **95**, 115633n (1981).
108. V. A. Mironov. A. D. Fedorovich and A. A. Akhrem, *Usp. Khim.*, **50**, 1272 (1981); *Chem. Abstr.*, **95**, 114226v (1981).
109. V. I. Minkin, I. E. Mikhailov, G. A. Dushenko, J. A. Yudilevich, R. M. Minyaev, A. Zschunke and K. Mügge, *J. Phys. Org. Chem.*, **4**, 31 (1991).
110. G. I. Borodkin, E. R. Susharin, M. M. Shakirov and V. G. Shubin, *Zh. Org. Khim.*, **21**, 1809 (1985); *Chem. Abstr.*, **104**, 108788t (1986).
111. G. I. Borodkin, E. R. Susharin, M. M. Shakirov and V. G. Shubin, *Zh. Org. Khim.*, **23**, 1610 (1987); *Chem. Abstr.*, **108**, 111539a (1988).
112. I. E. Mikhailov, G. A. Dushenko, V. I. Minkin and L. P. Olekhnovich, *Zh. Org. Khim.*, **20**, 1019 (1984); *Chem. Abstr.*, **101**, 110045e (1984).
113. I. E. Mikhailov, G. A. Dushenko and V. I. Minkin, *Zh. Org. Khim.*, **23**, 2522 (1987); *Chem. Abstr.*, **109**, 169681c (1988).
114. R. J. Bushby and D. W. Jones, *J. Chem. Soc., Chem. Commun.*, 688 (1979).
115. I. E. Mikhailov, G. A. Dushenko, Yu. A. Ustynyuk, L. P. Olekhnovich and V. I. Minkin, *Zh. Org. Khim.*, **20**, 2626 (1984); *Chem. Abstr.*, **102**, 131452w (1985).
116. I. E. Mikhailov, G. A. Dushenko and V. I. Minkin, *Zh. Org. Khim.*, **23**, 1109 (1987); *Chem. Abstr.*, **108**, 36970d (1988).
117. V. I. Minkin, I. E. Mikhailov and G. A. Dushenko, *J. Chem. Soc., Chem. Commun.*, 1181 (1988).
118. I. E. Mikhailov, O. E. Kompan, G. A. Dushenko and V. I. Minkin, *Mendeleev Commun.*, 121 (1991).
119. I. E. Mikhailov, G. A. Dushenko, V. I. Minkin, L. P. Olekhnovich, N. I. Borisenko and Yu. A. Zhdanov, *Dokl. Akad. Nauk SSSR*, **270**, 891 (1983); *Chem. Abstr.*, **99**, 121580s (1983).
120. I. E. Mikhailov, G. A. Dushenko, V. I. Minkin and L. P. Olekhnovich, *Zh. Org. Khim.*, **20**, 1657 (1984); *Chem. Abstr.*, **102**, 5386q (1985).
121. I. E. Mikhailov, G. A. Dushenko, V. I. Minkin and L. P. Olekhnovich, *Zh. Org. Khim.*, **20**, 2306 (1984); *Chem. Abstr.*, **102**, 131344n (1985).
122. O. E. Kompan, M. Yu. Antipin, Yu. T. Struchkov, I. E. Mikhailov, G. A. Dushenko, L. P. Olekhnovich and V. I. Minkin, *Zh. Org. Khim.*, **21**, 2032 (1985); *Chem. Abstr.*, **104**, 148438k (1986).
123. G. I. Borodkin, E. R. Susharin, M. M. Shakirov and V. G. Shubin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2797 (1985); *Chem. Abstr.*, **105**, 42066t (1986).
124. I. E. Mikhailov, G. A. Dushenko, Yu. A. Zhdanov, L. P. Olekhnovich and V. I. Minkin, *Dokl. Akad. Nauk SSSR*, **275**, 1431 (1984); *Chem. Abstr.*, **101**, 110048h (1984).
125. I. E. Mikhailov, O. E. Kompan, Yu. T. Struchkov, V. I. Minkin, G. A. Dushenko, A. A. Klenkin and L. P. Olekhnovich, *Zh. Org. Khim.*, **23**, 1029 (1987); *Chem. Abstr.*, **108**, 111533u (1988).
126. I. E. Mikhailov, V. I. Minkin, G. A. Dushenko, I. A. Kamenetskaya and L. P. Olekhnovich, *Dokl. Akad. Nauk SSSR*, **299**, 1399 (1988); *Chem. Abstr.*, **110**, 23044w (1989).
127. I. E. Mikhailov, G. A. Dushenko, I. A. Kamenetskaya, L. P. Olekhnovich and V. I. Minkin, *Zh. Org. Khim.*, **24**, 1998 (1988); *Chem. Abstr.*, **110**, 172472m (1989).
128. G. A. Dushenko, I. E. Mikhailov, I. A. Kamenetskaya, R. V. Skachkov, A. Zschunke, C. Mügge and V. I. Minkin, *Zh. Org. Khim.*, **30**, 1481 (1994); *Chem. Abstr.*, **123**, 338827b (1995).
129. I. E. Mikhailov, G. A. Dushenko, I. A. Kamenetskaya, O. E. Kompan, Yu. T. Struchkov and V. I. Minkin, *Mendeleev Commun.*, 83 (1991).
130. G. I. Borodkin, E. R. Susharin and V. G. Shubin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1687 (1986); *Chem. Abstr.*, **106**, 155691g (1987).

131. I. E. Mikhailov, V. I. Minkin, A. A. Klenkin, G. A. Dushenko, L. P. Olekhnovich and Yu. A. Zhdanov, *Dokl. Akad. Nauk SSSR*, **287**, 1404 (1986); *Chem. Abstr.*, **105**, 133134e (1986).
132. I. E. Mikhailov, A. A. Klenkin, V. I. Minkin and L. P. Olekhnovich, *Zh. Org. Khim.*, **22**, 865 (1986); *Chem. Abstr.*, **105**, 114465x (1986).
133. I. E. Mikhailov, V. I. Minkin, A. A. Klenkin, G. A. Dushenko, O. E. Kompan, A. I. Janovski and Yu. T. Struchkov, *Zh. Org. Khim.*, **26**, 28 (1990); *Chem. Abstr.*, **113**, 5451j (1990).
134. I. E. Mikhailov, V. I. Minkin, A. A. Klenkin, G. A. Dushenko, O. E. Kompan, Yu. T. Struchkov, A. I. Janovski, L. P. Olekhnovich and N. I. Borisenko, *Zh. Org. Khim.*, **24**, 2301 (1988); *Chem. Abstr.*, **111**, 96428e (1989).
135. I. E. Mikhailov, V. I. Minkin, A. A. Klenkin and L. P. Olekhnovich, *Zh. Org. Khim.*, **22**, 1331 (1986); *Chem. Abstr.*, **106**, 49447x (1987).
136. I. E. Mikhailov, G. A. Dushenko, O. E. Kompan, Yu. T. Struchkov, A. Zschunke, C. Mügge, V. N. Drozd and V. I. Minkin. *Mendeleev Commun.*, 120 (1994).
137. G. A. Dushenko, I. E. Mikhailov, A. Zschunke, N. Hakam, C. Mügge, R. V. Skachkov and V. I. Minkin, *Mendeleev Commun.*, 182 (1995).
138. J. A. Yudilevich, R. M. Minyaev, I. E. Mikhailov and V. I. Minkin, *Zh. Org. Khim.*, **25**, 245 (1989); *Chem. Abstr.*, **111**, 173353f (1989).
139. I. E. Mikhailov, G. A. Dushenko, A. V. Kisin, C. Mügge, A. Zschunke and V. I. Minkin, *Mendeleev Commun.*, 85 (1994).
140. V. I. Minkin, I. E. Mikhailov, G. A. Dushenko, O. E. Kompan and A. Zschunke, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 913 (1998).
141. G. A. Dushenko, I. E. Mikhailov, A. Zschunke, N. Hakam, C. Mügge and V. I. Minkin, *Mendeleev Commun.*, 50 (1997).
142. G. A. Dushenko, I. E. Mikhailov, A. Zschunke, N. Hakam, C. Mügge and V. I. Minkin, *Mendeleev Commun.*, 133 (1995).
143. M. Feigel, H. Kessler, D. Leibfritz and A. Walter, *J. Am. Chem. Soc.*, **101**, 1943 (1979).
144. T. A. Albright, P. Hofmann, R. Hoffmann, C. P. Lillya and P. A. Dobosh, *J. Am. Chem. Soc.*, **105**, 3396 (1983).
145. J. Silvestre and T. A. Albright, *J. Am. Chem. Soc.*, **107**, 6829 (1985).
146. I. N. Nazarov and L. A. Yanovskaya, *Usp. Khim.*, **27**, 241 (1958); *Chem. Abstr.*, **52**, 10964f (1958).
147. W. H. Sebrell and R. S. Harris (Eds.), *The Vitamins: Chemistry, Physiology, Pathology, Methods*, vol. I, 2nd. ed., Academic Press, New York, 1967.
148. H. O. Huisman, A. Smit, P. H. van Leeuwen and J. H. van Rij, *Recl. Trav. Chim. Pays-Bas*, **75**, 977 (1956).
149. W. Oroshnik, G. Karmas and A. D. Mebane, *J. Am. Chem. Soc.*, **74**, 295 (1952).
150. W. Oroshnik, G. Karmas and A. D. Mebane, *J. Am. Chem. Soc.*, **74**, 3807 (1952).
151. S. A. Osadchii, V. A. Drobysh, M. M. Shakirov, V. I. Mamatyuk and V. G. Shubin, *Zh. Org. Khim.*, **24**, 267 (1988); *Chem. Abstr.*, **109**, 229896p (1988).
152. S. A. Osadchii, V. A. Drobysh, M. M. Shakirov, V. I. Mamatyuk and V. G. Shubin, *Zh. Org. Khim.*, **24**, 1417 (1988); *Chem. Abstr.*, **110**, 192287h (1989).
153. S. A. Osadchii, M. M. Shakirov and V. G. Shubin, *Zh. Org. Khim.*, **29**, 930 (1993); *Chem. Abstr.*, **121**, 34567x (1994).
154. V. G. Shubin, M. M. Shakirov, S. M. Nagy and S. A. Osadchii, *Mendeleev Commun.*, 110 (1992).
155. J. Lukač and H. Helmgartner, *Helv. Chim. Acta*, **68**, 355 (1985).
156. G. Majetich and V. Khetani, *Tetrahedron Lett.*, **31**, 2243 (1990).
157. L. R. Hanton, S. D. Lorimer and R. T. Weavers, *Aust. J. Chem.*, **40**, 1795 (1987).
158. C. J. Collins and J. F. Eastman, in *The Chemistry of the Carbonyl Group* (Ed. S. Patai), Chap. 15, Wiley-Interscience, London, 1966, p. 761–821.
159. B. Miller, *Acc. Chem. Res.*, **8**, 245 (1975).
160. V. P. Vitullo, *J. Org. Chem.*, **34**, 224 (1969).
161. V. P. Vitullo and N. Grossman, *Tetrahedron Lett.*, 1559 (1970).
162. V. P. Vitullo and E. A. Logue, *J. Org. Chem.*, **37**, 3339 (1972).
163. V. P. Vitullo and E. A. Logue, *J. Org. Chem.*, **38**, 2265 (1973).
164. V. P. Vitullo and E. A. Logue, *J. Chem. Soc., Chem. Commun.*, 228 (1974).
165. B. Hagenbruch and S. Hünig, *Chem. Ber.*, **116**, 3884 (1983).
166. J. M. Brittain, P. B. D. de la Mare and P. A. Newman, *Tetrahedron Lett.*, **21**, 4111 (1980).

167. F. B. H. Ahmad, J. M. Bruce, J. Khalafy, V. Pejanovič, K. Sabetian and I. Watt, *J. Chem. Soc., Chem. Commun.*, 166 (1981).
168. F. B. H. Ahmad, J. M. Bruce, J. Khalafy and K. Sabetian, *J. Chem. Soc., Chem. Commun.*, 169 (1981).
169. R. Al-Hamdany, J. M. Bruce, R. T. Pardasani and I. Watt, *J. Chem. Soc., Chem. Commun.*, 171 (1981).
170. S. C. Cooper and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 2407 (1984).
171. R. Cassis, M. Scholz, R. Tapia and J. A. Valderrama, *Tetrahedron Lett.*, **26**, 6281 (1985).
172. V. I. Rosenberg, G. V. Gavrilova, B. I. Ginsburg, V. A. Nikanorov and O. A. Reutov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1916 (1982); *Chem. Abstr.*, **98**, 54072s (1983).
173. B. Miller, *J. Am. Chem. Soc.*, **92**, 432 (1970).
174. J. A. Berson and R. G. Salomon, *J. Am. Chem. Soc.*, **93**, 4620 (1971).
175. R. A. Baylouny, *J. Am. Chem. Soc.*, **93**, 4621 (1971).
176. P. Schiess and P. Fünfschillig, *Tetrahedron Lett.*, 5195 (1972).
177. A. J. Waring, J. H. Zaidi and J. W. Pilkington, *J. Chem. Soc., Perkin Trans. 1*, 1454 (1981).
178. V. P. Vitullo and M. J. Cashen, *Tetrahedron Lett.*, 4823 (1973).
179. J. R. Hanson and P. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 2937 (1984).
180. A. Rieker, *Angew. Chem.*, **83**, 449 (1971).
181. D. M. Gash and P. D. Woodgate, *Austral. J. Chem.*, **32**, 1863 (1979).
182. R. D. Malysheva, V. V. Ershov and A. A. Volod'kin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 610 (1983); *Chem. Abstr.*, **98**, 197378g (1983).
183. K. H. Dudley and R. W. Chiang, *J. Org. Chem.*, **34**, 120 (1969).
184. C. P. Falshaw, S. A. Lane and W. D. Ollis, *J. Chem. Soc., Chem. Commun.*, 491 (1973).
185. G. Märkl, M. Horn and W. Schlosser, *Tetrahedron Lett.*, **27**, 4019 (1986).
186. V. V. Ershov, A. A. Volod'kin and G. N. Bogdanov, *Usp. Khim.*, **32**, 154 (1963); *Chem. Abstr.*, **59**, 3800h (1963).
187. E. Curson, B. I. Golding, C. Pierpoint and B. W. Waters, *J. Organomet. Chem.*, **262**, 263 (1984).
188. R. Weiss and H. P. Kempcke, *Tetrahedron Lett.*, 155 (1974).
189. O. Cakmak, T. Hökelek, O. Büyükgüngör and M. Balci, *Tetrahedron Lett.*, **31**, 2345 (1990).
190. E. V. Lukovskaya, A. A. Bobyleva, T. I. Pekhk, N. F. Dubitskaya, I. A. Petrushenkova and N. A. Belikova, *Zh. Org. Khim.*, **24**, 1457 (1988); *Chem. Abstr.*, **110**, 172741y (1989).
191. L. E. Tatarova, V. B. Nigmatova, D. V. Korchagina. Yu. V. Gatilov, I. Yu. Bagryanskaya, T. V. Rybalova, O. B. Kun, V. L. Salenko, S. N. Anfilogova, N. A. Belikova and V. A. Barkhash, *Zh. Org. Khim.*, **25**, 2321 (1989); *Chem. Abstr.*, **112**, 197323t (1990).
192. S. N. Anfilogova, V. A. Andreev, T. I. Pekhk and N. A. Belikova, *Zh. Org. Khim.*, **25**, 1436 (1989); *Chem. Abstr.*, **112**, 178135s (1990).
193. V. B. Nigmatova, V. A. Andreev, T. I. Pekhk, N. A. Belikova, A. A. Bobyleva, S. N. Anfilogova, N. F. Dubitskaya and G. A. Karoza, *Zh. Org. Khim.*, **26**, 2552 (1990); *Chem. Abstr.*, **115**, 182685a (1991).
194. A. A. Bobyleva, E. V. Lukovskaya, T. I. Pekhk, G. A. Karoza and N. A. Belikova, *Zh. Org. Khim.*, **30**, 1632 (1994); *Chem. Abstr.*, **124**, 8272q (1996).
195. A. A. Bobyleva, I. A. Petrushenkova, E. V. Lukovskaya, T. I. Pekhk, N. F. Dubitskaya and N. A. Belikova, *Zh. Org. Khim.*, **25**, 1428 (1989); *Chem. Abstr.*, **112**, 177744c (1990).
196. N. S. Zefirov, N. K. Sadovaya, R. S. Akhmedova, I. V. Bodrikov, T. C. Morril, A. M. Nersisyan, V. B. Rybakov, N. D. Saraceno and Yu. T. Struchkov, *Zh. Org. Khim.*, **16**, 580 (1980); *Chem. Abstr.*, **93**, 94694z (1980).
197. N. S. Zefirov, N. V. Zyk, S. I. Kolbasenko and A. G. Kutateladze, *J. Org. Chem.*, **50**, 4539 (1985).
198. N. S. Zefirov, A. S. Koz'min, V. N. Kirin, V. V. Zhdankin and R. Caple, *J. Org. Chem.*, **46**, 5264 (1981).
199. T. Kumagai, M. Katayose and T. Mukai, *Chem. Lett.*, 899 (1987).
200. J. K. Whitesell, R. S. Matthews and P. A. Solomon, *Tetrahedron Lett.*, 1549 (1976).
201. G. Haufe, A. Wolf and K. Schulze, *Tetrahedron*, **42**, 4719 (1986).
202. G. Haufe and M. Mühlstädt, *Z. Chem.*, **19**, 170 (1979).
203. J. K. Sutherland, *Tetrahedron*, **30**, 1651 (1974).
204. F. Freeman, *Chem. Rev.*, **75**, 439 (1975).
205. D. E. Cane, *Acc. Chem. Res.*, **18**, 220 (1985).

206. D. V. Banthorpe, B. V. Charlwood and M. J. O. Francis, *Chem. Rev.*, **72**, 115 (1972).
207. E. M. Milvitskaya, A. V. Tarakanova and A. F. Plate, *Usp. Khim.*, **45**, 938 (1976); *Russ. Chem. Rev.*, **45**, 469 (1976); *Chem. Abstr.*, **85**, 176368v (1976).
208. P. A. Bartlett, *Tetrahedron*, **36**, 2 (1980).
209. A. Viola, J. J. Collins and N. Filipp, *Tetrahedron*, **37**, 3765 (1981).
210. W. T. Borden, R. J. Loncharich and K. N. Houk, *Annu. Rev. Phys. Chem.*, **39**, 213 (1988).
211. W. v. E. Doering, V. G. Toscano and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971).
212. K. Morokuma, W. T. Borden and D. A. Hrovat, *J. Am. Chem. Soc.*, **110**, 4474 (1988).
213. M. Dupuis, C. Murray and E. R. Davidson, *J. Am. Chem. Soc.*, **113**, 9756 (1991).
214. P. M. Kozlowski, M. Dupuis and E. R. Davidson, *J. Am. Chem. Soc.*, **117**, 774 (1995).
215. M. J. S. Dewar and C. Jie, *J. Chem. Soc., Chem. Commun.*, 1451 (1987).
216. M. J. S. Dewar and C. Jie, *Tetrahedron*, **44**, 1351 (1988).
217. M. J. S. Dewar and C. Jie, *J. Chem. Soc., Chem. Commun.*, 98 (1989).
218. M. Bearpark, F. Bernardi, M. Olivucci and M. A. Robb, *J. Am. Chem. Soc.*, **112**, 1732 (1990).
219. B. M. Gimarc and M. Zhao, *J. Org. Chem.*, **60**, 1971 (1995).
220. J. S. McKennis, L. Brener, J. S. Ward and R. Pettit, *J. Am. Chem. Soc.*, **93**, 4957 (1971).
221. G.-F. Chen and F. Williams, *J. Chem. Soc., Chem. Commun.*, 670 (1992).
222. H. D. Roth, *Z. Phys. Chem.*, **180**, 135 (1993).
223. H. Ikeda, T. Takasaki, Y. Takahashi and T. Miyashi, *J. Chem. Soc., Chem. Commun.*, 367 (1993).
224. T. G. Traylor and A. R. Miksztal, *J. Am. Chem. Soc.*, **109**, 2770 (1987).
225. W. R. Roth, H.-W. Lennartz, W. v. E. Doering, L. Birladeanu, C. A. Guyton and T. Kitagawa, *J. Am. Chem. Soc.*, **112**, 1722 (1990).
226. D. Hochstrate and F.-G. Klärner, *Justus Liebigs Ann. Chem.*, 745 (1995).
227. R. Gleiter and C. Sigwart, *J. Org. Chem.*, **59**, 1027 (1994).
228. R. Gleiter, T. Herb, O. Borzyk and I. Hyla-Kryspin, *Justus Liebigs. Ann. Chem.*, 357 (1995).
229. K. J. Shea, G. J. Stoddard, W. P. England and C. D. Haffner, *J. Am. Chem. Soc.*, **114**, 2635 (1992).
230. W. v. E. Doering, L. Birladeanu, K. Sarma, J. H. Teles, F.-G. Klärner and J.-S. Gehrke, *J. Am. Chem. Soc.*, **116**, 4289 (1994).
231. W. R. Dolbier, K. Palmer, H. Koroniak and H.-Q. Zhang, *J. Am. Chem. Soc.*, **113**, 1059 (1991).
232. W. R. Dolbier and K. W. Palmer, *J. Am. Chem. Soc.*, **115**, 9349 (1993).
233. N. Jing and D. M. Lemal, *J. Am. Chem. Soc.*, **115**, 8481 (1993).
234. W. G. Dauben and A. Chollet, *Tetrahedron Lett.*, **22**, 1583 (1981).
235. C. Herberg, H.-D. Beckhaus, T. Körtvelyesi and C. Rüchardt, *Chem. Ber.*, **126**, 117 (1993).
236. J. L. van der Baan, J. van der Louw, M. Wiersma and F. Bickelhaupt, *Tetrahedron Lett.*, **33**, 1377 (1992).
237. L. E. Overman and F. M. Knoll, *J. Am. Chem. Soc.*, **102**, 865 (1980).
238. R. Hamilton, T. R. B. Mitchell and J. J. Rooney, *J. Chem. Soc., Chem. Commun.*, 456 (1981).
239. T. Kawasaki, K. Watanabe, K. Masuda and M. Sakamoto, *J. Chem. Soc., Chem. Commun.*, 381 (1995).
240. K. Hafner, J. Hartung and C. Syren, *Tetrahedron*, **48**, 4879 (1992).
241. T. P. Sura and D. W. H. MacDowell, *J. Org. Chem.*, **58**, 4360 (1993).
242. K. F. Suzdalev and A. V. Koblik, *Khim. Geterocycl. Soedin.*, 603 (1990); *Chem. Abstr.*, **114**, 23761k (1991).
243. F. E. Ziegler and J. J. Piwinski, *J. Am. Chem. Soc.*, **102**, 880 (1980).
244. K. Takeda, *Tetrahedron*, **30**, 1525 (1974).
245. T. Hudlicki, C. H. Boros and E. E. Boros, *Synthesis*, 174 (1992).
246. R. N. Warrener, G. M. Elsey, I. G. Pitt, E. R. T. Tiekink and R. A. Russell, *Tetrahedron Lett.*, **35**, 1075 (1994).
247. R. Guevel and L. A. Paquette, *J. Am. Chem. Soc.*, **116**, 1776 (1994).
248. E. A. Chandross and C. J. Dempster, *J. Am. Chem. Soc.*, **92**, 703 (1970).
249. S. Lalitha, J. Chandrasekhar and G. Metha, *J. Org. Chem.*, **55**, 3455 (1990).
250. Yu. G. Osokin, M. Ya. Grinberg and V. S. Feldblum, *Dokl. Akad. Nauk SSSR*, **235**, 1319 (1977); *Chem. Abstr.*, **88**, 120652e (1978).
251. L. Crombie and K. M. Mistry, *J. Chem. Soc., Perkin Trans. 1*, 1981 (1991).

252. S. M. Ali, M. A. W. Finch, S. M. Roberts and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 679 (1979).
253. C. B. Chapleo and S. M. Roberts, *J. Chem. Soc., Chem. Commun.*, 680 (1979).
254. J.-P. Gesson, L. Hervaud and M. Mondon, *Tetrahedron Lett.*, **34**, 2941 (1993).
255. J. H. M. Lange, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **47**, 1495 (1991).
256. T.-C. Chou, P.-C. Hong and C.-T. Lin, *Tetrahedron Lett.*, **32**, 6351 (1991).
257. E. C. Gravett, J. A. K. Howard, K. Mackenzie, L. Shi-Xiong and P. B. Karadakov, *Tetrahedron*, **49**, 4699 (1993).
258. P. A. Wender and C. R. D. Correia, *J. Am. Chem. Soc.*, **109**, 2523 (1987).
259. G. Jommi, F. Orsini, M. Resmini and M. Sisti, *Tetrahedron Lett.*, **32**, 6969 (1991).
260. H. M. L. Davies, *Tetrahedron*, **49**, 5203 (1993).
261. S. Pantke-Böcker, G. Pohnert, I. Fischer-Lui and W. Boland, *Tetrahedron*, **51**, 7927 (1995).
262. W. R. Cantrell and H. M. L. Davies, *J. Org. Chem.*, **56**, 723 (1991).
263. H. M. L. Davies, N. J. S. Huby, W. R. Cantrell and J. L. Olive, *J. Am. Chem. Soc.*, **115**, 9468 (1993).
264. H. M. L. Davies, Z.-Q. Peng and J. H. Houser, *Tetrahedron Lett.*, **35**, 8939 (1994).
265. T. Hudlicky and P. V. Nguyen, *J. Org. Chem.*, **57**, 1933 (1992).
266. E. V. Dehmlow, D. Balschukat, P. P. Schmidt and R. Krause, *J. Chem. Soc., Chem. Commun.*, 1435 (1986).
267. D. C. Clark, W.-N. Chou and J. B. White, *J. Org. Chem.*, **55**, 3975 (1990).
268. W.-N. Chou and J. B. White, *Tetrahedron Lett.*, **32**, 157 (1991).
269. W.-N. Chou, J. B. White and W. B. Smith, *J. Am. Chem. Soc.*, **114**, 4658 (1992).
270. J. J. Titman, Z. Luz and H. W. Spiess, *J. Am. Chem. Soc.*, **114**, 3765 (1992).
271. S. Schlick, Z. Luz, R. Poupko and H. Zimmermann, *J. Am. Chem. Soc.*, **114**, 4315 (1992).
272. K. Rebsamen and G. Schröder, *Chem. Ber.*, **126**, 1419 (1993).
273. K. Rebsamen and G. Schröder, *Chem. Ber.*, **126**, 1425 (1993).
274. K. Rebsamen, H. Röttele and G. Schröder, *Chem. Ber.*, **126**, 1429 (1993).
275. J. F. M. Oth, H. Kwee, U. Prange and G. Schröder, *Tetrahedron Lett.*, 1565 (1976).
276. H. Quast, E. Geissler, T. Herkert, K. Knoll, E.-M. Peters, K. Peters and H. G. von Schnering, *Chem. Ber.*, **126**, 1465 (1993).
277. R. Aumann and M. Runge, *Chem. Ber.*, **125**, 259 (1992).
278. J. C. Barborak and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **92**, 3184 (1970).
279. J. B. Grutzner and S. Winstein, *J. Am. Chem. Soc.*, **92**, 3186 (1970).
280. H. Quast, J. Carlsen, R. Janiak, E.-M. Peters, K. Peters and H. G. von Schnering, *Chem. Ber.*, **125**, 955 (1992).
281. H. Quast, R. Janiak, E.-M. Peters, K. Peters and H. G. von Schnering, *Chem. Ber.*, **125**, 969 (1992).
282. H. Quast, J. Carlsen, H. Röschert, E.-M. Peters, K. Peters and H. G. von Schnering, *Chem. Ber.*, **125**, 2591 (1992).
283. H. Quast, A. Witzel, E.-M. Peters, K. Peters, and H. G. von Schnering, *Chem. Ber.*, **125**, 2613 (1992).
284. L. A. Paquette, M. A. Kesselmayer, G. E. Underiner, S. D. House, R. D. Rogers, K. Meerholz and J. Heinze, *J. Am. Chem. Soc.*, **114**, 2644 (1992).
285. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).
286. D. A. Evans and J. V. Nelson, *J. Am. Chem. Soc.*, **102**, 774 (1980).
287. M. L. Steigerwald, W. A. Goddard III and D. A. Evans, *J. Am. Chem. Soc.*, **101**, 1994 (1979).
288. G. A. Stashina, E. M. Vasil'vitskaya, G. D. Gamalevich, B. S. El'yanov, E. P. Serebryakov and V. M. Zhulin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 329 (1986); *Chem. Abst.*, **104**, 224412q (1986).
289. L. A. Paquette, *Angew. Chem.*, **102**, 642 (1990); *Angew. Chem., Int. Ed. Engl.*, **29**, 609 (1990).
290. L. A. Paquette and G. D. Maynard, *J. Am. Chem. Soc.*, **114**, 5018 (1992).
291. S.-Y. Wei, K. Tomooka and T. Nakai, *Tetrahedron*, **49**, 1025 (1993).
292. S.-Y. Wei, K. Tomooka and T. Nakai, *J. Org. Chem.*, **56**, 5973 (1991).
293. N. Greeves and K. J. Vines, *J. Chem. Soc., Chem. Commun.*, 1469 (1994).
294. N. Greeves and K. J. Vines, *Tetrahedron Lett.*, **35**, 7077 (1994).
295. E. Lee, Y. R. Lee, B. Moon, O. Kwon, M. S. Shim and J. S. Yun, *J. Org. Chem.*, **59**, 1444 (1994).
296. G. Ladouceur and L. A. Paquette, *Synthesis*, 185 (1992).

297. S. Hünig, M. Schäfer and W. Schweeberg, *Chem. Ber.*, **126**, 191 (1993).
298. S. Hünig, M. Schäfer and W. Schweeberg, *Chem. Ber.*, **126**, 205 (1993).
299. L. A. Paquette, D. R. Sauer, S. D. Edmondson and D. Friedrich, *Tetrahedron*, **50**, 4071 (1994).
300. L. A. Paquette, K. D. Combrink, S. W. Elmore and R. D. Rogers, *J. Am. Chem. Soc.*, **113**, 1335 (1991).
301. L. A. Paquette and R. C. Thompson, *J. Org. Chem.*, **58**, 4952 (1993).
302. S. W. Elmore and L. A. Paquette, *J. Org. Chem.*, **60**, 889 (1995).
303. L. A. Paquette, Z. Su, S. Bailey and F. J. Montgomery, *J. Org. Chem.*, **60**, 897 (1995).
304. S. W. Elmore and L. A. Paquette, *Tetrahedron Lett.*, **32**, 319 (1991).
305. L. A. Paquette and R. E. Maleczka, *J. Org. Chem.*, **56**, 912 (1991).
306. J. Doyon, W. He and L. A. Paquette, *J. Org. Chem.*, **59**, 2033 (1994).
307. L. A. Paquette and R. E. Maleczka, *J. Org. Chem.*, **57**, 7118 (1992).
308. J.-F. Devaux, I. Hanna and J.-Y. Lallemand, *J. Org. Chem.*, **58**, 2349 (1993).
309. L. A. Paquette and M.-A. Poupart, *J. Org. Chem.*, **58**, 4245 (1993).
310. L. A. Paquette, D. N. Deaton, Y. Endo and M.-A. Poupart, *J. Org. Chem.*, **58**, 4262 (1993).
311. S. F. Martin, J.-M. Assercq, R. E. Austin, A. P. Dantanarayana, J. R. Fishpaugh, C. Gluchowski, D. E. Guinn, M. Hartmann, T. Tanaka, R. Wagner and J. B. White, *Tetrahedron*, **51**, 3455 (1995).
312. B. B. Snider and A. J. Allentoff, *J. Org. Chem.*, **56**, 321 (1991).
313. L. A. Paquette, D. Koh, X. Wang and J. C. Prodger, *Tetrahedron Lett.*, **36**, 673 (1995).
314. G. Sathyamoorthi, K. Thangaraj, P. C. Srinivasan and S. Swaninathan, *Tetrahedron*, **46**, 3559 (1990).
315. S. Janardhanam and K. Rajagopalan, *J. Chem. Soc., Perkin Trans. 1*, 2727 (1992).
316. W. Fan and J. B. White, *J. Org. Chem.*, **58**, 3557 (1993).
317. X. Fu and J. M. Cook, *J. Org. Chem.*, **58**, 661 (1993).
318. G. Bojack and H. Künzer, *Tetrahedron Lett.*, **35**, 9025 (1994).
319. G. Metha, S. R. Karra and N. Krishnamurthy, *Tetrahedron Lett.*, **35**, 2761 (1994).
320. D. S. Brown and L. A. Paquette, *J. Org. Chem.*, **57**, 4512 (1992).
321. N. Bluthe, M. Malacria and J. Gore, *Tetrahedron Lett.*, **23**, 4263 (1982).
322. A. C. Braisted and P. G. Schultz, *J. Am. Chem. Soc.*, **116**, 2211 (1994).
323. R. W. Alder, D. Colclough, F. Grams and A. G. Orpen, *Tetrahedron*, **46**, 7933 (1990).
324. M. Brands, J. Bruckmann, C. Krüger and H. Butenschön, *J. Chem. Soc., Chem. Commun.*, 999 (1994).
325. S. Blechert, *Synthesis*, 71 (1989).
326. G. B. Bennett, *Synthesis*, 589 (1977).
327. S. R. Wilson and M. F. Price, *J. Am. Chem. Soc.*, **104**, 1124 (1982).
328. J. J. Gajewski, K. R. Gee and J. Jurayj, *J. Org. Chem.*, **55**, 1813 (1990).
329. S. E. Denmark, M. A. Harmata and K. S. White, *J. Am. Chem. Soc.*, **111**, 8878 (1989).
330. A. Mukherjee, Q. Wu and W. J. le Noble, *J. Org. Chem.*, **59**, 3270 (1994).
331. L. M. Harwood, A. J. Oxford and C. Thomson, *J. Chem. Soc., Chem. Commun.*, 1303 (1991).
332. N. Gairns, L. M. Harwood and D. P. Astles, *J. Chem. Soc., Perkin Trans. 1*, 3101 (1994).
333. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-t. Li, D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).
334. W. S. Johnson, N. P. Jensen and J. Hooz, *J. Am. Chem. Soc.*, **88**, 3859 (1966).
335. R. L. Markezich, W. E. Willy, B. E. McCarry and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 4414 (1973).
336. B. E. McCarry, R. L. Markezich and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 4416 (1973).
337. D. R. Morton, M. B. Gravestock, R. J. Parry and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 4417 (1973).
338. M. B. Gravestock, D. R. Morton, S. G. Boots and W. S. Johnson, *J. Am. Chem. Soc.*, **102**, 800 (1980).
339. W. S. Johnson, B. Frei and A. S. Gopalan, *J. Org. Chem.*, **46**, 1512 (1981).
340. W. S. Johnson, C. E. Ward, S. G. Boots, M. B. Gravestock, R. L. Markezich, B. E. McCarry, D. A. Okorie and R. J. Parry, *J. Am. Chem. Soc.*, **103**, 88 (1981).
341. W. S. Johnson, S. J. Telfer, S. Cheng and U. Schubert, *J. Am. Chem. Soc.*, **109**, 2517 (1987).
342. W. S. Johnson, B. Chenera, F. S. Tham and R. K. Kullnig, *J. Am. Chem. Soc.*, **115**, 493 (1993).

343. W. S. Johnson, R. A. Buchanan, W. R. Bartlett, F. S. Tham and R. K. Kullnig, *J. Am. Chem. Soc.*, **115**, 504 (1993).
344. M. Hanack, *Angew. Chem.*, **90**, 346 (1978).
345. W. S. Johnson, *Angew. Chem.*, **88**, 33 (1976).
346. R. R. Schmidt, T. Bär and R. Wild, *Synthesis*, 868 (1995).
347. J. C. Barrish, P. M. Wovkulich, P. C. Tang, A. D. Batcho and M. R. Uskokovič, **31**, *Tetrahedron Lett.*, 2235 (1990).
348. P. M. Wovkulich, K. Shankaran, J. Kiegiel and M. R. Uskokovič, *J. Org. Chem.*, **58**, 832 (1993).
349. K. Oshima, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 4446 (1973).
350. R. S. Garigipati, R. Cordova, M. Parvez and S. M. Weinreb, *Tetrahedron*, **42**, 2979 (1986).
351. W. Schroth, E. Hintzsche, R. Spitzner, D. Ströhl and J. Sieler, *Tetrahedron*, **51**, 13247 (1995).
352. W. Schroth, E. Hintzsche, R. Spitzner, D. Ströhl, K. Schmeiss and J. Sieler, *Tetrahedron*, **51**, 13261 (1995).
353. W. Schroth, E. Hintzsche, H. Viola, R. Winkler, H. Klose, R. Boese, R. Kempe and J. Sieler, *Chem. Ber.*, **127**, 401 (1994).
354. M. H. Hopkins and L. E. Overman, *J. Am. Chem. Soc.*, **109**, 4748 (1987).
355. L. D. M. Lolkema, H. Hiemstra, C. Semeyn and W. N. Speckamp, *Tetrahedron*, **50**, 7115 (1994).
356. L. D. M. Lolkema, C. Semeyn, L. Ashek, H. Hiemstra and W. N. Speckamp, *Tetrahedron*, **50**, 7129 (1994).
357. M. A. Walters, *J. Org. Chem.*, **61**, 978 (1996).
358. P. D. Bailey and M. J. Harrison, *Tetrahedron Lett.*, **30**, 5341 (1989).
359. M.-X. Wang and Z.-T. Huang, *J. Org. Chem.*, **60**, 2807 (1995).
360. G. R. Cook and J. R. Stille, *Tetrahedron*, **50**, 4105 (1994).
361. N. S. Barta, G. R. Cook, M. S. Landis and J. R. Stille, *J. Org. Chem.*, **57**, 7188 (1992).
362. M. A. Walters, C. S. McDonough, P. S. Brown and A. B. Hoem, *Tetrahedron Lett.*, **32**, 179 (1991).
363. S. Nishida, N. Asanuma, T. Tsuji and T. Imai, *Chem. Lett.*, 495 (1991).
364. S. Nishida, N. Asanuma, M. Murakami, T. Tsuji and T. Imai, *J. Org. Chem.*, **57**, 4658 (1992).
365. D. J. Hart and Y.-M. Tsai, *Tetrahedron Lett.*, **22**, 1567 (1981).
366. H. Ent, H. de Koning and W. N. Speckamp, *J. Org. Chem.*, **51**, 1687 (1986).
367. W. N. Speckamp and H. Hiemstra, *Tetrahedron*, **41**, 4367 (1985).
368. T. L. Gilchrist, A. M. d'A.Rocha Gonsalves and T. M. V. D. Pinho e Melo, *Tetrahedron Lett.*, **34**, 6945 (1993).
369. W. Deng and L. E. Overman, *J. Am. Chem. Soc.*, **116**, 11241 (1994).
370. S. R. Angle, J. M. Fevig, S. D. Knight, R. W. Marquis and L. E. Overman, *J. Am. Chem. Soc.*, **115**, 3966 (1993).
371. S. D. Knight, L. E. Overman and G. Pairaudeau, *J. Am. Chem. Soc.*, **117**, 5776 (1995).
372. E. J. Jacobsen, J. Levin and L. E. Overman, *J. Am. Chem. Soc.*, **110**, 4329 (1988).
373. C. Agami, F. Couty, J. Lin, A. Mikaeloff and M. Poursoulis, *Tetrahedron*, **49**, 7239 (1993).
374. J.-M. Valete, D. Dumas and J. Gore, *Tetrahedron Lett.*, **31**, 2277 (1990).
375. A. Gamba and R. Gandolfi, *Tetrahedron*, **49**, 6331 (1993).
376. J. Garin, E. Melendez, F. L. Merchan, T. Tejero, S. Uriel and J. Ayestaran, *Synthesis*, 147 (1991).
377. R. Grigg and J. Markandu, *Tetrahedron Lett.*, **32**, 279 (1991).
378. I. Lantos, W.-Y. Zhang, X. Shui and D. S. Eggleston, *J. Org. Chem.*, **58**, 7092 (1993).
379. I. Lantos and W.-Y. Zhang, *Tetrahedron Lett.*, **35**, 5977 (1994).
380. U. Salzner and S. M. Bachrach, *J. Org. Chem.*, **60**, 7101 (1995).

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CHAPTER **11**

Organometallic complexes of dienes and polyenes

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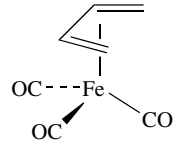
I. INTRODUCTION

The first complex of a conjugated diene was reported in 1930 by Reihlen and coworkers[1]. Reaction of butadiene with $Fe(CO)_5$ gave a yellow-brown oil with the molecular formula $(C_4H_6)Fe(CO)_3$. The elucidation of the structure of ferrocene eventually lead Hallam and Pauson[2] to propose a π-complex **(1)** for $(C_4H_6)Fe(CO)_3$ and this was eventually confirmed by crystal structure analysis at low temperature[3]. Since that time interest in

diene–metal complexes as starting materials for organic synthesis or as intermediates in stoichiometric or catalytic processes has led to the preparation and/or characterization of (conjugated diene)metal complexes of nearly all of the transition metals. This chapter will focus on monometallic transition metal complexes of cyclic and acyclic conjugated dienes and cyclobutadienes, particularly on structure, bonding, spectral characterization, fluxional behavior and reactivity.



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II. STRUCTURE AND BONDING

The bonding in conjugated diene- and cyclobutadiene–metal complexes differs from that for 'isolated' diolefin complexes due to differences in the π-type molecular orbitals for each system. For 'isolated' diolefins, there are two degenerate bonding symmetry combinations and two degenerate antibonding combinations (Figure 1). For a conjugated diene, these pairs of degenerate orbitals are each split into higher and lower energy cases due to interaction across the C2–C3 bond[4]. Both the s-*cis* and s-*trans* conformers may be considered for acyclic or non-constrained dienes (Figure 2). For square cyclobutadiene (D_{4h}), the four molecular orbitals consist of one bonding orbital, two degenerate non-bonding orbitals and one antibonding orbital (Figure 3)[5].

Overlap of the π-type orbitals with the corresponding appropriate metal fragment orbitals lead to new bonding and antibonding combinations. The frontier orbitals of two isolobal[6] cases are frequently encountered. For both the ML_3 and the CpM fragments the frontier orbitals consist of a doubly degenerate *e* set and a higher energy a_1 orbital (Figure 4)[7]. It should be noted that for the ML_3 fragment, these orbitals are tipped with respect to the orientation of the orbitals for the CpM fragment. Due to the double degeneracy of the *e* set of orbitals, diene complexes of these two fragments prefer coordination of the ligand in the s-*cis* η^4-1,3-diene fashion since the nodal plane of the $\pi 2$ orbital and the nodal plane of the $\pi 3$ orbital are perpendicular to each other. In comparison, the frontier

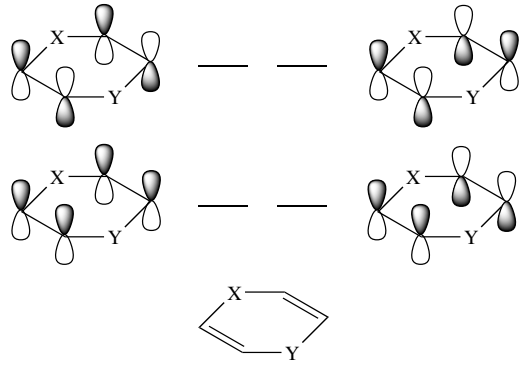


FIGURE 1. π-Molecular orbitals for unconjugated dienes

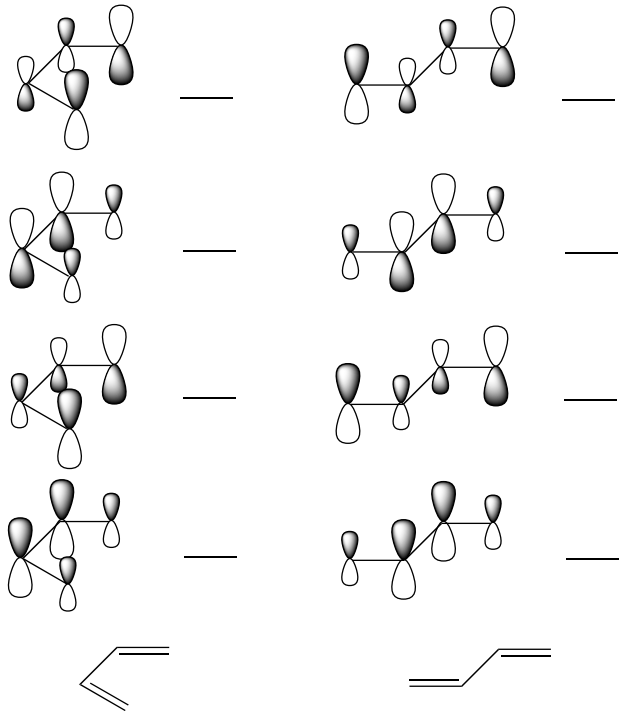


FIGURE 2. π-Molecular orbitals for conjugated dienes

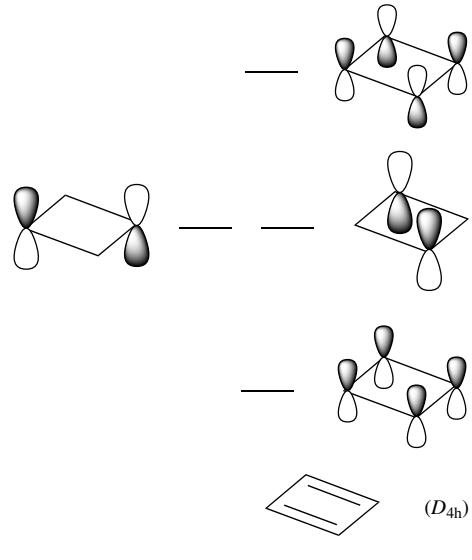


FIGURE 3. π-Molecular orbitals for cyclobutadiene

orbitals for the ML_4, ML_2Cp and the bent MCp_2 fragments (Figure 5) are characterized by sets of orbitals which primarily lie in a single plane[7,8]. This absense of a degenerate pair of orbitals for these fragments allows for a considerably wider range of complexation modes such as exemplified by non-conjugated dienes and s-*trans* η^4-1,3-dienes.

Complexation of the s-*cis* 1,3-diene conformer has been described as a hybrid of two extreme coordination modes: an η^4-diene **(2a)** and a σ^2,π metallacyclopent-3-ene **(2b)**.

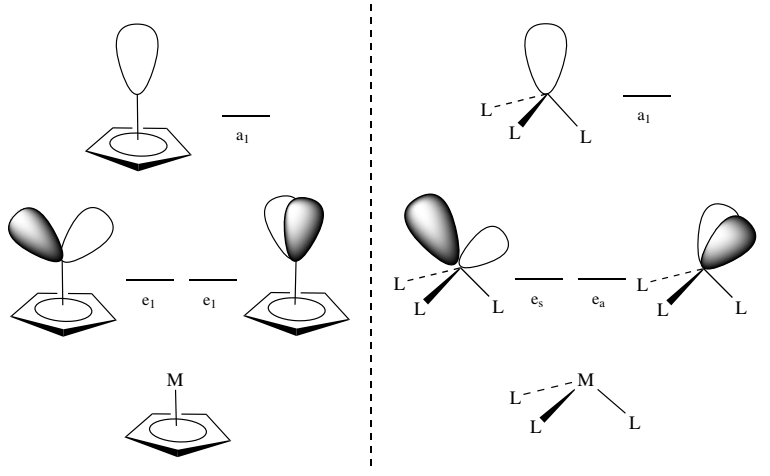


FIGURE 4. Molecular orbitals for MCp and ML_3 fragments

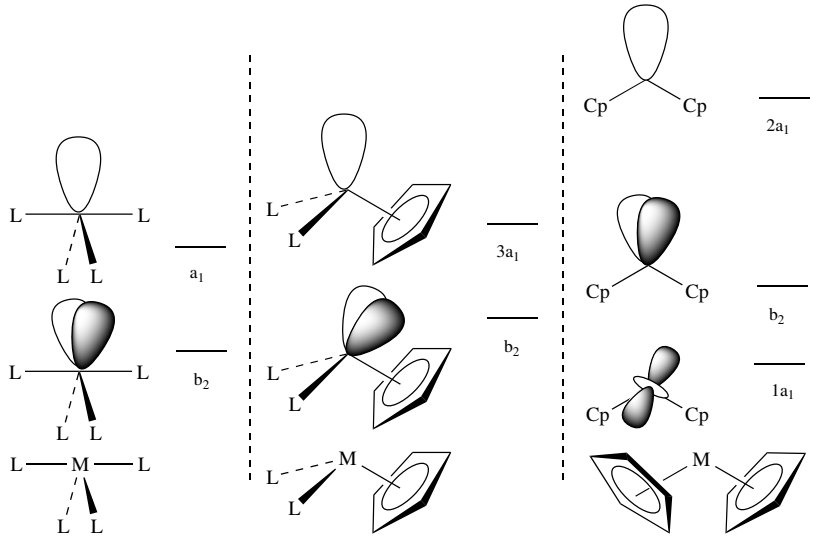
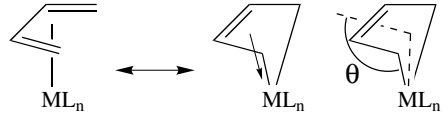


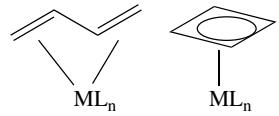
FIGURE 5. Molecular orbitals for ML_4, ML_2Cp and MCp_2 fragments

Complexes which may be best described by structure **2a** are distinguished by (1) nearly sp^2 hybridization at the terminal carbon atoms, (2) relatively similar lengths of the central (C2−C3) and the lateral bonds (C1−C2 and C3−C4) and (3) slightly longer distances for the metal to terminal carbon atoms (M−C1 and M−C4) vs the metal to internal carbon atoms (M−C2 and M−C3). In contrast, complexes which may be described as closer to **2b** are distinguished by (1) near sp^3 hybridization at the terminal carbon atoms, (2) distinctly shorter central bonds (C2−C3) and longer lateral bonds (C1−C2 and C3−C4) and (3) longer distances for the metal to internal carbon atoms (M−C2 and M−C3) vs the metal to terminal carbon atoms (M−C1 and M−C4). Nakamura and coworkers[9] have conducted a statistical analysis of the crystal structures of a series of s-*cis* (diene) complexes of various transition metals. They defined three parameters: the angle Θ between the C1−M−C4 plane and the diene plane (cf **2c**), the difference Δd between the average M−terminal carbon and average M−internal carbon distances, and the difference Δl between the average of C1−C2 and C3−C4 distances and the C2−C3 distance. The early transition metal complexes (Zr, Hf, Ta, Nb) are best described by the structure **2b** ($95^\circ < \Theta < 120^\circ$, -0.4 Å$< \Delta d < 0.0$ Å, 0.0 Å $< \Delta l < 0.2$ Å) while the later transition metal complexes (Mn, Fe, Os, Co, Rh, Ir) are best described by the structure **2a** ($80^\circ < \Theta < 85^\circ$, 0.0 Å $< \Delta d < 0.1$ Å, -0.1 Å $< \Delta l < 0.0$ Å).



(2a) **(2b)** **(2c)**

The crystal structures of a number of s-*trans* (diene)metal complexes **(3)** have been determined[10−14]. The diene ligand in all s-*trans* complexes is distinctly non-planar; the torsional angle between the two olefin groups is between 114° and 127°. In general, the terminal carbon to metal distance is greater than for the internal carbon to metal distance, and the C1−C2/C3−C4 bonds are shorter than the C2−C3 bond.



(3) **(4)**

Crystal structure data[15] indicate that in the vast majority of (cyclobutadiene)metal complexes **(4)** the cyclobutadiene ligand is approximately square-planar with nearly equal C−C bond distances (*ca* 1.46 Å) and bond angles of *ca* 90°. Within a given complex the cyclobutadiene carbon-to-metal distances are roughly equal.

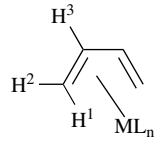
III. NMR SPECTROSCOPIC CHARACTERIZATION AND FLUXIONAL BEHAVIOR

A. Conjugated 1,3-Diene Complexes

1. ^1H NMR spectral data

In the following discussion, chemical shifts and coupling constants will be presented for the static structure of a complex. In general, the signals for protons attached to an s-*cis*

TABLE 1. ^{1}H NMR spectral data (chemical shift δ in ppm; coupling constants J in Hz) for (s-*cis*-butadiene)metal complexes



Entry	ML_n	Solvent/temp[a]	H^1	H^2	H^3	$^2J_{1-2}$	$^3J_{2-3}$	$^3J_{1-3}$	Reference
1	$Ti(\eta^8-C_8H_8)$	C_7D_8/30 °C	−0.19	4.12	3.72	−1.31	8.37	10.70	16
2	$Zr(\eta^8-C_8H_8)$	C_7D_8/30 °C	0.37	2.60	4.31	−4.14	9.41	11.09	16
3	$Hf(\eta^8-C_8H_8)$	C_7D_8/30 °C	0.45	1.79	4.85	−6.70	9.63	9.55	16
4	$ZrCp_2$	C_7D_8/−70 °C	−0.69	3.45	4.78	−10.0	9.5	10.5	17
5	$HfCp_2$	$CHFCl_2$/−120 °C	−0.73	2.74	5.0	*b*	*b*	*b*	18
6	$NbCp^*Cl_2$	C_6D_6/30 °C	0.46	1.35	7.07	6.0	6.5	7.5	19
7	$TaCpCl_2$	C_6D_6/30 °C	0.19	0.96	7.03	−6.5	7.5	6.5	9a
8	$Cr(CO)_4$	C_6D_6/RT	0.55	1.68	4.37	1.25	7.93	12.08	20
9	$MoCp(CO)_2^+$	C_3D_6O/−70 °C	2.28	3.07	6.45	*b*	7.4	9.6	21
10	$MoCp[P(OMe)_3]_2^+$	C_6D_6/[c]	0.86	2.26	5.60	*b*	*b*	*b*	22
11	$[Mn(CO)_3]^-$[d]	THF-d_8/25 °C	−1.3	0.6	4.4	*b*	4.0	7.0	23
12	$Fe(CO)_3$	C_6D_6/25 °C	−0.03	1.46	4.89	−2.42	6.93	9.33	24
13	$Fe(CO)_2PPh_3$	C_6D_6/[c]	−0.11	1.35	4.83	2.1	5.3	7.9	25
14	$Ru(CO)_3$	C_6D_6/[c]	0.12	1.44	4.88	−2.77	6.94	8.65	26
15	$Os(CO)_3$	C_6D_6/[c]	0.14	1.70	4.93	−3.48	6.86	7.78	26
16	$RuCp^*(OTf)$	$CDCl_3$/20 °C	2.32	3.86	4.70	*b*	6.2	10.3	27
17	$RuCp^*Br_2^+$	CD_3NO_2/−20 °C	2.41	3.97	7.27	1.2	7.5	7.8	27
18	$Co(CO)_3^+$	CD_3NO_2/[c]	2.5	3.6	6.7	3	3.5	10	28
19	CoCp	C_7D_8/30 °C	−0.37	1.69	4.91	−1.46	6.79	9.36	16
20	RhCp	$CDCl_3$/[c]	0.9	2.94	5.00	*b*	*b*	*b*	29

[a] $C_7D_8 = C_6D_5CD_3$; $C_3D_6O = (CD_3)_2CO$.
[b] Not reported.
[c] Temperature not reported, presumably ambient temperature.
[d] Data are for the (isoprene)ML_n complex.

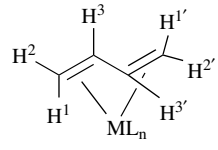
complexed diene appear upfield of those of the free ligand, and protons attached to the terminal carbons appear upfield of those attached to the internal diene carbons (Table 1). The proton NMR chemical shifts for a particular complex depend upon the metal, the charge of the complex, the orientation of the diene ligand with respect to the anisotropy of the peripheral ligands, the substituents present on the diene ligand, and the solvent. For isoelectronic complexes, the proton signals for anionic complexes appear upfield of neutral complexes, which appear upfield of cationic complexes (Table 1, entry 11, 12, 18). The nature of the diene bonding (i.e. η^4-π **2a** vs σ^2, π **2b**) is manifested in the $^2J_{gem}$ coupling constants. For complexes which are best described by **2b** (e.g. entries 4–7), the increased sp^3 character of the terminal carbons is reflected in larger magnitude J_{gem} (6–10 Hz) than for those complexes best described by the η^4-π **2a** bonding mode (e.g. entries 8, 12–14, 17–19; J_{gem} *ca*1–3 Hz). In general, for s-*cis* complexes **2**, the ^3J coupling constants are smaller than those of the corresponding free ligand.

There are considerably fewer examples of s-*trans* diene complexation (Table 2). For s-*trans* diene complexes, the signals for protons on the terminal carbons (C1/C4) of the diene generally appear downfield of those for the corresponding s-*cis* complex, while the signals for protons on the internal (C2/C3) carbons appear upfield of those for the corresponding s-*cis* complex (cf Table 1, entry 4 vs Table 2, entry 1; also Table 1, entry 9 vs Table 2, entry 2). This may reflect shorter metal–carbon distance of the internal carbons compared to the terminal carbons. In general, the $^3J_{a-c}$ coupling constants for s-*trans* diene complexes are larger than those observed for s-*cis* diene complexes.

2. ^{13}C NMR spectral data

The ^{13}C NMR signals of a diene are shifted far upfield upon complexation to a transition metal[33]. The terminal carbons (C1/C4) for a complexed diene are *ca* 50 to 80 ppm more shielded than the free ligand, while the internal carbons (C2/C3) are *ca* 20 to 60 ppm more shielded (Tables 3 and 4). The σ^2,π bonding mode **(2b)** which is found for Zr, Hf and Nb s-*cis* diene complexes is revealed in the diminished $^1J_{C-H}$ coupling to the terminal carbons (Table 3, entries 1–3) as compared to the later transition metal complexes. This decrease in the $^1J_{C-H}$ coupling constant is consistent with an increase in the p-character[35] for the hybridization of the terminal carbons in structures of type **2b**. Benn and Rufinska have measured and compared the $^1J_{C1-C2}$ and $^1J_{C2-C3}$ values for four complexes of isoprene[35]. For those complexes which exhibit the σ^2,π bonding mode **2b** [$ML_n = ZrCp_2$ and Hf(*t*-BuCp)$_2$] the $^1J_{C1-C2}$ values are considerably smaller than the $^1J_{C2-C3}$ values (by *ca* 20 Hz), while for those complexes which exhibit the $\eta^4 - \pi$ bonding mode **2a** [$ML_n = Fe(CO)_3$ and CoCp] there is only a small difference in magnitude (*ca* 2 Hz). These data are consistent with the concept that for complexes **2b**, the terminal carbons are closer to sp^3 hybridized and the internal carbons are close to sp^2 hybridized, while for complexes **2a** both the terminal and internal carbons have similar hybridization.

TABLE 2. ^1H NMR spectral data (chemical shift δ in ppm; coupling constants J in Hz) for (s-*trans*-diene)metal complexes



Entry	ML_n	Solvent/temp[a]	H^1	H^2	H^3	$^2J_{1-2}$	$^3J_{1-3}$	$^3J_{2-3}$	$^3J_{3-3}$	Reference
1	$ZrCp_2$	C_7D_8/38 °C	1.22	3.22	2.90	−4.0	7.1	16.4	*b*	17
2	$[MoCp^*(CO)_2]^{+c}$	CD_2Cl_2/−60 °C	3.24	4.24	3.65	*b*	6.8	12.9	7.0	30
3	$MoCp^*NO^c$	C_6D_6/amb[d]	2.85	2.43	1.51	2.5	6.8	14.0	11.4	31
4	$[RuCpCO]^{+c}$	CD_2Cl_2/−40 °C	4.31	4.21	4.15	*b*	6.8	12.7	7.7	32

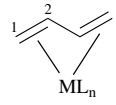
[a] $C_7D_8 = C_6D_5CD_3$.
[b] Not reported.
[c] Data are for the (1,3-pentadiene)ML_n complex.
[d] Ambient temperature.

TABLE 3. ^{13}C NMR spectral data (chemical shift δ in ppm; coupling constants J in Hz) for (s-*cis*-butadiene)metal complexes

Entry	ML_n	Solvent/temp	C^1	C^2	$^1J_{C_1-H}$	Reference
1	$ZrCp_2$	C_6D_6/30 °C	49	112	144	34
2	$HfCp_2$	C_6D_6/amb[b]	45	114.5	140	18
3	$NbCpCl_2$	C_6D_6/30 °C	60.1	123.0	145	19
4	$Cr(CO)_4$	C_6D_6/amb[b]	56.5	86.4	*a*	20
5	$MoCp[P(OMe)_3]_2^+$	C_6D_6/[b]	45.9	86.0	*a*	22
6	$[Mn(CO)_3]^-$[c]	THF-d_8/25 °C	38.5	78.6	152	23
7	$Fe(CO)_3$	C_6D_6/25 °C	40.53	85.49	161.5, 160	24
8	$Ru(CO)_3$	C_6D_6/[b]	32.7	86.3	159.6, 156.2	26
9	$Os(CO)_3$	C_6D_6/[b]	24.19	82.32	*a*	26
10	$RuCp^*Br_2^+$	CD_3NO_2/−20 °C	72.1	125.4	*a*	27
11	CoCp	C_7D_8/37 °C[d]	31.30	78.54	157	35

[a]Not reported.
[b]Temperature not reported, presumably an ambient temperature(amb).
[c]Data are for the (isoprene)ML_n complex.
[d]$C_7D_8 = C_6D_5CD_3$.

TABLE 4. ^{13}C NMR spectral data (chemical shift δ in ppm; coupling constants J in Hz) for (s-*trans*-diene)metal complexes

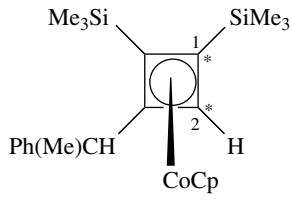


Entry	ML_n	Solvent/temp	C^1	C^2	$^1J_{C_1-H}$	Reference
1	$ZrCp_2$	C_7D_8/−10 °C[a]	59	96	149, 159	18
2	$[MoCp^*(CO)_2]^+$[b]	CD_2Cl_2/−45 °C	68.8	87.7 (94.6)	165.3	30
3	$MoCp^*NO$[b]	C_6D_6/amb[c]	58.50	88.42	158	31

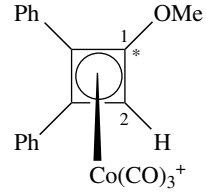
[a]$C_7D_8 = C_6D_5CD_3$.
[b]Data are for the (1,3-pentadiene)ML_n complex.
[c]Ambient temperature.

B. Cyclobutadiene Complexes

The ring protons of neutral cyclobutadiene–metal complexes generally appear in the range δ_H 3.5–5 ppm[15,36] while those of cationic cyclobutadiene–metal complexes appear further downfield in the range δ 6–7 ppm[37,38]. Notably, there is no detectable $^3J_{H-H}$ or, $^4J_{H-H}$ 'W' couplings observed for unsymmetrically substituted cyclobutadiene complexes. The unsubstituted ring carbons of cyclobutadiene complexes appear in the range δ_C 60–70 ppm, and $^1J_{C-H}$ couplings are in the range 185–200 Hz[33]. The $^1J_{C-C}$ coupling for two ^{13}C enriched cobalt cyclobutadiene complexes **5** (24.1 Hz)[39a] and **6** (40.8 Hz)[39b] have been reported, and these represent some of the lowest values for one-bond coupling between two formally trigonal carbon atoms.



(5)



(6)

* = Position of ^{13}C enrichment

C. Fluxional Behavior

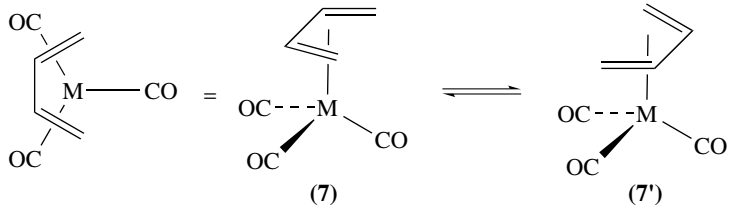
Dynamic intramolecular rearrangements are observed for a variety of diene–metal complexes at, or near, ambient temperature. This stereochemical non-rigidity may be detected by variable temperature NMR experiments[40] in which the signals observed for a static structure coalesce into time averaged signals for the fluxional process. For purposes of this section, processes with activation energies $> ca\ 25$ kcal mol^{-1} or which are irreversible will be considered to be isomerization phenomena and will be discussed in Section IV.

1. Ligand rotation[41]

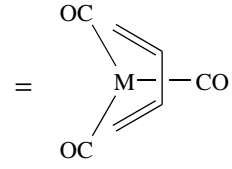
Except for MCp complexes, most (diene)metal complexes consistently exhibit particular molecular orientations in the solid state. While this is the case, rotation about the metal–ligand axis may be rapid in the solution phase. For example, the crystal structures of a variety of cyclic and acyclic (diene)$Fe(CO)_3$ complexes indicate a staggered geometry (**7**)[2,42]; one of the carbonyl ligands is oriented such that it bisects the 'open' end of the diene while the other two carbonyl ligands lie underneath the C1–C2 and C3–C4 diene bonds (equation 1). Molecular orbital theory[43a] rationalizes the preferred static structure on the basis that the tilt of the degenerate *e* pair of orbitals (Figure 4) provides the necessary asymmetry such that the mirror plane of the diene ligand is aligned with the *yz* mirror plane. A significant barrier to rotation about the metal–ligand axis is expected. This is due to the higher energy of the structure generated by 60° rotation, in which one of the carbonyl ligands is eclipsed with the central C–C bond (**7′**). Earlier calculations at the EHT level[43a] indicate this barrier to be 14.2 kcal mol^{-1}, while more recent DFT calculations[43b] indicate the barrier to be 9.6 kcal mol^{-1}. The ^{13}C NMR spectra of these complexes, at ambient temperature, exhibit only a single resonance for the carbonyl ligands, while at lower temperatures signals due to the static structure **7** are observed. The experimentally derived barriers[44] for this process are in the range of $\Delta G^{\ddagger}\ ca\ 9–13$ kcal mol^{-1}. For acyclic diene complexes, electron-withdrawing substituents on the terminal carbons tend to increase the barrier-to-ligand rotation, while electron donating substituents tend to decrease the barrier[44f]. Phospine substituted complexes [i.e. (diene)$Fe(CO)_2PR_3$] show a decreased barrier to rotation[25], while $Ru(CO)_3$ and $Ru(CO)_2PR_3$ complexes exhibit slightly higher barriers to rotation than their Fe counterparts[45].

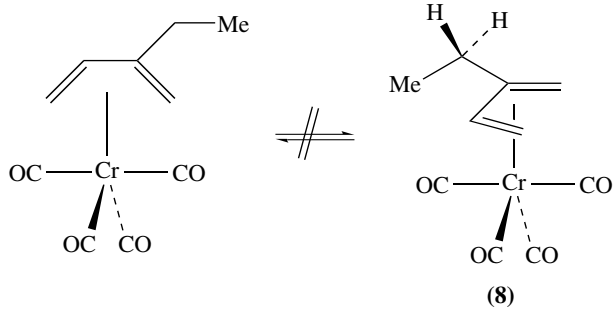
From their crystal structures, (1,3-diene)CrL_4 complexes[46] are found to be approximately octahedral coordinate. The low temperature (−90 °C) ^{13}C NMR spectrum of (butadiene)$Cr(CO)_4$, which consists of 3 M–CO signals (1 : 2 : 1 ratio), is consistent with this static structure. At higher temperature, these coalesce into a single signal[20]. The chiral complex (2-ethyl-1,3-butadiene)$Cr(CO)_4$ **(8)** shows similar behavior, however

the diastereotopic methylene proton signals of **8** remain distinct in its ^{1}H NMR spectrum at a temperature where scrambling of the carbonyl ligand signals is observed. These results[20,47] rule out a flip of the diene ligand from one face to the other (Section III.C.2), and strongly implicate a ligand rotation mechanism (equation 2). The experimentally derived barriers are *ca* 10–11 kcal mol^{-1}. Since all four carbonyl ligands scramble with each other simultaneously, ligand rotation by 90° must involve a synchronous change in C–Cr–C angles which is related to a Berry pseudorotation in trigonal bipyramidal structures.

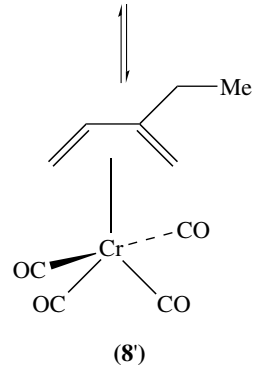


(1)

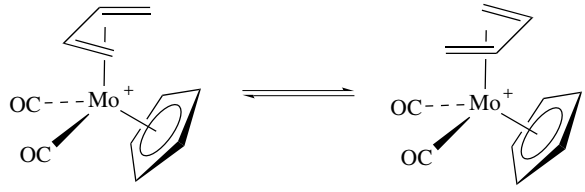




(2)



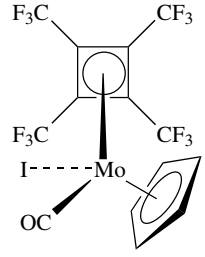
Fluxional behavior is observed for $(C_4H_6)MoCp(CO)_2^+$ (**9**). At low temperature (−60 °C) both *endo* and *exo* conformers (*ca* 5 : 1 ratio) are observed (equation 3), the signals of which coalesce at higher temperature ($\Delta G^{\ddagger} = 14.1$ kcal mol^{-1})[21]. Since the H_{syn} and H_{anti} signals (where *syn* and *anti* refer, respectively, to the substituent (or H) which is *syn* and *anti* with respect to the C2-substituent of the polyenyl ligand) remain distinct during this scrambling, a ligand rotation mechanism is proposed. For (1,3-pentadiene)$MoCp(CO)_2^+$, ligand rotation is observed along with a flip of the ligand ('envelope-flip', Section III.C.2). The ligand rotation occurs with a lower barrier than the envelope-flip process. The corresponding neutral (diene)WCp(CO)(acyl) complexes exhibit similar barriers to ligand rotation (13.8–14.6 kcal mol^{-1})[48].



(3)

(**9-*endo***) (**9-*exo***)

For conjugated (diene)metal complexes, the π-molecular orbitals of cyclobutadiene consist of a degenerate e_g pair (Figure 3). Because of this orthogonality, there is not a single electronically preferred conformer[43] and barriers for rotation of the cyclobutadiene ligand are generally low[15]. For (cyclobutadiene)$Fe(CO)_3$, in the solid state, NMR spin relaxation data indicate that there are two inequivalent lattice sites. For each of these inequivalent lattice sites, barriers for rotation of the cyclobutadiene have been measured to be 3.63 and 5.28 kcal mol^{-1}, respectively[49]. Davidson[50] has observed temperature-dependent NMR spectra for certain cyclobutadiene complexes. For cyclobutadiene complex **10**, four separate signals were observed in its ^{19}F NMR spectrum at −60 °C; these signals coalesce to a single signal at > 25 °C. Unfortunately, complexity due to $^{19}F-^{19}F$ coupling prevented a determination of the exact barrier for this fluxional process.

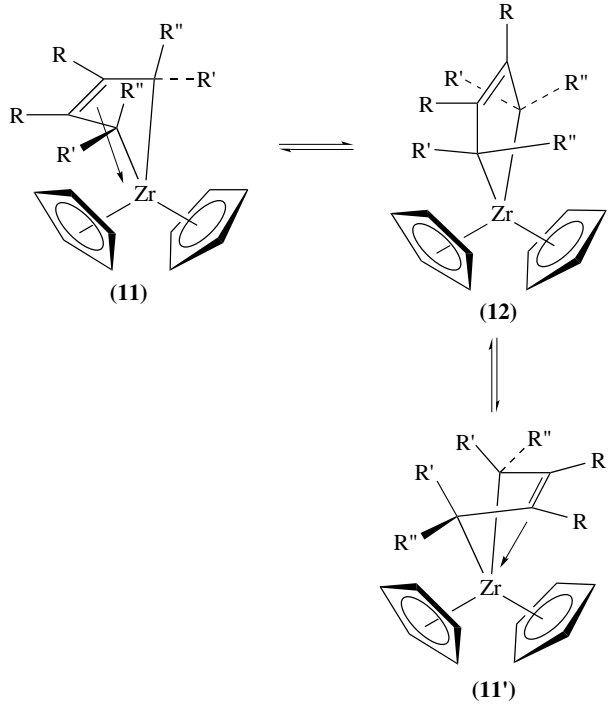


(**10**)

2. Metal migration from one face to the other ('envelope flip')

In solution, certain complexes are observed to undergo an 'envelope-flip' from one face of the diene ligand to the other. The ^1H NMR spectra of Cp_2Zr(s-*cis* diene) complexes (**11** $R' = R'' = H$) at ambient temperatures indicate a fluxional process which equilibrates the Cp signals as well as the terminal protons (equation 4). At lower temperature, signals for a

static structure are observed (i.e. two signals for the non-equivalent Cp groups and separate signals for the H_{syn} and H_{anti} terminal protons)[10,17,51–53]. An envelope-flip mechanism, involving a planar symmetric σ^2-metallacyclopent-3-ene intermediate **12**, is consistent with the fact that these sets of signals coalesce at the same rate. For Cp_2Zr(s-*cis* butadiene), the barrier for this process is 12.6 kcal mol^{-1}. The presence of substituents on the internal carbons (C2/C3) or on the cyclopentadienyl ligands (i.e. C_5Me_5) lowers the barrier for the envelope flip[10,53]. For Cp_2Zr(s-*cis* diene) complexes with substituents at the terminal carbons (C1/C4), the envelope-flip process is non-degenerate and generally the conformer which has the substituents in the less hindered *exo*-positions is greatly thermodynamically preferred[52,54]. Thus envelope-flip fluxionality is not observed in these cases. The corresponding Cp_2Hf(s-*cis* diene) complexes are also fluxional, however barriers for the envelope flip are considerably lower ($\Delta G^{\ddagger} = ca\,8$ kcal mol^{-1})[55].



(4)

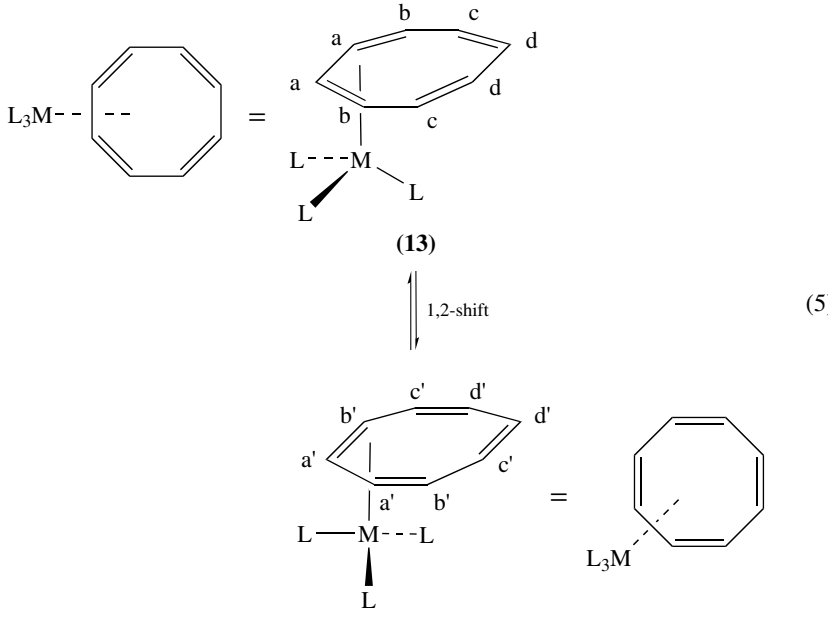
In the isoelectronic series (butadiene)M($\eta^8 - C_8H_8$) (M = Ti, Zr, Hf), the Hf complex exhibits an NMR spectrum at $> 30\,^{\circ}$C consistent with an envelope flip ($\Delta G^{\ddagger} =$ 17.6 kcal mol^{-1}). The same process can be detected for the Zr complex at $> 40\,^{\circ}$C only via magnetization transfer experiments ($\Delta G^{\ddagger} > 20$ kcal mol^{-1}). The Ti complex exhibits a static structure by NMR spectroscopy[16].

3. Metal migration about a π-complexed polyene ligand ('ring-whizzing')

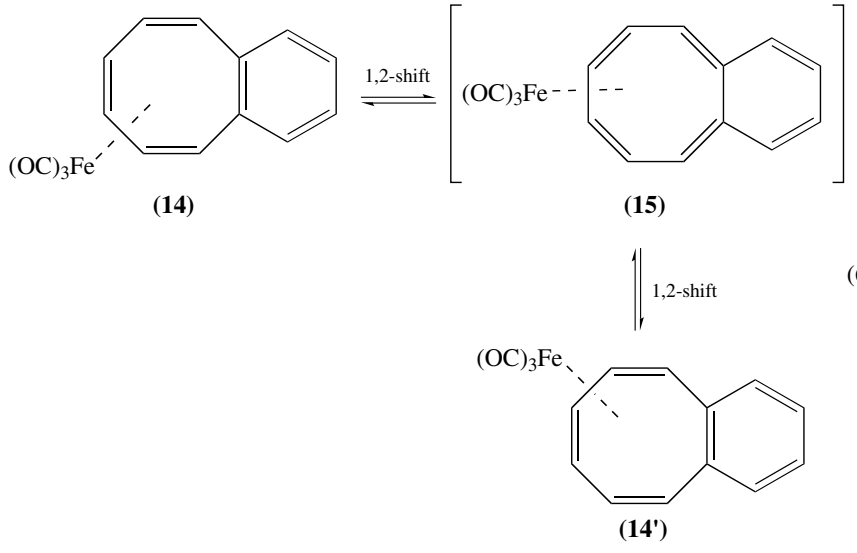
(η^4-Cyclooctatetraene)metal complexes **(13)** were some of the first recognized fluxional organometallic complexes. The (η^4-cyclooctatetraene)Mn(CO)$_3^-$ anion [**13**, ML_3 =

$Mn(CO)_3^-$] exhibits only one signal in its ^1H NMR spectrum. Unfortunately, a limiting spectrum could not be reached at $-110\,^\circ C$, at which temperature the salt precipitates from solution[56]. With this temperature as an upper limit, the barrier for migration about the ligand is < 8 kcal mol^{-1}.

While the crystal structure of **13** [$ML_3 = Fe(CO)_3$] indicates complexation as an η^4-diene ligand, the ^1H NMR spectrum of this complex exhibits a single signal (δ 5.24 ppm) at ambient temperature. At lower temperature ($-155\,^\circ C$) this signal eventually becomes two broad asymmetric signals, however, a definitive explanation of the fluxional process from these data is hampered by lack of a limiting spectrum[57]. In contrast, while (cyclooctatetraene)$Ru(CO)_3$ [**13**, $ML_3 = Ru(CO)_3$] likewise gives a single ^1H NMR signal at ambient temperature, a limiting ^1H NMR spectrum, consisting of four separate signals, is obtained at low temperature ($-147\,^\circ C$, $E_a = 9.4 \pm 1.5$ kcal mol^{-1})[58a]. Specific assignments for the upfield signals may be made by comparison to other (diene)$Ru(CO)_3$ complexes. A 1,2-shift mechanism (equation 5) was deduced on the basis that the signal assigned to the terminal η^4-protons (b or b′) initially broadens/exchanges more rapidly than that for the internal η^4-protons (a or a′). Analysis of the variable-temperature ^{13}C NMR spectrum of the ruthenium complex supports this proposal and gave the same activation barrier within error limits (8.6 kcal mol^{-1})[58b]. The variable-temperature ^{13}C NMR spectrum of the iron complex [**13**, $ML_n = Fe(CO)_3$] likewise indicated a 1,2-shift mechanism with a lower activation barrier (8.1 kcal mol^{-1})[58b]. Scrambling of the carbonyl ligands in **13** (M = Fe, Ru) occurs with essentially the same activation energy. Iron migration in the benzocyclooctatetraene complex **14** to **14′** (equation 6) has a considerably higher activation energy (18.6 kcal mol^{-1}). The higher barrier for this sequential set of 1,2-shifts is due to the higher energy intermediate **15**, in which aromaticity of the benzene ring is disrupted[59].

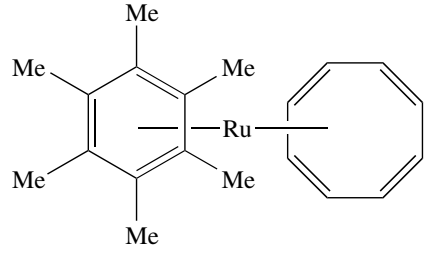


(5)



(14) **(15)** **(14')** (6)

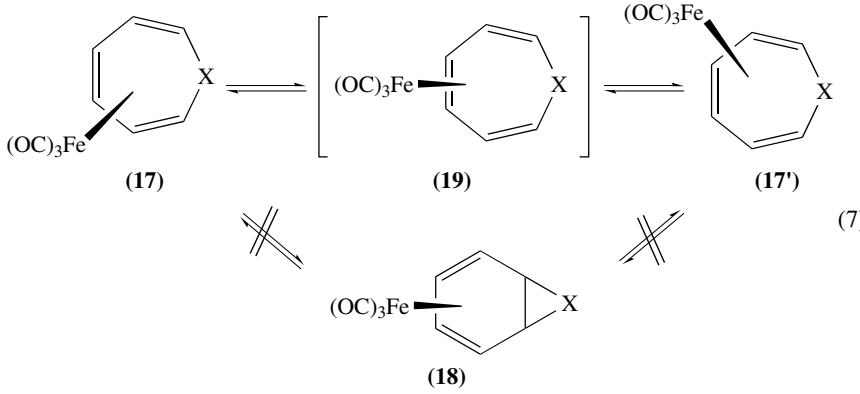
The crystal structure of (η^4-cyclooctatetraene)(hexamethylbenzene)ruthenium **(16)** indicates bonding as a tetrahapto ligand[60]. For this complex and similar iron–, ruthenium- and osmium–(η^4-cyclooctatetraene)(arene) complexes, their ^{1}H and ^{13}C NMR spectra exhibit only a single signal for the cyclooctatetraene ligand at temperatures as low as $-145\,^\circ$C. Using this temperature, the barrier-to-metal migration is estimated to be $\leqslant$6.6 kcal mol^{-1}.



(16)

Migration about the π-system is also observed in certain η^4-cyclic triene complexes **17** (equation 7). For the parent (η^4-cycloheptatriene)Fe(CO)$_3$ (**17**, X = CH$_2$), the barrier for this fluxional process is high enough that it is detectable only by Forsén–Hoffman spin-saturation techniques ($\Delta G^{\ddagger} = ca\,22.3$ kcal mol^{-1})[61a]. For (η^4-azepine)- and (η^4-oxepine)Fe(CO)$_3$ complexes (**17**, X = NCO$_2$Et or O), the barrier-to-iron migration is low enough to be measured by line-shape analysis of variable-temperature ^{1}H NMR spectra ($\Delta G^{\ddagger} ca 15.5–15.8$ kcal mol^{-1})[61b,c]. While metal migration occurs in (η^4-tropone)Fe(CO)$_3$ complexes (see Section IV.E.1.d), this process is too slow to result in coalescing signals in their NMR spectra. Early investigators had proposed that the metal migration

in complexes **17** to give **17′** occurred via sequential 1,2-shifts involving the norcaradiene complex **18** as an intermediate[61d]. However, EHT calculations[60] indicate that an electrocyclic ring closure of **17** to **18** is symmetry-forbidden. Furthermore, (heptafulvene) $Fe(CO)_3$ complexes (e.g. **17**, X = C=CHPh) , for which the norcaradiene ring intermediate would be expected to be more strained, show a lower barrier than for the parent cycloheptatriene system. The proposed intermediate is a symmetrical (η^2-cycloheptatriene) $Fe(CO)_3$ complex (**19**, X = CH_2) and EHT calculations indicate that the optimum geometry has the metal distorted toward the center of the cycloheptatriene ring[61a].

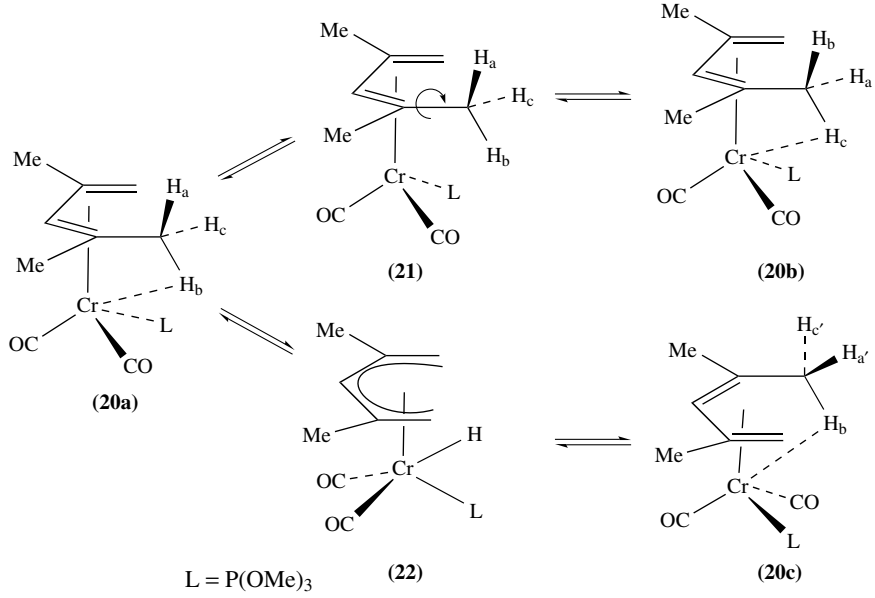


(7)

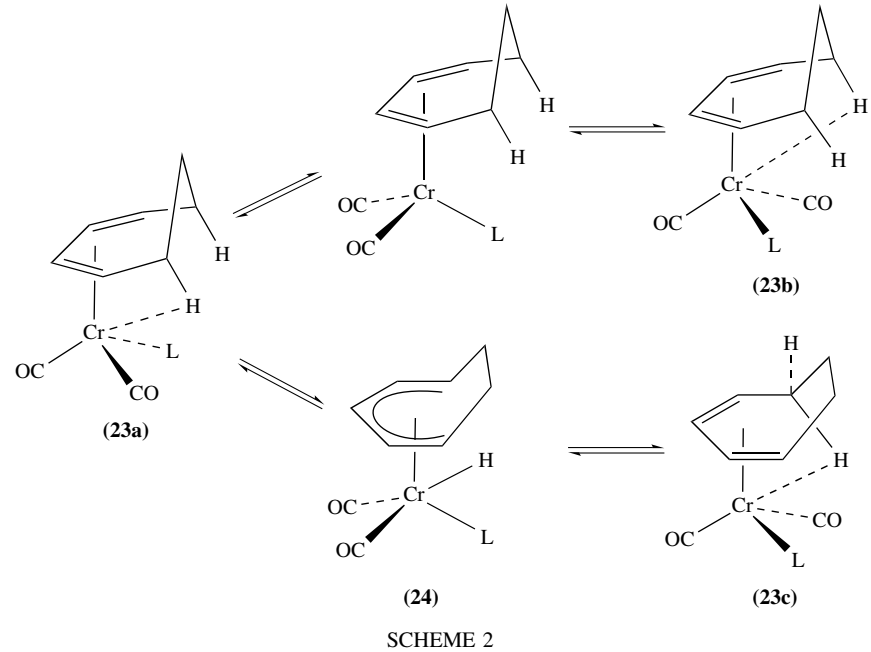
4. Bridging hydrogen exchange

The photochemically induced substitution of three CO ligands from $Cr(CO)_5P(OMe)_3$ by 2,4-dimethyl-1,3-pentadiene gives complex **20** (Scheme 1)[62a]. The crystal structure of **20** indicates that the ligand is bound as an (η^4-diene-μ-H) species (Cr−H distance = 1.94 Å). The three center-two electron donation inherent in the μ-H allows for coordinative saturation at Cr. At low temperature, the ^{1}H NMR spectrum of **20** consists of three separate signals for the three different protons of the *anti*-C5−methyl group, while at higher temperatures these three signals collapse to give rise to a single signal. This fluxionality is rationalized on the basis of hindered rotation about the C4−C5 bond due to a bridging hydrogen (agostic hydrogen). The barrier to this rotation ($\Delta G^{\ddagger} = 6.83$ kcal mol^{-1}) is due to formation of the coordinatively unsaturated 16-electron (η^4-diene) complex **21**. At still higher temperatures a second dynamic process occurs ($\Delta G^{\ddagger} =$ 16.3 kcal mol^{-1}) which is characterized by coalescence of the C2−Me and C4−Me signals as well as coalescence of the *anti*-C5 methyl signal with the signals for the C1 methylene protons. This process involves insertion of Cr into the H−C5 bond to generate a (η^5-pentadienyl)chromium hydride intermediate **22**. Since **22** possesses a plane of symmetry, the reverse of this insertion leads either to **20a** or to **20c**, thus accounting for the fluxionality.

Two related dynamic bridging hydrogen processes are observed for (η^4-cycloheptadiene-μ-H)$Cr(CO)_2L$ [**23**, L = CO, PMe_3, $P(OMe)_3$] (Scheme 2)[62b]. The lower energy process involves equilibration of the *endo* protons α to the complexed diene (i.e. **23a** to **23b**), while the higher energy process involves migration of the metal about the cyclic ligand (i.e **23a** to **23c**) via the (η^5-pentadienyl)chromium hydride intermediate **24**. The barriers for these two processes are similar to the analogous processes in the acyclic complex **22**.

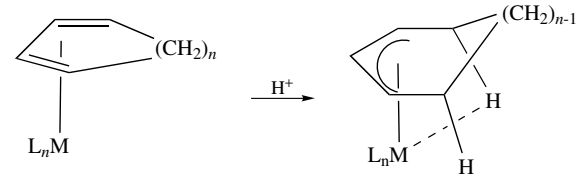


SCHEME 1



SCHEME 2

Similar bridging hydrogen exchange processes have been observed for neutral and cationic (η^3-allyl-μ-H)ML_n complexes **25** (Scheme 3)[23,58,63]. Many of these complexes are prepared by the protonation of the corresponding anionic or neutral (η^4-diene)ML_n complexes **26** (see Section V.C.1). Migration of the metal about a cyclic η^3-allyl ligand (i.e. **25a** to **25b**) is proposed to involve an (η^4-diene)ML_n hydride intermediate/transition state **27**.

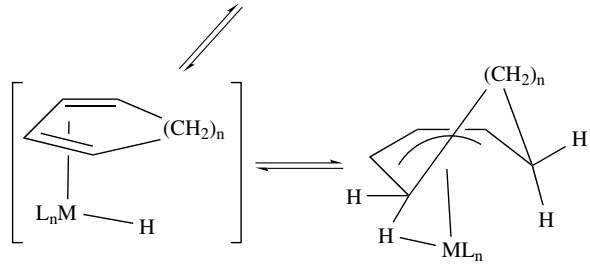


(26)

$ML_n = Mn(CO)_3^-$, $Fe(CO)_3$, $Fe(PR_3)_3$, Ru(arene), Os(arene) CoCp, RhCp, IrCp

(25a)

ground state for $ML_n = Mn(CO)_3$, $Fe(CO)_3^+$ $Fe(PR_3)_3^+$, $Ru(arene)^+$ $CoCp^+$, $RhCp^+$



(27)

ground state for $ML_n = Os(arene)^+$, $IrCp^+$

(25b)

SCHEME 3

IV. PREPARATION AND ISOMERIZATIONS OF CONJUGATED DIENE COMPLEXES

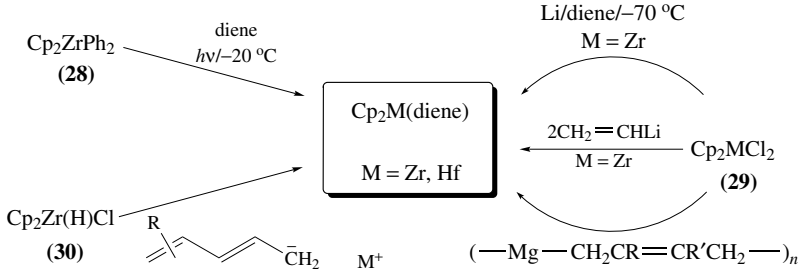
The preparation of conjugated diene complexes will be presented by groups. In addition, isomerization reactions, or degenerate rearrangements with activation energies >25 kcal mol^{-1}, will be considered in this section.

A. Complexes of Ti, Zr and Hf

1. (1,3-Diene)MCp_2 complexes (M = Zr, Hf)

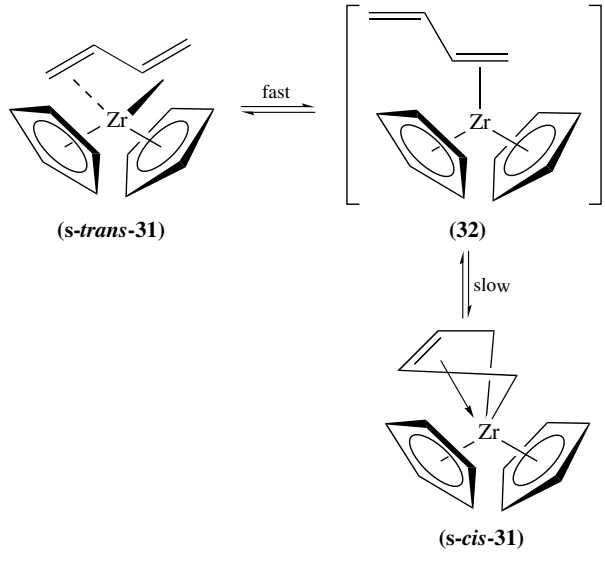
The preparations of acyclic and exocyclic diene complexes of $ZrCp_2$ and $HfCp_2$ were reported almost simultaneously by Erker and coworkers[10] and by Nakamura and coworkers[52a]. These complexes may be prepared (Scheme 4) (1) by direct complexation

of dienes to coordinatively unsaturated 'ZrCp$_2$' [generated either by photolysis of diphenylzirconocene **28** or by reduction of zirconocene dichloride **29** (M = Zr with Li metal][10,34,54,64], (2) by reaction of Cp_2MCl_2 (M = Zr, Hf) and substituted variants with (2-dien-1,4-diyl)magnesium reagents[17,18,50,53,65], (3) by reaction of substituted dienyl anions with zirconocene chloride hydride **(30)**[52], and (4) by reaction of zirconocene dichloride **29** with two equivalents of vinyl lithium[66]. There are no examples of endocyclic diene complexes of this type.



SCHEME 4

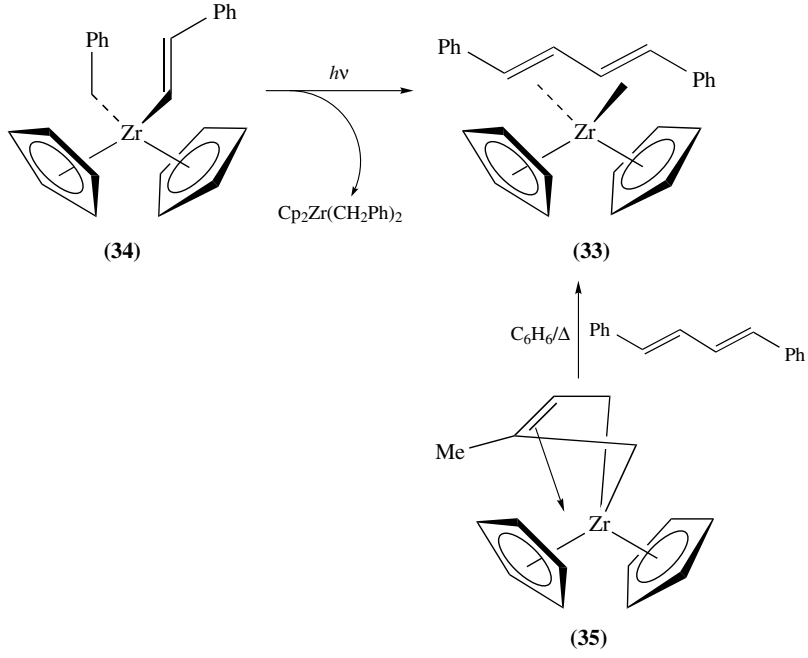
Preparation of the parent (butadiene)ZrCp$_2$ by either of the first two methods, *at low temperature* ($< -20\,^{\circ}C$), results in exclusive formation of the isomer s-*trans*-**31** (Scheme 5). Above $> -10\,^{\circ}C$ this begins to isomerize to an equilibrium mixture of s-*trans*-**31** and s-*cis*-**31** (55 : 45 ratio, $\Delta G^{\ddagger} = 22.7 \pm 0.3$ kcal mol^{-1})[18]. The isomerization of s-*trans*-**31** to s-*cis*-**31** is proposed to occur via the coordinatively unsaturated η^2-butadiene intermediate **32**. Since the s-*trans*-**31** isomer is the exclusive product at low



SCHEME 5

temperature, collapse of **32** to s-*trans*-**31** was deemed to be faster than collapse of **32** to s-*cis*-**32**. The parent butadiene complex **(31)** and (diene)$ZrCp_2$ complexes in which the diene bears substitution only at the terminal carbons (e.g. 1,3-pentadiene, 2,4-hexadiene) exist as both the s-*cis* and s-*trans* isomers at equilibrium. In comparison, for complexes in which the diene bears substitution at the internal carbons (e.g. isoprene, 2,3-dimethyl-1,3-butadiene, 2,3-diphenyl-1,3-butadiene etc.) the equilibrium is shifted exclusively toward the s-*cis* isomer[10,52].

Preparation of (1,4-diphenyl-1,3-butadiene)$ZrCp_2$ **(33)** may be accomplished by photolysis of (β-styryl)(benzyl)zirconocene **(34)**[67] or by displacement of isoprene from (isoprene)$ZrCp_2$ **(35)** at elevated temperature (Scheme 6)[17]. For complex **33**, the s-*trans*/s-*cis* equilibrium lies far toward the s-*trans* isomer (95 : 5).

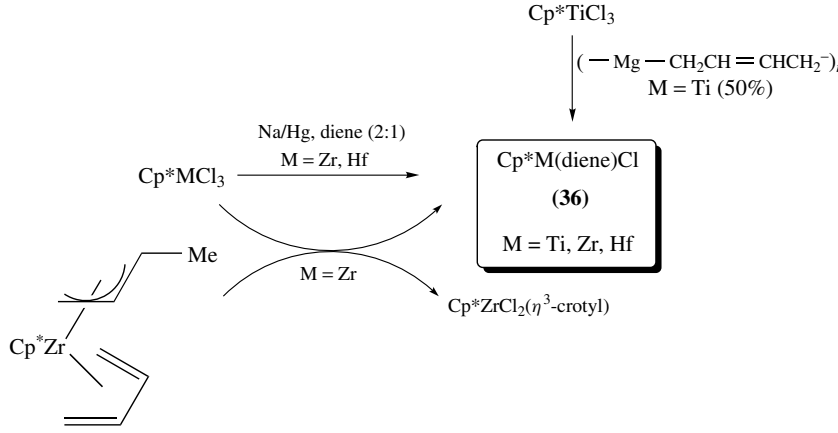


SCHEME 6

*2. (1,3-Diene)MCp*X complexes (M = Ti, Zr, Hf)*

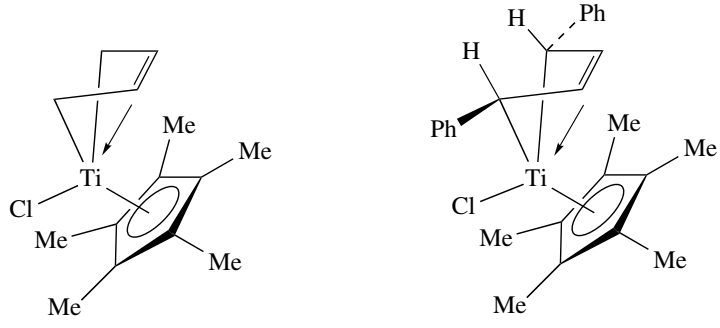
Coordinatively unsaturated 14-electron complexes of Ti, Zr and Hf, which contain an s-*cis* diene ligand **(36)**, have been prepared by Hessen and Teuben[68] and by Nakamura and coworkers[69]. The titanium complexes may be prepared by reaction of Cp^*TiX_3 with (2-dien-1,4-diyl)magnesium reagents (Scheme 7)[70]. In addition, these complexes may be prepared by direct complexation of a diene to 'Cp*TiX' [generated by reaction of Cp^*TiX_3 with two equivalents of a Grignard reagent][69b]. The analogous zirconium and hafnium complexes are primarily prepared by direct complexation of a diene to 'Cp*MCl' (generated by reduction of Cp^*MCl_3 with sodium amalgam)[70a,71]. When THF is used as solvent, these complexes are generally produced as solvated adducts which lose solvent

upon purification. The reaction of Cp^*MCl_3 with $Cp^*(\eta^3\text{-crotyl})M(butadiene)$[72] produces the above complexes **36** along with $Cp^*(\eta^3\text{-crotyl})MCl_2$; however, difficulties in separation render this method useful only for zirconium (Scheme 7)[71]. All of these complexes are described as being very air sensitive. There are no examples of endocyclic diene complexes of this type.

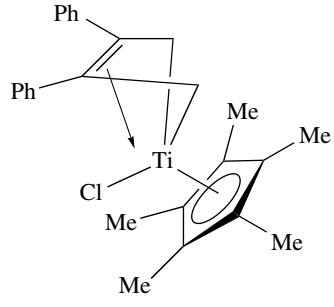


SCHEME 7

Crystal structures[69b,71] of titanium complexes **36a**, **36b** and **36c** and of hafnium complex **36d** indicate that the diene–metal interaction is best characterized by the σ^2, π bonding mode. In general, the diene ligand adopts an s-*cis* 'supine' conformation with respect to the Cp^* ligand (e.g. **36c** and **36d**). However, Nakamura and coworkers have noted that the Cp^*TiCl complexes of butadiene **(36a)**, 1,3-pentadiene and 1,4-diphenyl-1,3-butadiene **(36b)** adopt the s-*cis* 'prone' geometry in the solid state and in solution. Extended Hückel calculations of complex **36a** indicate that the 'prone' and 'supine' conformers are relatively close in energy[69b] and thus the preference for one of the two possible conformations may be determined by steric interactions between the Cp^* ligand and substituents present on the diene ligand. Isomerization between the two conformers is not observed.

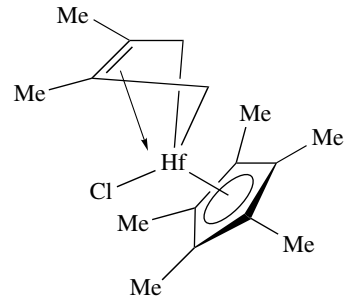


(**36a**) 'prone' (**36b**)



(36c)

'supine'



(36d)

B. Complexes of Nb and Ta

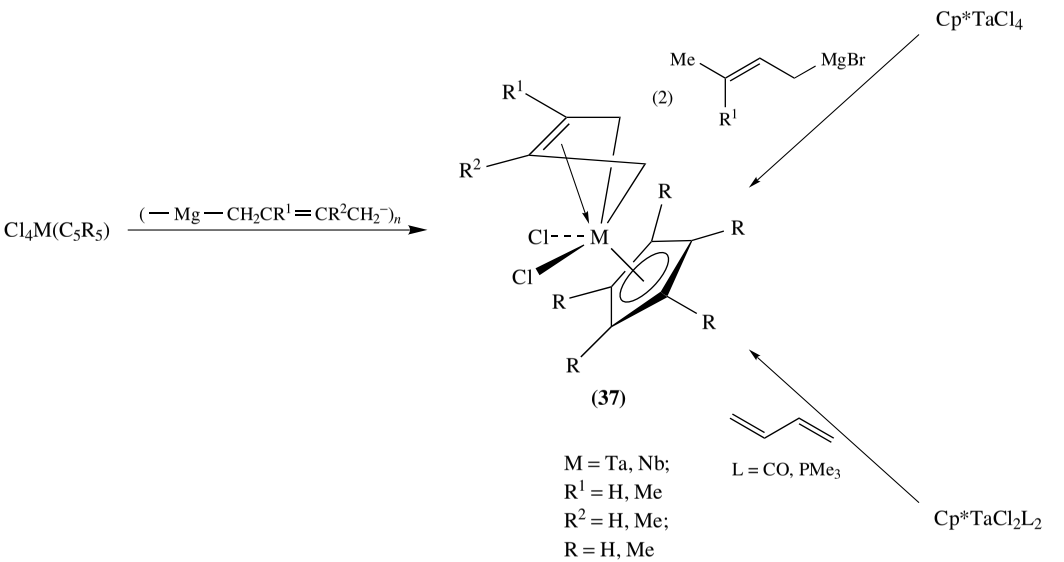
Mono- and bis-diene complexes of niobium and tantalum have been reported[73]. The mono-diene, 16 electron complexes **37** may be prepared (1) by the reaction of $CpMCl_4$ or Cp^*MCl_4 (M = Nb, Ta) with one equivalent of (2-dien-1,4-diyl)magnesium reagents[9a,19] or (2) by reaction of Cp^*TaCl_4 with two equivalents of a crotyl Grignard reagent (Scheme 8)[74]. The parent (butadiene)$TaCp^*Cl_2$ may also be prepared by ligand displacement of $Cp^*TaCl_2L_2$ (L = CO, PMe_3) with butadiene in solution (Scheme 8)[75]. For the mono–diene complexes, crystal structures indicate that these complexes adopt the 'supine' conformation in which the open end of the diene is directed toward the Cp ligand. No evidence has been found for either ligand rotation or envelope flip fluxionality/isomerization in these complexes.

The complex $(C_4H_6)Cp_2Ta^+MeB(C_6F_5)_3$ **(38)**, whose cationic part is isoelectronic with the neutral Zr and Hf complexes (Section IV.A.1), has been prepared by the reaction of complex **37** ($R = R^1 = R^2 = H$) with two equivalents of NaCp, followed by abstraction of the σ-bound cyclopentadienyl ligand (Scheme 9)[76]. Bonding of the butadiene ligand in **38** in the s-*trans* conformation was determined by X-ray diffraction analysis.

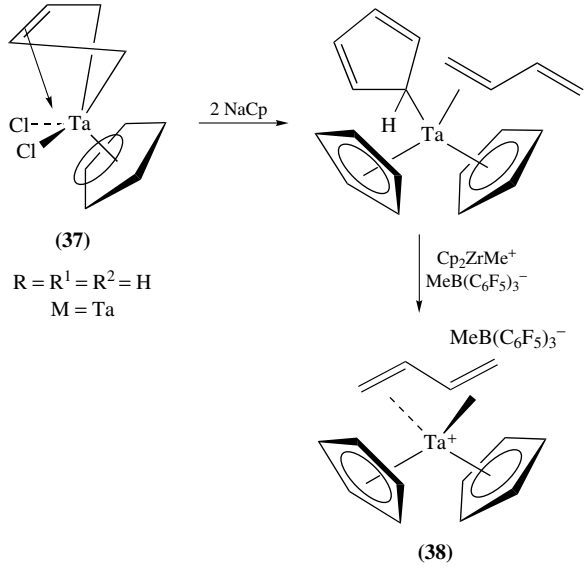
C. Complexes of Cr, Mo and W

1. Neutral metal–carbonyl complexes[47]

A wide variety of diene complexes of group 6 metal carbonyls have been prepared. Either attempted coordination of 1,3-cyclooctadiene (cod) via thermally induced ligand substitution of $Mo(CO)_6$ or $W(CO)_6$ or cocondensation of Cr vapor with 1,3-cod and CO gives the (1,5-cod)$M(CO)_4$ complexes in abysmally low yield (Scheme 10)[77]. These results indicate that isolated bisolefin $M(CO)_4$ complexes are more stable than the corresponding conjugated diene complexes. Significantly higher yields of the conjugated diene complexes are afforded under photochemical induced ligand displacement. Thus, photolysis of $M(CO)_6$ or $M(CO)_5L$ [M = Cr, Mo, W; L = $P(OMe)_3$, PMe_3, PBu_3] in the presence of a conjugated diene generates the corresponding (diene)$M(CO)_4$ **(39)**[20,78] or (diene)$M(CO)_3L$ **(40)**[79] complexes respectively in good yields (Scheme 10). In general, for acyclic diene complexes **40**, the phosphine/phosphite ligand is aligned along the 'mouth' of the conjugated diene, while for cyclohexadiene complexes the metal-to-phosphine/phosphite bond eclipses the C2–C3 bond. Similar photolyses of $M(CO)_4L_2$ [M = Cr, Mo, W; L_2 = $(P(OMe)_3)_2$, $(PMe_3)_2$, $(PBu_3)_2$, $Me_2PCH_2CH_2PMe_2$] produce the (diene)$M(CO)_2L_2$ complexes **(41)**[80]. The bisphosphine complexes **41** adopt structures


Cp*TaCl4
Me
MgBr
(2)
R1
R1
R2
R
R
Cl
M
Cl
R
R
R
(37)
M = Ta, Nb;
R1 = H, Me
R2 = H, Me;
R = H, Me
L = CO, PMe3
Cp*TaCl2L2

SCHEME 8



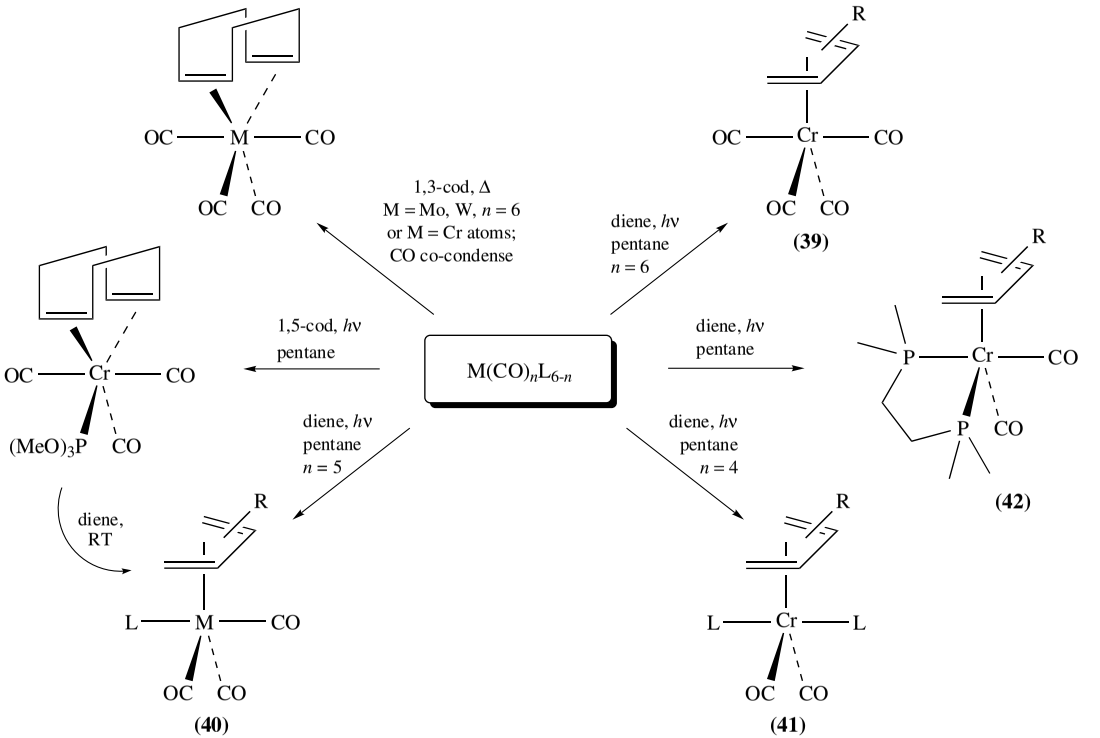
SCHEME 9

in which the phosphines occupy the two axial coordination sites, while the chelating bis(dimethylphosphino)ethane complexes **42** adopt structures in which one of the phosphorous atoms occupies the axial site aligned with the 'mouth' of the diene and the other phosphorous atom occupies an equatorial coordination site. The photochemical formation of ($\eta^4 - \mu$-H-diene)$Cr(CO)_2P(OMe)_3$ complexes (e.g. **20** or **23**) has previously been mentioned (Section III.C.4)[62].

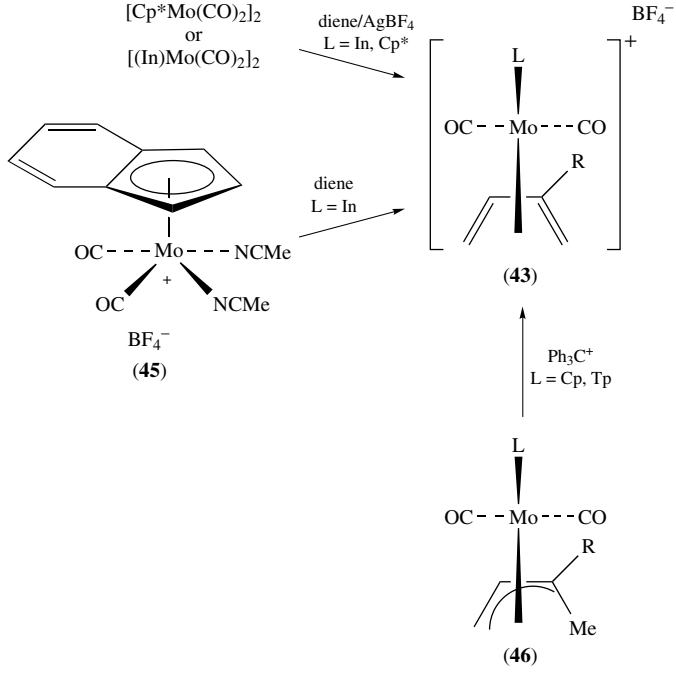
2. Cationic (diene)MCp(CO)$_2^+$ complexes (M = Mo, W)

A wide variety of s-*cis* acyclic **(43)** and cyclic **(44)** and (diene)$Mo(CO)_2L^+$ cations [L = Cp, Cp*, indenyl (In), trispyrazolylborohydride (Tp)] have been prepared. Direct complexation may be achieved by reaction of the stable cation [(η^5-indenyl)$Mo(CO)_2(NCMe)_2]^+$ BF_4^- **(45)** (prepared by the reaction of [(η^5-indenyl)$Mo(CO)_2]_2$ with $AgBF_4$ in MeCN) with a solution of the diene ligand (Scheme 11)[81]. It is not necessary to isolate **45**, since treatment of [(η^5-indenyl)$Mo(CO)_2]_2$ or [Cp*$Mo(CO)_2]_2$ with $AgBF_4$ in the presence of the diene ligand gives the corresponding cation **43** (L = indenyl)[82].

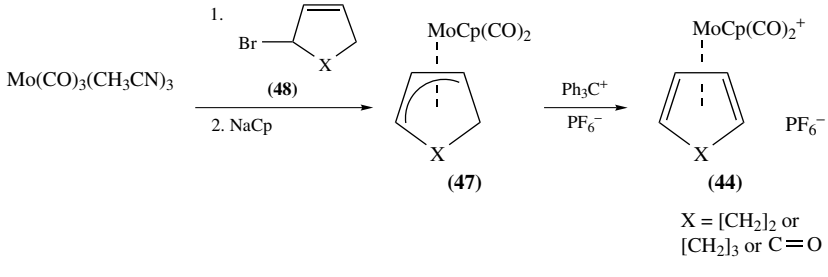
(Diene)$Mo(CO)_2L^+$ cations [L = Cp, Tp] may also be prepared by hydride abstraction from the corresponding neutral (η^3-allyl)$Mo(CO)_2L$ complexes, e.g. **(46)** or **(47)**, with triphenylmethyl cation[21,83] (Schemes 11 and 12). Hydride abstraction occurs only from a carbon in the *anti*-position of the η^3-allyl ligand. For this reason, hydride abstraction from cyclic (η^3-allyl)$(CO)_2$MoCp complexes **(47)**, in general, gives high yields of the corresponding cationic 1,3-cyclodiene complexes **44** (Scheme 12)[84]. The (η^3-allyl)$(CO)_2$MoCp precursors **47** are prepared by reaction of the appropriate allylic bromide **(48)** with $Mo(CO)_3(CH_3CN)_3$ [generated *in situ* from $Mo(CO)_6$ and CH_3CN] followed by treatment with cyclopentadienyl anion. Hydride abstraction occurs on the


M(CO)nL6-n
1,3-cod, Δ
M = Mo, W, n = 6
or M = Cr atoms;
CO co-condense
diene, hν
pentane
n = 6
(39)
1,5-cod, hν
pentane
diene, hν
pentane
(42)
diene, hν
pentane
n = 5
diene, hν
pentane
n = 4
diene,
RT
(40)
(41)

SCHEME 10



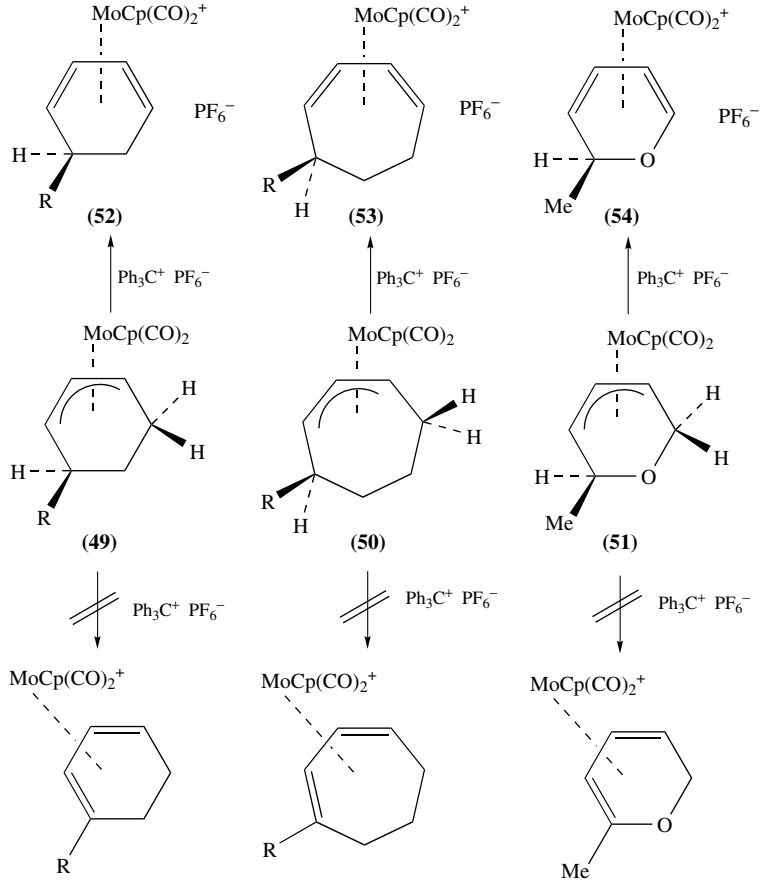
SCHEME 11



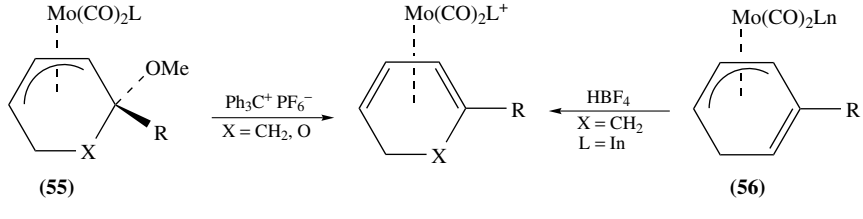
SCHEME 12

face opposite to molybdenum. This restriction has regiochemical implications for substituted cyclic η^3-allyl complexes. For example, complexes **49**, **50**, and **51** all undergo regioselective hydride abstraction with Ph_3C^+ to give the (diene)$(CO)_2MoCp^+$ cations **52**, R = Me, CH_2CO_2Me[84a,c], **53**, R = Me, allyl, $p-C_6H_4OMe$[84b] and **54**[85], respectively (Scheme 13).

Cyclic (diene)$Mo(CO)_2Cp$ (or In) cations have been prepared by trityl cation mediated alkoxide abstraction from cyclic (η^3-allyl)$Mo(CO)_2Cp$ (or In) complexes bearing a *syn* alkoxy in the α position (e.g. **55**, Scheme 14)[81b,86]. Additionally, protonation of (η^3-allyl)$Mo(CO)_2In$ (or Cp*) complexes bearing a vinyl group (e.g. **56**, Scheme 14) affords the corresponding (diene)Mo^+ cations[81b,87].

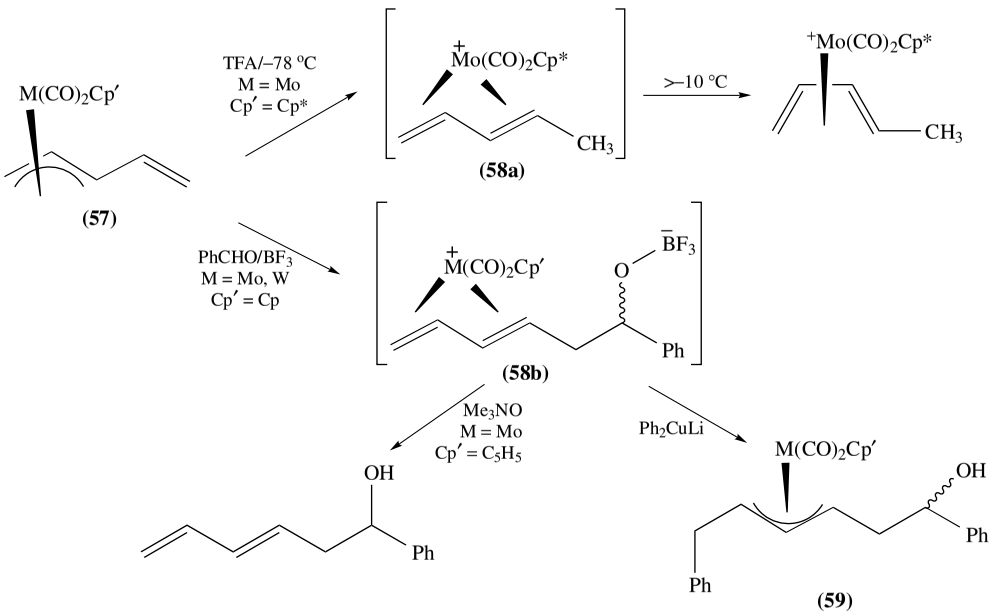


SCHEME 13



SCHEME 14

The reaction $< -40\,^{\circ}C$ of *syn*-vinyl substituted acyclic (η^3-allyl)$M(CO)_2Cp'$ complexes **57** (M = Mo, W; Cp′ = Cp, Cp*) with CF_3CO_2H or a mixture of BF_3 and an aldehyde generates the s-*trans* (diene)$M(CO)_2Cp'$ cations **58a** or **58b** respectively, which may be isolated by precipitation from ether (Scheme 15)[30,88]. At higher temperature

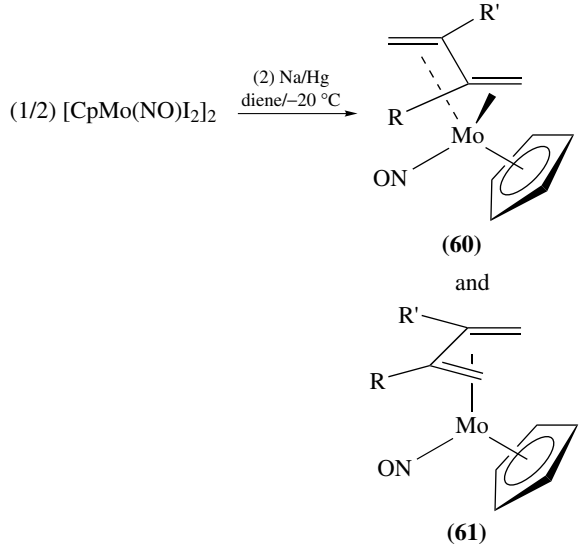

M(CO)2Cp′
(57)
TFA/–78 °C
M = Mo
Cp′ = Cp*
+Mo(CO)2Cp*
CH3
(58a)
>–10 °C
+Mo(CO)2Cp*
CH3
PhCHO/BF3
M = Mo, W
Cp′ = Cp
+M(CO)2Cp′
O
BF3
Ph
(58b)
Me3NO
M = Mo
Cp′ = C5H5
OH
Ph
Ph2CuLi
M(CO)2Cp′
OH
Ph
Ph
(59)

SCHEME 15

(>−10 °C), the s-*trans* pentadiene cation **58a** irreversibly rearranges to the s-*cis* diene cation **59**[30,88a]. The s-*trans* geometry of cations **58** has been ascertained by NMR spectroscopy at low temperature[30,88a] and by decomplexation of **58b** to give the *trans*-diene ligand[88b]. Reaction of nucleophiles, such as diphenylcuprate, with *in situ* generated **58b** gives the corresponding *syn*,*syn*-1,3-disubstituted allyl complex (**59**)[88].

3. (s-trans Diene)MoCp(NO) complexes

Reduction of the metal dimer $[CpMo(NO)I_2]_2$ with Na/Hg in the presence of a variety of acyclic dienes generates the (diene)MoCp(NO) complexes in moderate to low isolated yield (equation 8)[12,31,89]. For the majority of diene ligands, complexes **60** are formed exclusively as the s-*trans* isomers as evidenced by NMR spectroscopy and single-crystal X-ray diffraction analysis. In comparison, complexation of the 2,3-dimethyl-1,3-butadiene initially gives a separable mixture of the s-*trans* **(60)** and s-*cis*-complex **(61)**. The s-*cis* isomer isomerizes to the more thermodynamically stable s-*trans* isomer in solution (THF, $t_{1/2} = 5$ min; C_6H_6, $t_{1/2} = 24$ h).



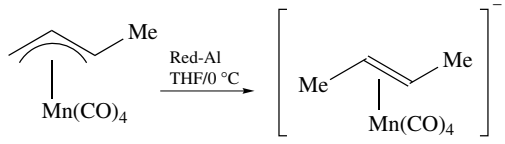
(8)

D. Complexes of Mn and Re

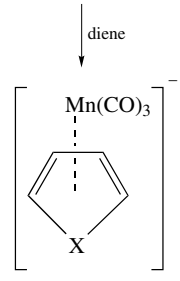
1. Anionic Mn–carbonyl complexes

(η^4-Diene)$Mn(CO)_3^-$ anions are stable in solution, and have been characterized by infrared and NMR spectroscopy. However, exposure of the anion solution to oxygen results in decomposition to give the free ligand. Reduction of (crotyl)$Mn(CO)_4$ **(62)** gives the manganese-carbonyl transfer reagent (*E*-2-butene)$Mn(CO)_4^-$. Reaction of 1,3-cycloheptadiene, 1,3-cyclooctadiene, 1,3,5-cycloheptatriene or 1,3,5,7-cyclooctatetraene

with (*E*-2-butene)$Mn(CO)_4^-$ affords complexes **63a–d** (equation 9)[58].



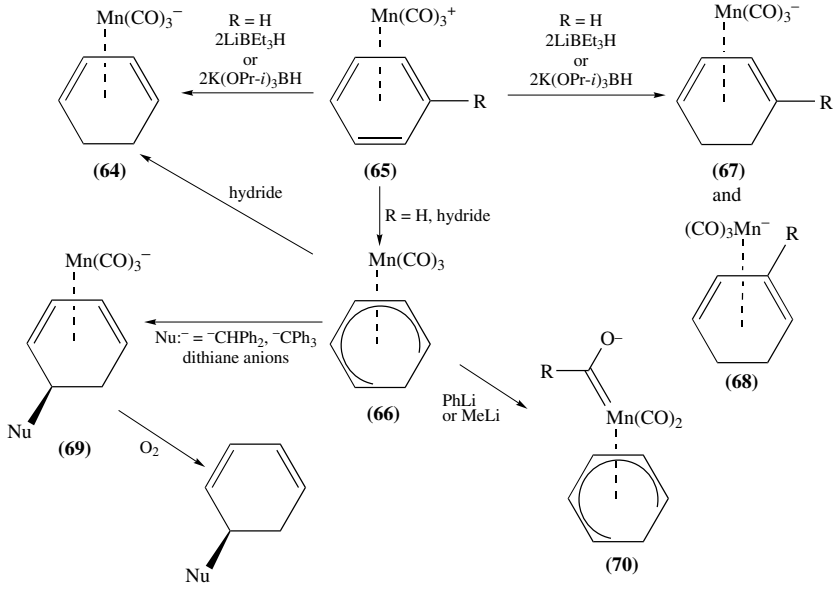
(62)



(9)

(63a) X = $[CH_2]_3$
(63b) X = $[CH_2]_4$
(63c) X = $CH_2CH{=}CH$
(63d) X = $[CH{=}CH]_2$

The 1,3-cyclohexadiene complex **64** may be prepared by addition of two equivalents of hydride to the $(C_6H_6)Mn(CO)_3^+$ cation **65** (R = H, Scheme 16)[90]. The first equivalent of hydride generates the neutral (η^5-cyclohexadienyl)$Mn(CO)_3$ complex



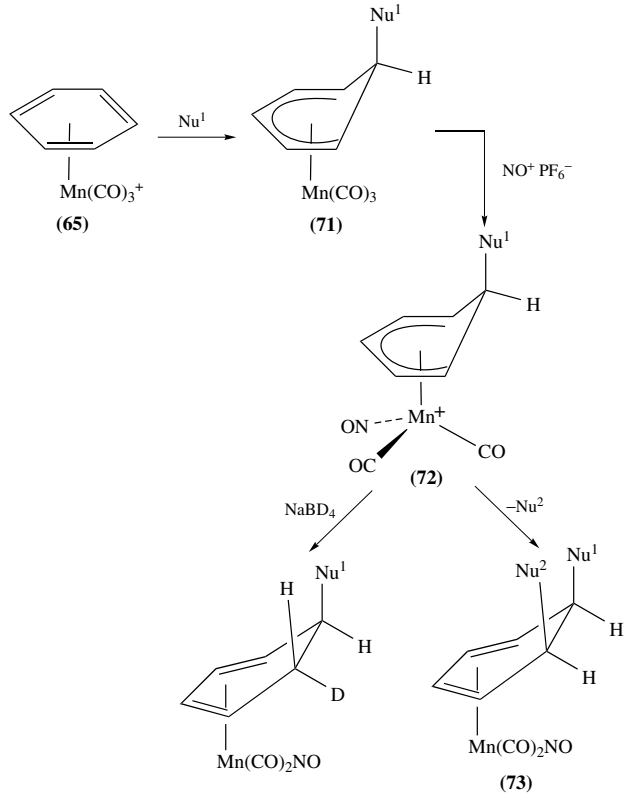
SCHEME 16

(66), which undergoes a second nucleophilic addition to give **64**. Reduction of substituted (arene)$Mn(CO)_3^+$ cations **65** (R = alkyl, aryl, alkoxy) with two equivalents of hydride leads to mixtures of isomeric (cyclohexadiene)$Mn(CO)_3^-$ anions **(67)** and **(68)**[90c,d]. Addition of certain stabilized nucleophiles (e.g. $LiCHPh_2$, $LiCPh_3$, $LiCMe_2CN$, $LiCMe_2CO_2Et$) to **66** gives the substituted cyclohexadiene anions **69**; air oxidation affords the free ligand[91]. In contrast, reaction of phenyl lithium or methyl lithium with **66** yields the acylate anion **70** via nucleophilic attack at one of the carbonyl ligands[92].

(Diene)$Mn(CO)_3^-$ anions are also prepared by deprotonation of the (η^3-allyl-μ-hydride) $Mn(CO)_3$ complexes (**25** $ML_n = Mn(CO)_3$) with potassium hydride[23,90a,c]. However, since complexes **25** $ML_n = Mn(CO)_3$ are generally prepared by protonation of the corresponding anions, this method is mostly of regenerative value.

2. Neutral Mn and Re carbonyl–nitrosyl complexes

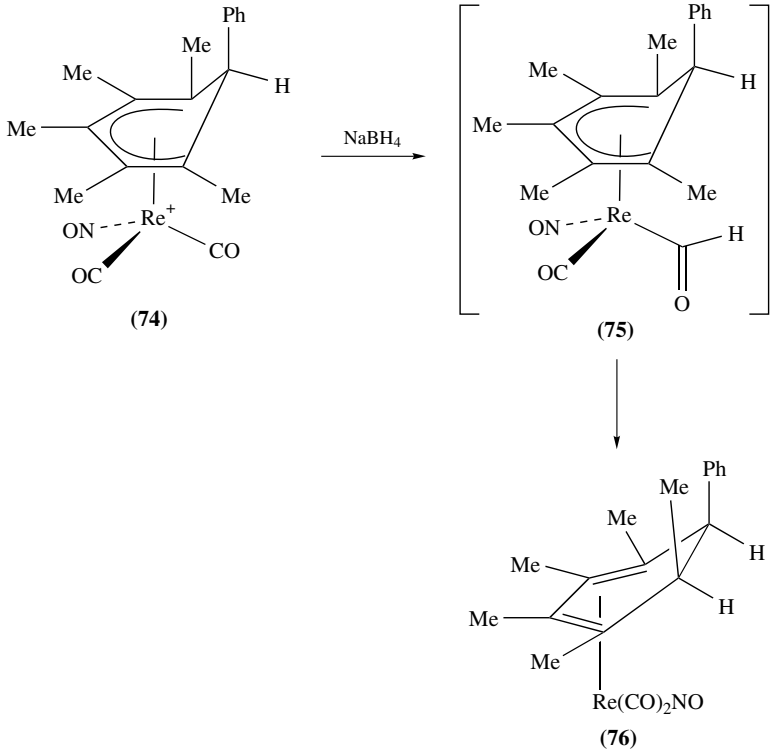
Neutral (cyclohexadienyl)manganese complexes **71**, generated by nucleophilic addition to (arene)$Mn(CO)_3^+$ cations **65**, undergo ligand substitution with nitrosyl hexafluorophosphate to give the corresponding (cyclohexadienyl)$Mn(CO)_2NO^+$ cations **72** (Scheme 17)[93]. Attack by a wide variety of nucleophiles on cations **72**



SCHEME 17

gives the neutral (cyclohexadiene)$Mn(CO)_2NO$ complexes **73**. Beginning with the (cycloheptadiene)$Mn(CO)_3^+$ cation, a similar sequence of reactions generates 5,7-disubstituted (1,3-cyclohexadiene)Mn complexes[94]. In a number of cases, nucleophilic attack on the face of the dienyl ligand opposite to the metal has been established by crystal structure analysis. Nucleophilic addition to (cyclohexadienyl)$Mn(CO)(PR_3)NO^+$ cations which are chiral at the metal occurs with modest diastereoselectivity (*ca* 33% de)[93e,g].

In contrast, spectroscopic and crystal structure analysis indicates that nucleophilic attack of hydride on **72** occurs on the face of the ligand which is coordinated to the metal (Scheme 17). No intermediate species could be detected for this latter reaction. Monitoring of the reduction of the rhenium analog **74** with sodium borohydride indicated the intermediacy of a rhenium formyl complex **75**, presumably formed by attack on a coordinated carbon monoxide. Signals for **75** eventually disappear and are replaced by those of the (diene)rhenium product **76** (Scheme 18)[95].

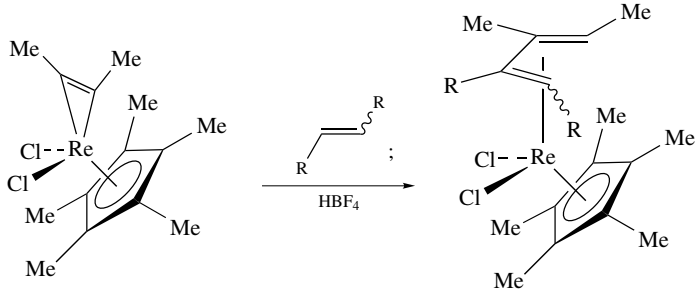


(74) **(75)** **(76)**

SCHEME 18

3. Miscellaneous

Herrmann and coworkers reported that the metallocyclopentene complex **77** reacts with ethylene or 2-butene to produce the (diene)rhenium complexes **78** (equation 10)[96].



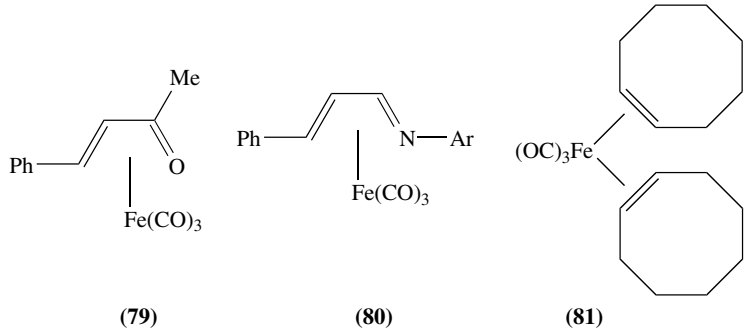
(77) (78) (10)

E. Complexes of Fe, Ru and Os

1. Neutral Fe–carbonyl and phosphine complexes

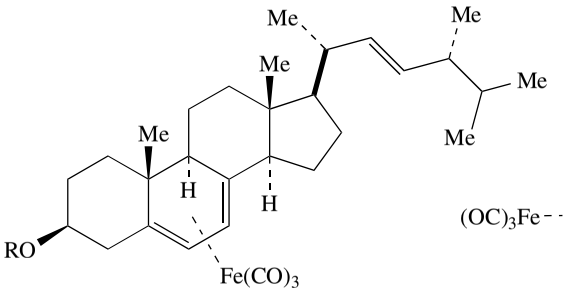
By far the greatest number of diene–metal complexes are of the type (diene)$Fe(CO)_3$. All of these complexes exhibit the s-*cis* η^4-diene coordination mode.

a. Preparation by direct complexation. In general, the most common method of preparation is by direct complexation of the free ligand using either $Fe(CO)_5$, $Fe_2(CO)_9$ or $Fe_3(CO)_{12}$, either thermally, photochemically, under the influence of ultrasonic stirring or by dry state-adsorption techniques[97,98]. Room temperature complexation using $Fe(CO)_5$ may be accomplished by decarbonylation with trimethylamine N-oxide[99]. Complexation of non-conjugated dienes under thermal conditions usually leads to isomerization to afford the conjugated (1,4-η^4-diene) complex[97b,100], except in cases where the non-conjugated diene is constrained in a bicyclic or polycyclic ring system. Complexation under mild reaction conditions can be achieved by using (α,β-enone)$Fe(CO)_3$ complexes **(79)**, (1-aza-1,3-diene)$Fe(CO)_3$ complexes **(80)** or bis(η^2-cyclooctene)$Fe(CO)_3$ **(81)** as metal transfer species[101].

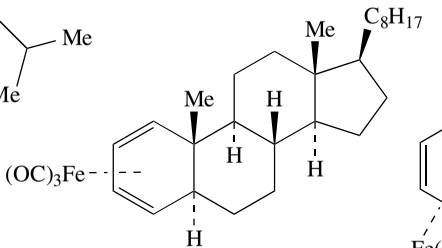


(79) **(80)** **(81)**

For diene ligands which are prochiral, complexation results in the formation of a racemic mixture. Resolution of this racemic mixture has been accomplished via either classical methods[102], chromatographic separation on chiral stationary phases[103] or kinetic resolution[104]. For certain acyclic or cyclic dienes possessing a pendent chiral center(s)



(82)



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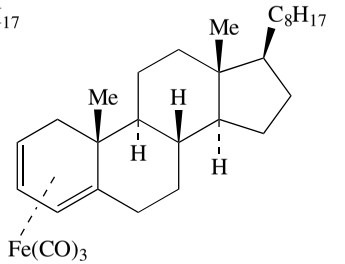

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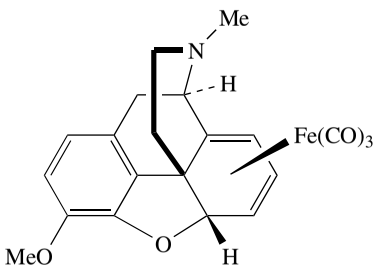

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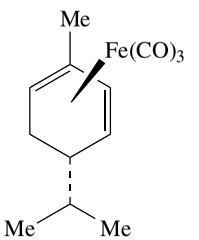

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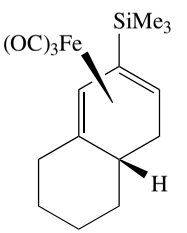
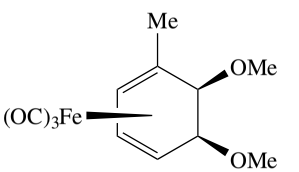
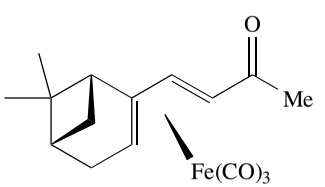


(87)



(88)



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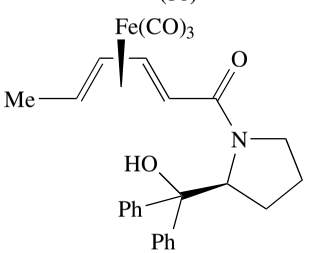

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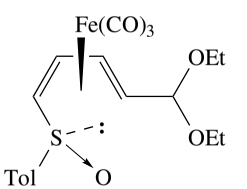

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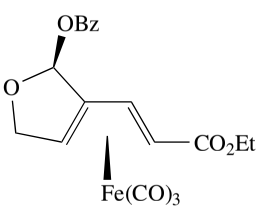

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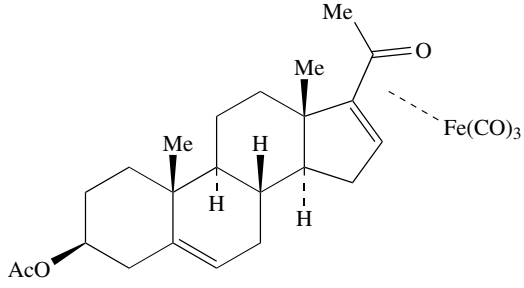

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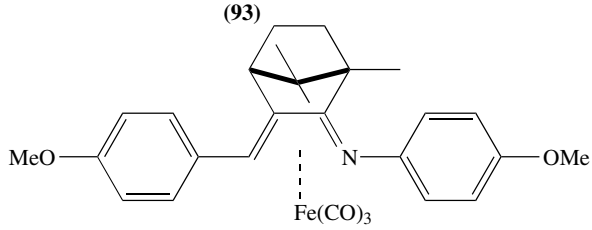
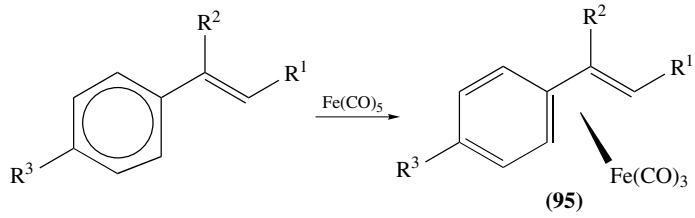


(94)

complexation may occur in a diastereoselective fashion (e.g. **82**–**92**)[105]. Enantioselective complexation (max. 64% ee) of prochiral dienes via optically active metal transfer reagents (e.g. **93**, **94**) has been reported[106].

Coordination of vinylarenes to an $Fe(CO)_3$ group gives rise to a complex **(95)** in which the metal is bound to the vinyl carbons and two of the carbons within the six-membered ring (equation 11)[107]. Crystal structure analysis indicates substantial bond localization in the uncomplexed portion of the ring. This has been interpreted as a loss of aromatic character due to participation of some of the π-electrons in coordination to iron.



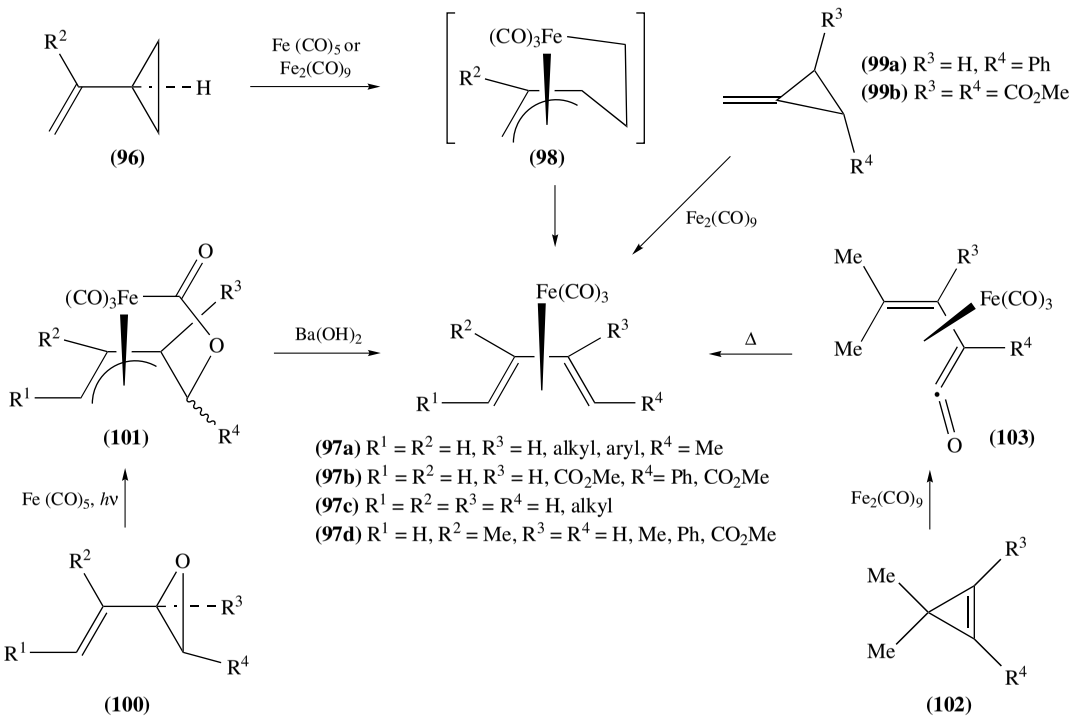
(11)

(95)

The reaction of *o*-halomethylene benzyl halides, 1,4-dihalobut-2-enes, cyclo-2-hexenols or 2,5-dihydrothiophene-1,1-dioxides with $Na_2Fe(CO)_4$ or $Fe_2(CO)_9$ results in the formation of (diene)$Fe(CO)_3$ complexes[108]. In each case, the precursor is transformed *in situ* into the free diene ligand, followed by complexation.

Metal vapor deposition of Fe atoms with a variety of acyclic and cyclic dienes, followed by treatment of the condensate with excess trimethylphosphite, give the corresponding (diene)$Fe[P(OMe)_3]_3$ complexes in low yield[109].

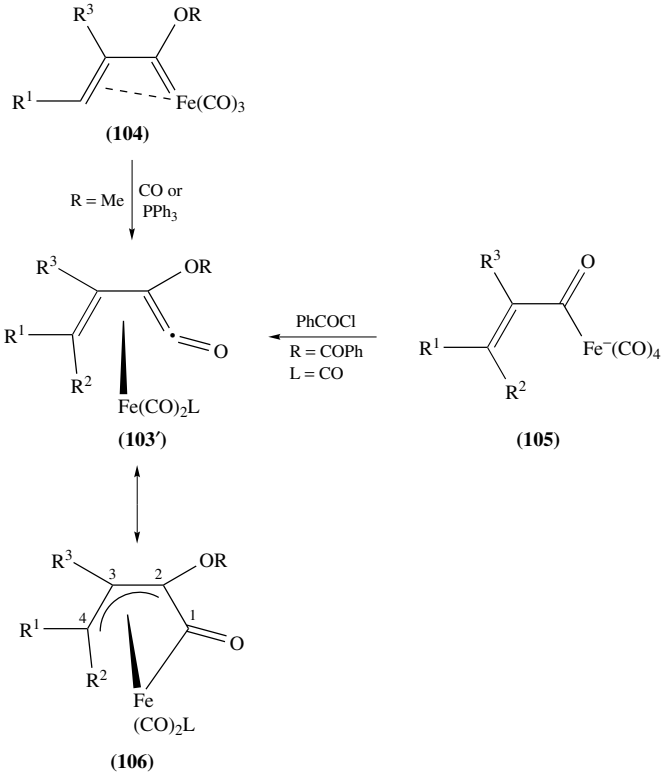
b. Diene formation within the coordination sphere of Fe. In certain cases, ring opening of strained cyclic compounds results in the formation of (η^4-diene)$Fe(CO)_3$ complexes (Scheme 19). The thermal reaction of vinylcyclopropanes **96** with $Fe(CO)_5$ or $Fe_2(CO)_9$


Fe (CO)5 or
Fe2(CO)9
(96)
(98)
(99a) R3 = H, R4 = Ph
(99b) R3 = R4 = CO2Me
Fe2(CO)9
Ba(OH)2
Δ
(101)
(97a) R1 = R2 = H, R3 = H, alkyl, aryl, R4 = Me
(97b) R1 = R2 = H, R3 = H, CO2Me, R4= Ph, CO2Me
(97c) R1 = R2 = R3 = R4 = H, alkyl
(97d) R1 = H, R2 = Me, R3 = R4 = H, Me, Ph, CO2Me
(103)
Fe (CO)5, hν
Fe2(CO)9
(100)
(102)

SCHEME 19

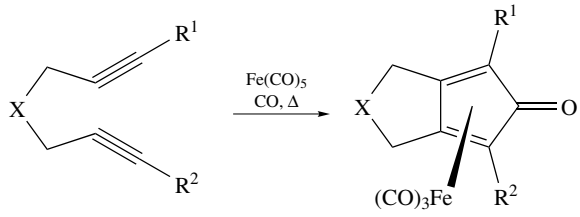
affords pentadiene complexes **97a**[110]. The intermediacy of a (pentenediyl)iron species **98** has been proposed. Reaction of methylenecyclopropanes **99a** and **99b** with $Fe_2(CO)_9$ yields diene complexes **97b**[111]. Ring opening of vinyloxiranes **100** with $Fe(CO)_5$ produces the corresponding π-allyl iron lactone complexes **101**. Treatment of **101** with barium hydroxide leads to diene complexes **97c** via decarboxylation[112]. Ring opening of 1,1-dimethylcyclopropenes **102** with $Fe_2(CO)_9$ proceeds with incorporation of a carbonyl ligand to afford the vinylketene complexes **103**[113]. Heating complexes **103** at reflux results in the loss of CO and hydride migration to give diene complexes **97d**[113c]. Direct thermolysis of **102** with $Fe_2(CO)_9$ produces the same products.

In addition to the ring opening of cyclopropenes noted above, vinylketene complexes **103′** have been prepared by (1) ligand initiated carbonyl insertion of vinyl carbene complexes **104** and (2) benzoylation of α,β-unsaturated acyl ferrates **105** (Scheme 20)[114]. X-ray diffraction analysis of these vinylketene complexes indicates that the structure may be best represented as a hybrid between an η^4-diene type complex **(103′)** and an η^3-allyl-η^1-acyl complex **(106)**. The Fe–C1 distance (*ca* 1.92 Å) is shorter than the Fe–C2, Fe–C3, or Fe–C4 distances (*ca* 2.1–2.2 Å)[113a–c]. In addition, the C–C–O ketene array is not linear (bend angle *ca* 135°).



SCHEME 20

Thermal cyclization of alkynes with $Fe(CO)_5$ proceeds predominantly with CO incorporation to afford (cyclopentadienone)$Fe(CO)_3$ complexes, however small amounts of cyclobutadiene complexes can be isolated (see Section VI.B.)[15]. 1,6-Heptadiyne and 1,7-octadiyne substrates **107** have been utilized to prepare bicyclo[3.3.0] and bicyclo[4.3.0] complexes **108** in excellent yield (equation 12)[115], while 1,8-nonadiynes gave bicyclo [5.3.0] complexes in low yield.

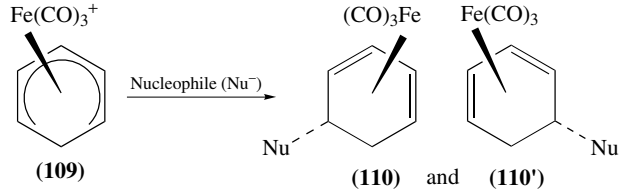


(107)

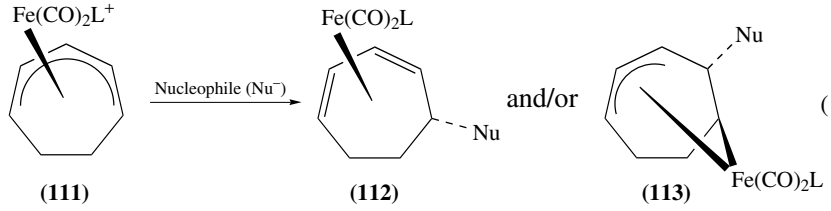
X = CH_2, $(CH_2)_2$, O, NR

(108) (12)

c. Preparation by nucleophilic addition to η^5-dienyl cations. The tricarbonyl(cyclohexadienyl)iron(1+) cation **(109)** is an excellent electrophile toward a wide variety of nucleophiles. Thus the reaction of **109**, and substituted variants, with halides, alkoxides, amines, phosphines and phosphites, organometallic anions, main group alkyl metals, enolates and electron-rich aromatics, proceeds via attack at the dienyl terminus to afford substituted (cyclohexadiene)$Fe(CO)_3$ complex **110** and its enantiomer **110′** (equation 13)[116]. Nucleophilic attack is generally observed to occur on the face of the dienyl ligand opposite to the coordinated metal. Compared to the reaction of cyclohexadienyl cation **109** the reaction of the (cycloheptadienyl)iron(1+) cations **(111)** with nucleophiles proceeds with differences in regioselectivity. While nucleophilic attack on the (dicarbonyl)phosphine- and (dicarbonyl)phosphite iron cations (**111**, L = PR_3) proceeds with excellent regioselectivity, nucleophilic attack on the tricarbonyl iron cation (**111**, L = CO) frequently affords mixtures of diene complexes **(112)** and pentenediyl complexes **(113)** (equation 14)[117].



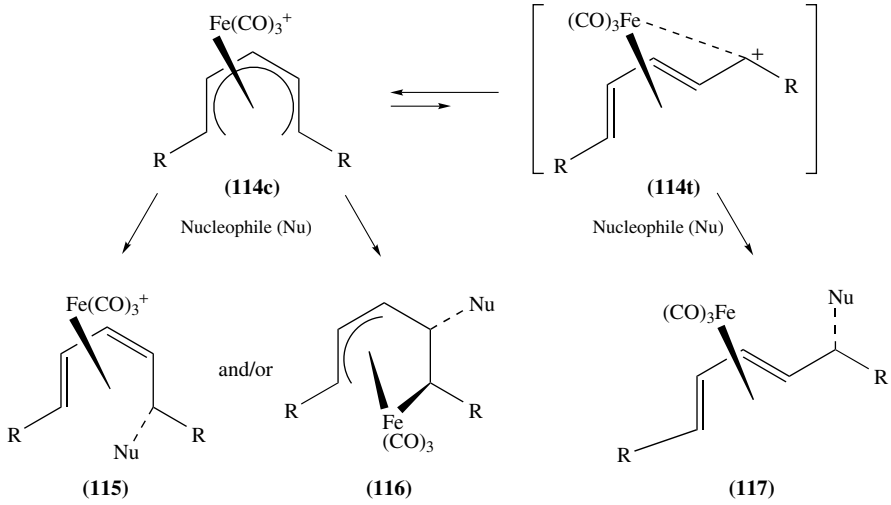
(109) **(110)** and **(110')** (13)



(111) **(112)** **(113)** (14)

Acyclic (pentadienyl)iron(1+) cations present additional possibilities for nucleophilic attack. The transoid form **114t** is known to exist in equilibrium with the more thermodynamically stable cisoid form **114c** (Scheme 21)[118]. Depending upon the nucleophile,

attack can take place on the cisoid form of the pentadienyl cation at either the termini or the internal atoms of the ligand to afford *E*,*Z*-diene complexes **115** or pentenediyl complexes **116**. Alternatively, nucleophilic attack on the transoid pentadienyl cation generates *E*,*E*-diene complexes **117**[119]. For symmetrically substituted dienyl cations **109**, **111**, and **114** nucleophilic attack on one of the terminal carbons of the ligand or the other results in the formation of mirror image products. Preferential (diastereoselective) attack on these symmetrical cations has been achieved using chiral nucleophiles[120]. For unsymmetrically substituted dienyl cations, the regioselectivity for nucleophilic attack is dependent upon the substituents present on the dienyl ligand, the nature of the nucleophile as well as on spectator ligands.

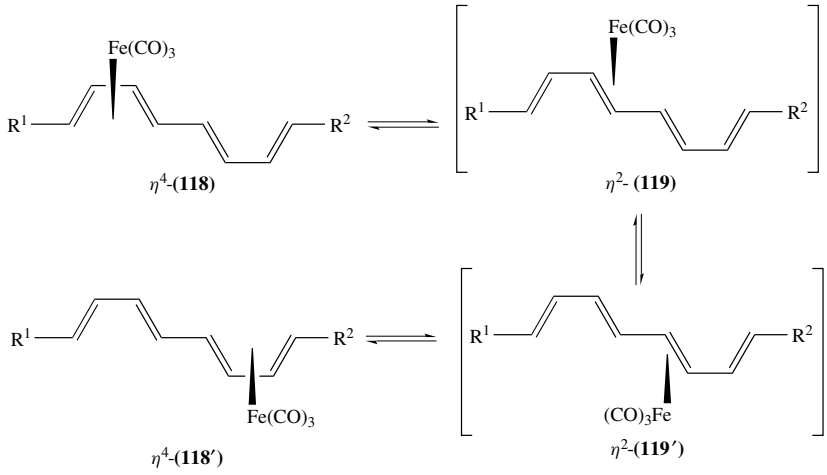


SCHEME 21

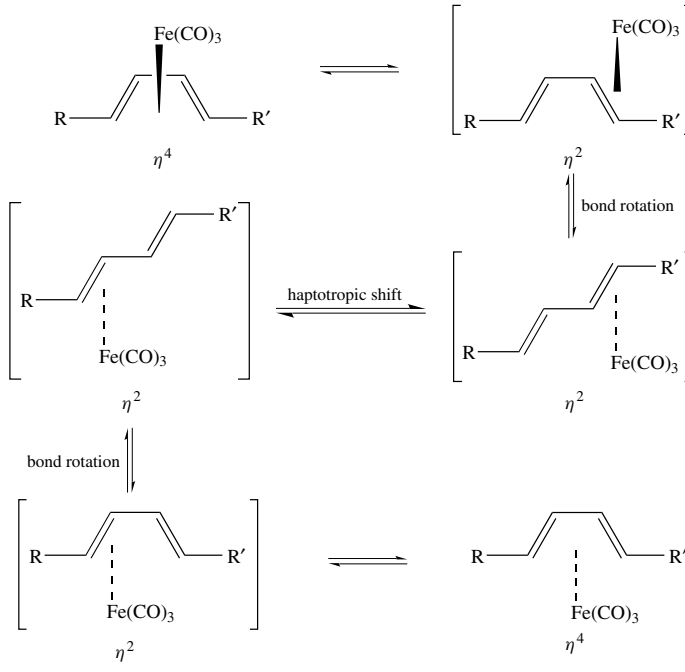
d. Isomerization reactions. Migration of iron about certain η^4-cyclic triene ligands occurs with relatively low energy barriers ($\Delta G^{\ddagger}$*ca* 15–23 kcal mol^{-1}, Section III.C.3). However, for (tropone)Fe(CO)$_3$ complexes iron migration occurs sufficiently slowly so that isomeric structures may be separated. The enantiomers of (tropone)Fe(CO)$_3$ may be separated by chiral chromatography[121]; the racemization of the resolved complex is observed to occur with an activation energy of 25.8 kcal mol^{-1}. Similar activation barriers have been reported for unsymmetrically substituted tropone complexes.

A significantly higher barrier (*ca* 32 kcal mol^{-1}) is observed for iron migration in linear polyene complexes, e.g. **118** → **118′** (Scheme 22). This isomerization is believed to proceed via $\eta^4 \rightarrow \eta^2$ coordination **(118 → 119)** followed by migration of the iron in the η^2 coordination mode **(119 → 119′)** (Scheme 22)[122]. While racemization of acyclic (diene)Fe(CO)$_3$ does not occur at ambient temperatures, it is observed at elevated temperatures. This process is also proposed to occur via η^2 coordination (Scheme 23); however the rate for racemization (*ca* 2.3–2.7 × 10^4 at 119 °C) is approximately half the rate of polyene migration[122].

(*E*,*Z*-Diene)Fe(CO)$_3$ complexes are configurationally stable under ambient conditions, however irreversible *Z* → *E* isomerization is observed at elevated temperatures. Since

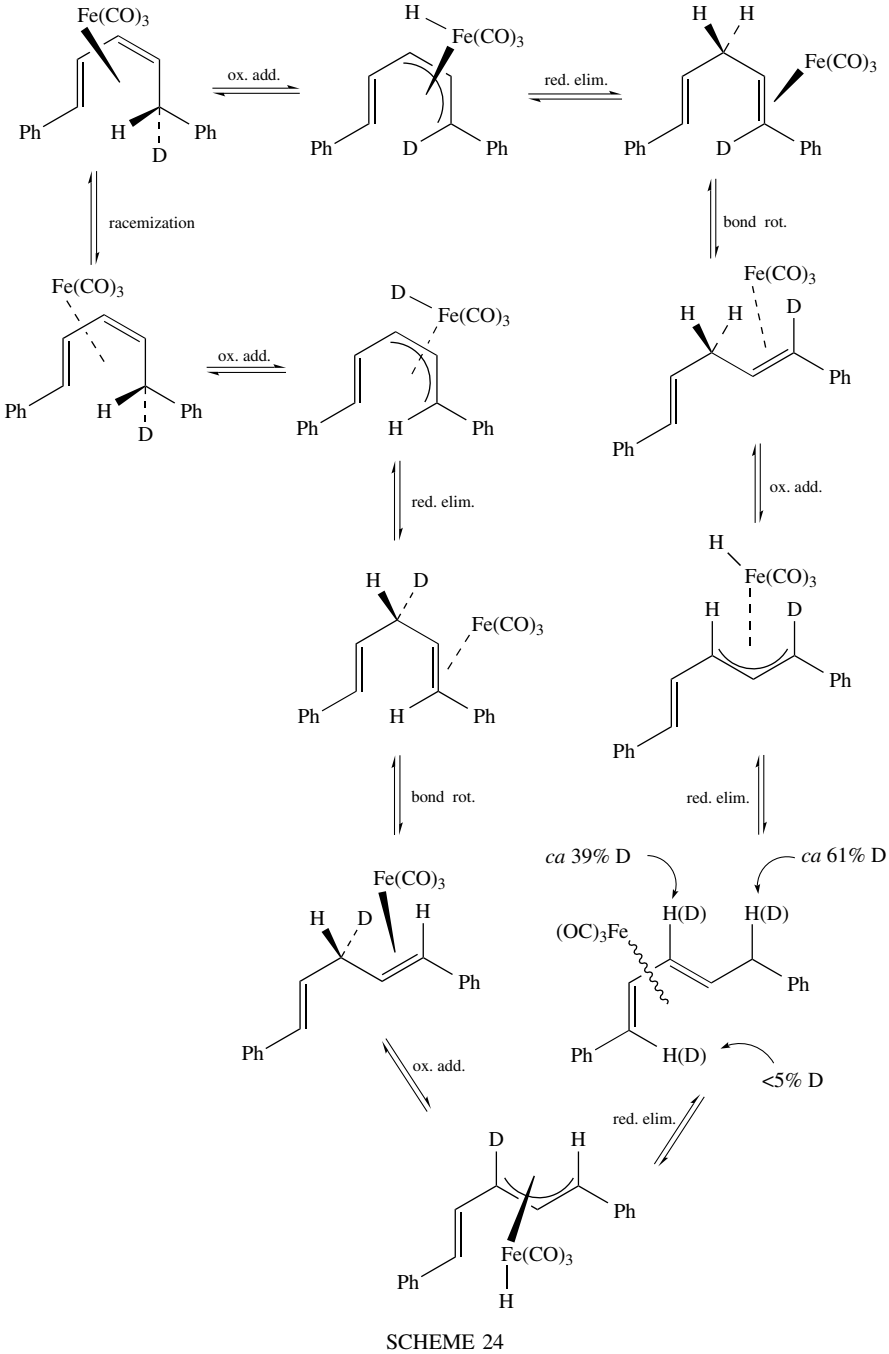


SCHEME 22



SCHEME 23

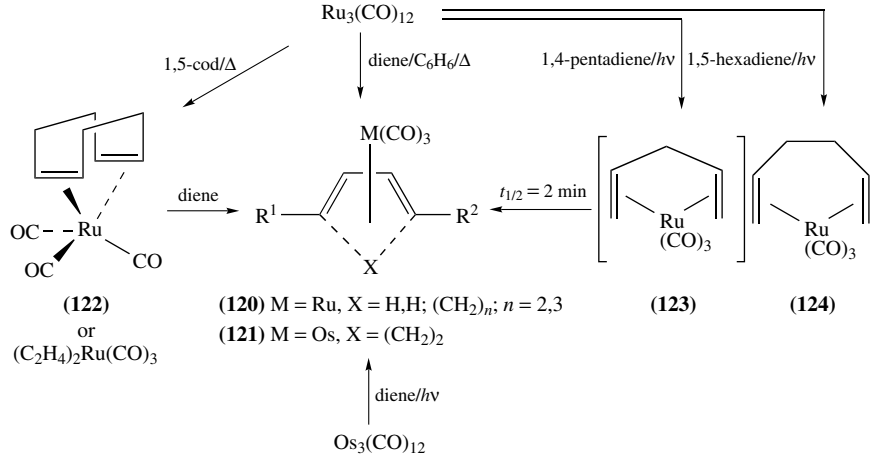
this isomerization occurs at one diene terminus and not at the other, an 'envelope flip' mechanism is excluded (Section III.C.2). In one study racemization was observed to occur at a rate slightly faster than $Z \rightarrow E$ isomerization. These results, along with deuterium labelling experiments, suggest a mechanism involving sequential oxidative insertion, reductive eliminations and bond rotations (Scheme 24)[123].


Fe(CO)3
ox. add.
red. elim.
racemization
bond rot.
Ph
H
D
ca 39% D
ca 61% D
H(D)
(OC)3Fe
<5% D

SCHEME 24

2. Neutral Ru and Os carbonyl complexes

The reaction of cyclic and acyclic 1,3-dienes with $Ru_3(CO)_{12}$ in refluxing benzene[124] or with $Os_3(CO)_{12}$ under photolytic conditions[26b,125] affords the corresponding (diene)Ru$(CO)_3$ complexes **(120)** or (diene)Os$(CO)_3$ complexes **(121)** respectively (Scheme 25). The thermal complexation of 1,5-cyclooctadiene with $Ru_3(CO)_{12}$ gives the non-conjugated (1,5-cod)Ru$(CO)_3$ complex **(122)** without rearrangement[126]. Heating **122** at reflux in benzene[26a,127], or reaction of $(C_2H_4)_2Ru(CO)_3$ at ambient temperature[128], in the presence of a 1,3-diene gives complexes **120**. Photolysis of $Ru_3(CO)_{12}$ with 1,4-pentadiene or 1,5-hexadiene affords the non-conjugated diene complexes **123** or **124**. Complex **123** is stable only at low temperatures, isomerizing rapidly ($t_{1/2} = 2$ min) at 25 °C to the 1,3-pentadiene complex[129], while complex **124** is stable for hours at 25 °C. These isomerizations are believed to occur via intermediates similar to those in Scheme 24. In contrast to the innumerable examples found in organoiron chemistry, there are only a limited number of examples for the preparation of substituted (cyclohexadiene)M$(CO)_3$ complexes from nucleophilic attack on (cyclohexadienyl)M$(CO)_3^+$ cations (M = Ru, Os)[125,130].

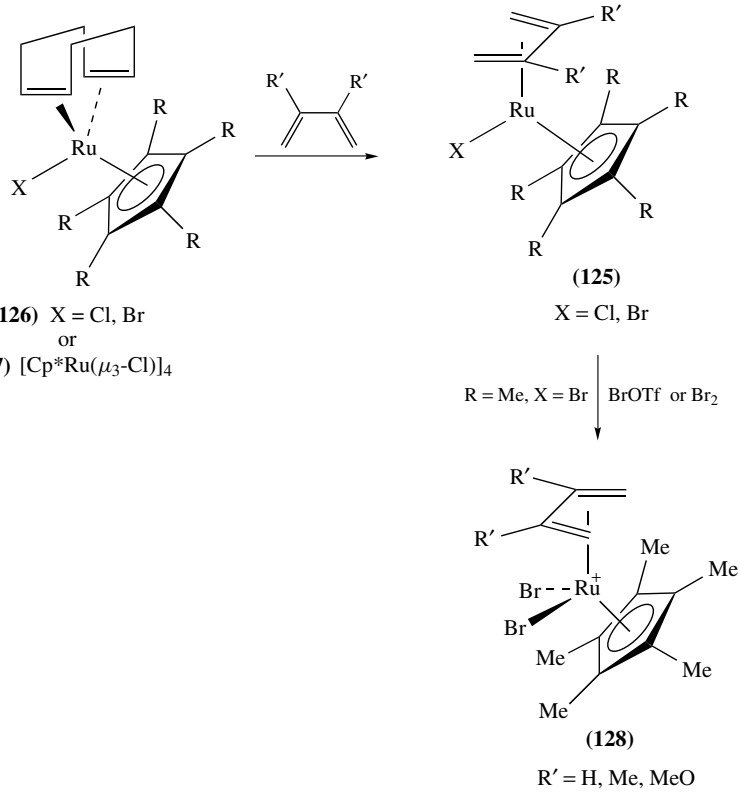


SCHEME 25

3. (Diene)RuCpX and related complexes

The preparation of cyclic or acyclic (diene)RuCp′X complexes **125** (Cp′ = C_5H_5 or C_5Me_5) via direct complexation has been reported (Scheme 26)[131]. This may be accomplished using either (1,5-cod)RuCpX **(126)** or the tetrameric species $[Cp^*Ru(\mu_3 - X)]_4$ **(127)**. Complexes **125** exhibit the s-*cis* η^4-diene coordination mode as evidenced by X-ray diffraction analysis. The ligands are oriented such that the open end of the diene is eclipsed with the Ru−X bond. Treatment of complexes **125** with $AgOSO_2CF_3$ or AgO_2CCF_3 effects replacement of the halide ligand X with either a triflate or trifluoroacetate ligand[27]. Oxidation of diene complexes **125** (R = Me), which lack alkyl substituents

at the terminal carbons, with Br_2 or bromonium triflate affords (diene)RuCp*Br_2^+ cations **128** (Scheme 26)[9b,27,132]. In contrast to complexes **125**, X-ray diffraction analyses of cations **128** provide evidence for coordination via the σ^2, π bonding mode. In addition, crystal structure data and NOE evidence indicate that the ligands in cations **128** are oriented such that the open end of the diene is eclipsed with the Cp* ligand.



(126) X = Cl, Br
or
(127) $[Cp^*Ru(\mu_3\text{-}Cl)]_4$

(125)
X = Cl, Br

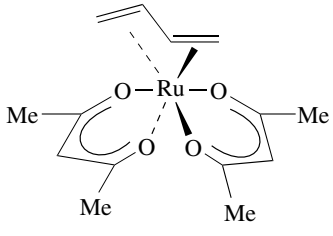
R = Me, X = Br | BrOTf or Br_2

(128)
R′ = H, Me, MeO

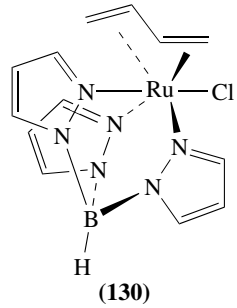
SCHEME 26

4. (s-trans Diene)Ru(II) complexes

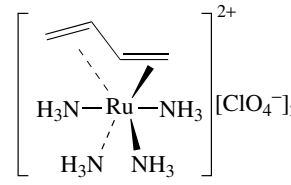
The preparation and characterization of several octahedral Ru(II) complexes containing s-*trans* coordinated dienes have been reported. The Zn mediated reduction of $Ru(acac)_3$ in the presence of a 1,3-diene affords (diene)$Ru(acac)_2$ complexes as a mixture of diastereomers (eg. **129**)[13a,b]. Reaction of $[(trispyrazolylborate)RuCl]_x$ or $[(NH_3)_4Ru(acetone)_2]_2^+$ $[ClO_4^-]_2$ with acyclic dienes yields complex **130** or cation **131** respectively[13c,14]. Coordination of the ligand as an s-*trans* diene was indicated either by crystal structure or by determining C_{2v} symmetry on the basis of NMR spectroscopy.



(129)



(130)

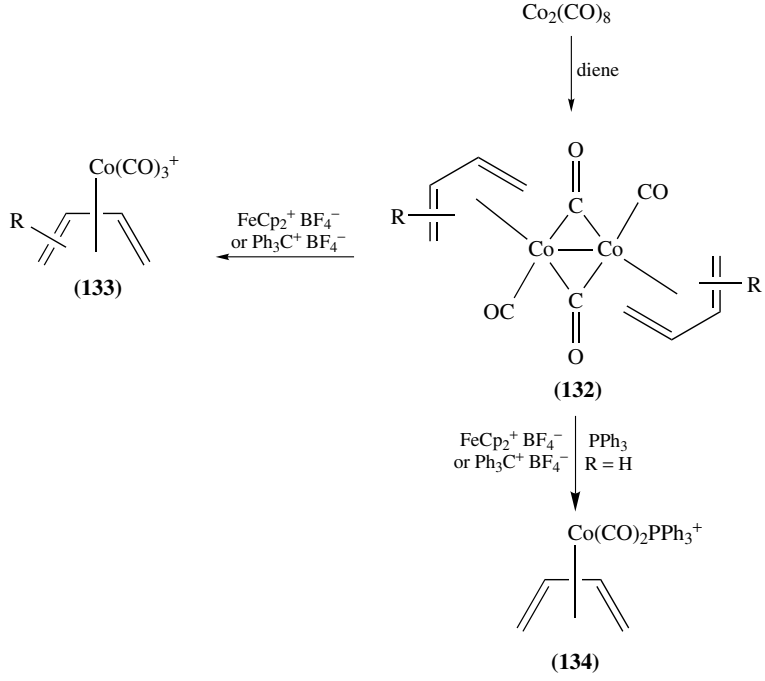


(131)

F. Complexes of Co, Rh and Ir

1. Cationic Co-carbonyl and phosphine complexes

The thermal reaction of 1,3-dienes with $Co_2(CO)_8$ gives the corresponding bimetallic dimers $[(diene)Co(CO)_2]_2$ **132** as orange red solids in good yields (Scheme 27)[28,133]. Oxidation of the dimeric complexes **132** with ferricinium tetrafluoroborate or triphenylcarbenium tetrafluoroborate gives the monomeric $(diene)Co(CO)_3^+$ cations **133** in modest



(133)

(132)

(134)

SCHEME 27

yields (20–45%)[28,134]. While this oxidation is limited by the amount of carbon monoxide present in **132**, performing the oxidation under CO atmosphere does not improve the yield. Oxidation of **132** in the presence of PPh_3 give the corresponding (diene)$Co(CO)_2PPh_3^+$ cations **134**. Reaction of cyclohexadiene with $HCo(CO)_4$ followed by hydride abstraction by trityl cation affords the (cyclohexadiene)$Co(CO)_3^+$ cation[134a]. The reduction of $Co[ClO_4]_2$ in the presence of excess phosphine and butadiene followed by anion metathesis gave (butadiene)$Co(PR_3)_3^+ Ph_4B^-$ salts as crystalline solids[135].

2. Neutral (diene)MCp complexes (M = Co, Rh, Ir)

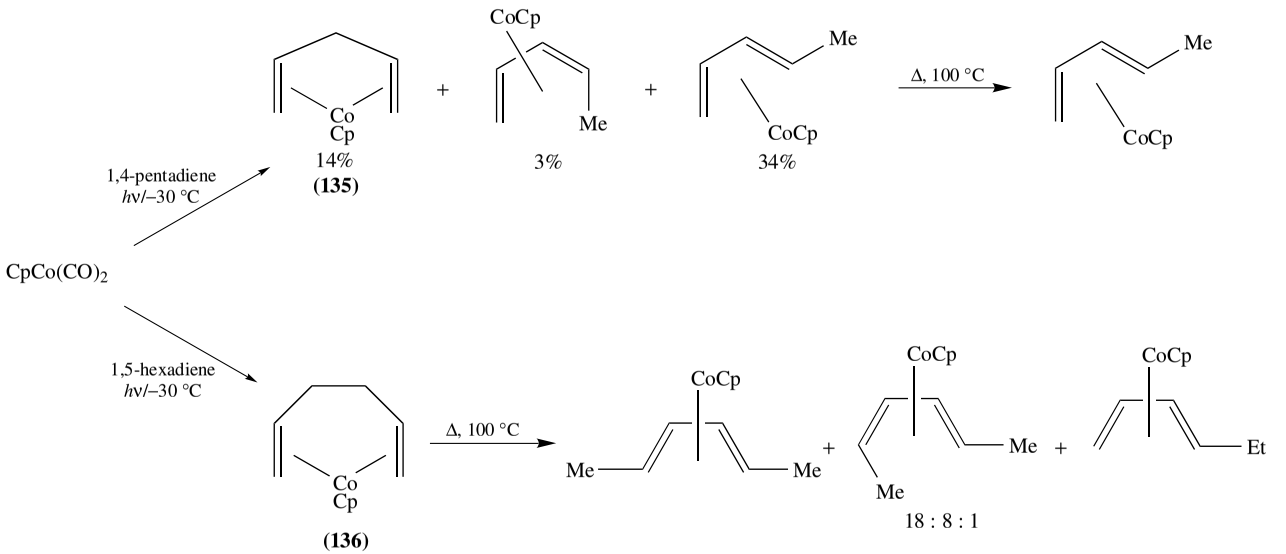
Cyclopentadiene(diene)cobalt complexes, the largest catagory of diene complexes of Co, may be prepared by direct complexation, by preparation of the dienes within the coordination sphere of Co and by nucleophilic addition to (η^5-dienyl)CoCp cations. In comparison to (diene)CoCp complexes, there are considerably fewer examples of (diene)RhCp and (diene)IrCp complexes known.

a. Preparation by direct complexation to Co. Direct complexation may be accomplished (1) by thermal or photochemical reaction of $CpCo(CO)_2$, $CpCo(PPh_3)_2$, $CpCo(C_2H_4)_2$ in the presence of the diene ligand[136], (2) by reduction of $[CpCoI_2]_2$ in the presence of a diene ligand[137], or (3) by reduction of $Co(acac)_3$ in the presence of a diene and monomeric cyclopentadiene[138]. Complexation of 1,4-pentadiene with $CpCo(CO)_2$ gave a mixture of 1,4-diene **(135)** and 1,3-diene complexes while use of 1,5-hexadiene gave only the non-conjugated complex **(136)** (Scheme 28)[136c]. The non-conjugated diene complexes may be isomerized into conjugated diene complexes under thermal conditions.

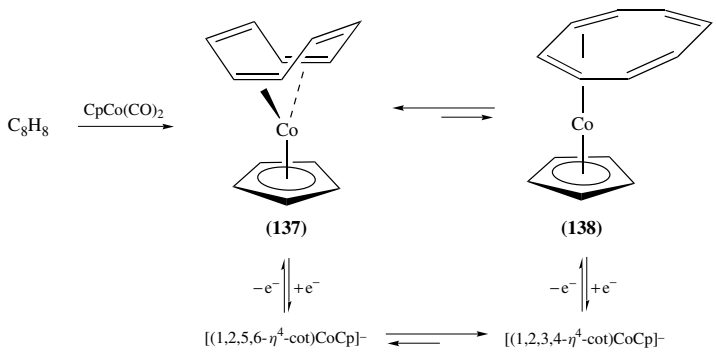
The complex (C_8H_8)CoCp, prepared from $CpCo(CO)_2$ and C_8H_8, was originally assigned the (1,2,5,6-η^4) structure **137** (Scheme 29)[139]. Further examination by Moraczewski and Geiger revealed that a minor amount of the (1,2,3,4-η^4) complex **138** existed in equilibrium with thermodynamically more stable **137**[139b]. The NMR spectrum of **138** consists of only two signals, consistent with a 'ring-whizzing' fluxionality. Electrochemical reduction of **137** gives the (1,2,5,6-η^4) anion, which isomerizes to the more stable (1,2,3,4-η^4) anion.

Migration of the metal along the polyene chain in (1,1-d_2-1,3,5-hexatriene)CoCp occurs with an activation energy of 25.6 kcal mol^{-1} (equation 15)[136b]. This barrier is *ca* 5–8 kcal mol^{-1} lower than that for metal migration in (triene)- or (tetraene)$Fe(CO)_3$ complexes (see Section IV.E.1.d).

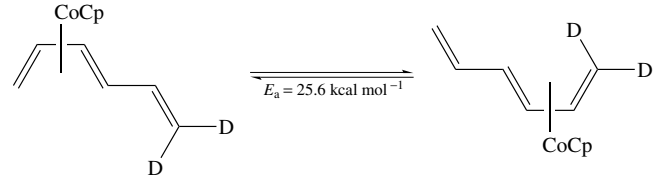
b. Preparation of dienes within the coordination sphere of Co. The $CpCo(CO)_2$ mediated [2 + 2 + 2] cyclization of an alkene with two alkynes leading to the formation of (hexadiene)CoCp complexes has been reviewed[140]. The reaction is considerably more efficient if two of the components are linked via an alkyl, aryl or heteroatom containing chain. The stereochemistry of substituents on the sp^3 hybridized carbons in the cyclohexadiene ring mirrors that originally present in the alkene component. As the product (cyclohexadiene)CoCp complexes may be decomposed under oxidation conditions to render the 'free' ligand, this cyclization has been utilized in the synthesis, or formal synthesis, of a variety of natural products (equations 16–18)[141].


CpCo(CO)2
1,4-pentadiene
hν/–30 °C
1,5-hexadiene
hν/–30 °C
Co
Cp
14%
(135)
CoCp
Me
3%
Me
CoCp
34%
Δ, 100 °C
Me
CoCp
Co
Cp
(136)
Δ, 100 °C
CoCp
Me
Me
CoCp
Me
Me
18 : 8 : 1
CoCp
Et

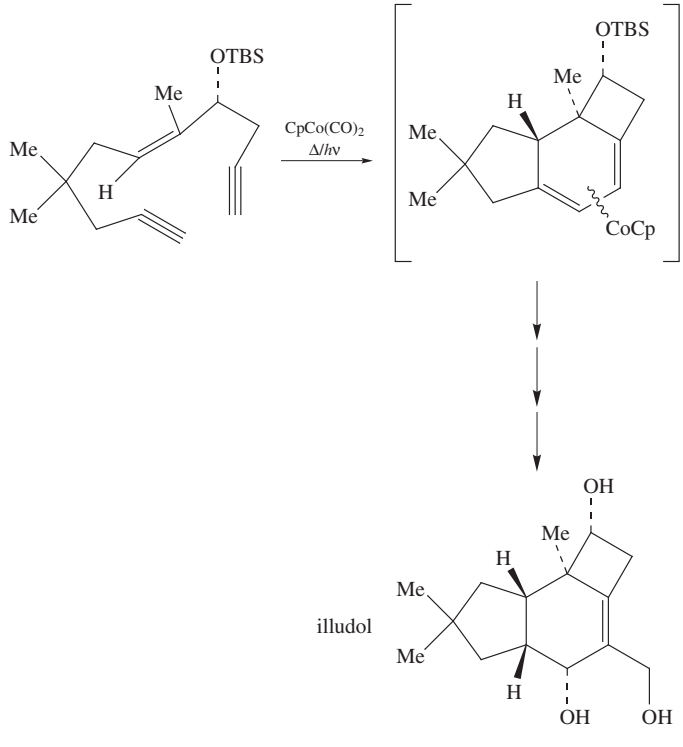
SCHEME 28



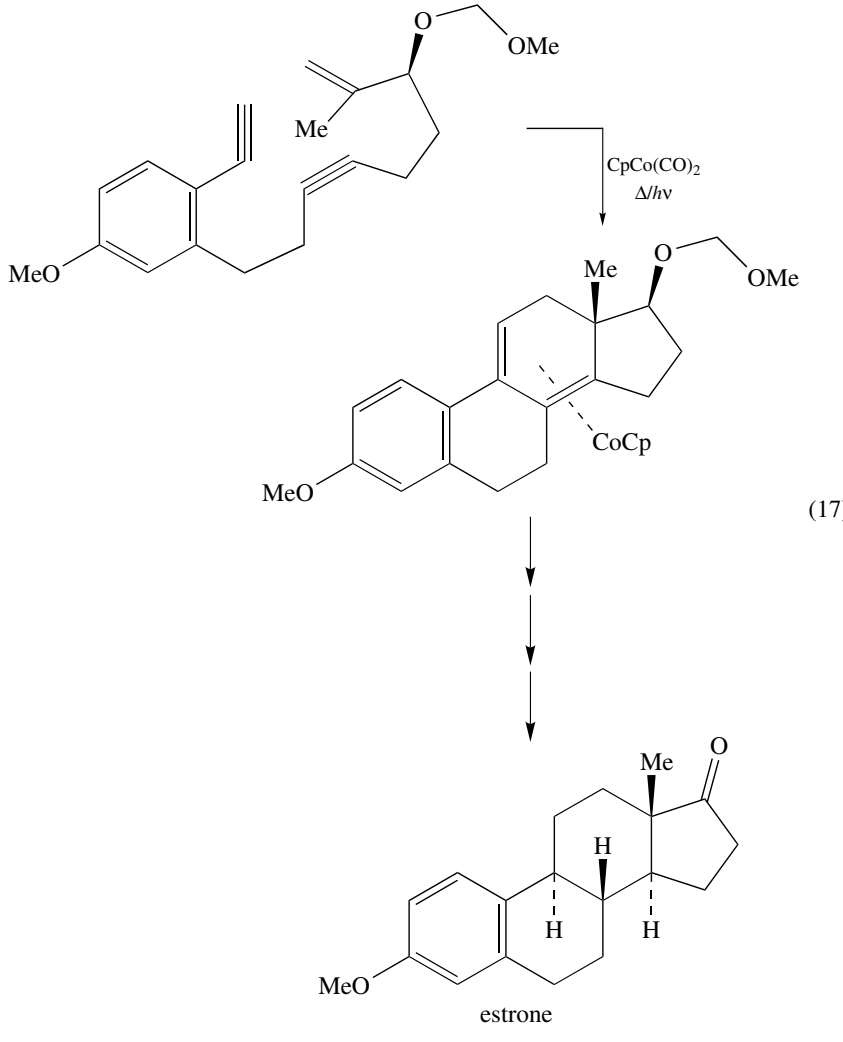
SCHEME 29



(15)



(16)



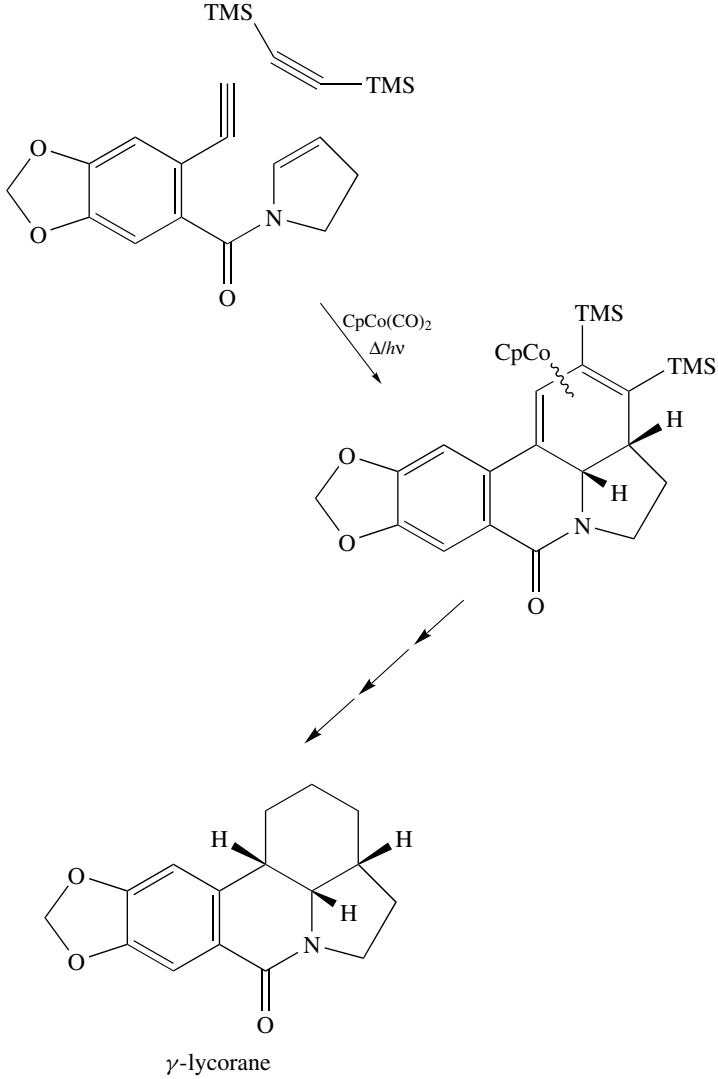
(17)

estrone

Low-temperature photochemical cyclization of alkynes bearing a bulky substituent, mediated by $CpCo(CO)_2$, proceeds with CO insertion to give cyclopentadienone complexes. Higher reaction temperatures lead to cyclotrimerization. The intramolecular variant of this reaction gives the bicyclic cyclopentadienones **139** and **139′** (equation 19)[142]. Cyclization of unsymmetrically substituted diynes with the chiral $R^*CpCo(CO)_2$ (R^* = 8-phenylmenthyl) leads to the formation of a mixture of diastereomers; modest diastereoselectivity was found.

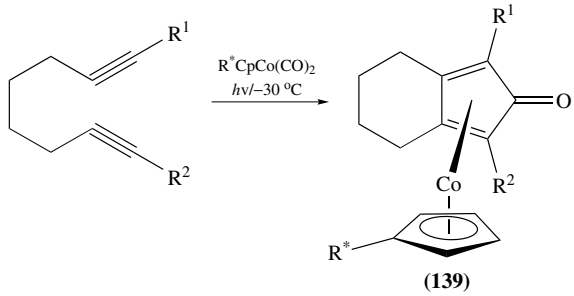
The reaction of $Cp(alkyne)CoPPh_3$ complexes **140** with 1 equivalent of ethyl diazoacetate in the presence of PPh_3 yields the cobaltacyclobutene **141**, which upon further reaction with the diazoacetate affords (diene)CoCp complexes **142** as a mixture of *E*,*E*-

and *E*,*Z*- isomers (Scheme 30)[143]. Treatment of **140** with excess of ethyl diazoacetate or diazoketones gives directly the diene complexes. At elevated temperatures, the complexes *E*,*Z*-**142a** and *E*,*Z*-**142b** interconvert with each other but not with *E*,*Z*-**142c**. This interconversion is proposed to occur via an 'envelope flip' mechanism (Section III.C.2). The photochemically induced isomerization of dideuteriated (diene)CoCp complex **143a** to **143b** provided further evidence for an 'envelope flip' mechanism (equation 20)[144]. The investigators noted that *syn–anti* isomerization occurs synchronously with diastereoisomerization.



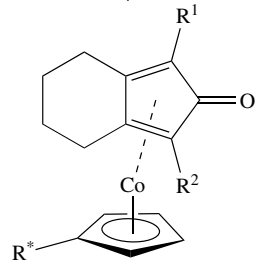
(18)

γ-lycorane



(139)

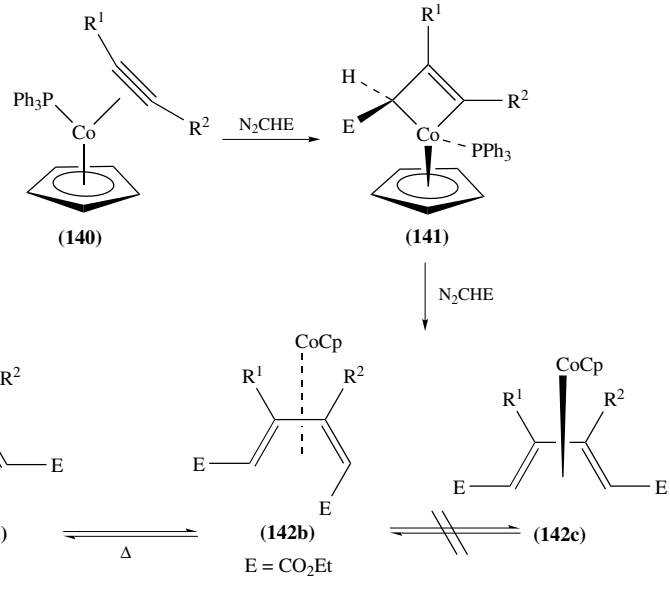
+



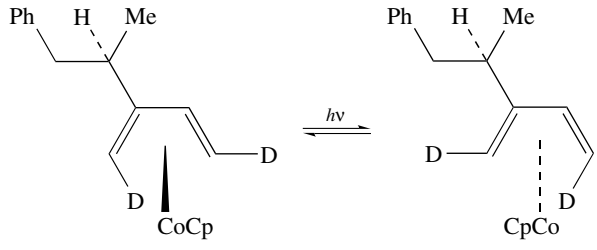
(139')

(19)

R* = 8-phenylmenthyl

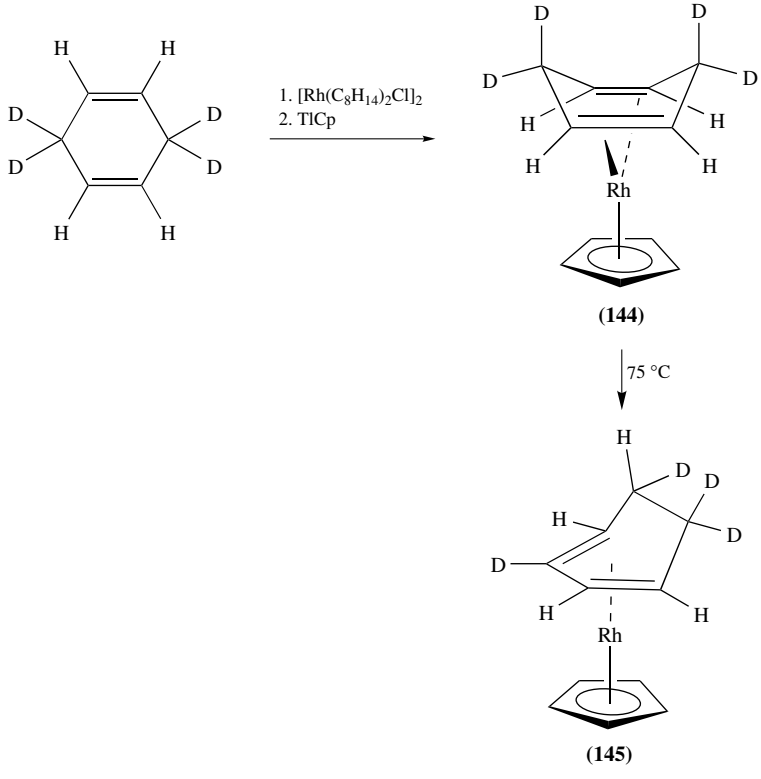


SCHEME 30



(143a) (143b) (20)

c. Preparation by direct complexation to Rh or Ir. Ligand substitution of ethylene in $[(C_2H_4)_2RhCl]_2$ or cyclooctene in $[(C_8H_{14})_2RhCl]_2$ with a diene or polyene gives the corresponding $[(diene)RhCl]_2$ dimer. Treatment of the dimer with cyclopentadienyl thallium gives the monomeric (diene)RhCp complexes[29]. Coordination of non-conjugated dienes (e.g. 1,4-cyclohexadiene) gives the non-conjugated diene complex (**144**, Scheme 31)[145]. Isomerization of **144** to the thermodynamically more stable conjugated diene complex **145** occurs at elevated temperatures ($\Delta G^{\ddagger} = 26$ kcal mol^{-1}). Deuterium labelling indicates a 1,3-hydride shift. Isomerization from a non-conjugated diene to a conjugated diene

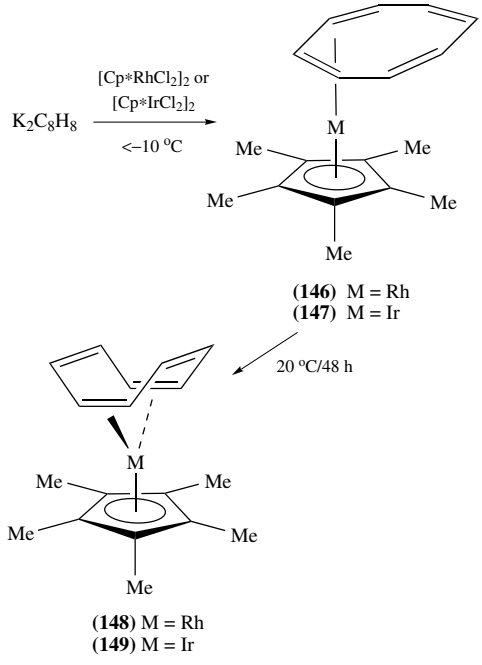


(144) (145)

SCHEME 31

in acyclic (diene)RhCp complexes occurs with a greater barrier ($\Delta G^{\ddagger} = 30$ kcal mol^{-1}) than for cyclic (diene)RhCp complexes. The energy for *anti* → *syn* isomerization is greater still ($\Delta G^{\ddagger} = 33$ kcal mol^{-1}). A mechanism similar to that for the isomerization of (diene)Fe(CO)$_3$ complexes (Scheme 24, Section IV.E.1.d) which involves the intermediacy of a π-allyl–metal–hydride intermediate is proposed.

Reaction of the cyclooctatetraene dianion with [Cp*RhCl$_2$]$_2$ or [Cp*IrCl$_2$]$_2$ at low temperature (< −10 °C) gave the (1,2,3,4-η^4) complexes **146** or **147**, respectively (Scheme 32)[146]. The NMR spectra of both **146** and **147** consists of only two signals even at −50 °C, indicative of fluxional 'ring-whizzing' with a low barrier. The initially obtained (1,2,3,4-η^4) complexes isomerize to (1,2,5,6-η^4) complexes **148** and **149**, respectively, after 48 h at 20 °C.



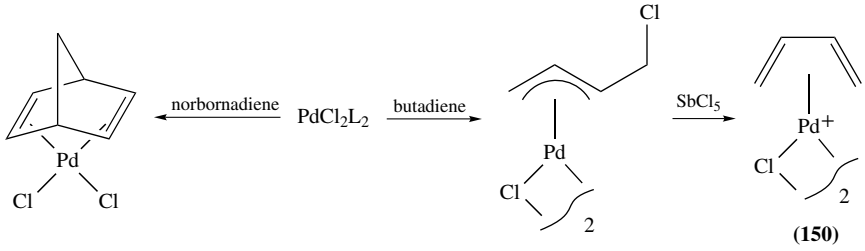
SCHEME 32

d. Preparation by nucleophilic addition to η^5-dienyl cations. There are limited examples of the addition of hydride, carbon or heteroatom nucleophiles to Cp$_2$M$^+$ cations or (cyclohexadienyl)MCp$^+$ cations to produce (cyclopentadiene)MCp or (cyclohexadiene) MCp products (M = Co, Rh)[136a,147]. While *endo* attack was originally proposed, crystal structure analysis eventually validated attack from the face of the ligand opposite to the metal.

G. Complexes of Ni, Pd and Pt

Non-conjugated dienes constrained within a rigid polycyclic system (e.g. norbornadiene) react with Na$_2$PdCl$_4$ or PdCl$_2$(PhCN)$_2$ to give the corresponding (diene)PdCl$_2$

complexes[148], while acyclic conjugated dienes undergo chloropalladation to form (π-allyl)PdCl dimers (Scheme 33)[149]. Ionization of (1-chloromethylallyl)PdCl with $SbCl_5$ generates the cationic (diene)Pd complex **150**. The reaction of 1,3-cyclooctadiene with $PdCl_2(PhCN)_2$ produces the non-conjugated (1,5-cyclooctadiene)$PdCl_2$ complex, demonstrating the greater stability of this coordination mode[150].



SCHEME 33

V. REACTIONS OF CONJUGATED DIENE COMPLEXES

(Diene)- and (polyene)metal complexes undergo a variety of reactions, including decomplexation and insertion reactions, and reactions with electrophiles or nucleophiles. In addition, the transition metal may serve as a protecting and/or stereodirecting group for a complexed diene. In order to compare similarities and differences in reactivity as a function of the coordinated metal, this section will be organized by reaction type rather than by metal group.

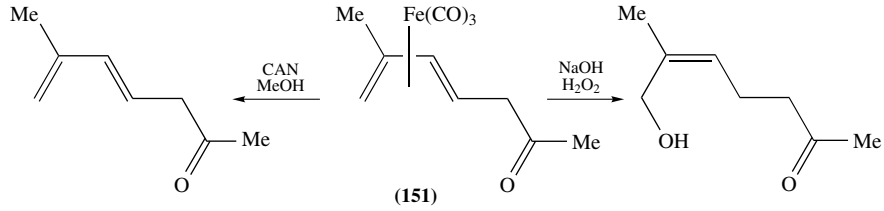
A. Decomplexation

1. Oxidative decomplexation

Liberation of a complexed diene ligand may be accomplished under oxidizing conditions. (Diene)$ZrCp_2$ complexes[151], (diene)TiCp*X complexes[69b], and (diene)$Mn(CO)_3^-$ anions[23,91] are all relatively sensitive and undergo oxidative decomplexation upon exposure to air to afford the free ligand. The majority of other diene–metal complexes are somewhat stable in air. In the case of the neutral complexes (diene)$Mn(CO)_2NO$[93f,g], (diene)$Fe(CO)_2L$ (L = CO, PR_3)[116–118], and (diene)CoCp[141b,142a], or cationic (diene)Mo $(CO)_2Cp^+$ complexes[81b,88b], stronger oxidizing agents such as $FeCl_3$, $CuCl_2$, $(NH_4)_2$ $Ce(NO_2)_6$ [CAN], or Me_3NO are necessary for the liberation of the diene ligand. While oxidation of (6-oxo-1,3-diene)$Fe(CO)_3$ complexes **(151)** with CAN gives the free ligand, oxidation with hydrogen peroxide gives allylic alcohols (Scheme 34)[152]. Oxidation of (cyclohexadiene)$Fe(CO)_3$ complexes **152**, prepared from the addition of aryl amines to (cyclohexadienyl)$Fe(CO)_3^+$ cations, with very active MnO_2 or I_2 proceeds with cyclization, decomplexation and oxidative aromatization to generate carbazole products (Scheme 35)[116d,153]. An extensive series of natural products has been prepared by this general method[116d].

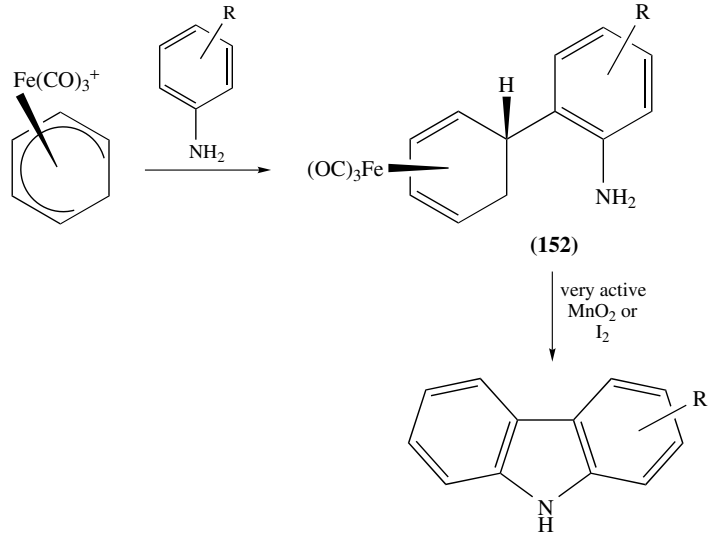
2. Reductive decomplexation

Exposure of (2,3-dimethyl-1,3-butadiene)HfCp*Cl **(36d)** to hydrogen (10 atm/$PhCH_3$/ 70 °C) gave a mixture of 2,3-dimethyl-2-butene and 2,3-dimethylbutane along with the



(151)

SCHEME 34



(152)

SCHEME 35

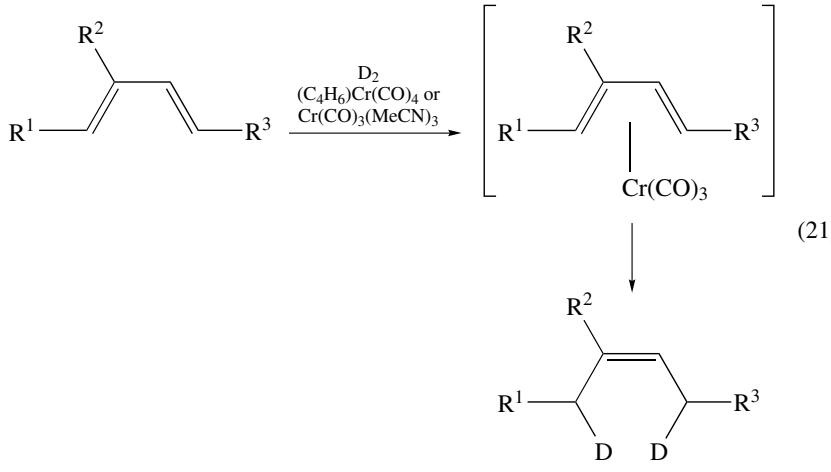
$[Cp^*Hf(H_2)Cl]_4$ tetramer[154]. Photochemical reduction of (diene)iron complexes in acetic acid gives the corresponding alkene[155]; this methodology has been used in the synthesis of the novel terpene lasiol[155b]. The regioselectivity for this reduction is good only if the diene is substituted by an electron withdrawing group.

(Diene)$Cr(CO)_4$ complexes serve as catalysts for the addition of hydrogen to 1,3-dienes to give 2*Z*-alkenes (equation 21)[78a]. Alternatively, $Cr(CO)_3(MeCN)_3$ may also be used as a catalyst for this reduction[156]. Use of deuterium instead of hydrogen affords the 1,4-dideuterio-2*Z*-alkene. The rate of reduction for uncomplexed acyclic dienes decreases in the order $E,E->E,Z->Z,Z$-dienes. This order parallels the ease of formation of the corresponding (diene)$Cr(CO)_4$ complexes. These results implicate the formation of a 16 valence electron [VE] (diene)$Cr(CO)_3$ intermediate as part of the catalytic cycle.

3. Carbonylative decomposition

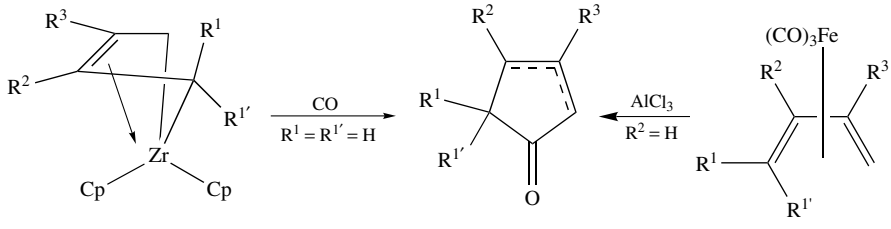
Direct displacement of a diene ligand by CO is rare and the only report of this involves treatment of (η^5-indenyl)(diene)$Mo(CO)_2^+$ cations with carbon monoxide (10 atm/50 °C) to generate the 'free' diene ligand[81b]. In this case, ligand substitution may be due to

a decrease in the metal-to-ligand backbonding due to the cationic charge. In addition, it is known that 18-VE (η^5-indenyl)metal complexes undergo ligand substitution via an associative mechanism due to $\eta^5 \rightarrow \eta^5$ ligand 'slippage'.



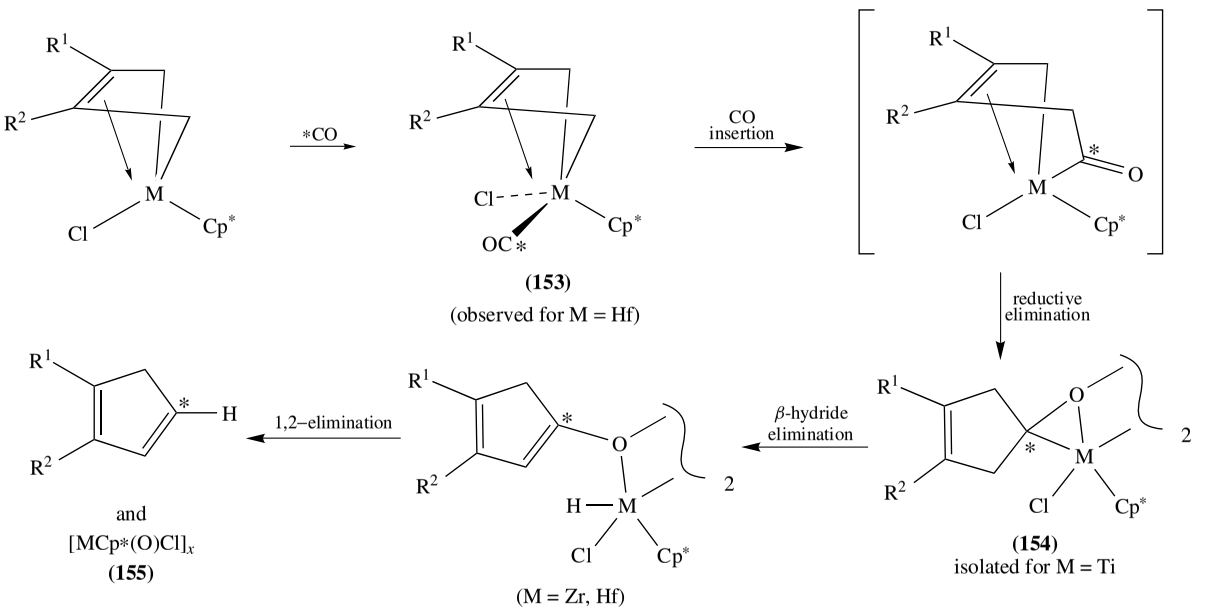
(21)

Carbonylation of (diene)$ZrCp_2$ complexes gives cyclopentenones (Scheme 36)[51]. Since the relative rates of this carbonylation parallel the relative rates for 'envelope flip' of these σ^2, π complexes, it might be speculated that initial coordination of CO to the σ^2-metallacyclopent-3-ene intermediate **12** is involved. (Diene)$Fe(CO)_3$ complexes undergo $AlCl_3$ mediated cyclocarbonylation to afford 2-cyclopentenones, however, the yields are acceptable only for 1,1,3-trisubstituted diene complexes (Scheme 36)[157].



SCHEME 36

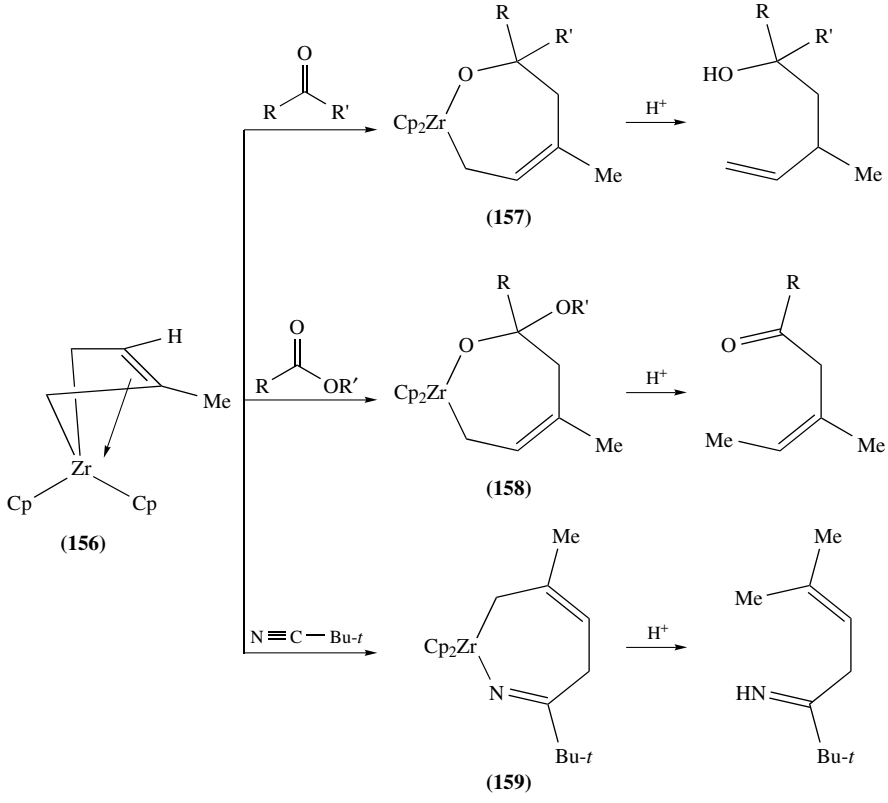
In contrast, exposure of 14-VE (diene)MCp^*Cl complexes (M = Zr, Hf) to CO (1 atm) results in the formation of cyclopentadienes[70]. The mechanism proposed for this transformation was elucidated with a carbon labeled CO (*CO) as requiring an initial coordination of CO to generate a (diene)$MCp^*(CO)Cl$ complex **153** (Scheme 37). For the hafnium complex, the intermediate **153** (M = Hf) was observed by infrared spectroscopy. Insertion of CO into the σ^2, π diene generates a metallacyclohexenone, which undergoes reductive elimination to generate the dimeric metallaoxirane species **154**. β-Hydride elimination from **154** (M = Zr, Hf) followed by 1,2-elimination produces substituted cyclopentadienes and the polymeric metal-oxide **155**. Treatment of (diene)$TiCp^*Cl$ with CO leads to isolation of the metallaoxirane complex **154** (M = Ti).


R1
R2
M
Cl
Cp*
*CO
Cl
M
Cp*
OC*
(153)
(observed for M = Hf)
CO
insertion
R1
R2
*
O
M
Cl
Cp*
reductive
elimination
R1
R2
O
*
M
Cl
Cp*
2
(154)
isolated for M = Ti
β-hydride
elimination
R1
R2
*
O
H
M
Cl
Cp*
2
(M = Zr, Hf)
1,2–elimination
R1
R2
*
H
and
[MCp*(O)Cl]x
(155)

SCHEME 37

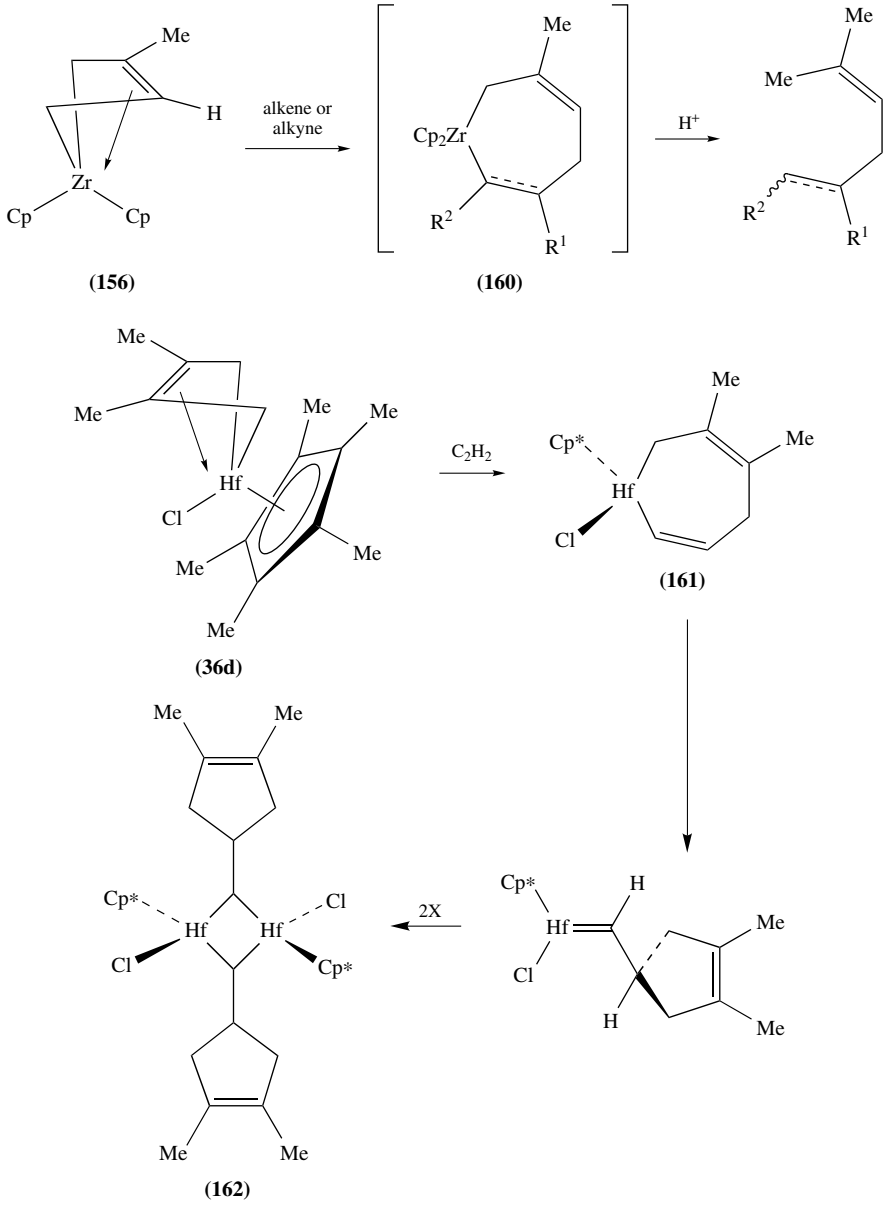
B. Insertion Reactions

Reaction of (isoprene)$ZrCp_2$ **(156)** with ketones[53,158,159], esters[160] and nitriles[159] gives addition products **157**, **158** and **159** respectively (Scheme 38). Protonolysis of **157**, **158** and **159** affords alcohols, ketones, and imines. The addition of ketones to (s-*trans*-C_4H_6)$ZrCp_2$ (s-*trans*-**31**) occurs more rapidly than to (s-*cis*-C_4H_6)$ZrCp_2$ (s-*cis*-**31**), and this evidence implicates a mechanism in which addition of the unsaturated functionality occurs via intermediacy of the η^2-bonded diene complex **32**. Similar insertion reactions have been reported for the (s-*trans*-C_4H_6)$TaCp_2^+$ cation (**38**)[76].



SCHEME 38

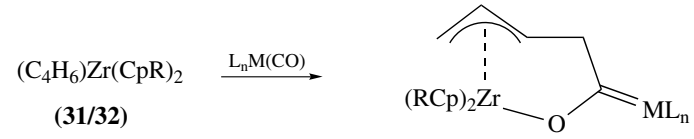
Insertion of alkenes or alkynes to complex **156** generates the metallacycloheptene or metallacycloheptadiene species **160** (Scheme 39)[161]. Protonolysis gives the corresponding hydrocarbons in good yields. In contrast, insertion of acetylene to (2,3-dimethylbutadiene) HfCp*Cl **(36d)** generates the metallacycloheptadiene intermediate **161** which rearranges to the bridging complex **(162)**[162]. The structure of **162** was assigned on the basis of X-ray diffraction analysis.



SCHEME 39

Reaction of (butadiene)$ZrCp_2$ **(31/32)**, and substituted Cp variants, with a wide range of metal–carbonyl complexes, generates the chelated metal–carbene complexes **163** (equation 22)[163]. The crystal structure of a number of these complexes has been determined

by X-ray diffraction analysis.



(31/32) (22)

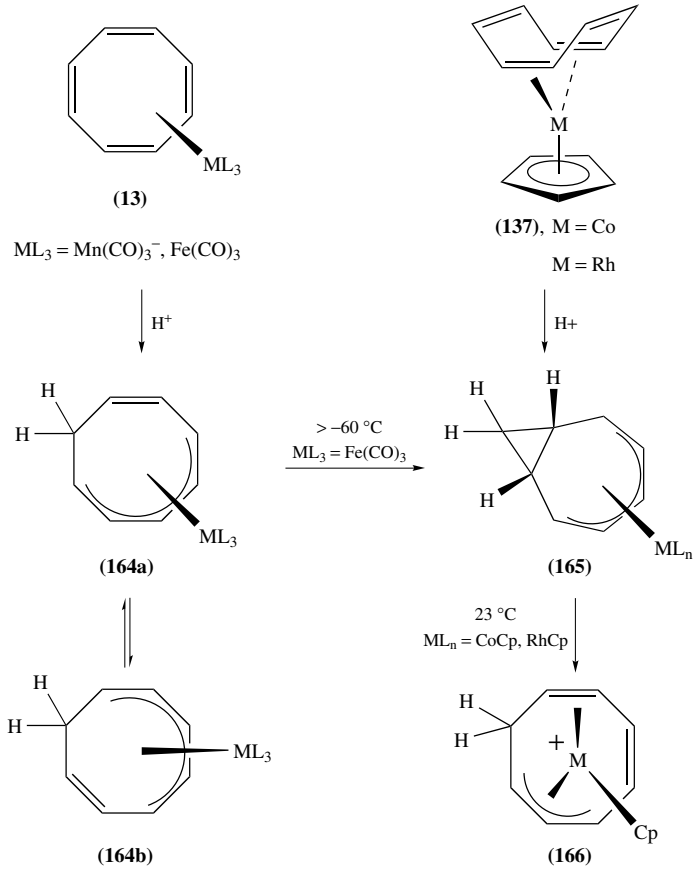
(163) ML_n = $V(CO)_3Cp$, $Cr(CO)_5$, $Mo(CO)_5$, $W(CO)_5$, $Fe(CO)_4$, $Fe(CO)_3PPh_3$, Co(CO)Cp, Rh(CO)Cp, $Pt(CO)(C_6F_5)_2$

C. Reactions with Electrophiles

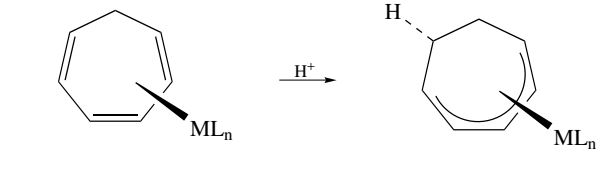
1. Protonation

Brookhart and others have studied the protonation of a variety of (polyene)- and (diene)metal complexes. Protonation of the $(\eta^4 - C_8H_8)Mn(CO)_3^-$ anion [**13**, ML_3 = $Mn(CO)_3^-$], leads to the (η^5-cyclooctatrienyl)$Mn(CO)_3$ complex [**164**, $ML_3 = Mn(CO)_3$, Scheme 40)[56]. This complex exhibits metal migration fluxionality with the uncomplexed olefin within the cyclooctatrienyl ring (eg. **164a** → **164b**). Low-temperature line-shape analysis indicated a free energy of activation for this process of 12.6 kcal mol^{-1}. Upon heating to 65 °C, partial isomerization of **164** to **165** [$ML_n = Mn(CO)_3$) is observed, however, the cyclooctatrienyl complex is still the major species present. Reaction of $(C_8H_8)Fe(CO)_3$ with acid at low temperature (−120 °C, FSO_3H/SO_2F_2) initially generates the (η^5-cyclooctatrienyl)$Fe(CO)_3$ cation [**164**, $ML_3 = Fe(CO)_3^+$] which may be spectroscopically observed[164]. Above −60 °C, cation **164** [$ML_3 = Fe(CO)_3^+$] *irreversibly* rearranges to the bicyclo[5.1.0]octadienyl cation **165** [$ML_n = Fe(CO)_3^+$] which was isolated as a salt. In comparison, protonation of (C_8H_8)CoCp **(137)** leads to the initial formation of a 1 : 1 mixture of the bicyclo[5.1.0]octadienyl cation **165** (ML_n = $CoCp^+$) and the (π-allyl-η^2-olefin) cation (**166**, M = Co)[165]. Upon standing at 23 °C for 48 h, the bicyclo[5.1.0]octadienyl cation completely converts into **166**. Protonation of (C_8H_8)RhCp initially gives only the cation **165** ($ML_n = RhCp^+$). However, as is the case for the Co complex, this eventually isomerizes completely to **166** (M = Rh) (Scheme 40). In contrast, protonation of anionic or neutral (polyene)ML_n complexes, other than those of C_8H_8, gives the corresponding (η^5-dienyl)ML_n complexes or cations (equation 23–25)[50,166,167].

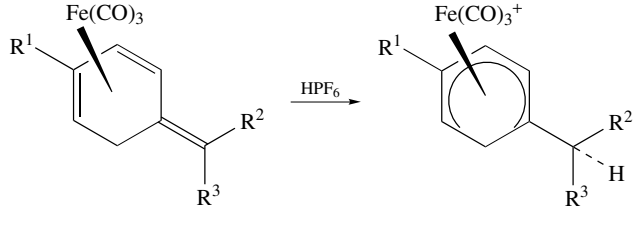
Acid mediated elimination of cyclic (dienyl ether)- and (dienol)$Fe(CO)_2L$ complexes leads to the formation of (cyclodienyl)$Fe(CO)_2L$ cations (equation 26 and 27)[105f,168]. Protonation of (pentadienol)- or (pentadienyl ether)$Fe(CO)_3$ complexes generates the corresponding (pentadienyl)$Fe(CO)_3^+$ cations **167** (Scheme 41)[118]. Lillya and coworkers have demonstrated that ionization of the hydroxyl substituent occurs with anchimeric assistance from iron, and that isomerization of the initially generated transoid pentadienyl cation **168** to the more stable cisoid cation occurs with retention of configuration about the C1−C2 bond[169]. The *in situ* generated transoid pentadienyl cations may also undergo reaction with heteroatom, hydride or carbon nucleophiles to afford substituted (*E*,*E*-diene)$Fe(CO)_3$ products **(169)**[170]. Acyclic (pentadienyl)MCp^+ cations (M = Rh, Ir) may be prepared by acidic dehydration of (dienol)MCp complexes[171].



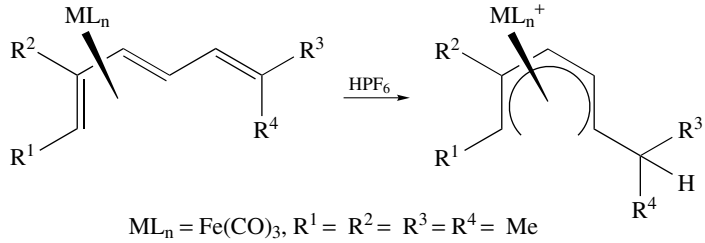
SCHEME 40



(23)



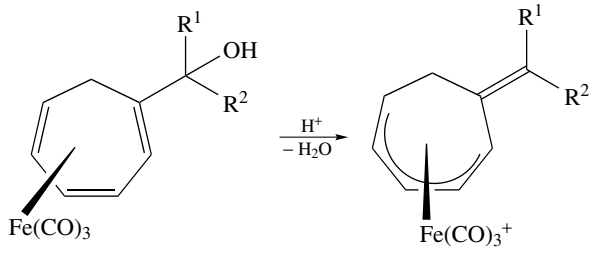
(24)



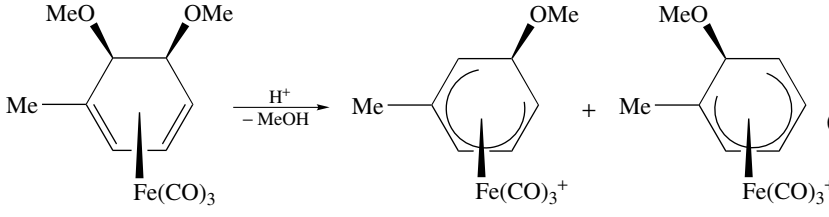
(25)

$ML_n = Fe(CO)_3$, $R^1 = R^2 = R^3 = R^4 = Me$

$ML_n = RhCp$, $R^1 = Ph$, $R^2 = R^4 = H$, $R^3 = COPh$



(26)



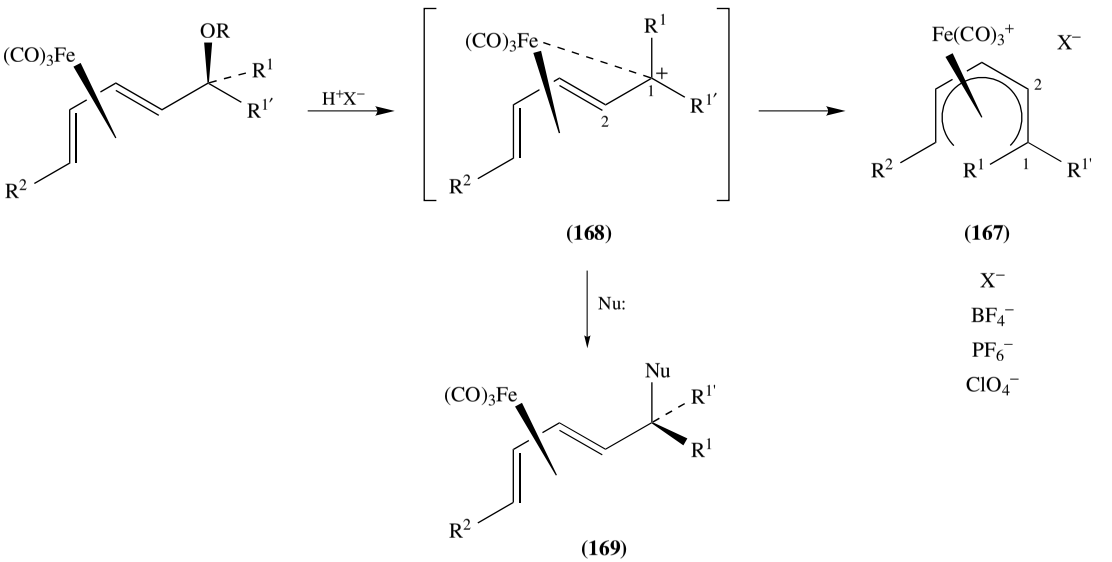
(27)

(1 : 1)

In contrast to the above reactions, protonation of (diene)ML_n complexes **(26)** occurs initially at the metal to give an (η^4-diene)ML_n(H) complex (**27**, Scheme 3)[23,58,63,90,136a]. For third-row transition metal complexes [**26**, ML_n = Os(arene), IrCp*] the M−H bond is stronger than a C−H bond, thus the ground state is this (diene)hydride complex. For the first- and second-row transition metals, [**26**, $ML_n = Mn(CO)_3^-$, $Fe(CO)_3$, $Fe(PR_3)_3$, CoCp, RhCp] the proton is transferred from the metal to the ligand to generate the corresponding (η^3-allyl-μ-hydride)ML_n complexes (**25a**, Scheme 3). As mentioned previously (Section III.C.4) the metal may migrate about a cyclic diene ligand via the intermediacy of (η^4-diene)ML_n(H) **27**. Use of deuteriated acid (instead of proton) leads to deuterium incorporation only at the methylene carbons on the same side as the metal. Protonation of acyclic (diene)$Fe(CO)_3$ complexes with HBF_4/CF_3CO_2H in the presence of CO results in the isolation of (π-allyl)$Fe(CO)_4^+$ cations, while protonation with HX leads to formation of the neutral (π-allyl)$Fe(CO)_3X$ complexes[172].

2. Reaction with carbon electrophiles

a. Triphenylmethylcarbenium ion. The reaction of cyclic (diene)ML_n complexes [ML_n = $Fe(CO)_2L$, $Ru(CO)_3$, $Os(CO)_3$, CoCp, RhCp] with triphenylmethyl carbenium ion (Ph_3C^+) results in abstraction of hydride from the *exo* face of the diene ligand to generate



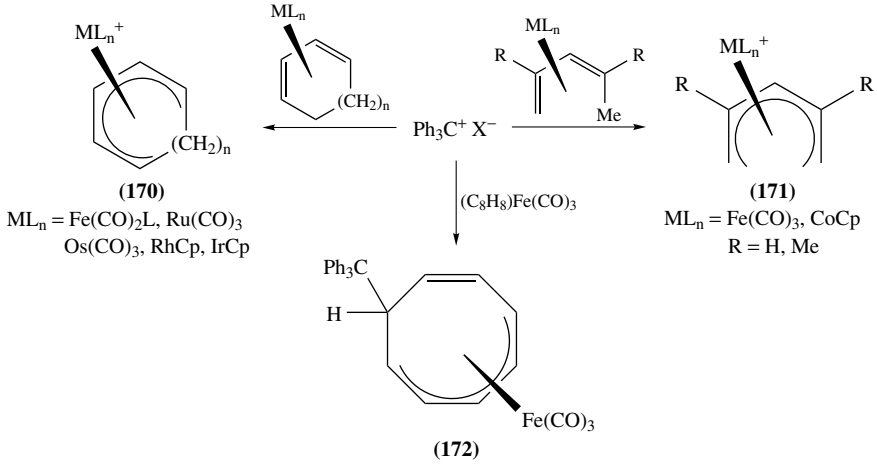
(168) **(167)**

X^-
BF_4^-
PF_6^-
ClO_4^-

(169)

SCHEME 41

(cyclodienyl)ML_n^+ cations (**170**, Scheme 42)[116,117,124a,125,136a,163b,173]. The regioselectivity of hydride abstraction from a variety of substituted (cyclohexadiene)$Fe(CO)_3$ complexes has been examined[116a–c]. There are only a few examples of hydride abstraction for the preparation of *acyclic* (pentadienyl)ML_n^+ cations **(171)**, since the success of this reaction requires the presence of a *cis*-alkyl substituent on the diene[138,174]. In comparison, reaction of Ph_3C^+ with $(C_8H_8)Fe(CO)_3$ generates the (η^5-cyclooctatrienyl)$Fe(CO)_3^+$ cation **172** via C–C bond formation rather than via hydride abstraction[175].

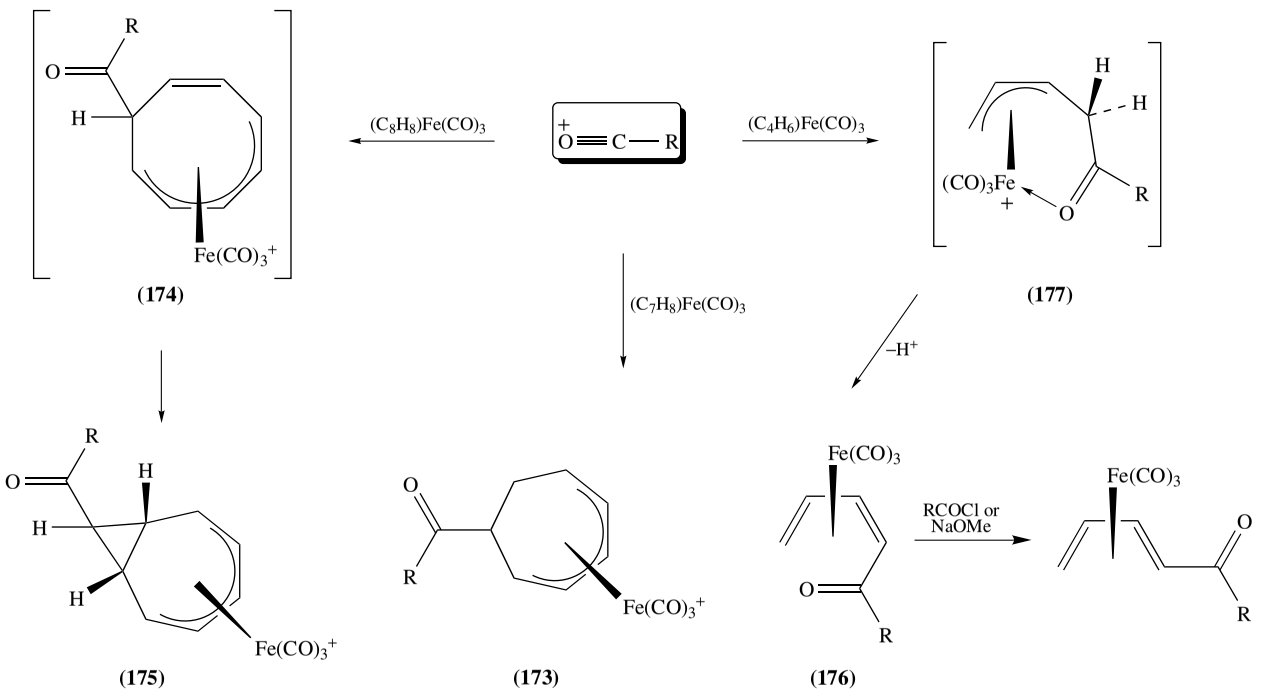


SCHEME 42

b. Acylium ions. Reaction of acylium ions with (cycloheptadiene)- or (cyclooctatetraene)$Fe(CO)_3$ occurs at an uncomplexed double bond to afford the acyl substituted (dienyl) $Fe(CO)_3^+$ cations **173** and **174** respectively (Scheme 43)[176]. While cation **174** is observable by NMR spectroscopy at low temperature, warming the solution results in cyclization to generate the final product **175**. In general, attempted acylation of uncomplexed 1,3-dienes results in polymerization. Coordination of the $Fe(CO)_3$ group moderates the electrophilic acylation of diene complexes to generate the corresponding *cis*-dienone complexes **176** (Scheme 43)[177]. Electrophilic attack occurs on the same face of the ligand as that bound to the metal to initially generate the cationic (η^3-allyl) complex **177**. Deprotonation gives **176**. The initially formed **176** may be subsequently isomerized to the more stable *trans*-dienone complex under the influence of additional acyl halide or base. Substitution is always observed to occur at the diene termini. In contrast to former assertions in the literature, Franck-Neumann and coworkers have reported that complexes bearing electron-withdrawing substituents slowly undergo acylation in the presence of two or more equivalents of $AlCl_3$[177a]. Electrophilic substitution of (diene)$Fe(CO)_3$ complexes with alkoxychloromethane or with orthochloroformates has been reported[178]. Acylation of the (cyclohexadiene)RhCp complex occurs at the cyclopentadienyl ligand[136a].

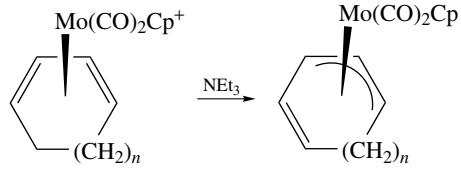
D. Deprotonation

A number of cationic (diene)metal complexes undergo α-deprotonation. Treatment of (cyclodiene)$Mo(CO)_2Cp^+$ cations (e.g. **44**) with NEt_3 or other non-nucleophilic bases

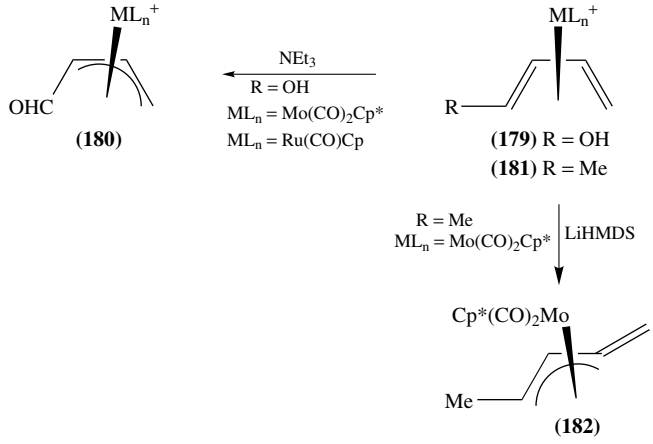

R
O
H
Fe(CO)3+
(174)
(C8H8)Fe(CO)3
+
O C R
(C4H6)Fe(CO)3
H
H
(CO)3Fe
+
O
R
(177)
(C7H8)Fe(CO)3
–H+
R
O
H
H
H
Fe(CO)3+
(175)
O
R
Fe(CO)3+
(173)
Fe(CO)3
O
R
(176)
RCOCl or
NaOMe
Fe(CO)3
O
R

SCHEME 43

yields the neutral (η^3-cyclodienyl)$Mo(CO)_2Cp$ complexes (**178**, equation 28)[81b,179]. Deprotonation of (1-hydroxy-1,3-butadiene) cations **179** [$ML_n = Mo(CO)_2Cp^*$, Ru(CO)Cp] with NEt_3 affords the *anti*-1-formyl-π-allyl products **180**[30,32] while the (1,3-pentadiene)Mo$(CO)_2Cp^{*+}$ cation **(181)** requires a stronger base for deprotonation to give **182** (Scheme 44)[87].



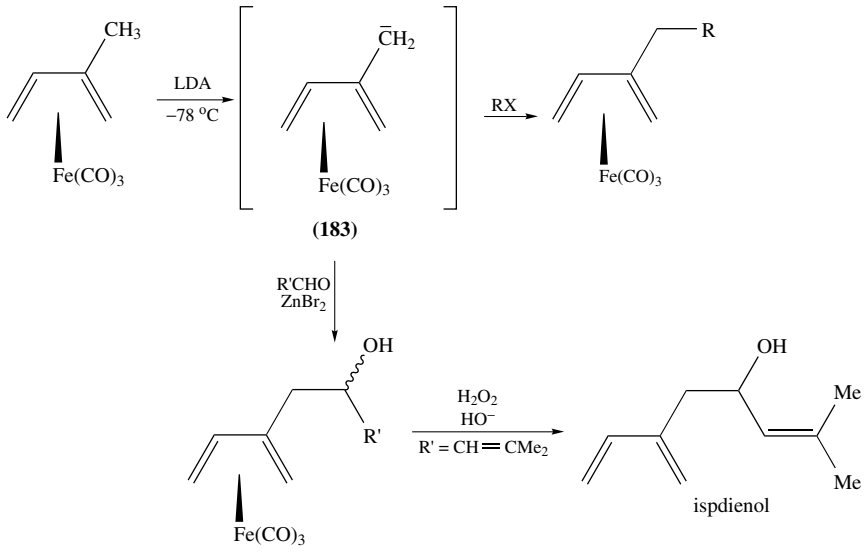
(44) $n = 1, 2$ **(178)** $n = 1, 2$ (28)



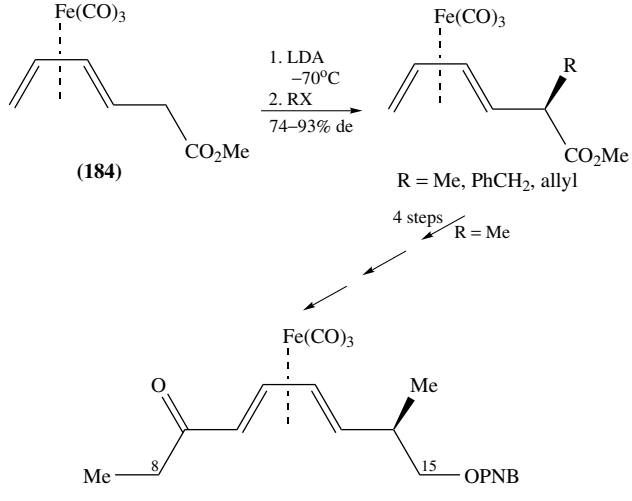
(180) **(179)** R = OH **(181)** R = Me **(182)**

SCHEME 44

In contrast, deprotonation of neutral (diene) metal complexes results in the formation of carbanions. Deprotonation of (isoprene)$Fe(CO)_3$ with LDA (−78 °C) generates the anion **183** (Scheme 45)[180]. The anion reacts directly with alkyl, benzyl or allyl halides or, in the presence of $ZnBr_2$, with aldehydes. The insect pheromone, ipsdienol, has been prepared by this method. In a similar fashion, deprotonation of cyclic and acyclic (diene)$Fe(CO)_3$ complexes bearing an electron-withdrawing group occurs α to this group and on the *exo* face of the complex. Alkylation of the resultant cyclic anions occurs in a diastereospecific fashion, also on the *exo* face of the ligand due to the steric bulk of the metal–ligand array[181]. This has been extended to acyclic dienes; alkylation of (methyl 3,5-hexadienoate)$Fe(CO)_3$ **(184)** occurs in a highly diastereoselective fashion (Scheme 46)[182]. This is proposed to occur via approach of the electrophile to the s-*trans* rotamer of the ester enolate anion on the face opposite to $Fe(CO)_3$. This methodology, along with electrophilic acylation (Section V.C.2.b), was utilized in the preparation of the C8–C15 segment of protomycinolide IV. Attempts to generate and alkylate a dithianyl anion adjacent to (butadiene)$Fe(CO)_3$ were unsuccessful[183].



SCHEME 45

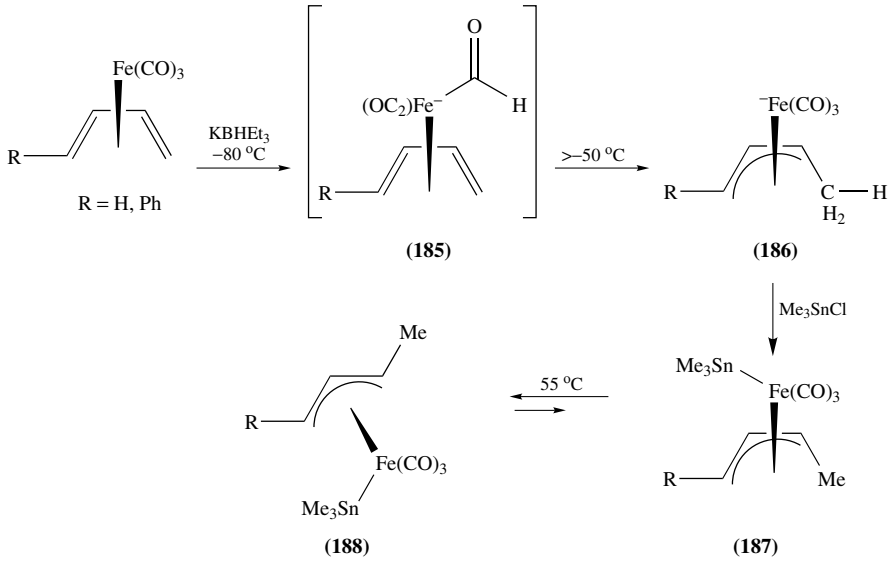


SCHEME 46

E. Nucleophilic Addition

1. Neutral (diene)iron complexes

Zerovalent transition metal carbonyl moieties may act as electron acceptors, and thus activate coordinated polyene ligands toward nucleophilic attack. Reaction of (C_4H_6)-$Fe(CO)_3$ with $KBHEt_3$ ($-80\,^{\circ}C$) proceeds via attack at a coordinated carbon monoxide to generate the anionic iron-formyl species **185** (Scheme 47)[184]. Upon warming to

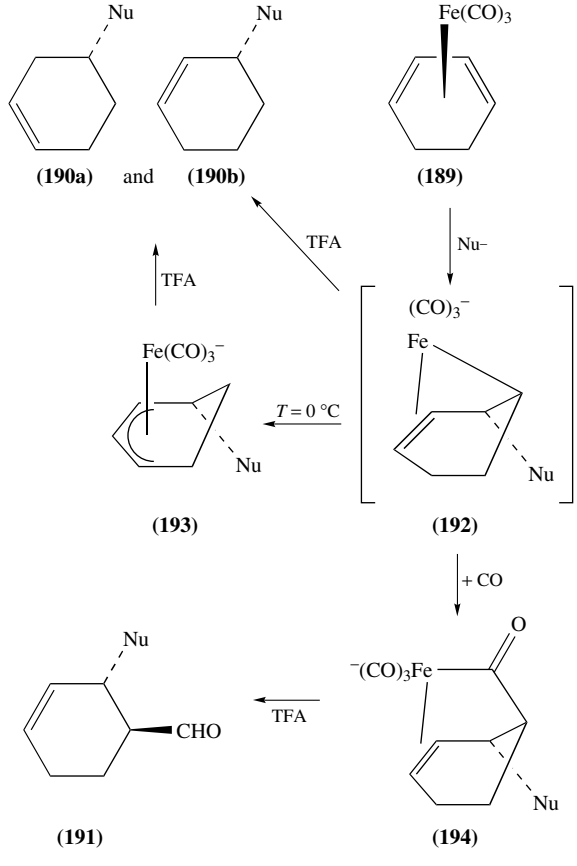


SCHEME 47

−50 °C, complex **185** isomerizes to the (*anti*-allyl)$Fe(CO)_3^-$ anion **(186)**, which may be trapped by reaction with Me_3SnCl to give the corresponding (*anti*-crotyl)$Fe(CO)_3SnMe_3$ complex **(187)**. Isomerization of **187** to the thermodynamically more stable (*syn*-crotyl) isomer **(188)** occurs only at a higher temperature (55 °C).

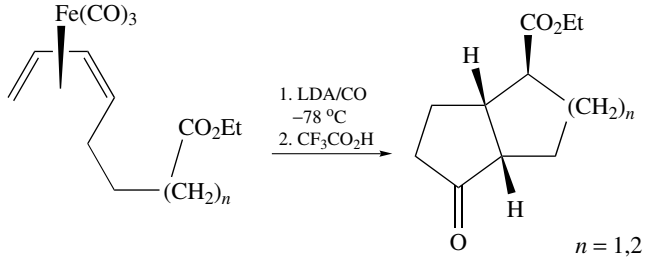
In contrast, reaction of (cyclohexadiene)$Fe(CO)_3$ **(189)** with strong carbon nucleophiles (conjugate acid $pK_a > ca\,28$) in THF/HMPA/−78 °C, followed by protic workup, gives cyclohexene products **190a** and **190b** (Scheme 48)[185]. If the reaction is run under an atmosphere of carbon monoxide, products incorporating CO (e.g. **191**) may be obtained. This reaction is proposed to occur via nucleophilic attack at an internal diene carbon on the face opposite to iron, to afford a (1,3,4-η^3-butenyl)$Fe(CO)_3^-$ anion **192** which has been partially characterized by ^1H NMR spectroscopy at low temperature (−60 °C)[186]. Upon warming the solution to 0 °C, the signals attributed to **192** disappear and are replaced by signals corresponding to the (allyl)$Fe(CO)_3^-$ species **193**. Protonation of either **192** or **193** gives the olefinic products **190a** and **190b**. Under a positive pressure of carbon monoxide, CO insertion into **192** gives the anionic acyl species **194** which has been characterized by IR and ^1H NMR spectroscopy[186]. Protonation of **194** yields **191**.

Examination of the reactivity of acyclic (diene)$Fe(CO)_3$ complexes indicates that this nucleophilic addition is reversible. The reaction of $(C_4H_6)Fe(CO)_3$ with strong carbon nucleophiles, followed by protonation, gives olefinic products **195** and **196** (Scheme 49)[187]. The ratio of **195** and **196** depends upon the reaction temperature and time. Thus, for short reaction time and low temperature (0.5 h, −78 °C) the product from attack at C2 (i.e. **195**) predominates while at higher temperature and longer reaction time (2 h, 0 °C) the product from attack at C1 (i.e. **196**) predominates . This selectivity is rationalized by kinetically controlled attack at the more electron-poor carbon (C2) at low temperature. Nucleophilic attack is reversible and, under conditions where an equilibrium is established, the thermodynamically more stable (allyl)$Fe(CO)_3^-$ is favored. The regioselectivity for nucleophilic attack on substituted (diene)$Fe(CO)_3$ complexes has been reported[187]. The

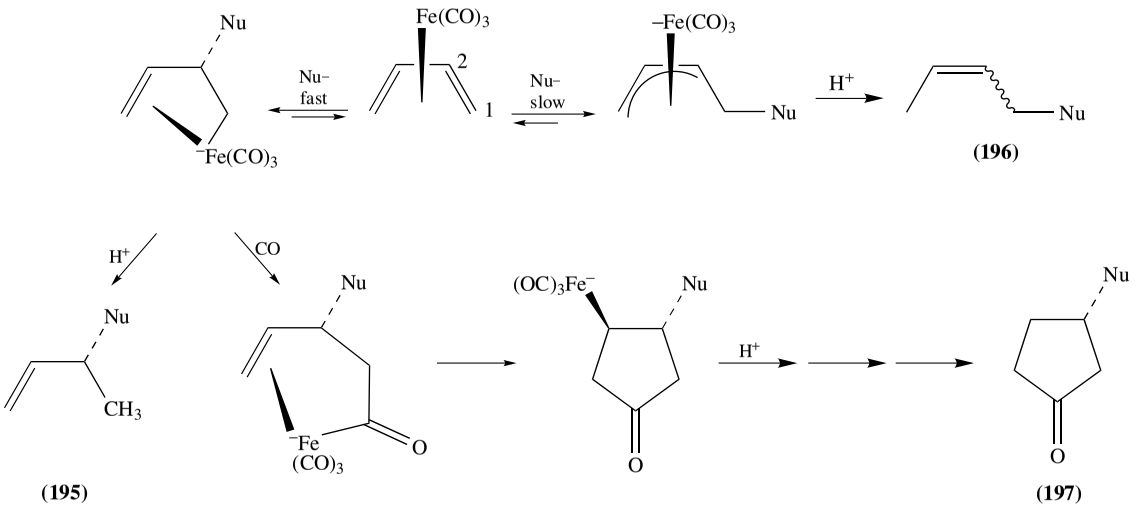


SCHEME 48

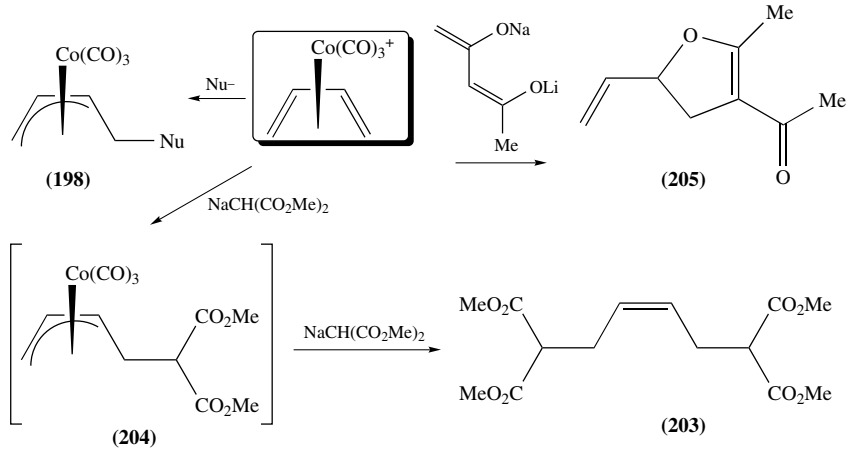
reaction of $(C_4H_6)Fe(CO)_3$ with carbon nucleophiles under CO pressure (*ca* 2 atm, $-78 \rightarrow 0\,^{\circ}C$) gives cyclopentanone products (**197**, Scheme 49)[188]. Intramolecular variants of this reaction have been reported for the preparation of bicyclo[*n*.3.0]alkanones (equation 29)[189].



(29)


Nu
Fe(CO)3
Nu–
fast
2
1
Nu–
slow
–Fe(CO)3
Nu
H+
Nu
(196)
H+
CO
Nu
CH3
(195)
Nu
–Fe
(CO)3
O
(OC)3Fe–
Nu
O
H+
Nu
O
(197)

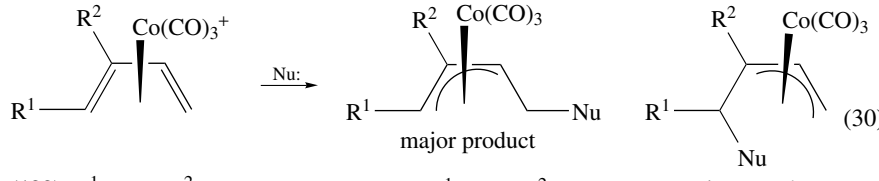
SCHEME 49



SCHEME 50

2. Cationic (diene)cobalt complexes

The reaction of (diene)$Co(CO)_3^+$ cations with a range of carbon and heteroatom nucleophiles has been examined. As might be expected, since these are positively charged species the range of nucleophiles which are reactive is more extensive than for neutral (diene)$Fe(CO)_3$ complexes (see Section V.E.1) and includes such nucleophiles as pyridine and phosphines. In contrast to the (diene)$Fe(CO)_3$ complexes, nucleophilic attack on the (diene)$Co(CO)_3^+$ cations occurs exclusively at the diene terminus to give neutral (*anti*-1-substituted-allyl)$Co(CO)_3$ complexes **198** in 'moderate to good yield' (Scheme 50)[28]. The regioselectivity for nucleophilic attack on substituted (diene)$Co(CO)_3^+$ cations has been examined[134b]. In general, for hydride, phenyl magnesium bromide or pyridine as nucleophile, attack at the less hindered diene terminus is preferred; 1-substituted (diene)$Co(CO)_3^+$ cations **199** give predominantly **200**, while 2-substituted (diene)$Co(CO)_3^+$ cations **201** give predominantly **202** (equation 30).



(199) $R^1 = Me$, $R^2 = H$ **(200)** $R^1 = Me$, $R^2 = H$

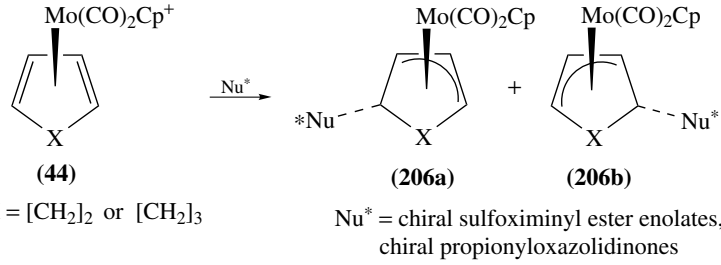
(201) $R^1 = H$, $R^2 = Et$ **(202)** $R^1 = H$, $R^2 = Et$

The neutral (allyl)$Co(CO)_3$ products are themselves susceptible to nucleophilic attack. Thus reaction of $(C_4H_6)Co(CO)_3^+$ with *two* equivalents of sodium dimethyl malonate anion gives the tetraester **203**, presumably via initial attack at C1 to generate the intermediate π-allyl complex **204** followed by regiospecific attack by the second equivalent at C4 (Scheme 50)[28]. The intramolecular variant of this reaction using a single equivalent of a dinucleophile, such as a β-dicarbonyl dianion or the corresponding 1,3-bis(silyloxy)diene, leads to the formation of vinyldihydrofuran products **205**[190]. For these reactions, it would

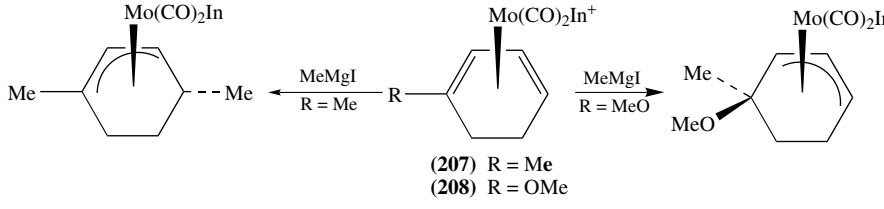
appear that initial electrophilic attack occurs at what is the less reactive nucleophilic site of the dianion/bis(silyloxy)diene. The mechanistic details of this annulation are not yet complete.

3. Cationic (diene)molybdenum complexes

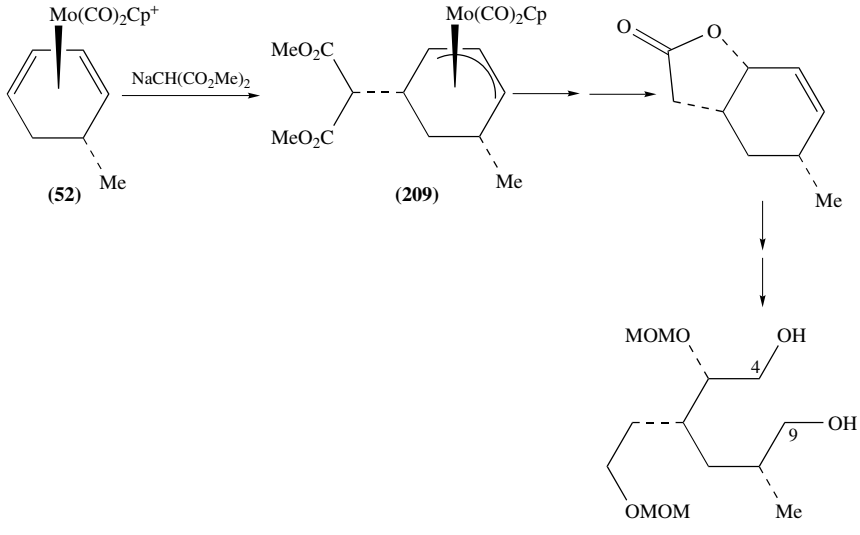
Cyclic (diene)$Mo(CO)_2L^+$ (L = Cp, Cp* or indenyl) cations react with a variety of carbon and heteroatom nucleophiles to generate (π-allyl)Mo complexes[84]. In a fashion similar to the (diene)Co^+ cations (Section V.E.2), nucleophilic atttack on the (diene)Mo^+ cations occurs exclusively at the terminal carbons of the diene. While the products from reaction of amine or alkoxide nucleophiles are difficult to handle, those resulting from reaction with carbon nucleophiles are relatively stable. In these cases, nucleophilic attack occurs on the face of the diene ligand opposite to the metal. For C_s symmetric cations **44** (X = $[CH_2]_2$ or $[CH_2]_3$), reaction with chiral nucleophiles(Nu*) gives mixtures of diastereomers **206a** and **206b** with moderate to good diastereoselectivity (10–86% de) (equation 31)[191]. The regioselectivity of nucleophilic attack on unsymmetrically substituted (cyclodiene)Mo^+ cations has been extensively studied. For 1-alkyl substituted complexes **(207)**, nucleophilic attack occurs at the unsubstitued terminus presumably due to steric hindrance, while for 1-alkoxy substituted complexes **(208)** attack occurs at the substitued terminus (Scheme 51)[81b]. A substituent on one of the sp^3 carbons of a (cyclohexadiene)Mo^+ cation (e.g. **52**) directs nucleophilic attack exclusively at the opposite terminus to give **209** (Scheme 52)[84a,c,179b,192]. Since complexes **52** may be readily prepared from the parent (cyclohexadiene)Mo^+ cations via nucleophilic addition, followed by hydride abstraction (see Scheme 13), these steps constitute a method for the preparation of a *cis*-1,3-disubstituted cyclohexene. This methodology has been utilized for the stereocontrolled synthesis of the C4–C9 segment of tylosin[192]. For similarly substituted (cycloheptadienyl)Mo^+ cations (e.g. **53**) nucleophilic attack occurs predominantly at the less hindered diene terminus. However, a minor amount of the other regioisomeric product is obtained depending upon the steric bulk of the nucleophile[84b].



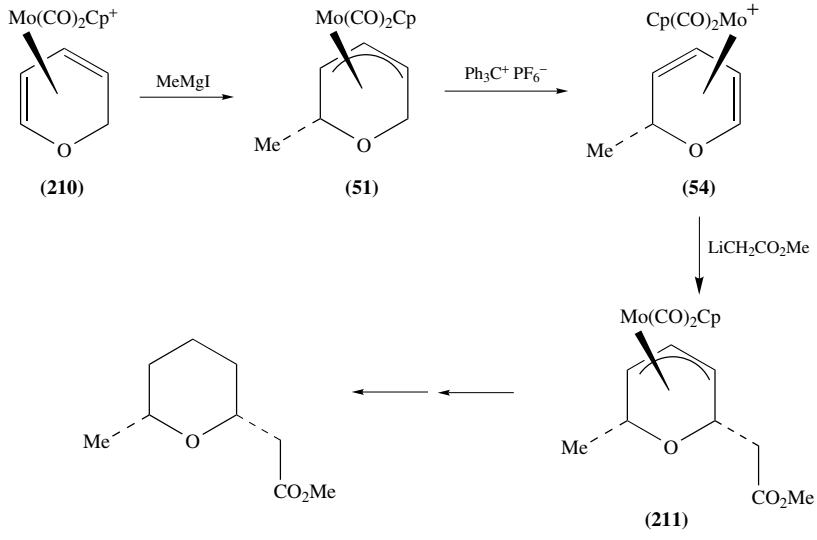
(31)



SCHEME 51



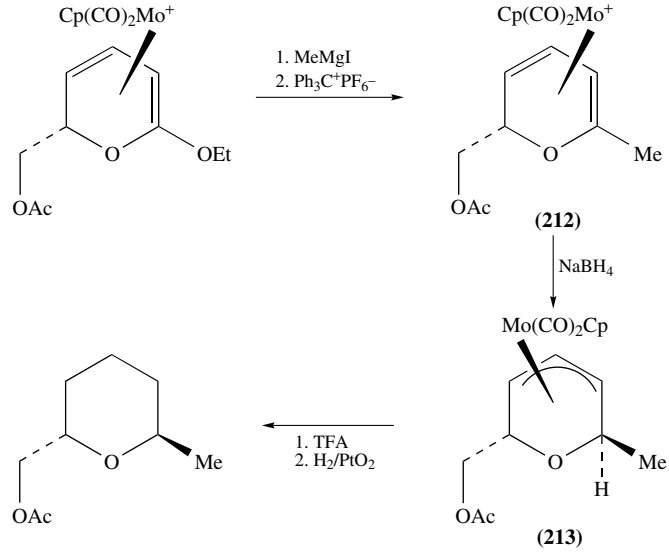
SCHEME 52



SCHEME 53

Liebeskind and coworkers have examined the reactivity of (2*H*-pyran)$Mo(CO)_2Cp^+$ cations **210**, which may be prepared in optically active form from carbohydrate precursors. Nucleophilic attack on cation **210** occurs at the diene terminus bonded to the ring oxygen to give π-allyl complexes **51** (Scheme 53)[85]. Hydride abstraction from **51** gives the cation **54**; addition of a second nucleophilie occurs regioselectively to give

a *cis*-2,6-disubstituted (pyranyl)Mo complex **211**. This methodology has been utilized for the preparation of a scent secretion of *Viverra civetta*. Preparation of a *trans*-2,6-disubstituted (pyranyl)Mo complex **(213)** is also possible via hydride addition to the substituted (2*H*-pyran)$Mo(CO)_2Cp^+$ cation **212** (Scheme 54)[86].



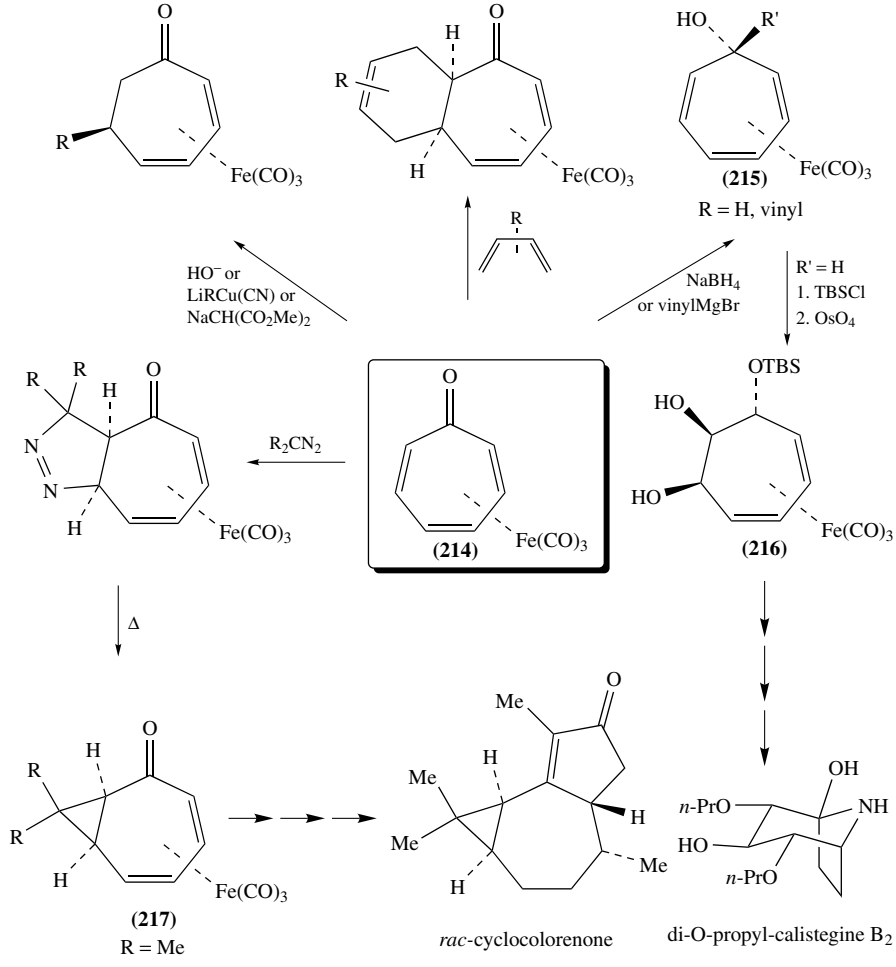
SCHEME 54

Nucleophilic addition to acyclic (diene)Mo^+ cations has been examined. For (isoprene) $Mo(CO)_2L$ (L = Cp, Cp*, In), the regioselectivity for nucleophilic attack has been found to depend on the nature of the nucleophile, the ligand L, the reaction solvent and the temperature[21,81a,83a,193]. The generation and *in situ* reactivity of transoid acyclic (diene)molybdenum and tungsten cations with nucleophiles has been previously mentioned (Section IV.C.2).

F. Use of the Metal as a Stereodirecting Functionality

In general, reagents approach a (diene)metal complex on the face opposite to the metal due to the steric bulk of the attached metal-ligand array. Due to the relatively low cost of iron, the vast majority of examples of these type of reactions utilize the $Fe(CO)_3$ fragment.

Tropone reacts with nucleophiles at C2 via an extended Michael addition and undergoes [6 + 2] cycloaddition reactions. In contrast, (tropone)$Fe(CO)_3$ **(214)** undergoes conjugate addition at C-3 and reacts with dienes via [4 + 2] cycloaddition (Scheme 55)[194]. Addition of borohydride or vinyl magnesium bromide to **214** gives cycloheptatrienols **(215)**[194a,195]. Osmylation and hydroboration/oxidation of cyclic trienes proceeds stereospecifically on the face opposite to the metal[195]. The partially protected (cycloheptadienetriol)iron complex **216** has been utilized in a synthesis of di-*O*-propyl-calistegine B_2. Complex **214** undergoes [3 + 2] cycloaddition with diazoalkanes to give the corresponding pyrazoline, which upon heating extrudes N_2 to give the bicyclo[5.1.0]octa-3,5-dien-2-one complex **(217)**[196]. Complex **217** (R = Me) has been used in a synthesis of cyclocolorenone[196b].

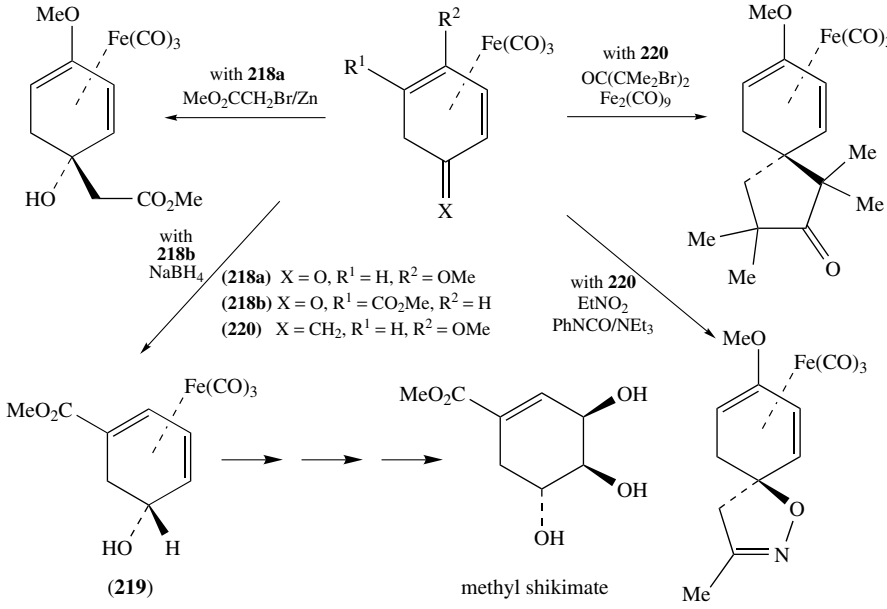


SCHEME 55

All of these reactions occur on the face of the ligand opposite to the sterically bulky $Fe(CO)_3$ moiety.

Nucleophilic additions to (cyclohexadienone)$Fe(CO)_3$ complexes **(218)** occur in a diastereospecific fashion (Scheme 56)[197]. For example, the Reformatsky reaction of ketone **(218a)** affords a simple diasteromeric alcohol product[197b]. The reduction of (1-carbomethoxycyclohexa-1,3-dien-5-one)$Fe(CO)_3$ **(218b)** to give **219** has been utilized in the enantioselective synthesis of methyl shikimate. In a similar fashion, cycloadditions of (2-methoxy-5-methylenecyclohexa-1,3-diene)$Fe(CO)_3$ **(220)** occur in a diastereospecific fashion[198].

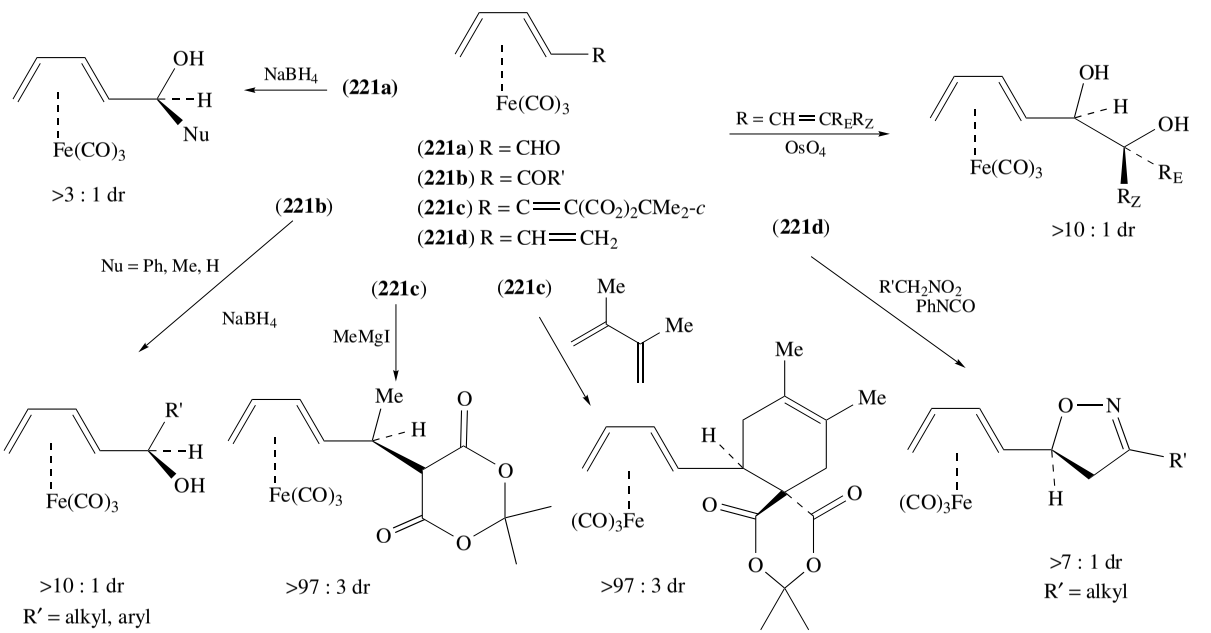
In comparison to the above *diastereospecific* reactions of cyclic polyene complexes, the reaction of acyclic (diene)$Fe(CO)_3$ complexes **(221)** with pendant unsaturated functionality has been found to occur in a *diastereoselective* fashion. The diastereoselectivity in



SCHEME 56

these reactions depends, in part, on the unsaturated functionality occupying a preferred, or more reactive, conformer about the diene-to-unsaturated functionality bond. Nucleophilic addition to (2*E*,4-dienal)$Fe(CO)_3$ complexes (**221a**) proceeds with variable diastereoselectivity, depending on both the complex and the nucleophile (Scheme 57)[199]. In general, the diastereomeric secondary alcohol products are easily separable by chromatography, with the Ψ-*exo* isomer being less mobile than the Ψ-*endo* isomer[200]. In comparison, reduction of the corresponding (*E*,*E*-dienone)$Fe(CO)_3$ complex (**221b**) proceeds with high diastereoselectivity (>90% de) to afford predominantly the Ψ-*endo* alcohol (Scheme 57)[201]. This high diastereoselectivity has been rationalized on the basis of the approach of borohydride to the dienone in the s-*trans* conformer on the face opposite to the bulky $Fe(CO)_3$ adjunct[201b,c]. Nucleophilic addition to complexed dienals has been utilized in the enantioselective syntheses of 5-HETE methyl ester[199b], AF toxin IIc[199c], LTB_4[199d], the LTB_4 antagonist SM 9064[199e] and lipoic acid methyl ester[199f], while reduction of a complexed dienone was utilized in an enantiospecific synthesis of LTA_4[201a]. Michael addition to activated (triene)$Fe(CO)_3$ complexes [**221c**] proceeds in a stereospecific fashion; only the *exo*-methyl adduct is obtained (Scheme 57)[202]. This reactivity has been utilized in the synthesis of (−)-verbenalol and (−)-epiverbenalol[202a] and the *as*-indacene unit of ikarugamycin[202b].

The cycloaddition of (triene)$Fe(CO)_3$ complexes occurs in a highly diastereoselective fashion via approach of the organic component to the complex in the s-*trans* conformation on the face opposite to the metal. Thus the Diels–Alder cycloaddition of the activated (triene)$Fe(CO)_3$ complex [**221c**] is reported to afford a single cycloadduct[203]. Intermolecular addition of nitrile oxides to triene complexes (**221d**) results in the formation of the corresponding isoxazolines in good yield, with good diastereoselectivity (*ca*


NaBH4
(221a)
R
Fe(CO)3
(221a) R = CHO
(221b) R = COR'
(221c) R = C═C(CO2)2CMe2-c
(221d) R = CH═CH2
R = CH═CREZRZ
OsO4
OH
H
OH
RE
RZ
>10 : 1 dr
(221b)
Nu = Ph, Me, H
NaBH4
R'
H
OH
>10 : 1 dr
R′ = alkyl, aryl
(221c)
MeMgI
Me
H
O
O
O
O
>97 : 3 dr
(221c)
Me
Me
(CO)3Fe
>97 : 3 dr
(221d)
R'CH2NO2
PhNCO
O—N
R'
H
(CO)3Fe
>7 : 1 dr
R′ = alkyl

SCHEME 57

80% de) (Scheme 57)[204]. This methodology has been used in an enantioselective synthesis of (+)-gingerol[204b], the carbon skeleton of (+)-streptenol D[204c] and the C11−C24 fragment of macrolactin A[170b].

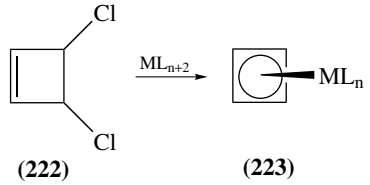
Osmylation of C−C double bonds adjacent to the (diene)$Fe(CO)_3$ functionality has been reported (Scheme 57)[205]. This methodology has been used in the enantiospecific synthesis of 5,6- and 11,12-diHETEs.

VI. PREPARATION OF CYCLOBUTADIENE–METAL COMPLEXES

The synthesis and reactivity of cyclobutadiene–metal complexes was extensively reviewed in 1977 by Efraty[15]. While the following two sections will mostly deal with newer developments, pertinent information from this review may be briefly presented in the following sections. Since most cyclobutadienes are highly reactive species, direct complexation of the ligand is generally not possible. Only one example has been reported; the reaction of $Fe_2(CO)_9$ with 1,2,3-tri-*t*-butyl-4-trimethylsilyl-1,3-cyclobutadiene gives the corresponding $Fe(CO)_3$ complex[206].

A. Preparation from Four-membered Ring Precursors

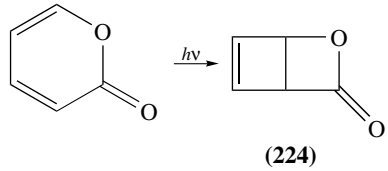
The reduction of 3,4-dichlorocyclobutene **(222)** in the presence of metal carbonyls has been utilized to prepare the parent complex [**223**, $ML_n = Cr(CO)_4$, $Mo(CO)_3$, $W(CO)_3$, $Fe(CO)_3$, $Ru(CO)_3$ or $Co_2(CO)_6$] (equation 32)[15]. More recently, reaction of $Ni(CO)_4$ with 3,4-dihalocyclobutenes (X = Br or I) or with **222** in the presence of $AlCl_3$ produced the corresponding (cyclobutadiene)nickel dihalides[207]. Methodology for the preparation of 1,2- or 1,3-disubstituted (cyclobutadiene)$Fe(CO)_3$ complexes from 1,2- or 1,3-disubstituted-3,4-dibromocyclobutenes has been presented[15,208]. In turn, the substituted dibromocyclobutenes are prepared from squaric esters. The reaction of *cis*-3,4-carbonyldioxycyclobutene and substituted variants with $Fe_2(CO)_9$ or $Na_2Fe(CO)_4$ also produces (cyclobutadiene)$Fe(CO)_3$ complexes[15,209]. Photolysis of α-pyrone generates 3-oxo-2-oxabicyclo [2.2.0]hex-5-ene **(224)** which undergoes photolysis with a variety of metal carbonyls to afford the parent cyclobutadiene complex **223** [$ML_n = CpV(CO)_2$, $Fe(CO)_3$, CoCp, or RhCp] (equation 33)[15,210].



(222) **(223)**

ML_n	
$Cr(CO)_4$	$Fe(CO)_3$
$Mo(CO)_4$	$Ru(CO)_3$
$W(CO)_4$	$Co_2(CO)_6$
	NiX_2

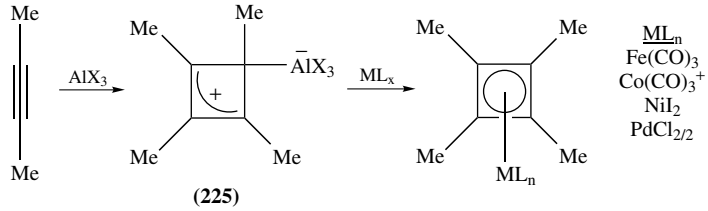
(32)



(224) **(223)**

ML_n
$CpV(CO)_2$
$Fe(CO)_3$
CoCp
RhCp

(33)



(225)

SCHEME 58

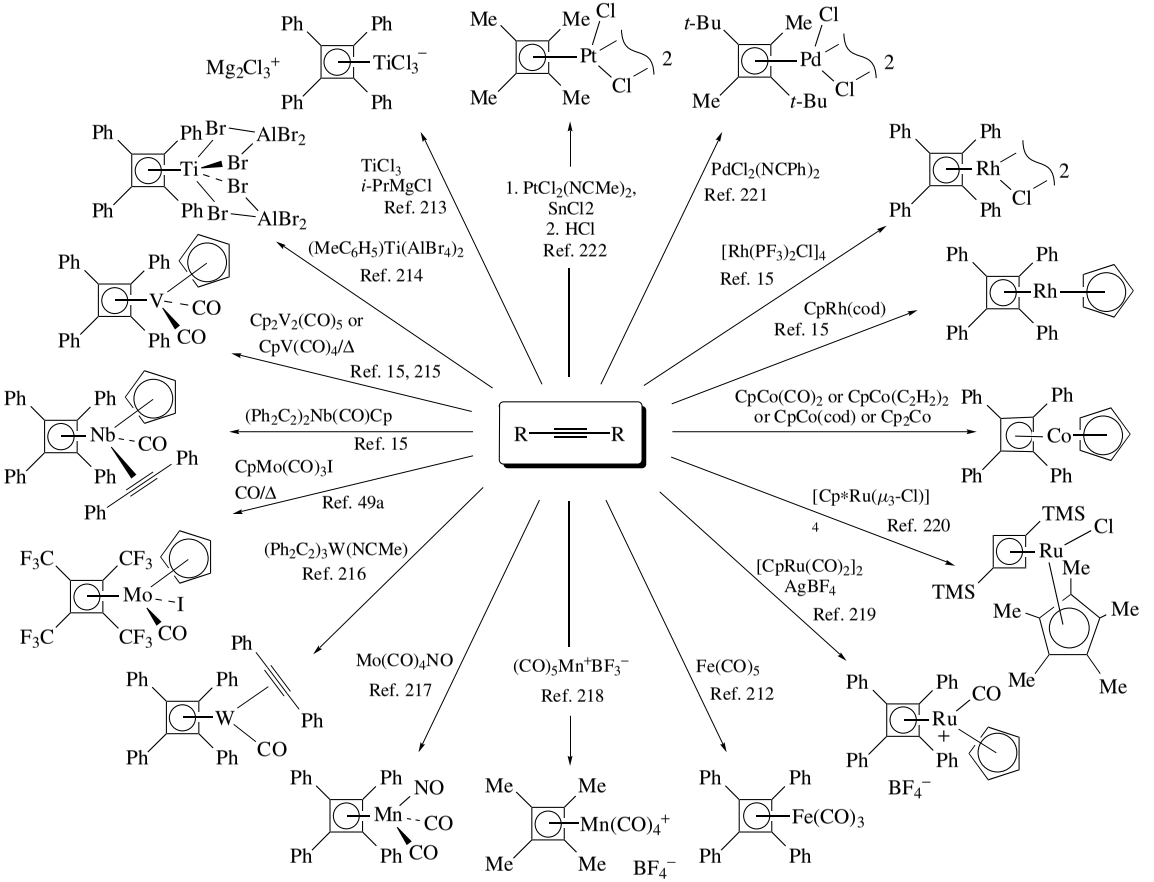
The reaction of alkynes with AlX_3 at $-78\,^{\circ}C$ has been shown, by NMR spectroscopy, to generate a zwitterionic σ-cyclobutadiene aluminum species **225** (Scheme 58)[211a]. Transfer of the cyclobutadiene ligand from **225** to a variety of transition metals has been reported[211].

B. Preparation by Alkyne Cyclodimerization

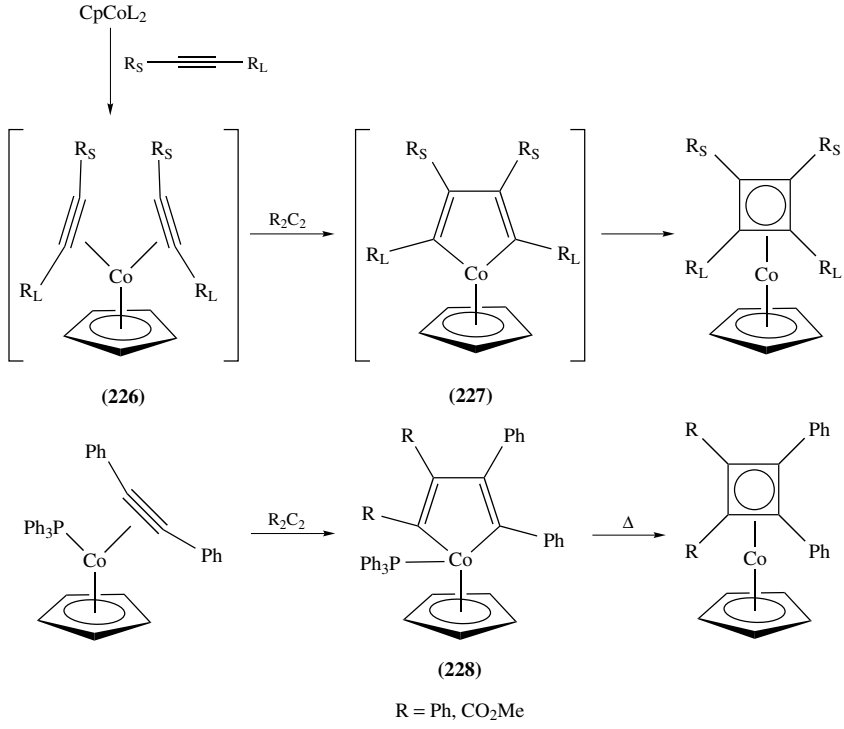
While one of the first preparations of a cyclobutadiene–metal complex involved the cyclodimerization of diphenylacetylene in the presence of $Fe(CO)_5$ at high temperature[212], the thermal reaction of alkynes with $Fe(CO)_5$ gives predominantly cyclopentadienone complexes (Section IV.E.1.b). The cyclization of alkynes by a wide variety of metal complexes has been reported (Scheme 59)[15,213–222].

Alkyne dimerizaton using CpCo(cod), $CpCo(C_2H_4)_2$ or $CpCo(CO)_2$ remains the method of choice for the preparation of (cyclobutadiene)CoCp complexes[223]. The overall mechanism for formation is believed to involve generation of a bis-alkyne complex **226** which undergoes reductive coupling to form a coordinatively unsaturated cobaltacyclopentadiene complex **227** (Scheme 60). A coordinatively saturated cobaltacyclopentadiene complex **228** has been isolated as the product from the reaction of $CpCo(PPh_3)(Ph_2C_2)$ with diphenylacetylene or with dimethyl acetylenedicarboxylate[224]. Heating of **228** at highly elevated temperatures results in the formation of differentially substituted (cyclobutadiene)CoCp complexes. For unsymmetrically substituted alkynes, coupling generally proceeds such that the more bulky substituents or electron-withdrawing substituents are located next to the cobalt. For cyclization with $CpCo(CO)_2$, one competing pathway to cyclobutadiene formation is the formation of cyclopentadienone complexes (cf Section IV.F.2.b, equation 19). Formation of these complexes may be avoided by use of the non-carbonyl reagents [e.g. CpCo(cod) or $CpCo(C_2H_4)_2$).

The cobalt mediated cyclodimerization of cyclic alkadiynes to afford tricyclic (cyclobutadiene)Co complexes **229** was previously examined by King and Efraty (Scheme 61)[225]. More recently, Gleiter and coworkers discovered that cyclization of 1,6-decadiyne, 1,8-tetradecadiyne or 1,10-octadecadiyne affords the tetra-bridged cyclobutadiene cyclophane complexes **230**, **231** and **232** in 12, 7 and 1% yields, respectively, in addition to complexes of type **229**[226]. The yield of the [3.3.3.3]-cyclophane could be increased to *ca* 30% if (η^5-indenyl)Co(cod) was used instead of $CpCoL_2$. X-ray diffraction analysis indicated that the distances between cyclobutadiene rings for **230**, **231** and **232** are 3.00 Å, 5.34 Å and 7.83 Å, respectively, and the Co–Co distances are 6.30 Å, 8.70 Å and 11.17 Å, respectively. In general, superphane formation occurs only for hydrocarbon cyclic diynes if the two alkyl chains contain an odd number of carbons and are of the same length. An exception to this generalization is the cyclodimerization of 1,5-cyclononadiyne with the sterically bulky $Cp^*Co(C_2H_4)_2$ to form **233** ($X = CH_2$) (Scheme 61)[227]. The cyclodimerization of certain large ring disilacyclodiynes **234** ($n = 5, 6$) with $Cp'Co(C_2H_4)_2$ was shown to


TiCl3 i-PrMgCl Ref. 213
1. PtCl2(NCMe)2, SnCl2 2. HCl Ref. 222
PdCl2(NCPh)2 Ref. 221
(MeC6H5)Ti(AlBr4)2 Ref. 214
[Rh(PF3)2Cl]4 Ref. 15
Cp2V2(CO)5 or CpV(CO)4/Δ Ref. 15, 215
CpRh(cod) Ref. 15
CpCo(CO)2 or CpCo(C2H2)2 or CpCo(cod) or Cp2Co
(Ph2C2)2Nb(CO)Cp Ref. 15
CpMo(CO)3I CO/Δ Ref. 49a
[Cp*Ru(μ3-Cl)]4 Ref. 220
(Ph2C2)3W(NCMe) Ref. 216
[CpRu(CO)2]2 AgBF4 Ref. 219
Mo(CO)4NO Ref. 217
(CO)5Mn+BF3− Ref. 218
Fe(CO)5 Ref. 212
R R

SCHEME 59



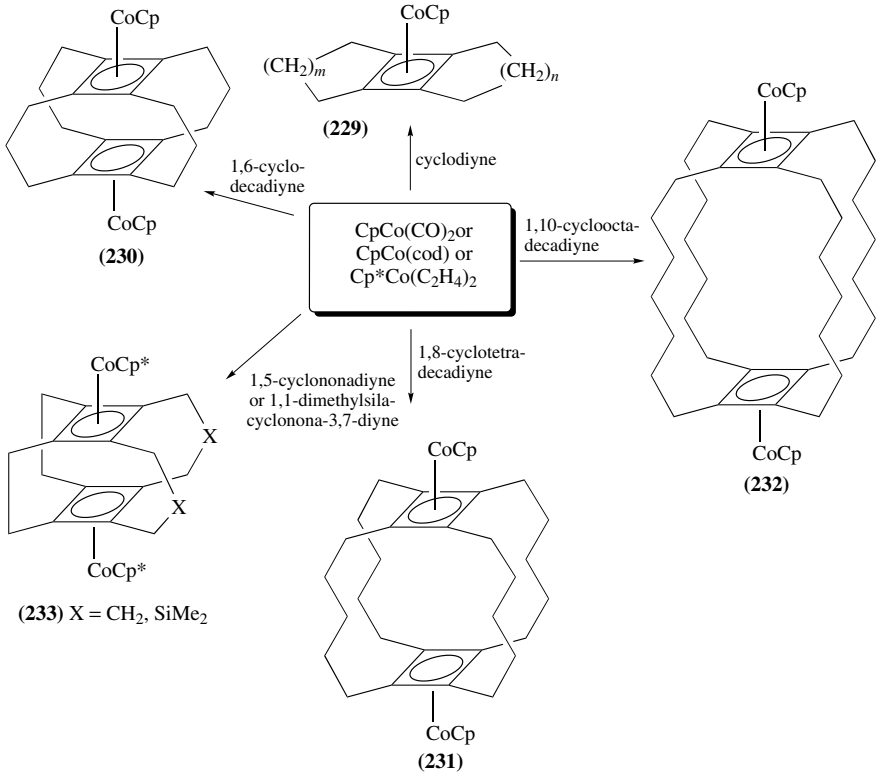
SCHEME 60

afford the corresponding silicon containing superphanes **235** (Scheme 62)[227b,c]. In contrast, reaction of the smaller 1,1,2,2-tetramethyl-1,2-disilacycloocta-3,7-diyne (**234**, $n = 2$) with $CpCo(cod)_2$ proceeded via intermolecular trimerization to generate the trimetallic complex **236**. Notably, the hydrocarbon bridges are all on one side of the macrocyclic structure. This is expected on the basis of the mechanism of cyclobutadiene formation which couples carbons carrying the sterically less bulky substituents together (cf Scheme 60). The crystal structure of **236** indicates that this compound possesses a conical shape; the diameters of the silyl bridged and the hydrocarbon bridged macrocyclic rings are 6.9 Å and 4.5 Å, respectively[227b].

Heteroatom-containing (cyclobutadiene)Co complexes (e.g. **237**, **238** and **239**) have been prepared by the reaction of heteroatom containing cobalt precursors with diphenylacetylene or by the reaction of cobalt precursors with phospha-alkynes[228].

C. Miscellaneous Methods of Preparation

Flash vapor pyrolysis of the (η^4-thiophene 1,1-dioxide)cobalt complexes results in extrusion of SO_2 to generate (cyclobutadiene)cobalt complexes (Scheme 63)[229]. The absence of ligand crossover products indicates that this reaction occurs in a unimolecular fashion. Pyrolysis of the diastereomerically pure complex **240** gave the cyclobutadiene complex as an equimolar mixture of diastereomers **241a** and **241b**. In addition, the recovered starting material (37%) was shown to have *ca* 40% scramble of the diastereomeric

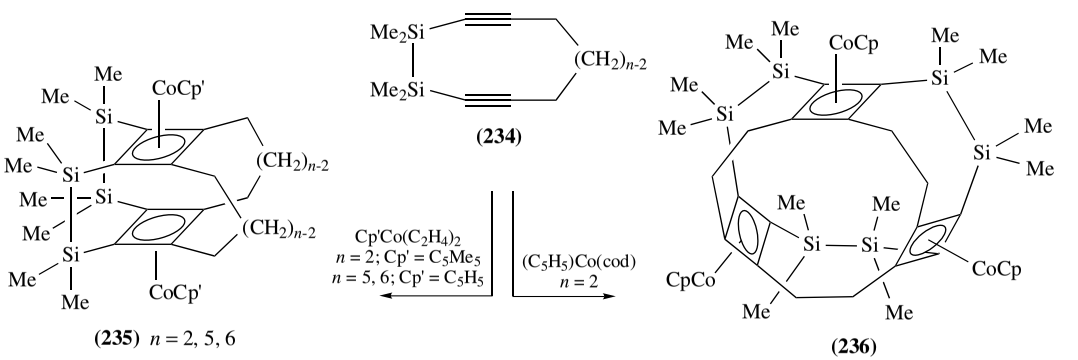


SCHEME 61

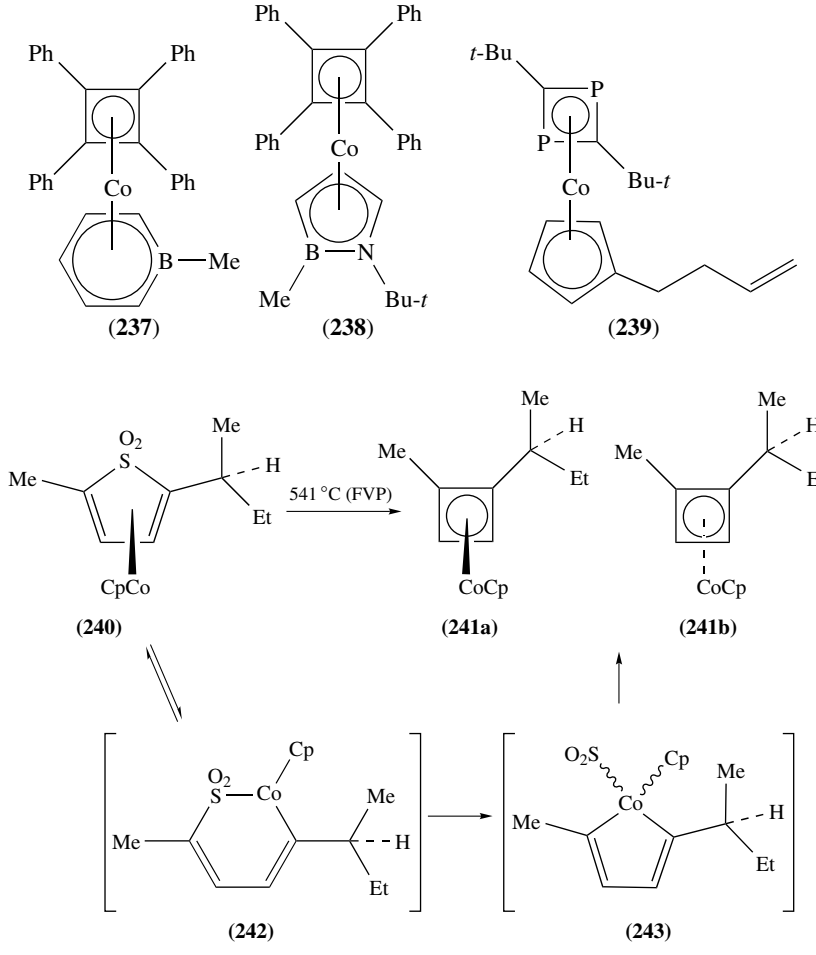
label. These results are consistent with a mechanism which involves reversible insertion of CoCp into the carbon–sulfur bond to generate a planar species **242**. Deinsertion of SO_2 from **242** generates the cobaltacyclopentadiene **243** which closes to the cyclobutadiene product.

The carbonyl oxygen in (3-oxocyclobutenyl)metal complexes is relatively polarized. Thus alkylation of the iron complex **244** or the cobalt complexes **245** with trialkyloxonium salts affords the corresponding (alkoxycyclobutadiene)metal cations **248** or **249**, respectively (Scheme 64)[38,230]. In a similar fashion, reaction of complexes **245** with BF_3 generates the zwitterionic complexes **250**. Olefination of the (3-oxocyclobutenyl)molybdenum complex **246** or tungsten complexes **247** gives the (3-methylenecyclobutenyl) complexes **251** (Scheme 64)[231]. Protonation of complexes **251** with HBF_4 give cationic (cyclobutadiene) species **252**.

Cyclopropene rings are stable, yet highly strained, ring systems. Under the influence of transition metals, facile ring-opening reactions may occur. The reaction of vinylcyclopropene **253** with $[RhCl(C_2H_4)_2]_2$ followed by treatment with $LiCp^*$ affords the metallacyclobutene complex **255** (Scheme 65)[232]. Heating **255** in chloroform generates the Cp^*Rh(cyclobutadiene) product **256**. In a somewhat similar fashion, reaction of vinylcyclopropene **254** with $Fe_2(CO)_9$ gave the η^2-complex **257**, which upon photolysis (but not thermolysis) gave a cyclobutadiene product **(258)**[233].


Me2Si
Me2Si
(CH2)n-2
(234)
Cp'Co(C2H4)2
n = 2; Cp' = C5Me5
n = 5, 6; Cp' = C5H5
(C5H5)Co(cod)
n = 2
CoCp'
(CH2)n-2
(CH2)n-2
CoCp'
(235) n = 2, 5, 6
CoCp
CpCo
CoCp
(236)

SCHEME 62



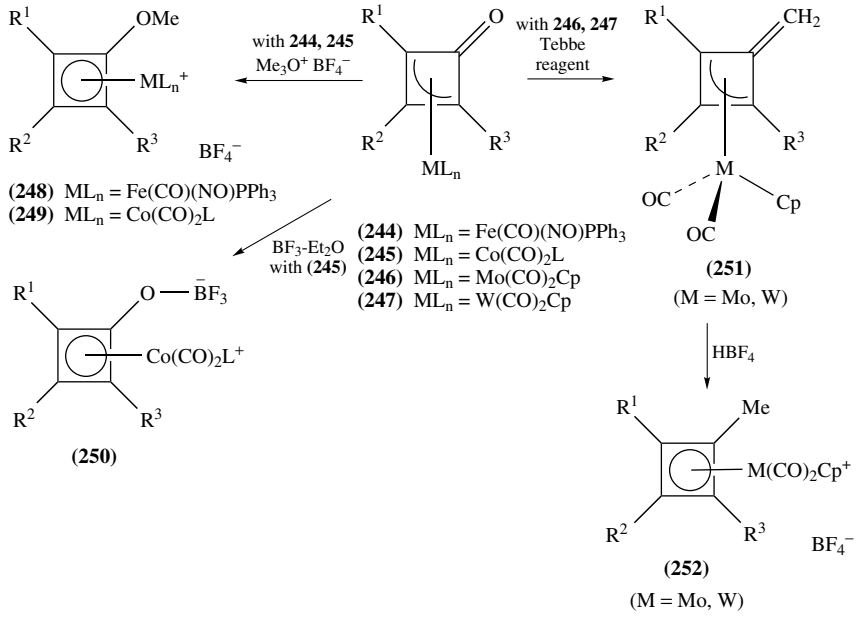
SCHEME 63

The (tetraphenylcyclobutadiene)PdX_2 dimer reacts with a variety of metal complexes via transfer of the cyclobutadiene ligand to another metal. These reactions and other ligand transfer reactions have been reviewed by Efraty[15].

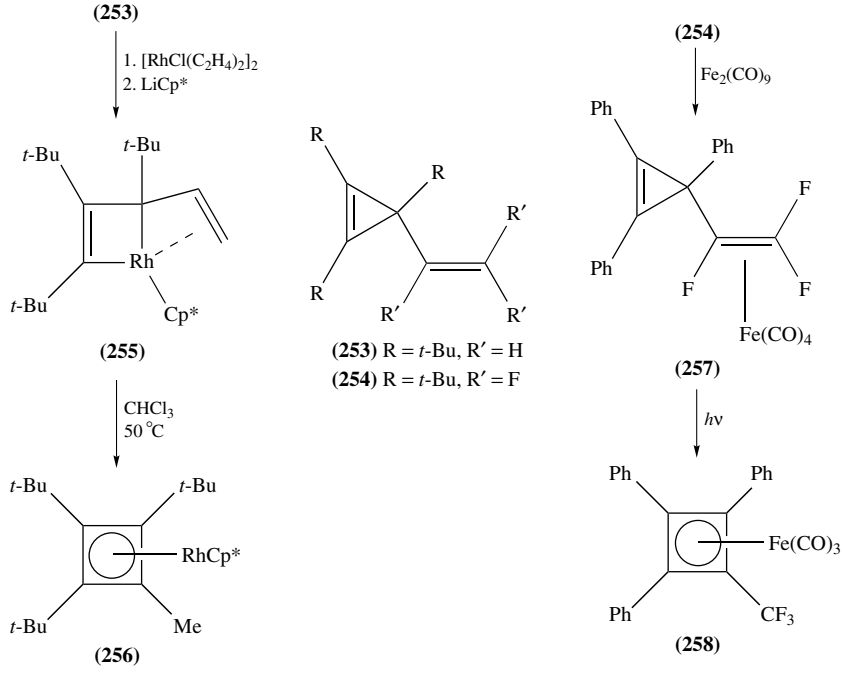
VII. REACTIONS OF CYCLOBUTADIENE–METAL COMPLEXES

A. Isomerizations

1,2-Disubstituted (cyclobutadiene)$Fe(CO)_3$ complexes in which the two substituents are different may exist as enantiomers. Racemic cyclobutadiene carboxylic acids or cyclobutadiene amine complexes of this type have been separated by classical resolution methodology[234]. These optically active (cyclobutadiene)$Fe(CO)_3$ complexes are stable with respect to racemization at 120 °C for 24 h. This stability contrasts with acyclic



SCHEME 64



SCHEME 65

(diene)$Fe(CO)_3$ complexes which have been shown to undergo racemization at this temperature (see Section IV.E.1.d).

In a similar fashion, 1-substituted-2,3-bis(trimethylsilyl) (cyclobutadiene)CoCp complexes in which the substituent contains a chiral center (e.g. **259**) exist as a mixture of diastereomers[235]. These diastereomers may be separated either by column chromatography or HPLC. Diastereoisomerization of either **259a** or **259b** requires extremely vigorous reaction conditions; either flash vacuum pyrolysis (>520 °C) or solution thermolysis (301 °C). The absence of ligand crossover products indicates that the diastereoisomerization occurs in a unimolecular fashion. Two possible pathways may be considered (Scheme 66). Pathway a involves insertion of cobalt into one side of the cyclobutadiene ligand to generate a cobaltacyclopentadiene intermediate. Notably, this type of intermediate is implicated in the cyclodimerization of alkynes to form (cyclobutadiene)CoCp complexes (see Scheme 60). Alternatively, in pathway b, a retro [2 + 2] cyclization would generate a bis-alkyne cobalt complex, which can undergo 'propeller' rotation about the alkyne-to-cobalt bond axis followed by [2 + 2] cyclization. Examination of the hexalabeled complex **260a** (two stereocenters, two different silyl groups, two ^{13}C labels) sheds light on these possibilities (Scheme 67). Thus, isomerization of **260a** leads only to isomer **261b** (but *not* to diastereomer **261a**) while isomerization of the **260b** leads only to **261a** (but not diastereomer **260a**). Since **260a** and **260b** should interconvert via the cobaltacyclopentadiene intermediate, the above results cannot be adequately explained by the 'pathway a' mechanistic possibility. The results are most consistent with a retro [2 + 2] alkyne cyclization ('pathway b') in such a fashion that the cyclobutadiene ring bond between the two silyl substituents is not broken.

Flash vacuum pyrolysis of deuterium-labeled [1,2-bis(ethynyl)cyclobutadiene]CoCp **262a** affords the rearranged product **262b** and recovered starting material (Scheme 68)[236]. None of the dideuteriated product **262c** or any of the potential [1,3-bis(ethynyl)cyclobutadiene] CoCp isomers were observed. These results are difficult to reconcile with a mechanism involving a bis(diyne)CoCp intermediate **(263)** and are most consistent with the intermediacy of either cyclooctadiendiyne complex **264** or cyclooctahexaene complex **265**.

B. Ligand Substitution

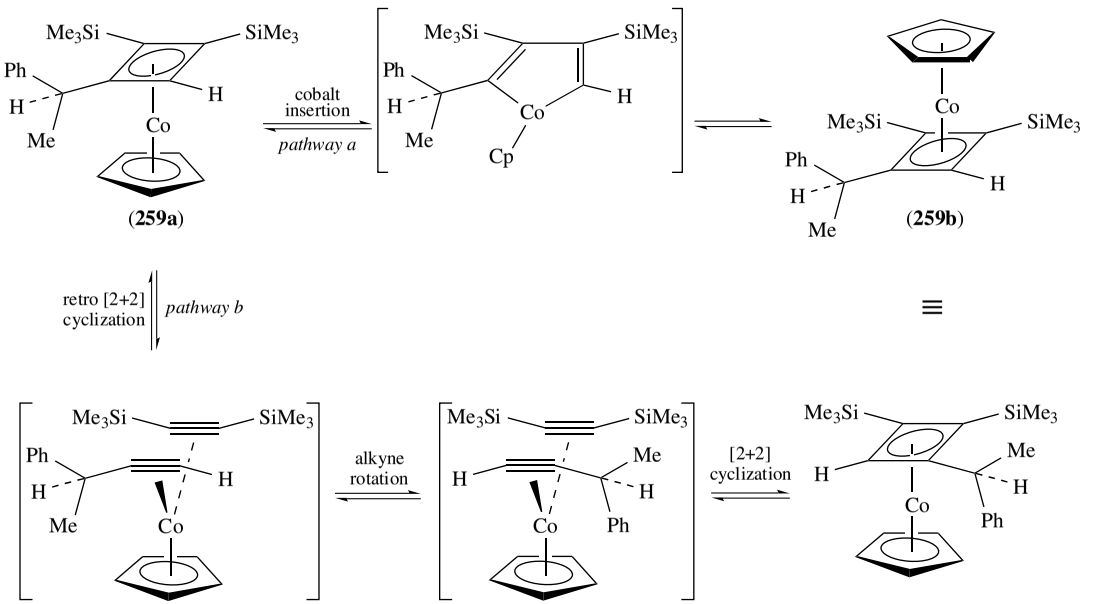
Tetramethyl- or tetraphenyl- (cyclobutadiene)nickel dihalides undergo reductive ligand substitution with nitrogen donor ligands such as 2,2′-bipyridine or 1,4-diaza-1,3-dienes with the addition of sodium metal[237]. The 2,2′-bipyridyl ligand is readily displaced and reaction of this complex with a variety of olefins and alkynes leads to cycloaddition reactions with the cyclobutadiene ligand.

Neutral (cyclobutadiene)$Co(CO)_2X$ complexes and (cyclobutadiene)$Co(CO)_3^+$ cations undergo displacement in the presence of arenes to generate (η^4-cyclobutadiene)(η^6-arene) Co^+ cations (Scheme 69)[38,211e,228a]. Neutral (cyclobutadiene)MoCp(CO)I complexes[50c] and (cyclobutadiene)$RuCp(CO)^+$ cations[219] also undergo ligand displacement of a coordinated carbon monoxide.

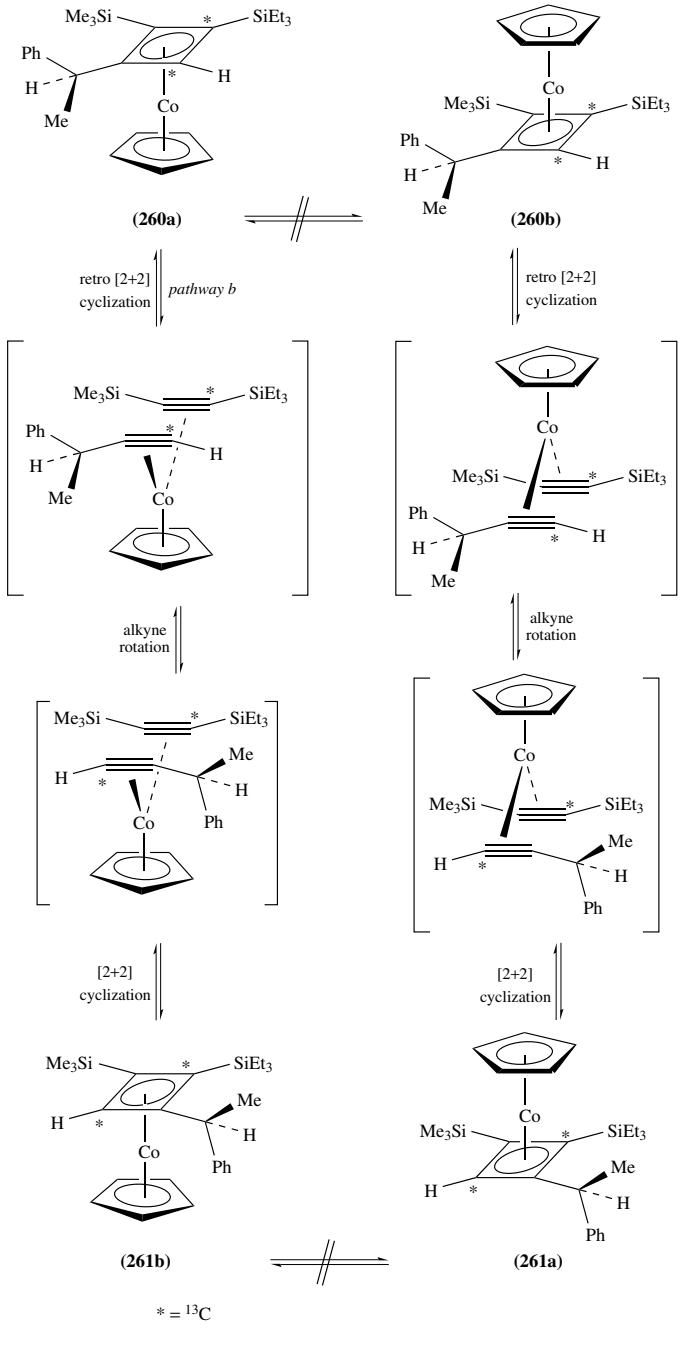
Neutral (cyclobutadiene)$Fe(CO)_3$ complexes undergo thermal and photochemical ligand substitution with phosphines, with alkenes such as dimethyl fumarate and dimethyl maleate and with the nitrosonium cation to generate the corresponding (cyclobutadiene)$Fe(CO)_2L$ complexes[15]. These types of complexes are presumably intermediates in the reaction of (cyclobutadiene)$Fe(CO)_3$ complexes with perfluorinated alkenes and alkynes to generate the insertion products **266** or **267** respectively (Scheme 70)[15,238].

C. Decomplexation

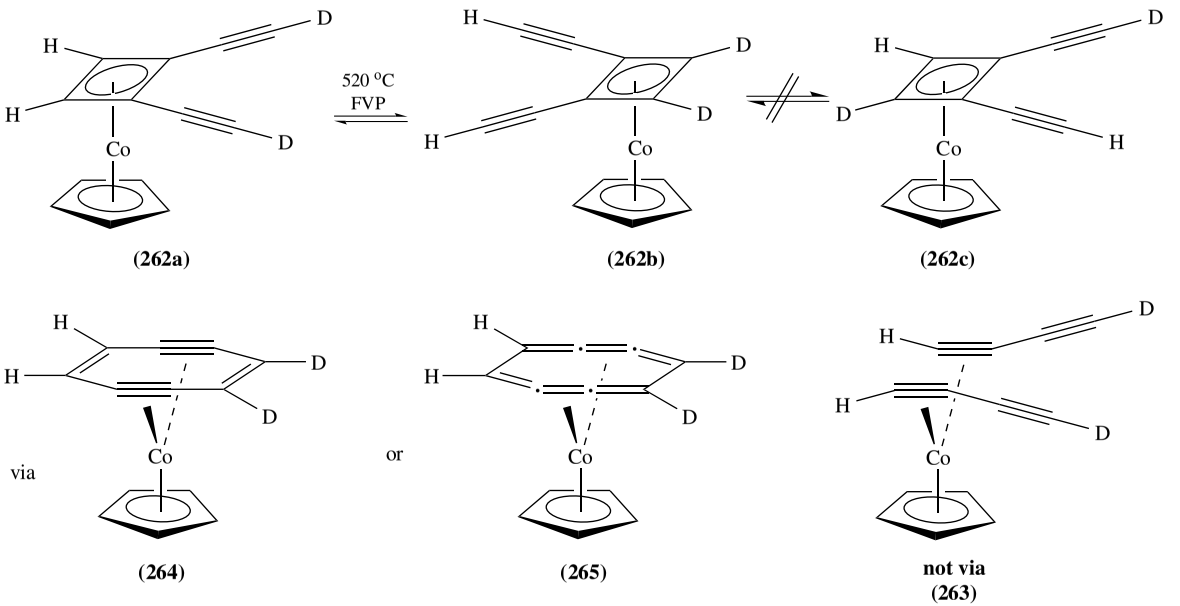
The majority of studies concerning decomplexation have been carried out on (cyclobutadiene)$Fe(CO)_3$ [**223**, $ML_n = Fe(CO)_3$] and substituted derivatives. As is the case


Me3Si
SiMe3
Ph
H
Me
Co
H
(259a)
cobalt
insertion
pathway a
Cp
(259b)
retro [2+2]
cyclization
pathway b
≡
alkyne
rotation
[2+2]
cyclization

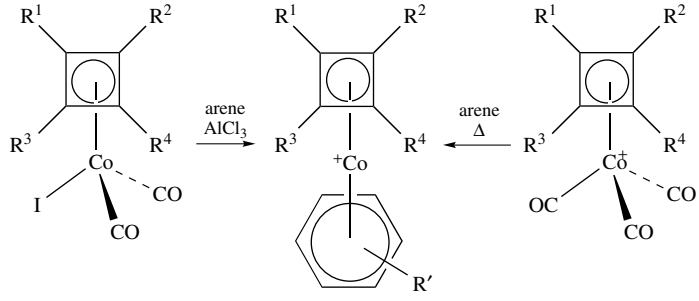
SCHEME 66


Me3Si
SiEt3
Ph
H
Me
Co
(260a)
(260b)
retro [2+2] cyclization
pathway b
alkyne rotation
[2+2] cyclization
(261b)
(261a)
* = 13C

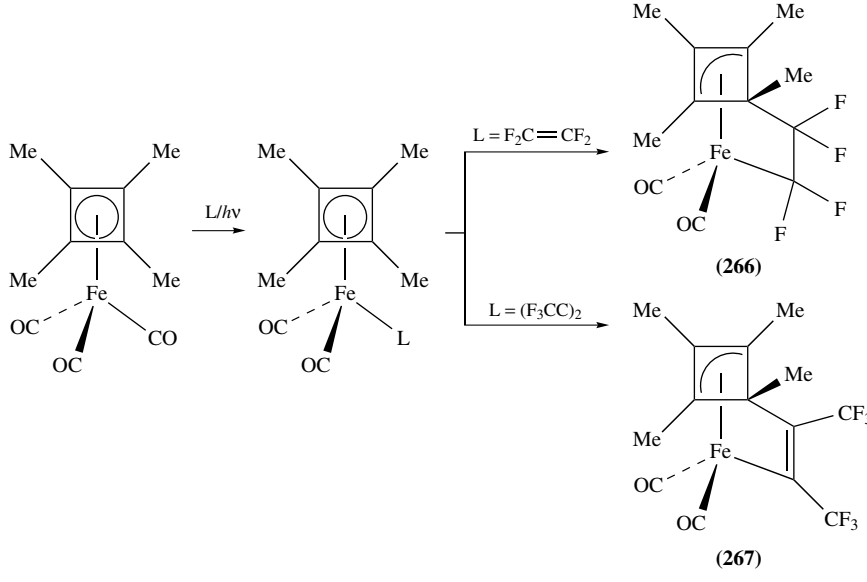
SCHEME 67



SCHEME 68



SCHEME 69



SCHEME 70

for acyclic butadiene and cyclohexadiene iron complexes (Section V.A.1), oxidation of (cyclobutadiene)$Fe(CO)_3$ liberates the organic ligand[239]. In the absence of other reactants the cyclobutadiene ligand undergoes dimerization to afford a mixture of *syn*- and *anti*-tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene (Scheme 71)[240]. In the presence of alkenes, alkynes or conjugated dienes, the liberated cyclobutadiene can act as either a diene or dienophile in Diels–Alder cycloadditions. Cycloaddition occurs in a stereospecific fashion with respect to the geometry of the alkene component and with *endo* selectivity. Oxidation of optically active (1,2-disubstituted cyclobutadiene)$Fe(CO)_3$ complexes leads to racemic products[234]. Thus the chemical oxidation appears to generate the ligand as a singlet diene. Additional evidence for the presence of the 'free' ligand was provided by the 'three phase test'. Transfer of the ligand from a polymer-bound (cyclobutadiene)iron complex by oxidation in the presence of a separately polymer-bound dienophile can only be accounted for by the

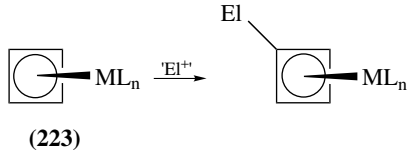
generation of the free ligand, since there is negligible contact between the functionalized sites of the two different polymeric supports[241]. The 'free' cyclobutadiene generated via the oxidation of (cyclobutadiene)$Fe(CO)_3$ has been utilized to prepare a variety of strained and theoretically interesting molecules (e.g. 'cubane', 'homocubanone', Dewar benzenes, and Dewar furan)[242].

Photolysis of substituted (cyclobutadiene)$Fe(CO)_3$ complexes (**268**, R = Me, CO_2Me, OEt) in the presence of alkynes affords substituted benzenes as a mixture of regioisomers[243]. The mechanism which is proposed involves initial loss of a carbon monoxide ligand and coordination of the alkyne (Scheme 72). Insertion of the alkyne into the cyclobutadiene–iron bond (cf Scheme 70) followed by reductive elimination affords a Dewar benzene intermediate. Secondary photolysis of the Dewar benzene gives the observed aromatic product. In a similar fashion, CAN oxidation of (cyclobutadiene) $Fe(CO)_3$ complexes **268** bearing a tethered alkyne or alkene (R = $CH_2OCH_2C{\equiv}CMe$, $CH_2OCH_2CH{=}CHPr$-*n*) generates tricyclic products **269** and **270** respectively (Scheme 72)[244]. The Dewar benzene product **(269)** opens to the substituted phthalan **271** under these oxidizing conditions.

D. Reactions with Electrophiles

The organic chemistry of (cyclobutadiene)metal complexes is much like that of ferrocene. Thus protonation of (cyclobutadiene)$Fe(CO)_3$ in HSO_3F/SO_2 generates a cationic species which exhibits a signal at $\delta -11.16$ ppm, consistent with a metal hydride species. However, spin–spin coupling of this signal to one of the ring protons is indicative that a bridging hydride species is more likely[245].

The reaction of (cyclobutadiene)metal complexes with X_2 results in the oxidative decomplexation to generate either dihalocyclobutenes or tetrahalocyclobutanes. In comparison, substitution of (cyclobutadiene)ML_n complexes **223** [ML_n = $Fe(CO)_3$, CoCp, and RhCp] with a variety of carbon electrophiles has been observed (equation 34)[15]. Electrophilic acylation of 1-substituted (cyclobutadiene)$Fe(CO)_3$ complexes gives a mixture of regioisomers predominating in the 1,3-disubstituted product and this has been utilized for the preparation of a cyclobutadiene cyclophane complex **272** (equation 35)[246]. For (cyclobutadiene)CoCp complexes, in which all of the ring carbons are substituted, electrophilic acylation occurs at the cyclopentadienyl ligand.



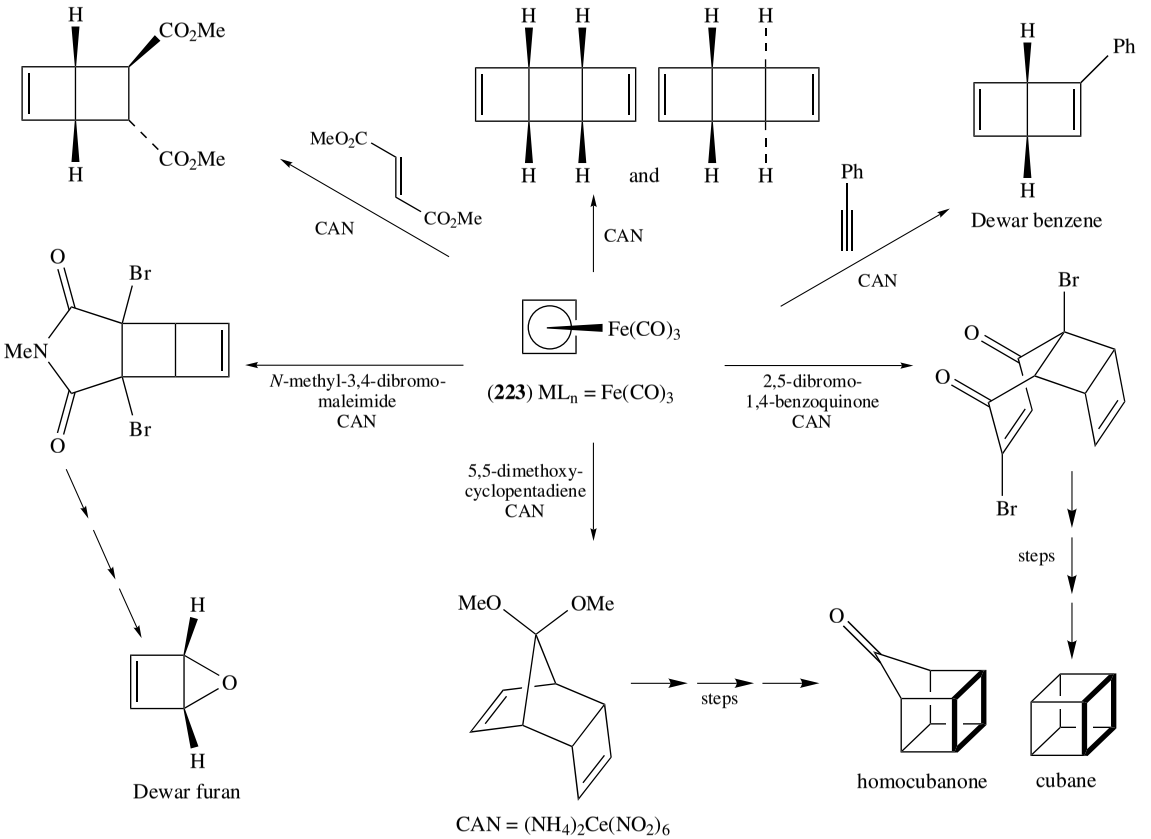
(223)

ML_n	'El^+'
$Fe(CO)_3$	COMe
CoCp	CHO
RhCp	CH_2Cl
	CH_2NMe_2
	HgCl
	SO_3H

(34)

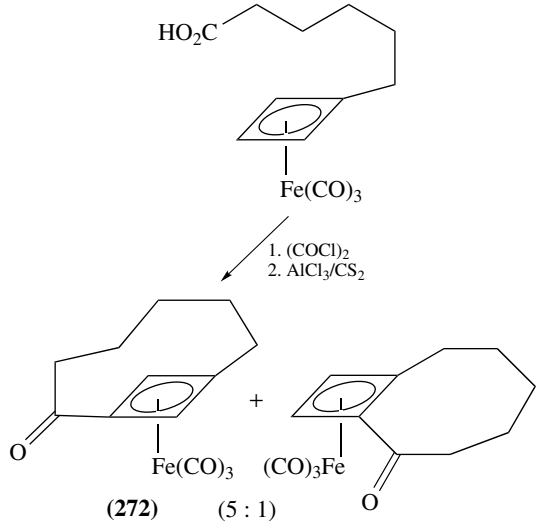
E. Reactions with Base or Nucleophiles

Deprotonation of (cyclobutadiene)$Fe(CO)_3$ with methyl lithium or *n*-butyl lithium is not possible[15], however lithiation is achieved by use of *s*-butyl lithium[247], or by transmetalation of (chloromercurycyclobutadiene)$Fe(CO)_3$. The metalated cyclobutadiene

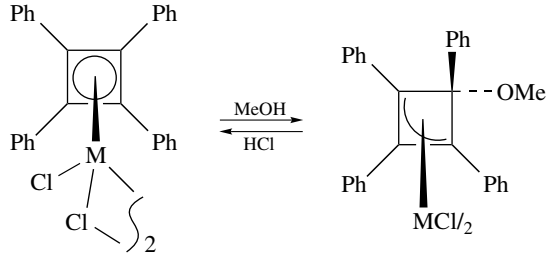

CO2Me
CO2Me
MeO2C
CO2Me
CAN
and
CAN
Ph
CAN
Ph
Dewar benzene
O
Br
MeN
O
Br
N-methyl-3,4-dibromo-
maleimide
CAN
Fe(CO)3
(223) MLn = Fe(CO)3
2,5-dibromo-
1,4-benzoquinone
CAN
Br
O
O
Br
5,5-dimethoxy-
cyclopentadiene
CAN
steps
H
O
H
Dewar furan
MeO
OMe
steps
O
homocubanone
cubane
CAN = (NH4)2Ce(NO2)6

SCHEME 71

can undergo reaction with Me_3SiCl, $(MeS)_2$, MeI, $(CH_2I)_2$ and ketones. Lithiation of (cyclobutadiene)CoCp with *n*-butyl lithium occurs predominantly at the cyclobutadiene ligand, as evidenced by carboxylation and esterification. However, a minor amount of product from lithiation at both the cyclobutadiene and cyclopentadienyl ligand is also isolated.

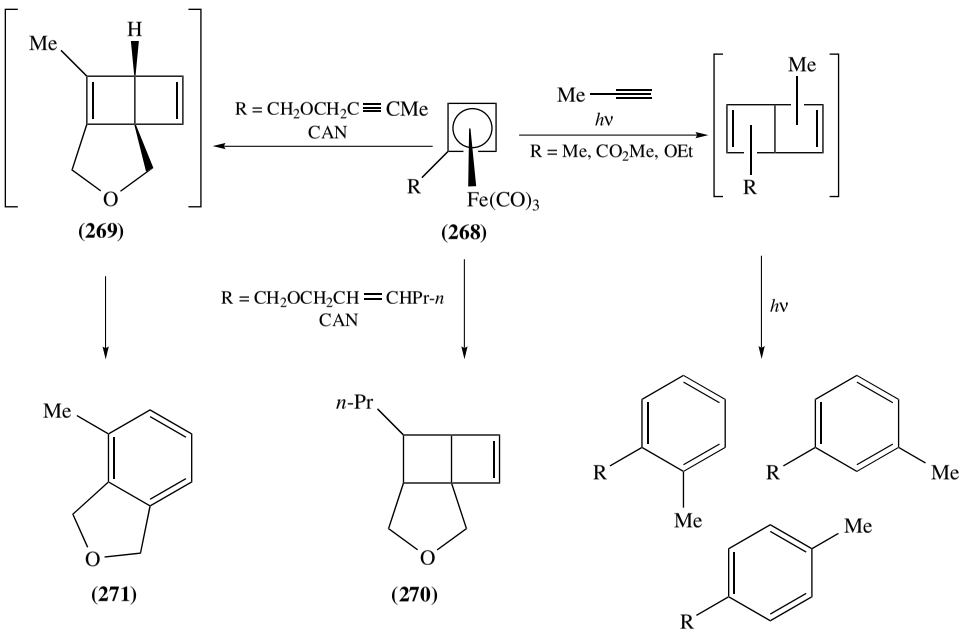


(272) (5 : 1) (35)

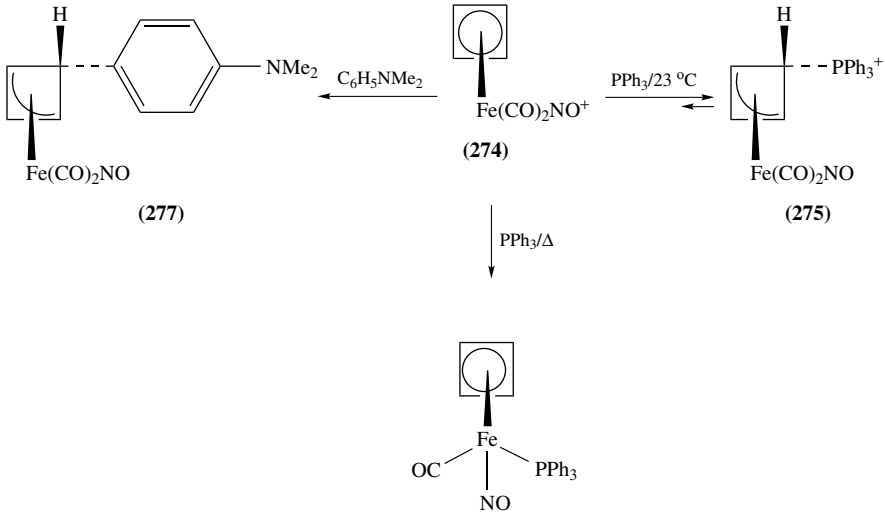


(273) M = Pd, Pt (36)

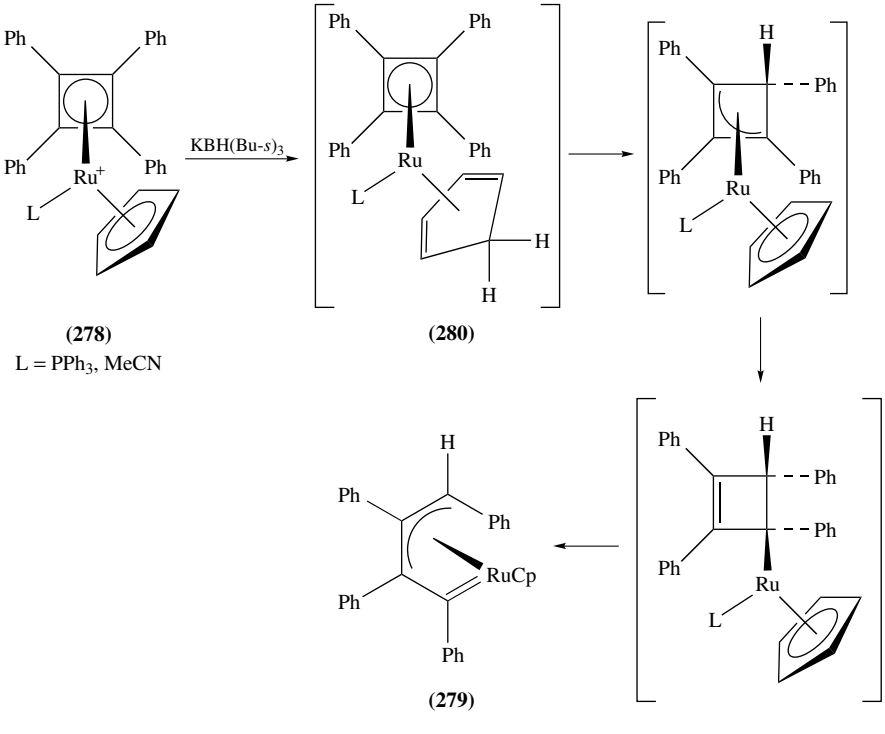
Although the reactivity of cyclobutadiene–metal complexes toward electrophiles has been studied extensively, there is relatively little known about their reactivity with nucleophiles. (Iodocyclobutadiene)$Fe(CO)_3$ reacts with alkoxide, sulfide or cyanide anions via displacement of the iodine. In the presence of palladium catalysts, (iodocyclobutadiene) $Fe(CO)_3$ undergoes coupling reactions with stannylalkynes to generate alkynylcyclobutadiene complexes[247]. Cyclobutadiene palladium- and platinum- chloride dimers **273** are reported to react with oxygen nucleophiles; the product is an *exo*-alkoxy-η^3-cyclobutenyl-metal species. This reaction is reversible upon addition of acid (equation 36)[248]. The (cyclobutadiene)$Fe(CO)_2NO^+$ cation **274** undergoes reaction with tertiary phosphines at 23 °C to form *exo*-phosphonium-η^3-cyclobutenyl iron complexes **275** (Scheme 73)[249]. This nucleophilic addition is reversible and, under more vigorous thermal conditions, the reaction proceeds via carbonyl substitution to yield the phosphine coordinated cation **276**. Reaction of **274** with *N*,*N*-dimethylaniline gives the η^3-cyclobutenyl iron complexes **277**.


Me
H
O
(269)
R = CH2OCH2C≡CMe
CAN
R
Fe(CO)3
(268)
Me
hν
R = Me, CO2Me, OEt
Me
R
R = CH2OCH2CH=CHPr-n
CAN
hν
Me
O
(271)
n-Pr
O
(270)
R
Me
R
Me
Me
R

SCHEME 72



SCHEME 73



SCHEME 74

Exo attack of the nucleophile on both **273** and **274** were unambiguously determined by crystal structure analysis.

Reaction of (tetraphenylcyclobutadiene)RuCpL$^+$ cations **278** with KBH(Bu-*s*)$_3$ gave product **279** from opening of the cyclobutadiene ring (Scheme 74)[250]. These reactions are believed to proceed via hydride attack on the cyclopentadienyl ligand to give **280**. Evidence for the intermediacy of **280** was obtained by NMR spectroscopy when L = P(OMe)$_3$. Migration of the hydride to the *endo* face of the cyclobutadiene would give a η^3-cyclobutenyl ruthenium species which undergoes ring opening to the final product.

VIII. REFERENCES

1. H. Reihlen, A. Grüghl, G. von Hessling and O. Pfrengle, *Justus Liebigs Ann. Chem.*, **482**, 161 (1930).
2. B. Hallam and P. Pauson, *J. Chem. Soc.*, 642 (1958).
3. O. S. Mills and G. Robinson, *Acta Crystalloger.*, **16**, 758 (1963).
4. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, New York, 1976.
5. T. Bally and S. Masamune, *Tetrahedron*, **36**, 343 (1980).
6. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **21**, 711 (1982).
7. (a) M. Elian and R. Hoffmann, *Inorg. Chem.*, **14**, 1058 (1975).
   (b) M. Elian, M. M. L. Chen, D. M. P. Mingos and R. Hoffmann, *Inorg. Chem.*, **15**, 1148 (1976).
8. J. W. Lauher and R. Hoffmann, *J. Am. Chem. Soc.*, **98**, 1729 (1976).
9. (a) H. Yasuda, K. Tatsumi, T. Okamoto, K. Mashima, K. Lee, A. Nakamura, Y. Kai, N. Kanehisa and N. Kasai, *J. Am. Chem. Soc.*, **107**, 2410 (1985).
   (b) C. Gemel, K. Mereiter, R. Schmid and K. Kirchner, *Organometallics*, **15**, 532 (1996).
10. G. Erker, J. Wicher, K. Engel, F. Rosenfeldt, W. Dietrich and C. Krüger, *J. Am. Chem. Soc.*, **102**, 6344 (1980).
11. Y. Kai, N. Kanehisa, K. Miki, N. Kasai, K. Mashima, K. Nagasuna, H. Yasuda and A. Nakamura, *J. Chem. Soc., Chem. Commun.*, 191 (1982).
12. A. D. Hunter, P. Legzdins, C. R. Nurse, F. W. B. Einstein and A. C. Willis, *J. Am. Chem. Soc.*, **107**, 1791 (1985).
13. (a) R. D. Ernst, E. Melendez, L. Stahl and M. Ziegler, *Organometallics*, **10**, 3635 (1991).
    (b) E. Melendez, R. Ilarraza, G. P. A. Yap and A. L. Rheingold, *J. Organomet. Chem.*, **522**, 1 (1996).
    (c) T. Sugaya, A. Tomita, H. Sago and M. Suno, *Inorg. Chem.*, **35**, 2692 (1996).
14. C. Gemel, K. Mereiter, R. Schmid and K. Kirchner, *Organometallics*, **16**, 2623 (1997).
15. A. Efraty, *Chem. Rev.*, **77**, 691 (1977).
16. R. Benn and G. Schroth, *J. Organomet. Chem.*, **228**, 71 (1982).
17. H. Yasuda, Y. Kajihara, K. Mashima, K. Nagasuna, K. Lee and A. Nakamura, *Organometallics*, **1**, 388 (1982).
18. U. Dorf, K. Engel and G. Erker, *Organometallics*, **2**, 462 (1983).
19. T. Okamoto, H. Yasuda, A. Nakamura, Y. Kai, N. Kanehisa and N. Kasai, *J. Am. Chem. Soc.*, **110**, 5008 (1988).
20. M. Kotzian, C. G. Kreiter and S. Özkar, *J. Organomet. Chem.*, **229**, 29 (1982).
21. J. W. Faller and A. M. Rosan, *J. Am. Chem. Soc.*, **99**, 4858 (1977).
22. K. B. Kingsbury, J. D. Carter, L. McElwee-White, R. L. Ostrander and A. L. Rheingold, *Organometallics*, **13**, 1635 (1994).
23. F. Timmers and M. Brookhart, *Organometallics*, **4**, 1365 (1985).
24. K. Bachmann and W. von Philipsborn, *Org. Magn. Reson.*, **8**, 648 (1976).
25. J. A. S. Howell, G. Walton, M.-C. Trivengadum, A. D. Squibb, M. G. Palin, P. McArdle, D. Cunningham, Z. Goldschmidt, H. Gottlieb and G. Strul, *J. Organomet. Chem.*, **401**, 91 (1991).
26. (a) S. Ruh and W. von Philipsborn, *J. Organomet. Chem.*, **127**, C59 (1977).
    (b) S. Zobl-Ruh and W. von Philipsborn, *Helv. Chim. Acta*, **63**, 773 (1980).
27. C. Gemel, D. Kalt, K. Mereiter, V. Sapunov, R. Schmid and K. Kirchner, *Organometallics*, **16**, 427 (1997).

28. L. S. Barinelli, K. Tao and K. M. Nicholas, *Organometallics*, **5**, 588 (1986).
29. S. M. Nelson, M. Sloan and M. G. B. Drew, *J. Chem. Soc., Dalton Trans.*, 2195 (1973).
30. S. A. Benyunes, M. Green and M. J. Grimshire, *Organometallics*, **8**, 2268 (1989).
31. N. J. Christensen, P. Legzdins, F. W. B. Einstein and R. H. Jones, *Organometallics*, **10**, 3070 (1991).
32. S. A. Benyunes, J. P. Day, M. Green, A. W. Al-Saadon and T. L. Waring, *Angew. Chem., Int. Ed. Engl.*, **29**, 1416 (1990).
33. B. E. Mann and B. F. Taylor, ^{13}C *NMR Data for Organometallic Compounds*, Academic Press, New York, 1981, pp. 210–218.
34. G. Erker, J. Wicher, K. Engel and C. Krüger, *Chem. Ber.*, **115**, 3300 (1982).
35. (a) S. Zobl-Ruh and W. von Philipsborn, *Helv. Chim. Acta*, **64**, 2378 (1981).
    (b) R. Benn and A. Rufinska, *J. Organomet. Chem.*, **323**, 305 (1987).
36. P. L. Pruitt, E. R. Biehl and P. C. Reeves, *J. Chem. Soc., Perkin Trans. 2*, 907 (1977).
37. A. Efraty, R. Bystrek, J. A. Geaman, S. S. Sandhu, Jr., M. H. A. Huang and R. H. Herber, *Inorg. Chem.*, **13**, 1269 (1974).
38. W. A. Donaldson, R. P. Hughes, R. E. Davis and S. M. Gadol, *Organometallics*, **1**, 812 (1982).
39. (a) G. Ville and K. P. Vollhardt, *J. Magn. Reson.*, **45**, 525 (1981).
    (b) W. A. Donaldson and R. P. Hughes, *J. Magn. Reson.*, **43**, 170 (1981).
40. (a) J. W. Faller, in *Advances in Organometallic Chemistry*, Vol. 16 (Eds. F. G. A. Stone and R. West), Academic Press, New York, 1977, pp. 211–239.
    (b) B. E. Mann, in *Comprehensive Organometallic Chemistry*, Vol. 3 (Eds. G. Wilkinson, F. G. A. Stone and E. W. Abel), Pergamon Press, New York, 1982, pp. 89–171.
41. J. A. S. Howell, in *Advances in Dynamic Stereochemistry*, Vol. 1 (Ed. M. F. Gielen), Chap. 4, Freund Publishing House, Ltd., London, 1985, pp. 111–205.
42. (a) F. A. Cotton, V. W. Day, B. A. Frenz, K. I. Hardcastle and J. M. Troup, *J. Am. Chem. Soc.*, **95**, 4522 (1973).
    (b) F. A. Cotton and J. M. Troup, *J. Organomet. Chem.*, **77**, 369 (1974).
    (c) F. H. Herbstein and M. G. Reisner, *Acta Crystallogr.*, **B33**, 3304 (1977).
43. (a) T. A. Albright, P. Hofmann and R. Hoffmann, *J. Am. Chem. Soc.*, **99**, 7546 (1977).
    (b) O. Gonzalez-Blanco and V. Branchadell, *Organometallics*, **16**, 475 (1997).
44. (a) C. G. Kreiter, S. Stüber and L. Wackerle, *J. Organomet. Chem.*, **66**, C49 (1974).
    (b) L. Kruczynski and J. Takats, *J. Am. Chem. Soc.*, **96**, 932 (1974).
    (c) D. Leibfritz and H. tom Dieck, *J. Organomet. Chem.*, **105**, 255 (1976).
    (d) J. Elzinga and H. Hogeveen, *Tetrahedron Lett.*, 2383 (1976).
    (e) J.-Y. Lallemand, P. Laszlo, C. Muzette and A. Stockis, *J. Organomet. Chem.*, **91**, 71 (1975).
    (f) P. Bischofberger and H.-J. Hansen, *Helv. Chim. Acta*, **65**, 721 (1982).
45. T. H. Whitesides and R. A. Budnick, *Inorg. Chem.*, **14**, 664 (1975).
46. C. G. Kreiter, M. Kotzian, U. Schubert, R. Bau and M. A. Bruck, *Z. Naturforsch. B*, **39B**, 1553 (1984).
47. C. G. Kreiter, in *Advances in Organometallic Chemistry*, Vol. 26 (Eds. F. G. A. Stone and R. West), Academic Press, New York, 1986, pp. 197–375.
48. C. G. Kreiter, K. Nist and J. Kögler, *Z. Naturforsch.*, **41B**, 599 (1986).
49. P. D. Harvey, I. S. Butler and D. F. R. Gilson, *Inorg. Chem.*, **25**, 1009 (1986).
50. (a) J. L. Davidson, *J. Chem. Soc., Chem. Commun.*, 113 (1980).
    (b) J. L. Davidson, *J. Chem. Soc., Dalton Trans.*, 2715 (1987).
    (c) J. L. Davidson, *J. Organomet. Chem.*, **419**, 137 (1991).
51. G. Erker, K. Engel, C. Krüger and A.-P. Chiang, *Chem. Ber.*, **115**, 3311 (1982).
52. (a) H. Yasuda, Y. Kajihara, K. Mashima, K. Lee and A. Nakamura, *Chem. Lett.*, 519 (1981).
    (b) H. Yasuda, K. Nagasuna, M. Akita, K. Lee and A. Nakamura, *Organometallics*, **3**, 1470 (1984).
53. Y. Kai, N. Kanehisa, K. Miki, N. Kasai, M. Akita, H. Yasuda and A. Nakamura, *Bull. Chem. Soc. Jpn.*, **56**, 3735 (1983).
54. G. Erker, K. Engel, U. Korek, P. Czisch, H. Berke, P. Caubère and R. Vanderesse, *Organometallics*, **4**, 1531 (1985).
55. C. Krüger, G. Müller, G. Erker, U. Dorf and K. Engel, *Organometallics*, **4**, 215 (1985).
56. M. Brookhart, S. K. Noh, F. J. Timmers and Y. H. Hong, *Organometallics*, **7**, 2458 (1988).

57. (a) C. G. Kreiter, A. Maasbol, F. A. L. Anet, H. D. Kaesz and S. Winstein, *J. Am. Chem. Soc.*, **88**, 3444 (1966).
(b) C. E. Keller, B. A. Shoulders and R. Pettit, *J. Am. Chem. Soc.*, **88**, 4760 (1966).
(c) F. A. Cotton, A. Davidson and J. W. Faller, *J. Am. Chem. Soc.*, **88**, 4507 (1966).
58. (a) F. A. Cotton, A. Davidson, T. J. Marks and A. Musco, *J. Am. Chem. Soc.*, **91**, 6598 (1969).
(b) F. A. Cotton and D. L. Hunter, *J. Am. Chem. Soc.*, **98**, 1413 (1976).
59. H. W. Whitlock, Jr. and H. Stucki, *J. Am. Chem. Soc.*, **94**, 8594 (1972).
60. M. A. Bennett, T. W. Matheson, G. B. Robertson, A. K. Smith and P. A. Tucker, *Inorg. Chem.*, **19**, 1014 (1980).
61. (a) K. J. Karel and M. Brookhart, *J. Am. Chem. Soc.*, **100**, 1619 (1978).
(b) H. Günther and R. Wenzl, *Tetrahedron Lett.*, 4155 (1967).
(c) R. Aumann, H. Averbeck and C. Krüger, *Chem. Ber.*, **108**, 3336 (1975).
(d) L. K. K. Li Shing Man and J. Takats, *J. Organomet. Chem.*, **117**, C104 (1976).
62. (a) G. Michael, J. Kaub and C. G. Kreiter, *Angew. Chem., Int. Ed. Engl.*, **24**, 502 (1985).
(b) G. Michael, J. Kaub and C. G. Kreiter, *Chem. Ber*, **118**, 3944 (1985).
63. (a) M. Brookhart, T. H. Whitesides and J. M. Crockett, *Inorg. Chem.*, **15**, 1550 (1976).
(b) M. A. Bennett and T. W. Matheson, *J. Organomet. Chem.*, **153**, C25 (1978).
(c) S. D. Ittel, F. A. Van-Catledge, C. A. Tolman and J. P. Jesson, *J. Am. Chem. Soc.*, **100**, 1317 (1978).
(d) S. D. Ittel, F. A. Van-Catledge and J. P. Jesson, *J. Am. Chem. Soc.*, **101**, 6905 (1979).
(e) B. Buchmann, U. Piantini, W. von Philipsborn and A. Salzer, *Helv. Chim. Acta*, **70**, 1487 (1987).
(f) M. A. Bennett, I. J. McMahon, S. Pelling, M. Brookhart and D. M. Lincoln, *Organometallics*, **11**, 127 (1992).
64. G. Erker, K. Engel and P. Vogel, *Angew. Chem., Int. Ed. Engl.*, **21**, 782 (1982).
65. G. Erker, T. Mühlenbernd, A. Rufinska and R. Benn, *Chem. Ber.*, **120**, 507 (1987).
66. R. Beckhaus and K.-H. Thiele, *J. Organomet. Chem.*, **317**, 23 (1986).
67. P. Czisch, G. Erker, H.-G. Korth and R. Sustmann, *Organometallics*, **3**, 945 (1984).
68. B. Hessen and J. H. Teuben, *J. Organomet. Chem.*, **358**, 135 (1988).
69. (a) J. Chen, Y. Kai, N. Kasai, H. Yamamoto, H. Yasuda and A. Nakamura, *Chem. Lett.*, 1545 (1987).
(b) H. Yamamoto, H. Yasuda, K. Tatsumi, K. Lee, A. Nakamura, J. Chen, Y. Kai and N. Kasai, *Organometallics*, **8**, 105 (1989).
70. (a) J. Blenkers, H. J. de Liefde Meijer and J. H. Teuben, *Organometallics*, **2**, 1483 (1983).
(b) B. Hessen, J. Blenkers, J. H. Teuben, G. Helgesson and S. Jagner, *Organometallics*, **8**, 2809 (1989).
71. J. Blenkers, B. Hessen, F. van Bolhuis, A. J. Wagner and J. H. Teuben, *Organometallics*, **6**, 459 (1987).
72. J. Blenkers, H. J. de Liefde Meijer and J. H. Teuben, *J. Organomet. Chem.*, **218**, 383 (1981).
73. A. Nakamura and K. Mashima, *J. Organomet. Chem.*, **500**, 261 (1995).
74. K. Mashima, Y. Yamanaka, S. Fujikawa, H. Yasuda and A. Nakamura, *J. Organomet. Chem.*, **428**, C5 (1992).
75. (a) M. D. Curtis, J. Real and D. Kwon, *Organometallics*, **8**, 1644 (1989).
(b) V. C. Gibson, T. P. Kee and W. Clegg, *J. Chem. Soc., Dalton Trans.*, 3199 (1990).
76. H. C. Strauch, G. Erker and R. Frölich, *Organometallics*, **17**, 5746 (1998).
77. (a) G. Leigh and E. O. Fischer, *J. Organomet. Chem.*, **4**, 461 (1965)
(b) J. R. Blackborow, C. R. Eady, F.-W. Grevels, E. A. Körner von Gustorf, A. Scrivanti, O. S. Wolfbeis, R. Benn, D. J. Brauer, C. Krüger, P. J. Roberts and Y.-H. Tsay, *J. Chem. Soc., Dalton Trans.*, 661 (1981).
78. (a) I. Fischler, M. Budzwait and E. A. Körner von Gustorf, *J. Organomet. Chem.*, **105**, 325 (1976).
(b) S. Özkar, N. K. Tunali and C. G. Kreiter, *J. Organomet. Chem.*, **428**, 345 (1992).
79. (a) C. G. Kreiter and S. Özkar, *J. Organomet. Chem.*, **152**, C13 (1978).
(b) M. Kotzian, C. G. Kreiter, G. Michael and S. Özkar, *Chem. Ber.*, **116**, 3637 (1983).
(c) S. Özkar and C. G. Kreiter, *J. Organomet. Chem.*, **303**, 367 (1986).
(d) D. J. Wink, N.-F. Wang and B. T. Creagan, *Organometallics*, **8**, 561 (1989).
(e) C. G. Kreiter, M. Kotzian, S. Özkar and I. Abu-Mour, *J. Organomet. Chem.*, **431**, 159 (1991).

80. (a) F. Hohmann, H. tom Dieck, T. Mack and D. Leibfritz, *J. Organomet. Chem.*, **132**, 255 (1977).
(b) S. Özkar and C. G. Kreiter, *J. Organomet. Chem.*, **256**, 57 (1983).
(c) C. G. Kreiter and M. Kotzian, *J. Organomet. Chem.*, **289**, 295 (1985).
(d) S. Özkar, C. Kayran and C. G. Kreiter, *J. Organomet. Chem.*, **434**, 79 (1992).
81. (a) M. Bottrill and M. Green, *J. Chem. Soc., Dalton Trans.*, 2365 (1977).
(b) M. Green, S. Greenfield and M. Kersting, *J. Chem. Soc., Chem. Commun.*, 18 (1985).
(c) J. S. Baxter, M. Green and T. V. Lee, *J. Chem. Soc., Chem. Commun.*, 1595 (1989).
82. (a) A. J. Pearson and V. D. Khetani, *J. Org. Chem.*, **53**, 3395 (1988).
(b) A. J. Pearson and V. D. Khetani, *J. Am. Chem. Soc.*, **111**, 6778 (1989).
83. (a) A. J. Pearson and A. R. Douglas, *Organometallics*, **17**, 1446 (1998).
(b) K. Mauthner, C. Slugovc, K. Mereiter, R. Schmid and K. Kirchner, *Organometallics*, **15**, 181 (1996).
(c) E. Bjurling and C.-M. Andersson, *Tetrahedron Lett.*, **40**, 1981 (1999).
84. (a) J. W. Faller, H. H. Murray, D. L. White and K. H. Chao, *Organometallics*, **2**, 400 (1983).
(b) A. J. Pearson and M. N. I. Khan, *Tetrahedron Lett.*, **26**, 1407 (1985).
(c) L. S. Liebeskind and A. Bombrun, *J. Am. Chem. Soc.*, **113**, 8736 (1991).
(d) J. W. Faller, in *Encyclopedia of Reagents for Organic Synthesis* (Ed. L. A. Paquette), Vol. 3, Wiley, New York, 1995, pp. 1637–1639.
85. S. Hansson, J. F. Miller and L. S. Liebeskind, *J. Am. Chem. Soc.*, **112**, 9660 (1990).
86. A. Rubio and L. S. Leibeskind, *J. Am. Chem. Soc.*, **115**, 891 (1993).
87. S. A. Benyunes, M. Green, M. McPartlin and C. B. M. Nation. *J. Chem. Soc., Chem. Commun.*, 1887 (1989).
88. (a) M.-H. Cheng, Y.-H. Ho, G.-H. Lee, S.-M. Peng and R.-S. Liu, *J. Chem. Soc., Chem. Commun.*, 697 (1991).
(b) S.-H. Lin, Y.-J. Yang and R.-S. Liu, *J. Chem. Soc., Chem. Commun.*, 1004 (1991).
(c) M.-H. Cheng, Y.-H. Ho, S.-L. Wang, C.-Y. Cheng, S.-M. Peng, G.-H. Lee and R.-S. Liu, *J. Chem. Soc., Chem. Commun.*, 45 (1992).
89. (a) A. D. Hunter, P. Legzdins, F. W. B. Einstein, A. C. Willis, B. E. Bursten and M. G. Gatter, *J. Am. Chem. Soc.*, **108**, 3843 (1986).
(b) N. J. Christensen, A. D. Hunter and P. Legzdins, *Organometallics*, **8**, 930 (1989).
90. (a) W. Lamanna and M. Brookhart, *J. Am. Chem. Soc.*, **103**, 989 (1981).
(b) M. Brookhart, W. Lamanna and M. B. Humphrey, *J. Am. Chem. Soc.*, **104**, 2117 (1982).
(c) M. Brookhart, W. Lamanna and A. R. Pinhas, *Organometallics*, **2**, 638 (1983).
(d) M. Brookhart and A. Lukacs, *J. Am. Chem. Soc.*, **106**, 4161 (1984).
91. B. C. Roell, Jr., K. F. McDaniel, W. S. Vaughn and T. S. Macy, *Organometallics*, **12**, 224 (1993).
92. R. S. Padda, J. B. Sheridan and K. Chaffee, *J. Chem. Soc., Chem. Commun.*, 1226 (1990).
93. (a) Y. K. Chung, H. S. Choi, D. A. Sweigart and N. G. Connelly, *J. Am. Chem. Soc.*, **104**, 4245 (1982).
(b) Y. K. Chung, E. D. Honig, W. T. Robinson, D. A. Sweigart, N. G. Connelly and S. D. Ittel, *Organometallics*, **2**, 1479 (1983).
(c) Y. K. Chung, D. A. Sweigart, N. G. Connelly and J. B. Sheridan, *J. Am. Chem. Soc.*, **107**, 2388 (1985).
(d) S. D. Ittel, J. F. Whitney, Y. K. Chung, P. G. Williard and D. A. Sweigart, *Organometallics*, **7**, 1323 (1988).
(e) R. D. Pike, W. J. Ryan, G. B. Carpenter and D. A. Sweigart, *J. Am. Chem. Soc.*, **111**, 8535 (1989).
(f) W. H. Miles and H. R. Brinkman, *Tetrahedron Lett.*, **33**, 589 (1992).
(g) T.-Y. Lee, Y. K. Kang, Y. K. Chung, R. D. Pike and D. A. Sweigart, *Inorg. Chim. Acta*, **214**, 125 (1993).
94. E. D. Honig and D. A. Sweigart, *J. Chem. Soc., Chem. Commun.*, 691 (1986).
95. (a) R. D. Pike, T. J. Alavosus, C. A. Camaioni-Neto, J. C. Williams, Jr. and D. A. Sweigart, *Organometallics*, **8**, 2631 (1989).
(b) R. D. Pike, W. J. Ryan, N. S. Lennhoff, J. Van Epp and D. A. Sweigart, *J. Am. Chem. Soc.*, **112**, 4798 (1990).
96. W. A. Herrmann, R. A. Fischer and E. Herdtweck, *Organometallics*, **8**, 2821 (1989).

97. (a) R. B. King, in *The Organic Chemistry of Iron*, Vol. 1 (Eds. E. A. Körner von Gustorf, F.-W. Grevels and I. Fischler), Academic Press, New York, 1978, p. 525.
(b) G. F. Emerson, J. E. Mahler, R. Kochhar and R. Pettit, *J. Org. Chem.*, **29**, 3620 (1964).
(c) S. V. Ley, C. M. R. Low and A. D. White, *J. Organometal. Chem.*, **302**, C13 (1986).
(d) G. F. Docherty, G. R. Knox and P. L. Pauson, *J. Organomet. Chem.*, **568**, 287 (1998).
98. (a) A. J. Birch, P. E. Cross, J. Lewis and D. A. White, *Chem. Ind.*, 838 (1964).
(b) A. J. Pearson, *Synlett*, 10 (1990).
99. Y. Shvo and E. Hazum, *J. Chem. Soc., Chem. Commun.* 829 (1975).
100. (a) J. Kiji and M. Iwamoto, *Bull. Chem. Soc. Jpn.*, **41**, 1483 (1968).
(b) C. W. Ong, W. T. Liou and W. S. Hwang, *J. Organomet. Chem.*, **384**, 133 (1990).
101. H.-J. Knölker, in *Encyclopedia of Reagents for Organic Synthesis*, Vol. 1 (Ed. L. A. Paquette), Wiley, New York, 1995, pp. 333–335.
102. (a) A. Musco, P. Palumbo and G. Paiaro, *Inorg. Chim. Acta*, **5**, 157 (1971).
(b) A. J. Birch and B. M. R. Bandara, *Tetrahedron Lett.*, **21**, 2981 (1980);
(c) A. Monpert, J. Martelli, R. Grée and R. Carrié, *Tetrahedron Lett.*, **22**, 1961 (1981).
103. (a) H.-J. Knölker, P. Gonser and T. Koegler, *Tetrahedron Lett.*, **37**, 2405 (1996).
(b) M. Xu and C. D. Tran, *J. Chromatogr.*, **543**, 233 (1991).
104. (a) J. A. S. Howell, M. G, Palin, G. Jaouen, S. Top, H. El Hafa and J. M. Cense, *Tetrahedron: Asymmetry*, **4**, 1241 (1993).
(b) M. Uemura, H. Nishimura, S. Yamada, Y. Hayashi, K. Nakamura, K. Ishihara and A. Ohno, *Tetrahedron: Asymmetry*, **5**, 1673 (1994).
(c) N. W. Alcock, D. H. G. Crout, C. M. Henderson and S. E. Thomas, *J. Chem. Soc., Chem. Commun.*, 746 (1988).
(d) W. R. Roush and J. C. Park, *Tetrahedron Lett.*, **31**, 4707 (1990).
105. (a) A. J. Birch and H. Fitton, *Aust. J. Chem.*, **22**, 971 (1969).
(b) H. Alper and C.-C. Huang, *J. Organomet. Chem.*, **50**, 213 (1973).
(c) D. H. R. Barton, A. A. L. Gunatilaka, T. Nakanishi, H. Patin, D. A. Widdowson and B. R. Worth, *J. Chem. Soc., Perkin Trans. 1*, 821 (1976).
(d) P. McArdle and T. Higgins, *Inorg. Chim. Acta*, **30**, L303 (1978).
(e) L. A. Paquette and R. G. Daniels, *Organometallics*, **1**, 757 (1982).
(f) P. W. Howard, G. R. Stephenson and S. C. Taylor, *J. Organomet. Chem.*, **370**, 97 (1989).
(g) A. Salzer, H. Schmalle, R. Stauber and S. Streiff, *J. Organomet. Chem.* **408**, 403 (1991).
(h) A. J. Pearson, K. Chang, D. B. McConville and W. J. Youngs, *Organometallics*, **13**, 4 (1994).
(i) H.-G. Schmalz, E. Hessler, J. W. Bats and G. Dürner, *Tetrahedron Lett.*, **35**, 4543 (1994).
(j) R. S. Paley, A. de Dios, L. A. Estroff, J. A. Lafontaine, C. Montero, D. J. McCulley, M. B. Rubio, M. P. Ventura, H. L. Weers, R. F. de la Pradilla, S. Castro, R. Dorado and M. Morento, *J. Org. Chem.*, **62**, 6326 (1997).
106. (a) H.-J. Knölker and H. Hermann, *Angew. Chem., Int. Ed. Engl.*, **35**, 341 (1996).
(b) F. Maywald and P. Eilbracht, *Synlett*, 380 (1996).
(c) A. J. Birch, W. D. Raverty and G. R. Stephenson, *Organometallics*, **3**, 1075 (1984).
107. (a) R. Victor, R. Ben-Shoshan and S. Sarel, *Tetrahedron Lett.*, 4257 (1970).
(b) R. Victor, R. Ben-Shoshan and S. Sarel, *J. Org. Chem.*, **37**, 1930 (1972).
(c) R. E. Davis and R. Pettit, *J. Am. Chem. Soc.*, **92**, 716 (1970).
108. (a) R. C. Kerber and E. C. Ribakove, *Organometallics*, **10**, 2848 (1991).
(b) D. Farcasiu and G. Marino, *J. Organomet. Chem.*, **253**, 243 (1983).
(c) M.-C. P. Yeh, T. Chou, H.-H. Tso and C.-Y. Tsai, *J. Chem. Soc., Chem. Commun.*, 897 (1990).
109. (a) A. D. English, J. P. Jesson and C. A. Tolman, *Inorg. Chem.*, **15**, 1730 (1976).
(b) S. D. Ittel, F. A. Van-Catledge and J. P. Jesson, *J. Am. Chem. Soc.*, **101**, 3874 (1979).
110. (a) S. Sarel, R. Ben-Shoshan and B. Kirson, *J. Am. Chem. Soc.*, **87**, 2517 (1965).
(b) R. Ben-Shoshan and S. Sarel, *J. Chem. Soc., Chem Commun.*, 883 (1969).
(c) R. Aumann, *J. Organomet. Chem.*, **47**, C29 (1973).
(d) R. Aumann, *J. Am. Chem. Soc.*, **96**, 2631 (1974).
111. (a) T. H. Whitesides and R. W. Slaven, *J. Organomet. Chem.*, **67**, 99 (1974).
(b) A. R. Pinhas, A. G. Samuelson, R. Risemberg, E. V. Arnold, J. Clardy and B. K. Carpenter, *J. Am. Chem. Soc.*, **103**, 1668 (1981).
112. R. Aumann, H. Ring, C. Krüger and R. Goddard, *Chem. Ber.*, **112**, 3644 (1979).

113. (a) G. Dettlaf, U. Behrens and E. Weiss, *Chem. Ber.*, **111**, 3019 (1978).
(b) P. Binger, B. Cetinkaya and C. Krüger, *J. Organomet. Chem.*, **159**, 63 (1978).
(c) M. G. Newton, N. S. Pantaleo, R. B. King and C.-K. Chu, *J. Chem. Soc., Chem. Commun.*, 10 (1979).
(d) M. Franck-Neumann, C. Dietrich-Buchecker and A. K. Khémiss, *J. Organomet. Chem.*, **220**, 187 (1981).
(e) M. Franck-Neumann, C. Dietrich-Buchecker and A. Khemiss, *Tetrahedron Lett.*, **22**, 2307 (1981).
114. (a) T.-A. Mitsudo, T. Sasaki, Y. Watanabe, Y. Takegami, S. Nishigaki and K. Nakatsu, *J. Chem. Soc., Chem. Commun.*, 252 (1978).
(b) T. Mitsudo, A. Ishihara, M. Kadokura and Y. Watanabe, *Organometallics*, **5**, 238 (1986).
115. (a) A. J. Pearson, R. J. Shively, Jr. and R. A. Dubbert, *Organometallics*, **11**, 4096 (1992).
(b) A. J. Pearson and R. J. Shively, Jr., *Organometallics*, **13**, 578 (1994).
(c) A. J. Pearson and A. Perosa, *Organometallics*, **14**, 5178 (1995).
(d) H.-J. Knölker, J. Heber and C. H. Mahler, *Synlett*, 1002 (1992).
(e) H.-J. Knölker and J. Heber, *Synlett*, 924 (1993).
116. (a) A. J. Pearson, *Acc. Chem. Res.*, **13**, 463 (1980).
(b) A. J. Birch and L. F. Kelly, *J. Organomet. Chem.*, **285**, 267 (1985).
(c) G. R. Stephenson, S. T. Astley, I. M. Palotai, P. W. Howard, D. A. Owen and S. Williams, in *Organic Synthesis via Organometallics* (Eds. K. H. Dötz and R. W. Hoffmann), Wieweg, Braunschweig, 1991, pp. 169–185.
(d) H.-J. Knölker, *Synlett*, 371 (1992).
(e) C. Tao, in *Encyclopedia of Reagents for Organic Synthesis* (Ed. L. A. Paquette), Vol. 7, Wiley, New York, 1995, pp. 5043–5045.
117. (a) A. J. Pearson, S. L. Kole and T. Ray, *J. Am. Chem. Soc.*, **106**, 6060 (1984).
(b) M. M. Hossain and A. K. Saha, in *Encyclopedia of Reagents for Organic Synthesis* (Ed. L. A. Paquette), Vol. 3, Wiley, New York, 1995, pp. 1635–1637.
(c) P. Eilbracht and A. Hirshfelder, in *Advances in Metal-Organic Chemistry* (Ed. L. S. Liebeskind), Vol. 5, JAI Press Inc., London, 1996, pp. 55–118.
118. (a) W. A. Donaldson, in *Encyclopedia of Reagents for Organic Synthesis* (Ed. L. A. Paquette), Vol. 7, Wiley, New York, 1995, pp. 5048–5050.
(b) W. A. Donaldson, *Aldrichimica Acta*, **30**, 17 (1997).
(c) R. Grée and J. P. Lellouche, in *Advances in Metal-Organic Chemistry* (Ed. L. S. Liebeskind), Vol. 4, JAI Press Inc., London, 1995, pp. 129–273.
119. T. S. Sorenson and C. R. Jablonski, *J. Organomet. Chem.*, **25**, C62 (1970).
120. A. J. Pearson, S. L. Blystone, H. Nar, A. A. Pinkerton, B. A. Roden and J. Yoon, *J. Am. Chem. Soc.*, **111**, 134 (1989).
121. (a) A. Tajiri, N. Morita, T. Asao and M. Hatano, *Angew. Chem., Int. Ed. Engl.*, **24**, 329 (1985).
(b) N. Morita and T. Asao, *Tetrahedron Lett.*, **27**, 3873 (1986).
(c) M. G. Banwell and H. M. Schuhbauer, *Organometallics*, **15**, 4078 (1996).
122. (a) H. W. Whitlock, Jr., C. Reich and W. D. Woessner, *J. Am. Chem. Soc.*, **93**, 2483 (1971).
(b) H. W. Whitlock, Jr. and R. L. Markezich, *J. Am. Chem. Soc.*, **93**, 5290 (1971).
(c) A. A. El-Awady, *J. Inorg. Nucl. Chem.*, **36**, 2185 (1974).
123. T. H. Whitesides and J. P. Neilan, *J. Am. Chem. Soc.*, **98**, 63 (1976).
124. (a) B. F. G. Johnson, R. D. Johnston P. L. Josty, J. Lewis and I. G. Williams, *Nature*, **213**, 901 (1967).
(b) O. Gambino, M. Valle, S. Aime and B. A. Vaglio, *Inorg. Chim. Acta*, **8**, 71 (1974).
(c) K. S. Claire, O. W. Howarth and A. McCamley, *J. Chem. Soc., Dalton Trans.*, 2615 (1994).
125. E. G. Bryan, A. L. Burrows, B. F. G. Johnson, J. Lewis and G. M. Schiavon, *J. Organomet. Chem.*, **129**, C19 (1977).
126. A. J. P. Domingos, J. A. S. Howell, B. F. G. Johnson and J. Lewis, *Inorg. Synth.*, **28**, 52 (1990).
127. (a) A. J. P. Domingos, B. F. G. Johnson and J. Lewis, *J. Organomet. Chem.*, **49**, C33 (1973).
(b) A. J. P. Domingos, B. F. G. Johnson and J. Lewis, *J. Chem. Soc., Dalton Trans.*, 2288 (1975).
128. S. L. Ingham and S. W. Magennis, *J. Organomet. Chem.*, **574**, 302 (1999).
129. Y.-M. Wuu, C. Zou and M. S. Wrighton, *Inorg. Chem.*, **27**, 3039 (1988).

130. T. I. Odiaka, *J. Chem. Soc., Dalton Trans.*, 1049 (1985).
131. (a) M. O. Albers, D. J. Robinson, A. Shaver and E. Singleton, *Organometallics*, **5**, 2199 (1986).
(b) P. J. Fagan, W. S. Mahoney, J. C. Calabrese and I. D. Williams, *Organometallics*, **9**, 1843 (1990).
132. C. Gemel, K. Mereiter, R. Schmid and K. Kirchner, *Organometallics*, **14**, 1405 (1995).
133. (a) E. O. Fischer, P. Kuzel and H. P. Fritz, *Z. Naturforsch, B*, **16**, 138 (1961).
(b) G. Winkaus and G. Wilkinson, *J. Chem. Soc.*, 602 (1961).
134. (a) F. M. Chaudhary and P. L. Pauson, *J. Organomet. Chem.*, **69**, C31 (1974).
(b) R. Pankayatselvan and K. M. Nicholas, *J. Organomet. Chem.*, **384**, 361 (1990).
135. M. Bressan, R. Ettorre and P. Rigo, *J. Organomet. Chem.*, **144**, 215 (1978).
136. (a) B. F. G. Johnson, J. Lewis and D. J. Yarrow, *J. Chem. Soc., Dalton Trans.*, 2084 (1972).
(b) J. A. King, Jr. and K. P. C. Vollhardt, *J. Organomet. Chem.*, **369**, 245 (1989).
(c) J. A. King, Jr. and K. P. C. Vollhardt, *J. Organomet. Chem.*, **460**, 91 (1993).
(d) J. A. King, Jr. and K. P. C. Vollhardt, *J. Organomet. Chem.*, **470**, 207 (1994).
137. W.-S. Lee and H. H. Brintzinger, *J. Organomet. Chem.*, **209**, 401 (1981).
138. R. D. Ernst, H. Ma, G. Sargeson, T. Zahn and M. L. Ziegler, *Organometallics*, **6**, 848 (1987).
139. (a) A. Nakamura and N. Hagihara, *Bull. Chem. Soc. Jpn.*, **33**, 425 (1960).
(b) J. Moraczewski and W. E. Geiger, Jr., *J. Am. Chem. Soc.*, **103**, 4779 (1981).
140. (a) D. B. Grotjahn, in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds. E. W. Abel, F. G. A. Stone and G. Wilkinson), Chap. 7.3, Elsevier Science Inc., New York, 1995, pp. 741–770.
(b) P. L. Pauson, in *Encyclopedia of Reagents for Organic Synthesis* (Ed. L. A. Paquette), Vol. 3, Wiley, New York, 1995, pp. 1639–1647.
141. (a) E. P. Johnson and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **113**, 381 (1991).
(b) E. D. Sternberg and K. P. C. Vollhardt, *J. Org. Chem.*, **49**, 1574 (1984).
(c) D. B. Grotjahn and K. P. C. Vollhardt, *Synthesis*, 579 (1993).
142. (a) E. R. F. Gesing, J. P. Tane and K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, **19**, 1023 (1980).
(b) R. L. Halterman and K. P. C. Vollhardt, *Organometallics*, **7**, 883 (1988).
143. (a) P. Hong, K. Aoki and H. Yamazaki, *J. Organomet. Chem.*, **150**, 279 (1978).
(b) J. M. O'Conner, H. Ji, M. Iranpour and A. L. Rheingold, *J. Am. Chem. Soc.*, **115**, 1586 (1993).
(c) J. M. O'Conner, M.-C. Chen and A. L. Rheingold, *Tetrahedron Lett.*, **38**, 5241 (1997).
(d) J. M. O'Conner, M.-C. Chen, M. Frohn, A. L. Rheingold and I. A. Guzei, *Organometallics*, **16**, 5589 (1997).
144. B. Eaton, J. A. King, Jr. and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **108**, 1359 (1986).
145. (a) J. Evans, B. F. G. Johnson and J. Lewis, *J. Chem. Soc., Dalton Trans.*, 2668 (1972).
(b) M. Arthurs, M. Sloan, M. G. B. Drew and S. M. Nelson, *J. Chem. Soc., Dalton Trans.*, 1794 (1975).
(c) M. Arthurs, C. M. Regan and S. M. Nelson, *J. Chem. Soc., Dalton Trans.*, 2053 (1980).
(d) M. G. B. Drew, C. M. Regan and S. M. Nelson, *J. Chem. Soc., Dalton Trans.*, 1034 (1981).
146. A. K. Smith and P. M. Maitlis, *J. Chem. Soc., Dalton Trans.*, 1773 (1976).
147. (a) M. L. H. Green, L. Pratt and G. Wilkinson, *J. Chem. Soc.*, 3753 (1959).
(b) E. O. Fischer and G. E. Herberich, *Chem. Ber.*, **94**, 1517 (1961).
(c) R. J. Angelici and E. O. Fischer, *J. Am. Chem. Soc.*, **85**, 3733 (1963).
(d) G. E. Herberich and J. Schwarzer, *Chem. Ber.*, **103**, 2016 (1970).
(e) G. E. Herberich and R. Michelbrink, *Chem. Ber.*, **103**, 3615 (1970).
148. P. M. Maitlis, P. Espinet and M. J. H. Russell, in *Comprehensive Organometallic Chemistry*, Vol. 6 (Eds. G. Wilkinson and F. G. A. Stone), Chap. 38.6, Pergamon Press, New York, 1982, pp. 363–384.
149. (a) J. Lukas, P. W. N. M. van Leeuwen, H. C. Volger and A. P. Kouwenhoven, *J. Organomet. Chem.*, **47**, 153 (1973).
(b) S. D. Robinson and B. L. Shaw, *J. Chem. Soc.*, 4806 (1963).
150. H. A. Tayim and A. Vassilian, *J. Chem. Soc., Chem. Commun.*, 630 (1970).
151. H. Yasuda, K. Nagasuna, K. Asami and A. Nakamura, *Chem. Lett.*, 955 (1983).
152. J. Böhmer, W. Förtsch and R. Schobert, *Synlett*, 1073 (1997).

153. (a) A. J. Birch, A. J. Liepa and G. R. Stephenson, *Tetrahedron Lett.*, 3565 (1979).
(b) H.-J. Knölker and W. Fröhner, *Tetrahedron Lett.*, **37**, 9183 (1996).
154. M. Booij, J. Blenkers, J. C. M. Sinnema, A. Meetsma, F. van Bolhuis and J. H. Teuben, *Organometallics*, **7**, 1029 (1988).
155. (a) M. Franck-Neumann, D. Martina and F. Brion, *Angew. Chem., Int. Ed. Engl.*, **17**, 690 (1978).
(b) W. A. Donaldson and M.-J. Jin, *Tetrahedron*, **49**, 8787 (1993).
156. M. A. Schroeder and M. S. Wrighton, *J. Organomet. Chem.*, **74**, C29 (1974).
157. (a) M. Franck-Neumann, E. L. Michelotti, R. Simler and J.-M. Vernier, *Tetrahedron Lett.*, **33**, 7361 (1992).
(b) M. Franck-Neumann and J.-M. Vernier, *Tetrahedron Lett.*, **33**, 7365 (1992).
158. (a) G. Erker, K. Engel, J. L. Atwood and W. E. Hunter, *Angew. Chem., Int. Ed. Engl.*, **22**, 494 (1983).
(b) G. Erker and U. Dorf, *Angew. Chem., Int. Ed. Engl.*, **22**, 777 (1983).
159. H. Yasuda, Y. Kajihara, K. Mashima, K. Nagasuna and A. Nakamura, *Chem. Lett.*, 671 (1981).
160. M. Akita, H. Yasuda and A. Nakamura, *Chem. Lett.*, 217 (1983).
161. H. Yasuda, Y. Kajihari, K. Nagasuna, K. Mashima and A. Nakamura, *Chem. Lett.*, 719 (1981).
162. B. Hessen, F. van Bolhuis and J. H. Teuben, *Organometallics*, **6**, 1352 (1987).
163. (a) G. Erker and R. Lecht, *J. Organomet. Chem.*, **311**, 45 (1986).
(b) G. Erker, R. Lecht, J. L. Peterson and H. Bönnemann, *Organometallics*, **6**, 1962 (1987).
(c) G. Erker and B. Menjón, *Chem. Ber.*, **123**, 1327 (1990).
164. M. Brookhart, E. R. Davis and D. L. Harris, *J. Am. Chem. Soc.*, **94**, 7853 (1972).
165. J. Evans, B. F. G. Johnson, J. Lewis and D. J. Yarrow, *J. Chem. Soc., Dalton Trans.*, 2375 (1974).
166. (a) R. Edwards, J. A. S. Howell, B. F. G. Johnson and J. Lewis, *J. Chem. Soc., Dalton Trans.*, 2105 (1974).
(b) A. J. Pearson, S. Balasubramanian and K. Srinivasan, *Tetrahedron*, **49**, 5663 (1993).
(c) W. A. Donaldson, L. Shang, M. Ramaswamy, C. A. Droste, C. Tao and D. W. Bennett, *Organometallics*, **14**, 5119 (1995).
(d) P. Powell, *J. Organomet. Chem.*, **244**, 393 (1983).
167. C. E. Anson, R. D. A. Hudson, S. A. Osborne, D. G. Smyth and G. R. Stephenson, *Tetrahedron Lett.*, **39**, 7603 (1998).
168. B. F. G. Johnson, J. Lewis, P. McArdle and G. L. P. Randall, *J. Chem. Soc., Dalton Trans.*, 2076 (1972).
169. (a) D. G. Gresham, D. J. Kowalski and C. P. Lillya, *J. Organomet. Chem.*, **144**, 71 (1978).
(b) P. A. Dobosh, D. G. Gresham, D. J. Kowalski, C. P. Lillya and E. S. Magyar, *Inorg. Chem.*, **17**, 1775 (1978).
170. (a) T. Benvegnu, L. Schio, Y. Le Floc'h and R. Grée, *Synlett*, 505 (1994).
(b) V. Prahlad and W. A. Donaldson, *Tetrahedron Lett.*, **37**, 9169 (1996).
(c) M. Uemura, T. Minami, Y. Yamashita, K. Hiyoshi and Y. Hayashi, *Tetrahedron Lett.*, **28**, 641 (1987).
(d) W. R. Roush and C. K. Wada, *Tetrahedron Lett.*, **35**, 7347 (1994).
171. P. Powell, *J. Organomet. Chem.*, **165**, C43 (1979).
172. (a) T. H. Whitesides, R. W. Arhart and R. W. Slaven, *J. Am. Chem. Soc.*, **95**, 5792 (1973).
(b) A. Salzer and A. Hafner, *Helv. Chim. Acta*, **66**, 1774 (1983).
173. E. D. Sternberg and K. P. C. Vollhardt, *J. Org. Chem.*, **49**, 1564 (1984).
174. (a) J. E. Mahler and R. Pettit, *J. Am. Chem. Soc.*, **85**, 3955 (1963).
(b) A. J. Pearson and T. Ray, *Tetrahedron*, **41**, 5765 (1985).
175. B. F. G. Johnson, J. Lewis and J. W. Quail, *J. Chem. Soc., Dalton Trans.*, 1252 (1975).
176. (a) B. F. G. Johnson, J. Lewis and G. L. P. Randall, *J. Chem. Soc. (A)*, 422 (1971).
(b) B. F. G. Johnson, J. Lewis, P. McArdle and G. L. P. Randall, *J. Chem. Soc., Dalton Trans.*, 456 (1972).
177. (a) M. Franck-Neumann, M. Sedrati and M. Mokhi, *New J. Chem.*, **14**, 471 (1990).
(b) R. E. Graf and C. P. Lillya, *J. Organomet. Chem.*, **122**, 377 (1976).
(c) E. O. Greaves, G. R. Knox, P. L. Pauson, S. Toma, G. A. Sim and D. I. Woodhouse, *J. Chem. Soc., Chem. Commun.*, 257 (1974).
(d) A. J. Birch, W. D. Raverty, S.-Y. Hsu and A. J. Pearson, *J. Organomet. Chem.*, **260**, C59 (1984).

178. M. Franck-Neumann, P. Bissinger and P. Geoffroy, *Tetrahedron Lett.*, **34**, 4643 (1993).
179. (a) A. J. Pearson, S. Mallik, R. Mortezaei, M. W. D. Perry, R. J. Shively, Jr. and W. J. Youngs, *J. Am. Chem. Soc.*, **112**, 8034 (1990).
(b) S.-H. Wang, Y.-C. Cheng, G.-H. Lee, S.-M. Peng and R.-S. Liu, *Organometallics*, **12**, 3282 (1993).
180. M. F. Semmelhack and E. J. Fewkes, *Tetrahedron Lett.*, **28**, 1497 (1987).
181. (a) G. M. Williams, D. E. Rudisill, B. A. Barnum, K. Hardcastle, R. H. Heyn, C. J. Kozak and J. W. McMillan, *J. Am. Chem. Soc.*, **112**, 205 (1990).
(b) A. J. Birch and L. F. Kelly, *J. Org. Chem.*, **50**, 712 (1985).
(c) A. J. Pearson and K. Srinivasan, *J. Chem. Soc., Chem. Comm.*, 392 (1991).
182. (a) W. A. Donaldson, R. Craig and S. Spanton, *Tetrahedron Lett.*, **33**, 3967 (1992).
(b) J. T. Wasicak, R. A. Craig, R. Henry, B. Dasgupta, H. Li and W. A. Donaldson, *Tetrahedron*, **53**, 4185 (1997).
183. M. Franck-Neumann, D. Martina and M.-P. Heitz, *J. Organomet. Chem.*, **315**, 59 (1986).
184. S. Chang, P. S. White and M. Brookhart, *Organometallics*, **12**, 3636 (1993).
185. (a) M. F. Semmelhack and J. W. Herndon, *Organometallics*, **2**, 363 (1983).
(b) M. F. Semmelhack, J. W. Herndon and J. P. Springer, *J. Am. Chem. Soc.*, **105**, 2497 (1983).
186. M. F. Semmelhack and J. W. Herndon, *J. Organomet. Chem.*, **265**, C15 (1984).
187. (a) M. F. Semmelhack and H. T. M. Le, *J. Am. Chem. Soc.*, **106**, 2715 (1984).
(b) M.-C. P. Yeh and C.-C. Hwu, *J. Organomet. Chem.*, **419**, 341 (1991).
(c) S.-S. P. Chou, C.-H. Hsu and M.-C. P. Yeh, *Tetrahedron Lett.*, **33**, 643 (1992).
188. M. F. Semmelhack, J. W. Herndon and J. K. Liu, *Organometallics*, **2**, 1885 (1983).
189. (a) M.-C. P. Yeh, B.-A. Sheu, H.-W. Fu, S.-I. Tau and L.-W. Chuang, *J. Am. Chem. Soc.*, **115**, 5941 (1993).
(b) M.-C. P. Yeh, L.-W. Chuang, C.-C. Hwu, J.-M. Sheu and L.-C. Row, *Organometallics*, **14**, 3396 (1995).
190. L. S. Barinelli and K. M. Nicholas, *J. Org. Chem.*, **53**, 2114 (1988).
191. (a) A. J. Pearson, S. L. Blystone and B. A. Roden, *Tetrahedron Lett.*, **28**, 2459 (1987).
(b) A. J. Pearson, V. D. Khetani and B. A. Roden, *J. Org. Chem.*, **54**, 5141 (1989).
192. A. J. Pearson, M. N. I. Khan, J. C. Clardy and H. Cun-heng, *J. Am. Chem. Soc.*, **107**, 2748 (1985).
193. (a) A. J. Pearson, M. S. Holden and R. D. Simpson, *Tetrahedron Lett.*, **27**, 4121 (1986).
(b) A. J. Pearson and M. K. M. Babu, *Organometallics*, **13**, 2539 (1994).
194. (a) J. H. Rigby and C. O. Ogbu, *Tetrahedron Lett.*, **31**, 3385 (1990).
(b) N. Morita, S. Ito and T. Asao, *J. Organomet. Chem.*, **460**, 67 (1993).
(c) M.-C. P. Yeh, C.-C. Hwu, C.-H. Ueng and H.-L. Lue, *Organometallics*, **13**, 1788 (1994).
195. (a) A. J. Pearson and K. Srinivasan, *J. Org. Chem.*, **57**, 3965 (1992).
(b) J. Soulié, J.-F. Betzer, B. Muller and J.-Y. Lallemand, *Tetrahedron Lett.*, **36**, 9485 (1995).
196. (a) M. Franck-Neumann and D. Martina, *Tetrahedron Lett.*, 1759 (1975).
(b) M. Saha, B. Bagby and K. M. Nicholas, *Tetrahedron Lett.*, **27**, 915 (1986).
197. (a) R. J. H. Cowles, B. F. G. Johnson, J. Lewis and A. W. Parkins, *J. Chem. Soc., Dalton Trans.*, 1768 (1972).
(b) A. J. Birch, L. F. Kelly and D. V. Weerasuria, *J. Org. Chem.*, **53**, 278 (1988).
198. C. W. Ong and T.-L. Chien, *Organometallics*, **15**, 1323 (1996).
199. (a) R. Grée, *Synthesis*, 341 (1989).
(b) C. Tao and W. A. Donaldson, *J. Org. Chem.*, **58**, 2134 (1993).
(c) M. Laabassi, L. Toupet and R. Grée, *Bull. Soc. Chim. Fr.*, **129**, 47 (1992).
(d) K. Nunn, P. Mosset, R. Grée and R. W. Saalfrank, *Angew. Chem., Int. Ed. Engl.*, **27**, 1188 (1988).
(e) A. Teniou and R. Grée, *Bull. Soc. Chim. Belg.*, **100**, 411 (1991).
(f) C. Crévisy, B. Herbage, M.-L. Marrel, L. Toupet and R. Grée, *Eur. J. Org. Chem.*, 1949 (1998).
200. D. G. Gresham, C. P. Lillya, P. C. Uden and F. H. Walters, *J. Organomet. Chem.*, **142**, 123 (1977).
201. (a) M. Franck-Neumann and P.-J. Colson, *Synlett*, 891 (1991).
(b) N. A. Clinton and C. P. Lillya, *J. Am. Chem. Soc.*, **92**, 3058 (1970).
(c) D. E. Kuhn and C. P. Lillya, *J. Am. Chem. Soc.*, **94**, 1682 (1972).

202. (a) M. Laabassi and R. Grée, *Tetrahedron Lett.*, **29**, 611 (1988).
(b) W. R. Roush and C. Wada, *J. Am. Chem. Soc.*, **116**, 2151 (1994).
(c) W. R. Roush and C. K. Wada, *Tetrahedron Lett.*, **35**, 7351 (1994).
203. T. Benvegnu, J. Martelli, R. Grée and L. Toupet, *Tetrahedron Lett.*, **31**, 3145 (1990).
204. (a) T. Le Gall, J.-P. Lellouche, L. Toupet and J.-P. Beaucourt, *Tetrahedron Lett.*, **30**, 6517 (1989).
(b) T. Le Gall, J.-P. Lellouche and J.-P. Beaucourt, *Tetrahedron Lett.*, **30**, 6521 (1989).
(c) B. Dasgupta and W. A. Donaldson, *Tetrahedron: Asymmetry*, **9**, 3781 (1998).
205. (a) A. Gigou, J.-P. Lellouche, J.-P. Beaucourt, L. Toupet and R. Grée, *Angew. Chem., Int. Ed. Engl.*, **28**, 755 (1989).
(b) A. Gigou, J.-P. Beaucourt, J.-P. Lellouche and R. Grée, *Tetrahedron Lett.*, **32**, 635 (1991).
206. G. Maier and D. Born, *Angew. Chem., Int. Ed. Engl.*, **28**, 1050 (1989).
207. C. Fröhlich and H. Hoberg, *J. Organomet. Chem.*, **222**, 337 (1981).
208. C. M. Adams, J. E. Schemenaur, E. S. Crawford and S. A. Joslin, *Synth. Commun.*, **22**, 1385 (1992).
209. R. H. Grubbs and T. A. Pancoast, *Synth. React. Inorg. Met.-Org. Chem.*, **8**, 1 (1978).
210. M. D. Rausch and A. V. Grossi, *J. Chem. Soc., Chem. Commun.*, 401 (1978).
211. (a) H. Hogeveen and D. M. Kok, *Tetrahedron Lett.*, **21**, 659 (1980).
(b) K. S. Fongers, H. Hogeveen and R. F. Kingma, *Synthesis*, 839 (1982).
(c) H. Hoberg and H. J. Riegel, *J. Organomet. Chem.*, **229**, 85 (1982).
(d) H. Hoberg, H. J. Riegel and K. Seevogel, *J. Organomet. Chem.*, **229**, 281 (1982).
(e) M. R. Cook, P. Härter, P. L. Pauson and J. Sraga, *J. Chem. Soc., Dalton Trans.*, 2757 (1987).
212. (a) W. Hübel and E. H. Braye, *J. Inorg. Nucl. Chem.*, **10**, 250 (1959).
(b) W. Hübel, E. H. Braye, A. Clauss, E. Weiss, U. Krüerke, D. A. Brown, S. D. King and C. Hoogzand, *J. Inorg. Nucl. Chem.*, **19**, 204 (1959).
213. M. E. E. Meijer-Veldman, J. L. DeBoer, H. J. de Liefde Meijer, A. M. M. Schreurs, J. Kroon and A. L. Spek, *J. Organomet. Chem.*, **269**, 255 (1984).
214. F. Calderazzo, F. Marchetti, G. Pampaloni, W. Hiller, H. Antropiusová and K. Mach, *Chem. Ber.*, **122**, 2229 (1989).
215. L. N. Lewis and K. G. Caulton, *J. Organomet. Chem.*, **252**, 57 (1983).
216. W.-Y. Yeh, C.-L. Ho, M. Y. Chiang and I.-T. Chen, *Organometallics*, **16**, 2698 (1997).
217. M. D. Rausch, B. H. Edwards, J. L. Atwood and R. D. Rogers, *Organometallics*, **1**, 1567 (1982).
218. K. Raab, M. Appel and W. Beck, *J. Organomet. Chem.*, **291**, C28 (1985).
219. M. Crocker, M. Green, A. G. Orpen and D. M. Thomas, *J. Chem. Soc., Chem. Commun.*, 1141 (1984).
220. B. K. Campion, R. H. Heyn and T. D. Tilley, *Organometallics*, **9**, 1106 (1990).
221. (a) E. A. Kelly, P. M. Bailey and P. M. Maitlis, *J. Chem. Soc., Chem. Commun.*, 289 (1977).
(b) E. A. Kelly and P. M. Maitlis, *J. Chem. Soc., Dalton Trans.*, 167 (1979).
(c) J. D'Angelo, J. Ficini, S. Martinon, C. Riche and A. Sevin, *J. Organomet. Chem.*, **177**, 265 (1979).
222. J. Moreto and P. M. Maitlis, *J. Chem. Soc., Dalton Trans.*, 1368 (1980).
223. P. Pauson, in *Encyclopedia of Reagents for Organic Synthesis* (Ed. L. A. Paquette), Wiley, New York, 1995, Vol. 2, pp. 1444–1447 and Vol. 3, pp. 1639–1647.
224. (a) K. Yasafuku and H. Yamazaki, *J. Organomet. Chem.*, **121**, 405 (1976).
(b) K. Yasufuku and H. Yamazaki, *J. Organomet. Chem.*, **127**, 197 (1977).
(c) H. Yamazaki and Y. Wakatsuki, *J. Organomet. Chem.*, **149**, 377 (1978).
225. R. B. King and A. Efraty, *J. Am. Chem. Soc.*, **92**, 6071 (1970).
226. (a) R. Gleiter, M. Karcher, M. L. Ziegler and B. Nuber, *Tetrahedron Lett.*, **28**, 195 (1987).
(b) R. Gleiter, B. Treptow, D. Kratz and B. Nuber, *Tetrahedron Lett.*, **33**, 1733 (1992).
(c) R. Gleiter, G. Pflästerer and B. Nuber, *J. Chem. Soc., Chem. Commun.*, 454 (1993).
(d) R. Gleiter and G. Pflästerer, *Organometallics*, **12**, 1886 (1993).
227. (a) R. Gleiter and M. Merger, *Angew. Chem., Int. Ed. Engl.*, **36**, 2426 (1997).
(b) G. Haberhauer, F. Rominger and R. Gleiter, *Angew. Chem., Int. Ed. Engl.*, **37**, 3376 (1998).
(c) R. Gleiter, H. Stahr and B. Nuber, *Tetrahedron Lett.*, **36**, 4607 (1995).
228. (a) G. E. Herberich and A. K. Naithani, *J. Organomet. Chem.*, **241**, 1 (1983).
(b) G. Schmid and M. Schütz, *J. Organomet. Chem.*, **492**, 185 (1995).

(c) R. M. Matos, J. F. Nixon and J. Okuda, *Inorg. Chim. Acta*, **222**, 13 (1994).
229. R. S. Drage and K. P. C. Vollhardt, *Organometallics*, **4**, 389 (1985).
230. U. Behrens, K.-J. Jens, J. Kopf, T. Valéri and E. Weiss, *J. Organomet. Chem.*, **348**, 379 (1988).
231. R. P. Hughes, J. W. Reisch and A. L. Rheingold, *Organometallics*, **3**, 1761 (1984).
232. R. P. Hughes, A. S. Kowalski and B. T. Donovan, *J. Organomet. Chem.*, **472**, C18 (1994).
233. R. C. Hemond and R. P. Hughes, *J. Chem. Soc., Chem. Commun.*, 319 (1988).
234. (a) E. K. G. Schmidt, *Angew. Chem., Int. Ed. Engl.*, **12**, 777 (1973).
(b) R. H. Grubbs and R. A. Grey, *J. Chem. Soc., Chem. Commun.*, 76 (1973).
(c) R. H. Grubbs and R. A. Grey, *J. Am. Chem. Soc.*, **95**, 5765 (1973).
235. G. A. Ville, K. P. C. Vollhardt and M. J. Winter, *Organometallics*, **3**, 1177 (1984).
236. J. R. Fritsch and K. P. C. Vollhardt, *Organometallics*, **1**, 590 (1982).
237. (a) U. Griebsch and H. Hoberg, *Angew. Chem., Int. Ed. Engl.*, **17**, 950 (1978).
(b) H. Hoberg and C. Fröhlich, *J. Organomet. Chem.*, **209**, C69 (1981).
238. A. Bond, M. Bottrill, M. Green and A. J. Welch, *J. Chem. Soc., Dalton Trans.*, 2372 (1977).
239. W. A. Donaldson, in *Encyclopedia of Reagents for Organic Synthesis* (Ed. L. A. Paquette), Vol. 7, Wiley, New York, 1995, pp. 5041–5042.
240. L. Watts, J. D. Fitzpatrick and R. Pettit, *J. Am. Chem. Soc.*, **88**, 623 (1966).
241. J. Rebek, Jr. and F. Gaviña, *J. Am. Chem. Soc.*, **97**, 3453 (1975).
242. (a) J. C. Barborak, L. Watts and R. Pettit, *J. Am. Chem. Soc.*, **88**, 1328 (1966).
(b) J. C. Barborak and R. Pettit, *J. Am. Chem. Soc.*, **89**, 3080 (1967).
(c) L. Watts, J. D. Fitzpatrick and R. Pettit, *J. Am. Chem. Soc.*, **87**, 3253 (1965).
(d) I. G. Pitt, R. A. Russell and R. N. Warrener, *J. Am. Chem. Soc.*, **107**, 7176 (1985).
243. (a) P. L. Pruitt, E. R. Biehl and P. C. Reeves, *J. Organomet. Chem.*, **134**, 37 (1977).
(b) A. V. Gist and P. C. Reeves, *J. Organomet. Chem.*, **215**, 221 (1981).
244. (a) R. H. Grubbs and T. A. Pancoast, *J. Am. Chem. Soc.*, **99**, 2382 (1977).
(b) J. A. Tallarico, M. L. Randall and M. L. Snapper, *J. Am. Chem. Soc.*, **118**, 9196 (1996).
(c) M. L. Snapper, J. A. Tallarico and M. L. Randall, *J. Am. Chem. Soc.*, **119**, 1478 (1997).
245. G. A. Olah and G. Liang, *J. Org. Chem.*, **41**, 2659 (1976).
246. C. M. Adams, E. S. Crawford and E. Salim, *Tetrahedron Lett.*, **33**, 3963 (1992).
247. (a) U. H. F. Bunz and V. Enkelmann, *Organometallics*, **13**, 3823 (1994).
(b) U. H. F. Bunz and J. E. C. Wiegelmann-Kreiter, *Chem. Ber.*, **129**, 785 (1996).
248. (a) P. M. Maitlis, A. Efraty and M. L. Games, *J. Am. Chem. Soc.*, **87**, 719 (1965).
(b) F. Canziani, P. Chini, A. Quarta and A. DiMartino, *J. Organomet. Chem.*, **26**, 285 (1971).
249. (a) A. Efraty, J. Potenza, S. S. Sandhu, Jr., R. Johnson, M. Mastropaolo, R. Bystrek, D. Z. Denney and R. H. Herber, *J. Organomet. Chem.*, **70**, C24 (1974).
(b) J. A. Potenza, R. Johnson, D. Williams, B. H. Toby, R. A. LaLancette and A. Efraty, *Acta Crystalloger., Sect. B*, **B37**, 442 (1981).
(c) D. M. Birney, A. M. Crane and D. A. Sweigart, *J. Organomet. Chem.*, **152**, 187 (1978).
(d) J. C. Calabrese, S. D. Ittel, H. S. Choi, S. G. Davis and D. A. Sweigart, *Organometallics*, **2**, 226 (1983).
250. (a) M. Crocker, M. Green, A. G. Orpen, H.-P. Neumann and C. J. Schaverien, *J. Chem. Soc., Chem. Commun.*, 1351 (1984).
(b) M. Crocker, M. Green, K. R. Nagle, A. G. Orpen, H.-P. Neumann, C. E. Morton and C. J. Schaverien, *Organometallics*, **9**, 1422 (1990).

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CHAPTER **12**

Reduction of dienes and polyenes

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I. INTRODUCTION

Reduction of dienes and polyenes has attracted much attention since it is important from both practical and theoretical aspects. In these reactions the major interest is the selective reduction of a double bond in the presence of another. In general, saturation of all the multiple double bonds of nonaromatic compounds can be carried out with any of the catalysts which are suitable for low-pressure reductions or with some reducing chemicals.

The selective partial hydrogenation of polyenes is interesting from both preparative and commercial points of view. Success depends on the nature of the polyene as well as on a careful choice of catalyst and conditions.

There are several industrial processes in which reduction of dienes and polyenes is involved. The three most well known ones are the following: the hydrotreating of pyrolysis gases and gasoline[1], the hydrogenation of fats and fatty oils[2] and the hydrogenation of nitrile-butadiene rubber[3]. In all of these processes selectivity is a key issue. For example, in the purification of ethylene and propylene from acetylene and diene traces, the selectivity of the Pd catalyst influences the yield of the olefinic products. Similarly, the selectivity of the hydrogenation of fatty oils towards *cis* oleic acid containing glycerides determines basically the quality and value of the saturated products.

Besides these processes, several reduction methods or hydrogenation technologies of dienes and polyenes are used for the fine chemicals industry.

II. METHODS OF REDUCTION

A. Catalytic Hydrogenation

The olefinic C=C double bond is easy to reduce, under mild conditions, with most of the hydrogenation catalysts, with noble metals, with different forms of nickel as heterogeneous catalysts, with Rh, Pt, Co complexes and with Ziegler catalysts as homogeneous catalysts. In the hydrogenation of dienes and polyenes the selectivity is the most important issue, i.e. how can one double bond be saturated with retention of the other(s). When high selectivity is required, homogeneous catalysts are used. Nevertheless, as known, their separation from the reaction mixture is a difficult task.

In the industrial processes for the hydrogenation of dienes and polyenes, heterogeneous catalysts are used in most cases, although their selectivity is not perfect.

1. Homogeneous catalyzed hydrogenation of dienes and polyenes

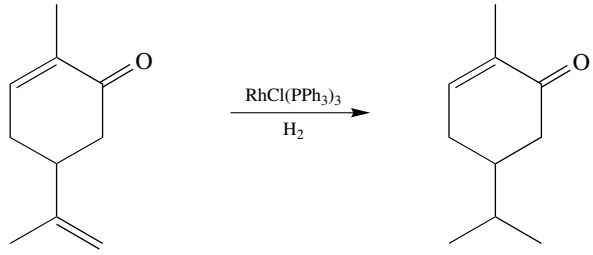
The hydrogenation of olefins with soluble metal complexes has been studied extensively[4,5]. This intensive study seems anomalous because soluble catalysts are seldom used for olefin hydrogenation in industry and in organic synthesis. The importance of homogeneous catalysts is great in asymmetric reactions (L-Dopa, Dual herbicide synthesis) where the high stereoselectivity of optically active catalysts is the major advantage.

Another potential use of homogeneous hydrogenation catalysts is the hydrogenation of dienes and trienes to monoolefins, where they display high specificity. Such an example is the conversion of the easily available butadiene dimers and trimers to polymer intermediates[6].

The hydrogenation of unsaturated polymers like polyisoprene is based on the mobility of a soluble catalyst in the reaction medium. In the hydrogenation of such unsaturated polymers the soluble catalyst brings its active site to the C=C bonds in the polymer chain. In contrast, a heterogeneous catalyst requires that the polymer chain unfold to gain access to a catalytically active site on the surface of a metal particle.

For practical hydrogenation of olefins four classes of metal complexes are preferred: (a) Rh complexes, the $RhCl(PPh_3)_3$, the so-called Wilkinson catalyst and the $[Rh(diene)-(PR_3)_2]^+$ complexes, (b) a mixture of Pt and Sn chlorides, (c) anionic cyanocobalt complexes and (d) Ziegler catalysts, prepared from a transition metal salt and an alkylaluminum compound.

The Wilkinson catalyst reduces external double bonds much faster than the internal ones as in the hydrogenation of carvone (equation 1)[7].



(1)

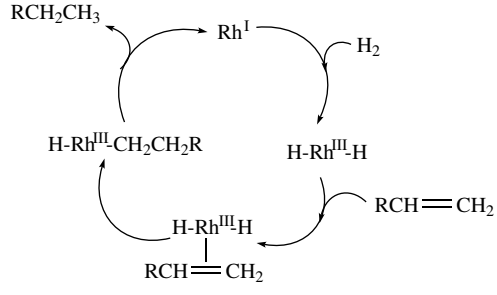
As this catalyst is slow in the hydrogenation of internal olefins, the closely related $[Rh(diene)-(PR_3)_2)]^+$ catalysts are useful with highly substituted olefins, for example in asymmetric hydrogenations[8].

The Pt–Sn complexes were studied extensively in the hydrogenation of vegetable oils to remove excessive unsaturation[9].

For hydrogenation in water with an inexpensive catalyst, solutions containing cobalt salts and excess cyanide are useful[10,11]. The catalysts are selective for conjugated C=C bonds and are relatively unreactive with unconjugated dienes such as 1,5-cyclooctadiene.

The Ziegler-type systems are useful for the hydrogenation of unsaturated polymers, so they have industrial application[12].

The mechanism of olefin hydrogenation is rather simple: the olefin and the H_2 are brought together as ligands in the coordination sphere of the metal and a rearrangement of the H–M-olefin complex to a metal-alkyl is followed by hydrogenolytic cleavage of the M–C bond (Scheme 1). The catalysts differ in the mode of cleaving H_2 to form the metal-hydride ligand and in the mechanism of cleavage of the metal-alkyl bond to form alkane. The Rh, Pt–Sn and Co based catalysts differ in the H_2 cleavage mechanism[13].



SCHEME 1

The Rh complex undergoes oxidative addition while activating hydrogen. With the anionic Pt catalyst the process occurs by heterolytic cleavage of hydrogen (equation 2)[14].

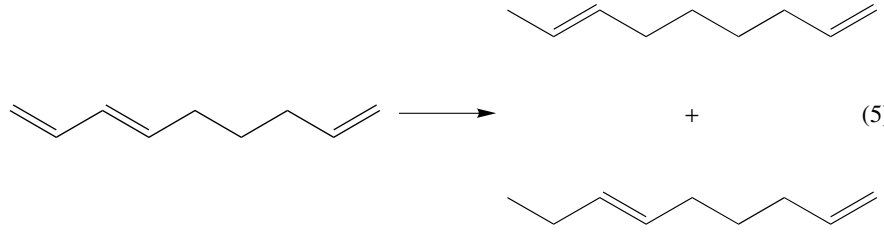
$$H_2 + [Pt(SnCl_3)_5]^{3-} \rightleftharpoons H^+ + [HPt(SnCl_3)_4]^{3-} + SnCl_3^- \quad (2)$$

The third major mechanism is based on homolytic cleavage of the dihydrogen molecule by metal–metal (Co) bonded species or by a paramagnetic complex (equations 3 and 4)[15].

$$Co_2(CO)_8 + H_2 \rightleftharpoons 2HCo(CO)_4 \quad (3)$$

$$2[Co(CN)_5]^{3-} \rightleftharpoons [Co_2(CN)_{10}]^{6-} \xrightarrow{H_2} 2[HCo(CN)_5]^{3-} \quad (4)$$

A practical example for polyene hydrogenation is the reduction of 1,5,9-cyclododecatriene to cyclododecene. The starting compound is a readily available butadiene trimer; it can be converted to cyclododecene, the precursor of dodecanedioic acid and laurolactam, two commercial polyamide intermediates. The two soluble catalysts, which are superior in selectivity compared with the Pd/Al_2O_3 catalyst used in the industrial process, are $[Co(CO)_3(PBu_3)$ and $NiI_2(PPh_3)_2]$, which are prepared from nonprecious metals. These catalysts effect partial hydrogenation of either conjugated or unconjugated dienes and trienes[14,16–21]. Another group of catalysts, $[Co(CN)_5]^{3-}$, [Cr(CO)(methyl benzoate)], $Cr(CO)_6$, $[Cr(CO)_2(C_2H_5)_2]_2$, hydrogenate only conjugated dienes and trienes (equation 5)[10,22].

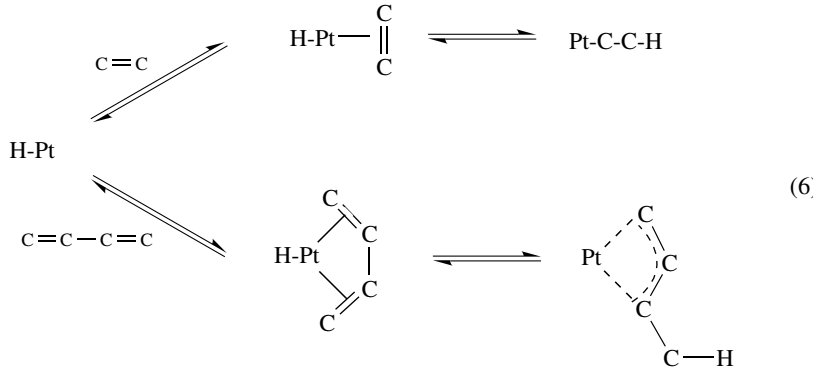


(5)

The major distinction between the two classes of catalysts is that the members of the former group are olefin isomerization catalysts, while the cobalt cyanide and the chromium catalysts are not[23–25].

The isomerization catalysts are hydride complexes, and they can convert the unconjugated dienes or polyenes to conjugated systems through double-bond migration. This process occurs by an M–H addition–elimination process.

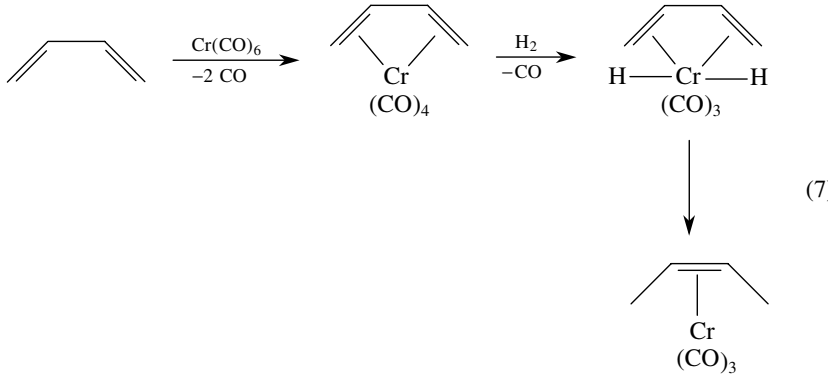
The selectivity for hydrogenation of dienes in the presence of monoolefins arises from the exceptional stability of π-allyl complexes. In the case of Pt catalysts the reactions shown can compete with one another (equation 6)[14]. The second pathway is favored, especially when the olefin or diene must compete with excess ligands (phosphine, CO, $SnCl_3^-$) for a coordination site. This is why the diene is almost completely hydrogenated before the concentration of olefin increases to the point that the olefin gains access to the catalyst. A similar phenomenon can be responsible for selectivity in hydrogenation of dienes with heterogeneous catalysts.



(6)

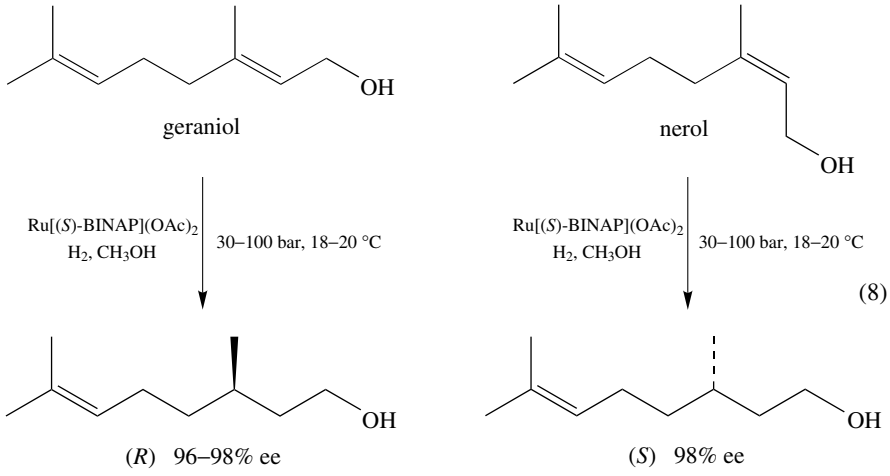
The $Cr(CO)_6$ and $Cr(CO)_3$(arene) catalysts hydrogenate conjugated dienes by 1,4-addition of hydrogen. The diene coordinates in a *cisoid* configuration (equation 7)[23]. This

proposal is supported by the high selectivity for 1,4-addition and the *cis* conformation of the olefinic product.



(7)

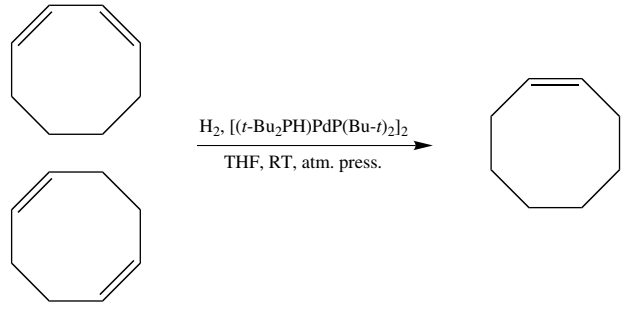
A characteristic example for the application of homogeneous catalysts in enantioselective and regioselective hydrogenation of dienic compounds is the hydrogenation of geraniol and nerol to citronellol with Ru-BINAP catalyst (equation 8)[26,27]. The high enantiomeric excesses (96–98%), the nearly quantitative yields (>95%) and the very low catalyst/substrate ratio (1 : 50000) are attractive attributes of this process.



(8)

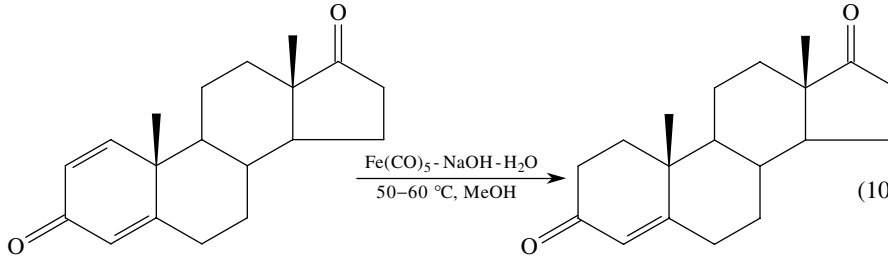
Besides the catalysts mentioned in the introductory part of this topic, other catalytic systems were used successfully in diene hydrogenation. An example is $NiH(PPh_3)(AlCl_4)$, which hydrogenated 1,4-cyclohexadiene to cyclohexene in toluene at 40 °C[28].

A selective hydrogenation of conjugated dienes was carried out with a Pd complex which was preactivated with oxygen. Besides the conversion of dienes with good selectivity (98%), diene esters, ketones and nitro compounds were also hydrogenated with fairly good selectivities (equation 9)[29].



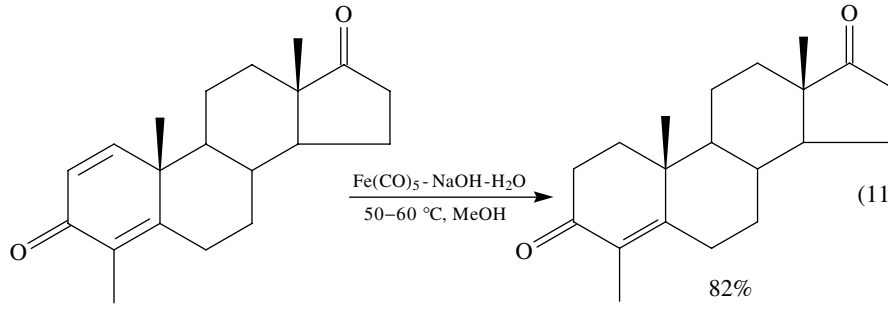
(9)

The iron carbonyl complex $[Fe(CO)_5]$ in basic media hydrogenated steroidal dienes selectively (equations 10–12)[30].



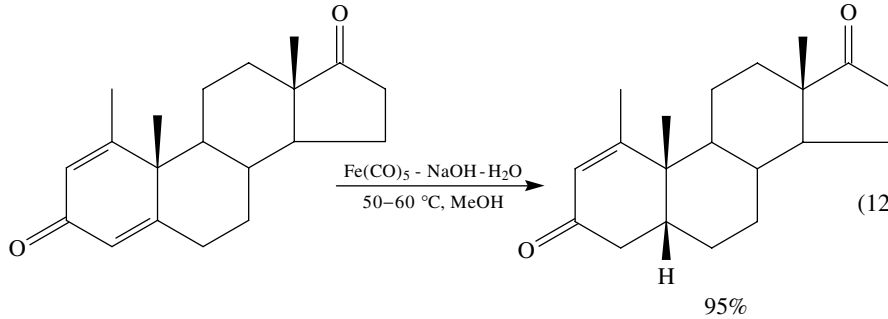
(10)

85%



(11)

82%



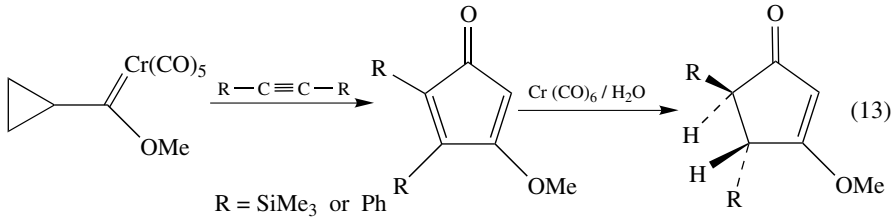
(12)

95%

Low melting tetraalkylammonium salts of $SnCl_3^-$ and $GeCl_3^-$ anions are convenient solvents for some homogeneous catalytic reactions of olefins. These salts, when fused, dissolve up to 7% $PtCl_2$ to give deep red solution which catalyze among other reactions the hydrogenation of 1,5,9-cyclododecatriene with considerable selectivity to cyclododecene at 150 °C and 100 bar hydrogen pressure. The catalytic solution of $PtCl_2$ in $[(C_2H_5)_4N][SnCl_3]$ appears to contain $SnCl_3^-$ complexes of platinum, including the known $[Pt(SnCl_3)_5]^{3-}$ and $[HPt(SnCl_3)_4]^{3-}$ anions[14].

There were several attempts to use homogeneous catalysts in the hydrogenation of fatty acid esters. Pt, Pd and Mo complexes were investigated. The monoene selectivity and the activity of Pt catalysts were good, but their separation from the product remained an unsolved problem. They were active in a double-bond migration reaction which, however, was accompanied by the disadvantageous *cis–trans* isomerization[9,31].

An interesting example is the stereoselective reduction of a cyclopentadienone derivative with a chromium carbonyl itself without hydrogen (equation 13)[32].



(13)

2. Heterogeneous catalyzed hydrogenation of dienes and polyenes

For the hydrogenation of dienes and polyenes the most frequently applied catalysts are heterogeneous metal catalysts. Their advantage is the high reaction rate, good selectivity under optimized conditions and the easy separation.

For olefin hydrogenation Horiuti and Polányi[33] proposed a scheme, which is generally being accepted and which accounts for two aspects of this reaction, i.e. double-bond migration and *cis–trans* isomerization. The elementary steps of this scheme are the following: the dissociative adsorption of hydrogen, the diadsorption of olefin and the addition of one hydrogen atom to the olefin, forming a so called 'half-hydrogenated species'. If this undergoes a configurational change, *cis–trans* isomerization may occur. Transformation of the monoadsorbed species to form a different diadsorbed species may also occur, resulting in double-bond migration. (Monoadsorbed and diadsorbed mean attachment to the catalyst surface by one and two covalent bonds, respectively.) Migration and isomerization are favored by a low hydrogen concentration at the surface and diminished by high hydrogen availability at the surface.

Catalysts differ in their ability to promote double-bond migration and *cis–trans* isomerization, in their thermodynamic and mechanistic selectivities in diene hydrogenation and in their tendencies to catalyze 1,2-, 3,4-, or 1,4-addition[34].

The reason for the selectivity is that dienes are adsorbed with strengths comparable to those of alkynes. The large selectivities that various metals show in the hydrogenation of allene (propadiene), 1,3-butadiene and 1,4-pentadiene are similar to those observed with alkynes. Pd is again outstanding in diene hydrogenation, its behavior being similar to that shown in the hydrogenation of alkynes. However, the hydrogenation of dienes is a more complex process, and the relative amounts of isomeric alkenes vary considerably from one metal to another, and with the reaction conditions due to varying amounts of 1,2- and 1,4-addition[35,36].

The mechanistic studies were carried out mainly with butadiene and two mechanisms were suggested depending first of all on the *trans/cis* ratio of the formed 2-butene. On Pd and sometimes on Co catalysts the *trans/cis* ratio is high and the mechanism is based on formating of *syn*- and *anti*-π-allyl intermediates which cannot interconvert on the surface. On other metals, where the *trans/cis* ratio is about unity, the intermediates are π-alkenes or σ-alkyls that may interconvert more freely[36].

The hydrogenation of butadiene is structure-sensitive on Pd and Rh but lacks particle-size dependence in the case of platinum. The strong complexation of the diene to atoms of low coordination number is a possible explanation for this phenomenon where it occurs[37,38].

Three factors determine the activity and selectivity in the hydrogenation of alkadienes[39]: (a) the particle size through the effect of complexation of reactants to active sites containing low coordination number atoms, (b) the particle size, through self-poisoning by carbonaceous residues, and (c) with palladium, a particle-size effect through the solubility of hydrogen and the formation of the unselective β-PdH derivatives.

The selectivity of metal catalysts improves in some reactions with alloying; for example the alumina-supported Pd–Cu catalyst hydrogenates butadiene to 1-butene with 99% selectivity, i.e. the isomerization is less than 1%. The explanation is that hydrogen adsorption decreased on the Cu-containing catalysts[40]. Similarly, better selectivities were observed with a polymer anchored Pd, or a Pd–Co catalyst in the gas-phase hydrogenation of butadiene and cyclopentadiene in a hollow-fiber reactor[41,42] and in the liquid-phase hydrogenation of 1,5-hexadiene with Pd–Ag catalyst[43].

The intermetallic compounds $CePd_3$ and $ZrPd_3$ exhibited higher selectivity for butene formation than Pd. On Pd the hydrogen and butadiene are adsorbed on similar sites, whereas on the intermetallic compounds different sites may be involved in these adsorption processes[44].

Another explanation for the selectivity of Pd in reduction to 1-butene is the phenomenon of self-poisoning. Carbonaceous materials and oligomers are formed on the catalyst surface. Butadiene, due to its high adsorption ability, is able to be adsorbed on metallic sites in the presence of the oligomers. However, *n*-butenes could not compete with the oligomers. A large quantity of hydrocarbonaceous deposit decreases the surface fugacity of the diene due to hindrance of transport and in consequence enhances the overhydrogenation of diene[45,46].

Recently, silica supported nickel–boron catalyst was tested in the hydrogenation of cyclopentadiene and was found to be selective in giving cyclopentene[47].

The liquid-phase hydrogenation of dienes and polyenes is also an extensively studied topic. The behavior of metals in such reactions is similar to that in the gas-phase reactions, i.e., Pd is the most selective catalyst.

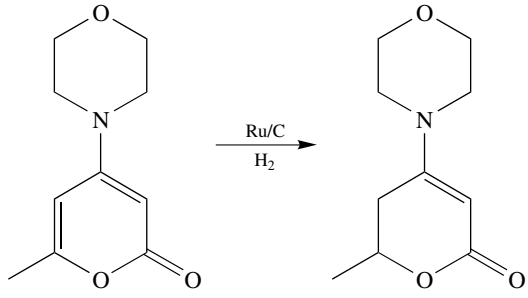
In the industrial scale of hydrogenation of fats and oils, the most frequently used catalysts are Ni based. The 20–30% Ni is supported on silica. When partial hydrogenation is needed, the temperature applied is between 140 and 200 °C and the pressure between 4 and 10 bar. The total hydrogenation requires higher temperature and pressure (200 °C, 20 bar). Nickel is not a perfect catalyst due to its relative low activity and also due to the formation of Ni-soaps. Recently, a colloidal Pd catalyst was applied successfully in a two-phase system for this type of hydrogenation, at room temperature and atmospheric pressure. The complete conversion of multiunsaturated compounds could be achieved during 15–45 minutes. In dimethylformamide as the second phase solvent, 92% monoene yield with a 70/30 *cis/trans* ratio could be produced[48].

Recently, Ir/Al_2O_3 catalyst was tested in the hydrogenation of linoleic acid at 140 °C and 300 torr hydrogen pressure. The Δ-12 double bond showed the highest reactivity in the reduction process[49].

In the hydrogenation of 1,3-pentadiene the selectivity sequence is the following[50]:

$$Pd > Rh > Ru \cong Pt > Ir.$$

An exception is the hydrogenation with Ru/C catalyst shown in equation 14[51]. Another exception is the Pd-catalyzed hydrogenation of 1,3-cyclohexadiene, where benzene and cyclohexane are formed[52].

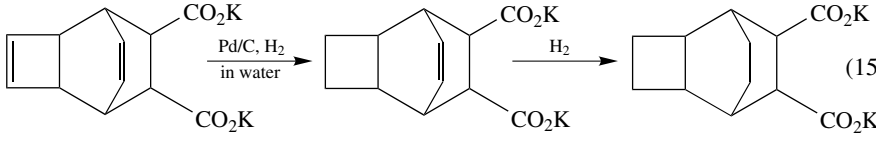


(14)

In order to increase the selectivity in diene hydrogenation, low-temperature basic additives and the use of less polar solvents may help. In special cases, treatment of the catalysts with the salts of heavy metals (Zn, Cd, Pb) can be the method used to modify the activity and selectivity[53]. Rh and Ir catalysts could be selectively poisoned with CO-containing hydrogen, in order to saturate 1,3-butadiene to 1-butene without isomerization[54].

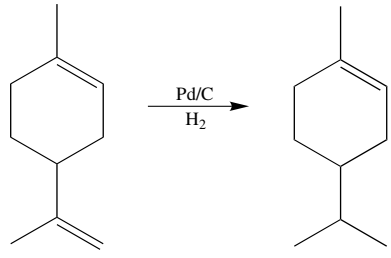
Iron introduced into Pd/Al_2O_3 catalyst by controlled surface reaction promoted the activity of the catalyst in the liquid-phase hydrogenation of isoprene. When Fe was introduced by impregnation or coimpregnation, it had an opposite effect[55].

The hydrogenation of the double bond is facilitated by steric strain (equation 15)[53].



(15)

It is generally observed that the less hindered double bond in a diolefin is preferentially hydrogenated as found in the reaction of limonene (equation 16)[56].

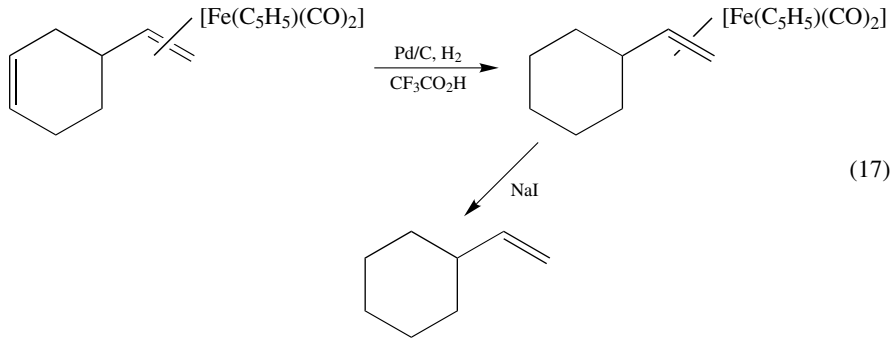


(16)

In most cases during the hydrogenation of dienes and polyenes there is an easily observed decrease in the rate of hydrogenation after the uptake of one mole of hydrogen. When this decrease is not easily detectable, it is worthwhile to stop the reaction after

the uptake of one mol hydrogen, because it may enable one to prepare successfully the half-hydrogenated product in a fairly good yield.

An interesting method is to protect one double bond by addition of cyclopentadienyl dicarbonyl iron during hydrogenation and afterwards to regenerate the product (equation 17)[57].



(17)

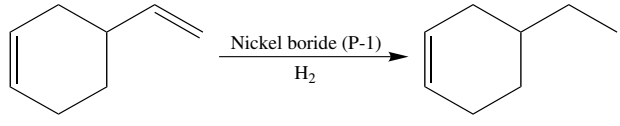
Not only metals but some oxide catalysts are active in diene hydrogenation: ZnO modified by $Sn(CH_3)_4$ afforded 1-butene in hydrogenation of butadiene at room temperature[58]. Reduced and sulfided molibdena on alumina catalyst hydrogenated butadiene and cyclohexadiene selectively[59]. When the transition metal complex $Mo(CO)_6$ was encapsulated in NaY zeolite cages, it converted *trans*-1,3-pentadiene to *cis*-2-pentene and 1,4-pentadiene to *cis*-1,3-pentadiene at 150 °C[60]. $Cr(CO)_3$ encaged in LiX or NaX zeolite was efficient and selective in butadiene hydrogenation to *cis*-2-butene[61].

Copper, gold and Pt/TiO_2 catalysts were tested in the hydrogenation of norbornadiene. When the latter catalyst is thermally treated at high temperature, strong metal support interaction takes place and the catalyst adsorbs a negligible amount of hydrogen. The common characteristic of these catalysts is that they cannot activate hydrogen, but the diene hydrogenation is rather fast. A plausible explanation is that the surface olefin–metal complex is directly involved in activating the molecular hydrogen[62].

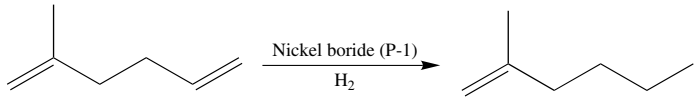
Catalysts formed by reacting nickel(II) acetate with NaH or $NaBH_4$ can be applied as hydrogenation catalysts in selective hydrogenations of dienes[63–65].

In aqueous medium, the reduction of nickel(II) acetate with $NaBH_4$ produces nickel boride[66]. This fine black precipitate, designated P-1 nickel, is a more active catalyst than Raney nickel for double-bond hydrogenations. The P-1 nickel catalyst produces less double-bond migration than standard Raney nickel, it is not pyrophoric and is more readily prepared than Raney nickel.

P-1 nickel can also be used for the selective hydrogenation of dienes. For instance, 4-vinylcyclohexene was hydrogenated with high selectivity (98%) to 4-ethylcyclohexene (equation 18), whilst 2-methyl-1-hexene was obtained with 93% selectivity from 2-methyl-1,5-hexadiene over it (equation 19)[66].

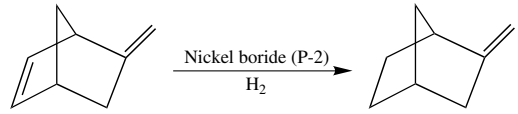


(18)



(19)

In ethanol nickel(II) acetate treated with $NaBH_4$ produces a nearly colloidal black suspension[63]. Variation of the solvent in the preparation of the nickel catalyst results in an amorphous nickel boride catalyst[67,68]. This P-2 nickel catalyst is much more sensitive to the double-bond structure[69,70]. In the hydrogenation of the strained double bonds of norbornadienes, P-2 nickel shows high selectivity (95%) and low isomerization characteristics (equations 20 and 21).



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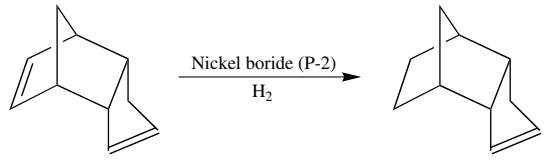


(21)

A complex reducing agent was prepared from NaH, RONa and nickel(II) acetate[64,65]. This catalyst (referred to as Nic), similarly to the P-1 and P-2 nickel catalysts, is a selective catalyst in diene reductions. The reactive parts of Nic are metal hydrides[71] and the key step in the hydrogenation is the formation of M−H bonds. The sodium salt of the alcohol added plays an important role as an activating agent in reductions using Nic. Whereas P-1 and P-2 nickels are selective and sensitive to the double-bond structure and show a rather low propensity toward isomerization, Nic has no propensity toward disproportionation.

B. Chemical Reduction

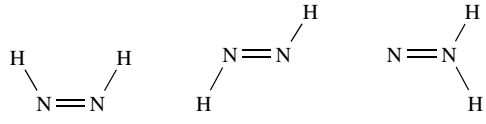
For the chemical reduction of dienes and polyenes diimide, ionic hydrogenating agents, metal hydrides containing reducing agents and alkali metals are used. The regioselectivity and the stereoselectivity can be different in these reductions depending on the nature of reagents.

1. Reduction by diimide

In the 1960s diimide was recognized as a new reducing agent in the reduction of double bonds[72−76].

Since diimide exists as a transient intermediate and cannot be isolated under normal conditions, procedures for reduction by diimide necessarily involve generation of the reagent *in situ*[74,75,77]. Diimide can be generated by (i) oxidation of hydrazine, (ii) acid decomposition of azodicarboxylate salts and (iii) thermal or base-catalyzed decomposition of substituted benzenesulfonyl hydrazides.

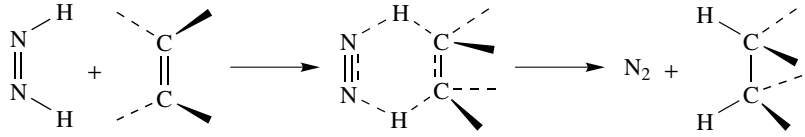
Diimide has three isomers: *cis*- and *trans*-diimide as well as 1,1-diimide (aminonitrene) (Figure 1)[77−80]. Although *trans*-diimide is the only isolated and characterized diimide, *cis*-diimide must be formed as a reactive intermediate in the reduction system[72,77].



cis-diimide *trans*-diimide 1,1-diimide

FIGURE 1

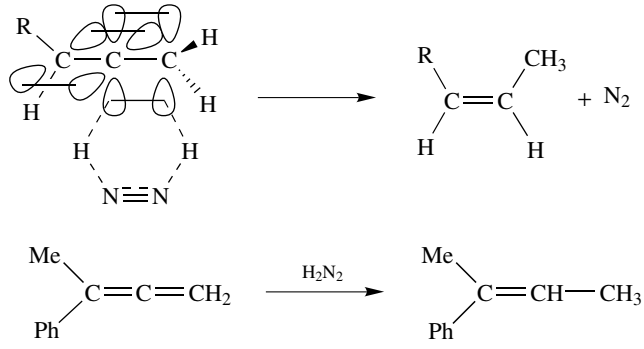
Transfer of hydrogen occurs exclusively in a *syn* manner and it has been concluded that the reduction of a multiple bond by diimide involves a synchronous transfer of a pair of hydrogens to a single face of the carbon–carbon double bond via a six-membered cyclic transition state to give a *syn* adduct (equation 22)[77,81].



(22)

Diimide can act as both a hydrogen acceptor and donor, undergoing disproportionation as a side-reaction which produces a considerable amount of nitrogen gas. From a practical point of view the occurrence of this disproportionation reaction requires the use of an excess of the diimide precursor.

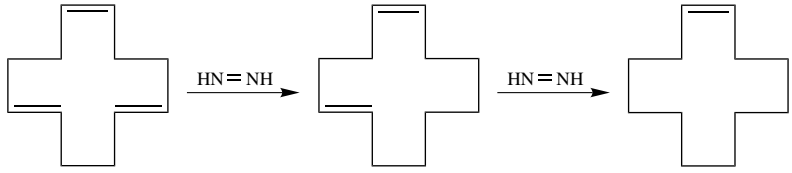
The reduction of dienes by diimide depends on the nature of the substitution of the diene. Several studies of relative reactivity have been carried out and they indicated that an increasing degree of alkyl substitution on the double bond results in decreasing reactivity[82]. In the case of allenes, the reduction of the less substituted allenic double bonds and the formation of the thermodynamically less stable *cis* olefin can be explained by the steric control of the approach of the diimide (equation 23)[83].



(23)

In the reduction of phenylallenes it was found that the phenyl group inhibits sterically the *cis* coplanar approach of diimide, while in alkylallenes the alkyl group activates electronically the remote double bond[81].

In general, *trans* double bonds are more reactive than *cis* double bonds, and diimide reduction is not accompanied by migration or by *cis–trans* isomerization of the double bonds (equation 24)[77].



(24)

It was shown that conjugated dienes are more reactive than monoenes in their reduction by diimide[84]. According to the data of Table 1, conjugation increases the relative reactivity in reduction of dienes (k_{rel}) compared with the reduction of monoenes, but the more substituted double bond is less reactive.

2. Ionic hydrogenation

Ionic hydrogenation reactions[85] involve the use of a hydrogenating pair consisting of a proton donor and a hydride ion donor. The ionic hydrogenation is based on the principle that the carbenium ion formed by the protonation of the double bond abstracts a hydride ion from the hydride source.

The hydrogenating pair consisting of a proton source and a hydride ion source has to meet several requirements[86]. The proton donor must be sufficiently acidic to protonate the carbon–carbon double bond of the substrate to form a carbocation, but not so acidic as to protonate the hydride source. The intermediate carbocation must be electrophilic enough to abstract a hydride ion from the hydride source, but it should not react with any other nucleophile source in the reaction system, including the conjugate anion of the proton donor. In these respects the pairs involving trifluoroacetic acid and organosilanes proved to be the most useful. The donating ability of organosilanes in ionic hydrogenation reactions is a function of the substituents on the silicon atom, and it decreases in the following sequence[87–89]:

$$Et_3SiH > (n\text{-}C_8H_{17})_3SiH > Et_2SiH_2 > Ph_2SiH_2 > Ph_3SiH > PhSiH_3.$$

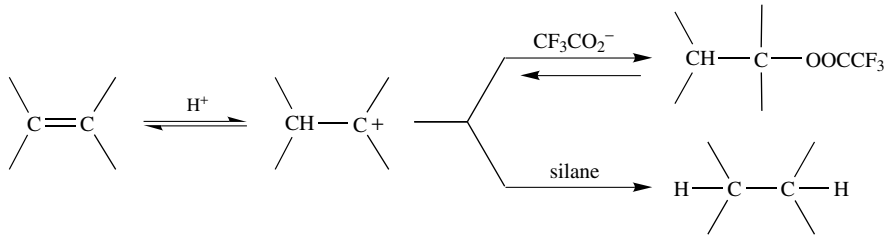
The ionic hydrogenation of unsaturated carbon–carbon bonds proceeds according to Scheme 2.

The rate-determining step in ionic hydrogenation is the protonation of the C=C bond[90]. The unsaturated substrate must be capable of forming a stable carbocation by protonation with CF_3CO_2H which strongly limits the application of this reaction. Unsaturated compounds which are branched at the alkenic carbon atom can be easily reduced[86,91], but unbranched compounds are not reduced under conditions of ionic hydrogenation reaction[91,92].

TABLE 1. Relative reactivities[a] in the reduction of dienes by diimide

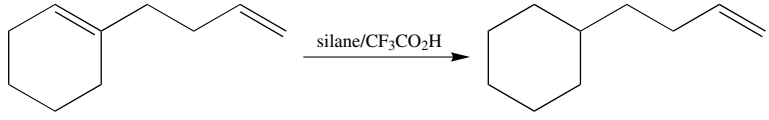
Dienes	k_{rel}
Cyclohexene	1.0
1,3-Cyclohexadiene	47.4
1,4-Cyclohexadiene	2.8
2-Methyl-1,3-butadiene	13.6
2,3-Dimethyl-1,3-butadiene	3.1
2,5-Dimethyl-2,4-hexadiene	0.5

[a]Relative to cyclohexene.



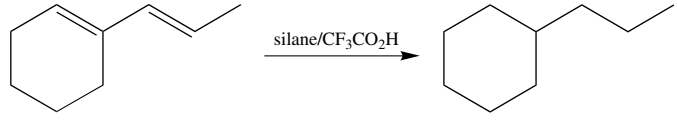
SCHEME 2

In a nonconjugated diene, where the C=C bonds are separated by two or more methylene groups, only the double bond containing a branched carbon atom is reduced (equation 25)[85].



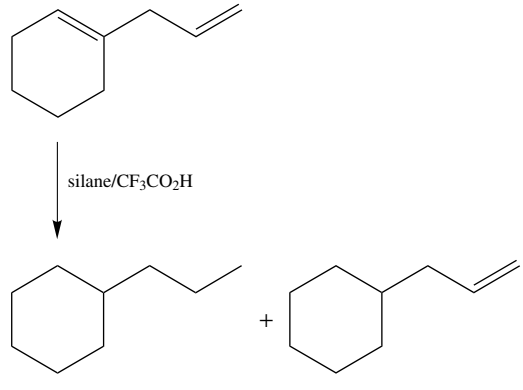
65% (25)

In a conjugated diene, where one of the carbon atoms is branched, both alkenic bonds are hydrogenated in the trifluoroacetic acid/silane reaction mixture to give the corresponding saturated hydrocarbon (equation 26)[85].



70% (26)

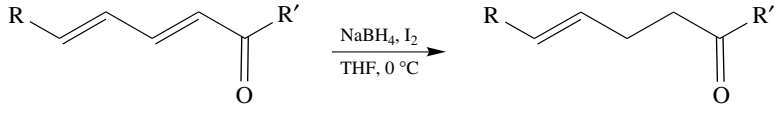
When the alkenic bonds are separated by one methylene group, the branched alkenic bond is mainly reduced but the completely hydrogenated product is also formed (equation 27)[85].



15% 55% (27)

3. Reduction by metal hydrides and dissolving metals

In the reduction of dienes and polyenes, combinations of a metal hydride and transition metal halides can also be used. Sodium borohydride and cobalt(II) halides were applied in the selective reduction of unsaturated carbon–carbon double bonds[93]. $LiAlH_4$, in the presence of Zr^{IV}-, Ti^{IV}- or V^{IV}-halides, is a selective reducing agent of dienes[94,95]. The following reactions were carried out with sodium borohydride and iodine (equation 28)[96].

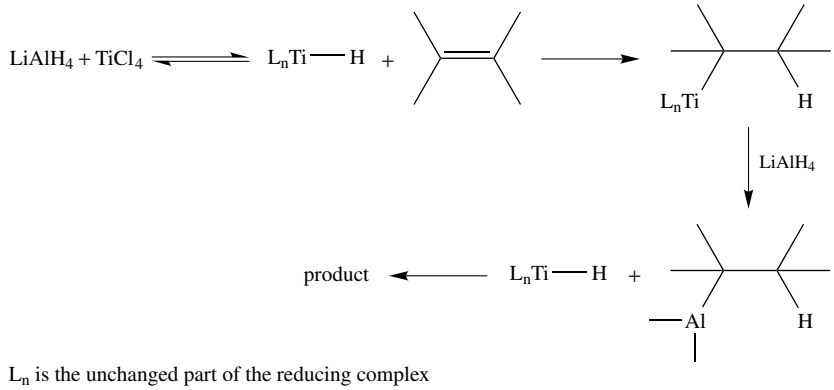


(28)

R	R′
3,4-Methylenedioxyphenyl	Piperidyl, *i*-BuNH
C_5H_{11}	*i*-BuNH

The first step of the reduction by cobalt(II) chloride and $NaBH_4$ involves the production of cobalt hydride species which is capable of exchanging hydrogen ligands with the medium. The second step is a hydrometallation reaction followed by a reductive cleavage of the carbon-cobalt bond. The hydrocobaltation seems to be reversible, as indicated by deuterium label incorporation[93].

Titanium tetrachloride is a very effective catalyst for the addition of $LiAlH_4$ or alane to the olefinic double bond. The mechanism of this reaction involves intermediate transition metal hydrides, as in the case of reaction of $NaBH_4$ and Co^{II}-salts. The hydrotitanation of the double bonds is probably followed by a rapid metal exchange reaction (Scheme 3)[94].



L_n is the unchanged part of the reducing complex

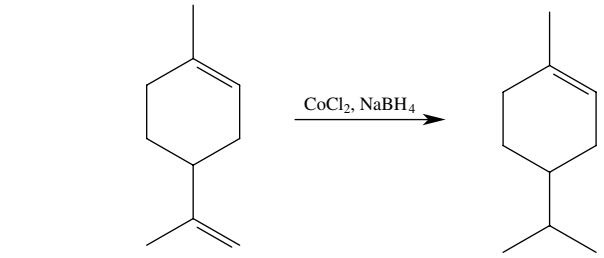
SCHEME 3

The combination of Co^{II}-salts with $NaBH_4$ is a selective reducing agent of a disubstituted side-chain olefinic double bond in the presence of a trisubstituted endocyclic double bond, which is demonstrated in the reduction of limonene (equation 29)[93,97].

The selectivity decreases in the following sequence: mono- > di- > tri- and tetrasubstituted alkenes, an order which can be ascribed to the operation of steric effects.

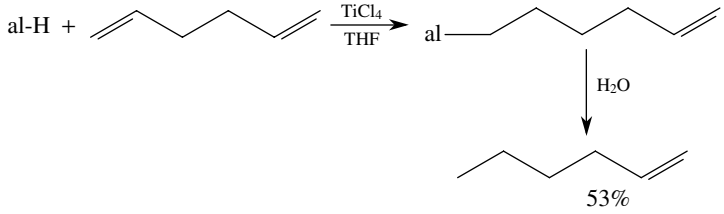
In the reaction of $LiAlH_4$ with nonconjugated dienes in the presence of titanium(IV) or zirconium(IV) chloride, selective reduction of the less hindered double bond was observed

(equation 30)[94,95].

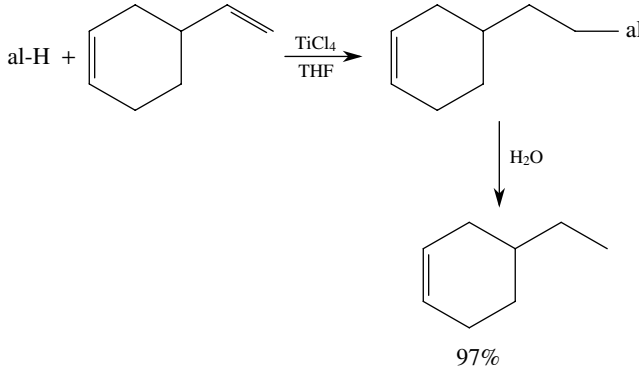


(29)

79%



53%



(30)

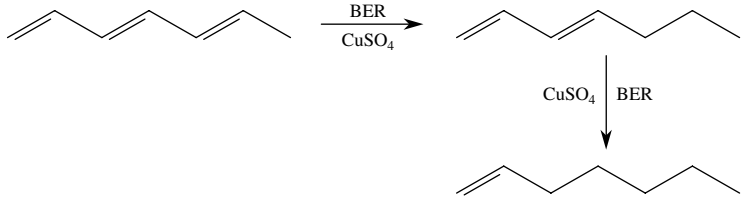
97%

al-H = $LiAlH_4$

The relative rates for reduction of double bonds are in the following order:

$$RHC{=}CH_2 > R'RC{=}CH_2 > RHC{=}CHR'.$$

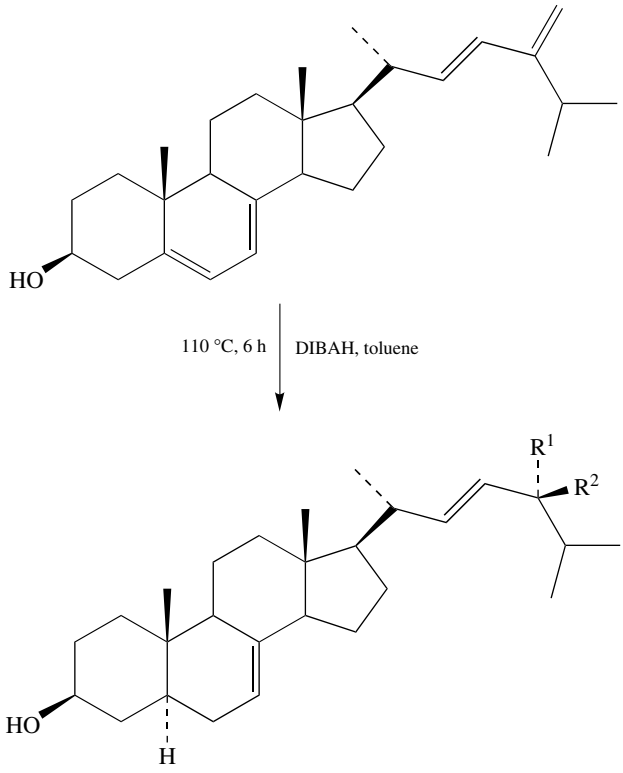
A special mild reducing agent called BER is prepared by treating an anion exchange resin with aqueous $NaBH_4$. Addition of $CuSO_4$ allows selective reductions of dienes and polyenes (equation 31)[98].



(31)

The reduction of conjugated dienes by dissolving metals is not extensively reported. This method appears to be nonselective, giving rise to a mixture of the expected olefins and polyolefins as by-products[99].

Recently, diisobutylaluminium hydride (DIBAH) was found to be a selective reducing agent in the reduction of steroidal 5,7 and 22,24(28) dienes (equation 32)[100].



(32)

R^1 = Me, R^2 = H

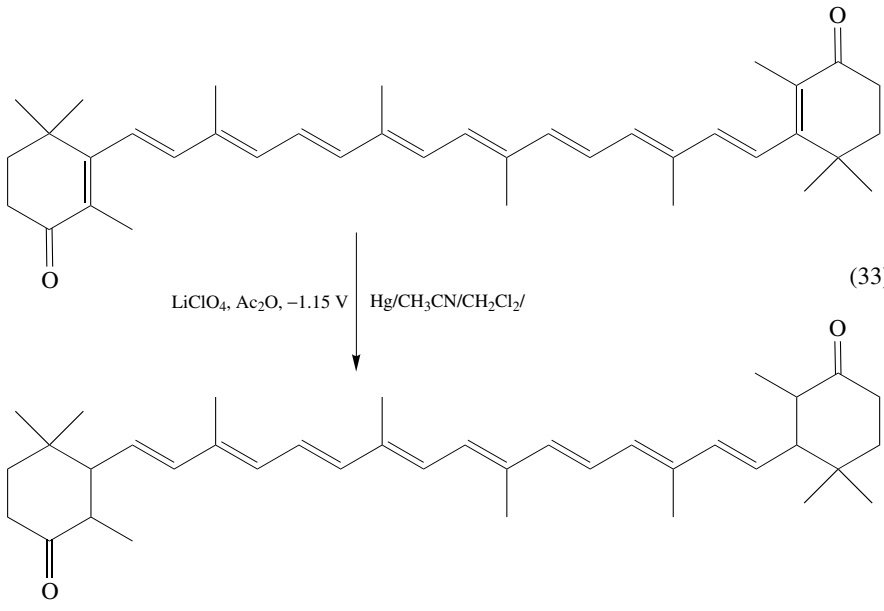
R^1 = H, R^2 = Me

C. Electrochemical Reduction

The electrocatalytic reduction of dienes, like that of monoenes, is difficult when the double bond is not activated. Polyolefins with isolated double bonds cannot be reduced on mercury cathode, while double bonds conjugated to another π-system can be reduced.

The reduction is usually made in a multi-compartment electrochemical cell, where the reference electrode is isolated from the reaction solution. The solvent can be water, alcohol or their mixture. As organic solvent *N*,*N*-dimethylformamide or acetonitrile is used. Mercury is often used as a cathode, but graphite or low hydrogen overpotential electrically conducting catalysts (e.g. Raney nickel, platinum and palladium black on carbon rod, and Devarda copper) are also applicable.

It is possible to get 4,4′-dioxo-5,5′,6,6′-tetrahydrocarotene by reduction of 4,4′-dioxo-β-carotene at a mercury cathode (equation 33)[101].

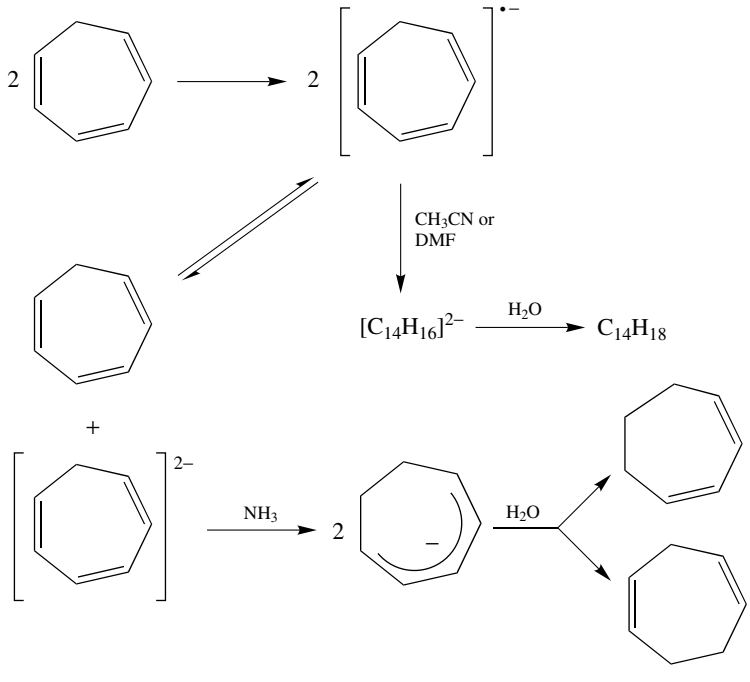


(33)

Cyclooctatetraene was reduced electrochemically to cyclooctatetraenyl dianion. In DMF the product is mostly (92%) 1,3,5-cyclooctatriene at −1.2 V. If the potential is lowered the main product is 1,3,6-cyclooctatriene. Previous experiments, in which the anion radical was found to be disproportionated, were explained on the basis of reactions of the cyclooctatetraene dianion with alkali metal ions to form tightly bound complexes, or with water to form cyclooctatrienes. The first electron transfer to cyclooctatetraene is slow and proceeds via a transition state which resembles planar cyclooctatetraene[102].

The reduction of cycloheptatriene was studied in aprotic solvents at a platinum electrode. A reversible wave at −2.5 V for the production of the radical anion was observed in ammonia containing 0.1 M KI. Quasi-reversible or irreversible reduction was observed in acetonitrile and in *N*,*N*-dimethylformamide (equation 34)[103].

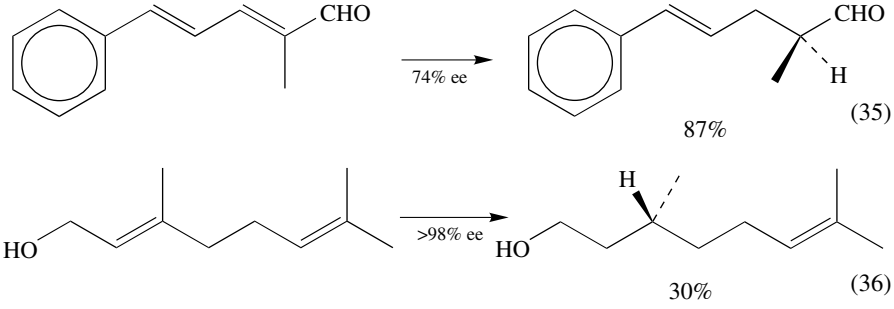
Soybean oil can be hydrogenated electrocatalytically at a moderate temperature, without an external supply of pressurized H_2 gas. In the electrocatalytic reaction scheme, atomic hydrogen is produced on an active Raney nickel powder cathode surface by the electrochemical reduction of water molecules from the electrolytic solution. The concentration of the hydrogen in the catalyst metal surface can easily be controlled by adjusting the applied current (or electric potential), which may lead to improved product selectivity; the catalyst will be cathodically polarized during reactor operation, resulting in less corrosion and lower concentrations of nickel ion contaminants in the oil product; since only a little free hydrogen gas is present, the risk of explosion and fire is reduced. The adsorbed hydrogen then reacts with triglycerides to form the hydrogenated product. The electrohydrogenated oil is characterized by a high stearic acid content and a low percentage of total *trans* isomers, as compared with that produced in a traditional hydrogenation process[104].

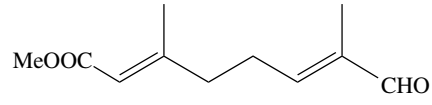


D. Enzymatic Reduction

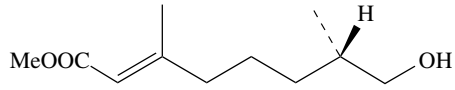
Besides the most widely used catalytic reductions of dienes and polyenes there are some other ways to saturate the C=C double bonds in these molecules. One of these rarely used methods is the enzymatic or microbial reduction. In the presence of bacteria and fungi the reactions progress just as over any classical catalysts.

Several catalysts are used in the field of microbial reductions. The common features of these catalysts are the high selectivity and their use only on a laboratorial scale. They are applied, for example, in the stereoselective synthesis of pharmaceutical intermediates. The reductions are exclusively selective either in the hydrogenation of the C=C double bond or in that of other reducible groups. One of the most widely used catalysts is baker's yeast. In the following hydrogenations, which are catalyzed by *Saccharomyces cerevisiae*, high enantioselectivities were achieved (equations 35–38)[105–108].



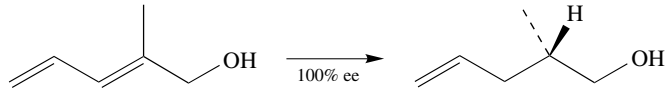


>97% ee



35%

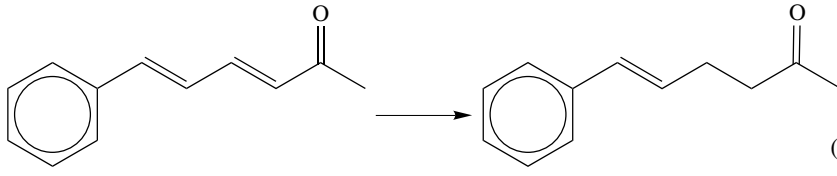
(37)



25–30%

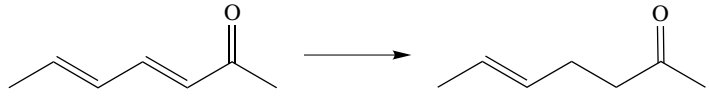
(38)

Baker's yeast can also be used in the saturation of α,β-unsaturated ketones. The reactions described share the following features: (i) remote double bonds are not hydrogenated, (ii) the reaction rate is affected by substitution on or near the double bond and (iii) after a prolonged reaction time reduction of the oxo group can also take place (equations 39 and 40)[109].



75%

(39)



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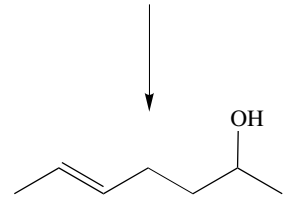
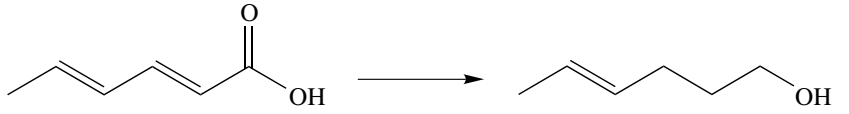


60%

(40)

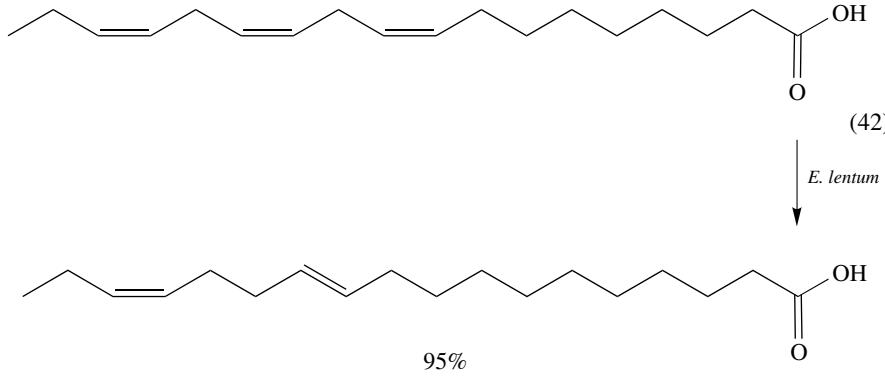
Fungi are capable of producing *trans*-4-hexenol from sorbic acid (equation 41)[110]. This bioconversion comprises two reaction steps. First, the carboxy function is reduced

to alcohol and then the saturation of the α,β-double bond proceeds. The remote double bond remains unchanged. The hydrogenation of sorbic acid can be performed with *Mucor sp.* A-73, as well as with other fungi belonging to the genera *Penicillinum*, *Rhizopus*, *Trichoderma*, *Aspergillus*, *Geotrichum* and *Monascus*[111].



90% (41)

Double bonds of other groups of molecules, such as fatty acids, are reduced with *Butyrivibrio fibrisolvens*[112,113] or *Eubacterium lentum*[114,115]. Under anaerobic conditions *B. fibrisolvens* is able to hydrogenate linoleic acid to octadecenoic acid[112]. This is a multistep reduction, in which isomerization and hydrogenation take place consecutively. α-Linolenic acid was also isomerized with *B. fibrisolvens* to produce a conjugated trienoic acid (9-*cis*,11-*trans*,15-*cis*-octadecatrienoic acid) which was hydrogenated to a nonconjugated *cis–trans* dienoic acid[113]. *Eubacterium lentum* can regioselectively hydrogenate at the 9-position of linoleic, α-linolenic and γ-linolenic acids. Thus, α-linolenic acid ($\Delta^{9,12,15}$) was reduced to 11-*trans*,15-*cis*-octadecadienoic acid with 95% yield (equation 42)[114,115].



(42)

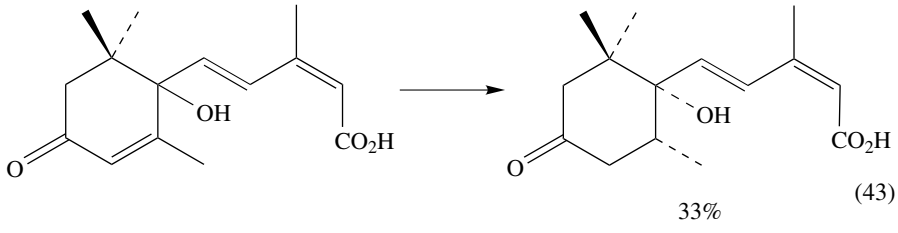
95%

The hydrogenation of the monoterpenes (−)- and (+)-carvone was studied extensively. Several microorganisms were used in these reductions. They catalyzed the production of all possible stereoisomers, but some of them only in small quantities. The distribution of the products depended on the catalyst applied[116].

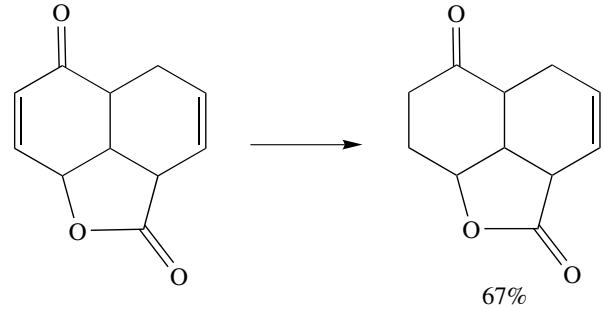
Finally, there are some examples for reduction of various compounds, which are of biochemical interest. Racemic abscisic acid was reduced with *Aspergillus niger* affording (−)-(1′*S*,2′*R*)-2′,3′-dihydroabscisic acid with >95% ee (equation 43)[117].

The reduction of Woodward's lactone with *Saccharomyces cerevisiae* produced an intermediate which is used for the preparation of hypotensive alkaloids (equation 44)[118].

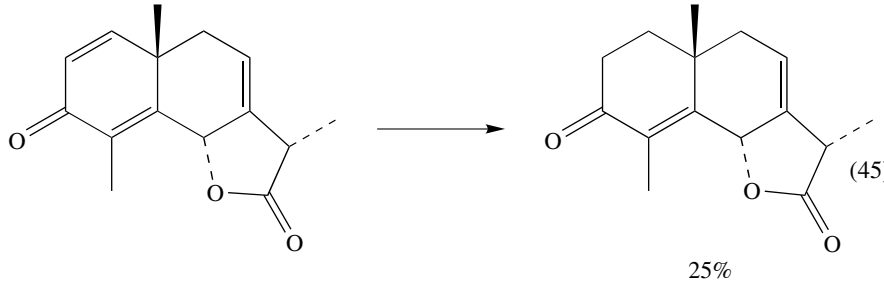
α-Santonin, a sesquiterpene lactone, was reduced with *Pseudomonas cichorii S* (equation 45)[119].



33% (43)



67% (44)



25% (45)

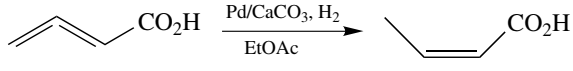
III. REDUCTION OF DIENES AND POLYENES WITH DIFFERENT STRUCTURES

A. Allenes

Allenes are reduced in two distinct stages. In the first stage, the major products are olefins, accompanied by a small amount of the alkane, while in the second stage the olefins produced are reduced to alkanes. The selectivity of reduction varies with the metal[34], and for allene itself at various temperatures it decreased in the following series of metals:

$$Pd > Rh \approx Pt > Ru > Os \gg Ir.$$

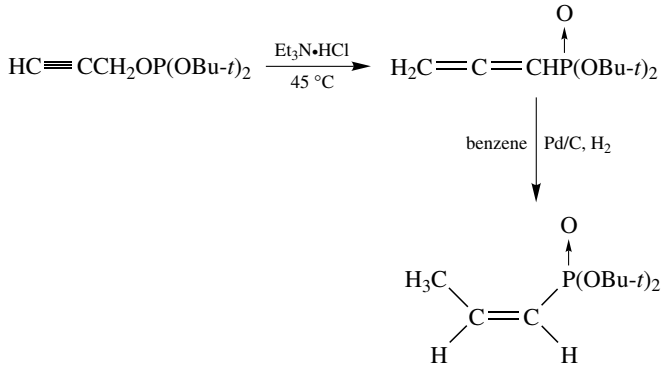
Allenes with terminal double bonds are selectively reduced in the terminal position, whereas internal allenes afford a mixture of the corresponding olefins[120]. Some hydrogenations resulted in the *cis* alkene derivative (equation 46)[121].



(46)

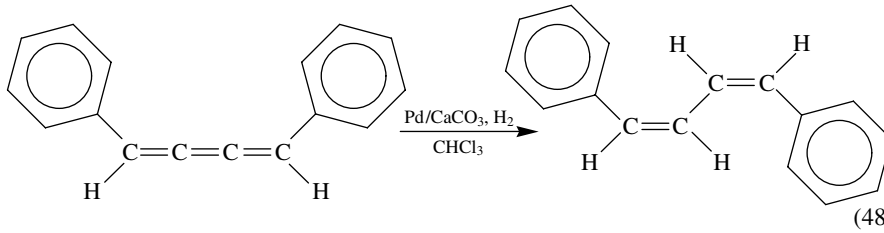
Similarly, 1,2-cyclononadiene in methanol with 10% palladium on carbon catalyst gave *cis*-cyclononene[122]. The *cis* isomer is not necessarily the primary product of allene hydrogenation, since the initially formed *trans* isomer is rapidly isomerized under the reaction conditions. Bond and Sheridan showed that allene resembles acetylene in its ease of hydrogenation[123]. They suggested that it is selectively adsorbed and held more strongly by the catalyst than 1-propene. Allene was selectively hydrogenated with Pd, Pt and Ni in the presence of 1-propene without its further reduction.

An example of the synthetic use of allene hydrogenation is the preparation of the antibiotic phosphonomycin (equation 47)[124].



(47)

In the reduction of trienes, only the central double bond was hydrogenated (equation 48)[125]. The product was a *cis*,*cis*-1,3-butadiene derivative. Similar results were obtained in the hydrogenation of the tetraphenyl derivative with a Pd catalyst modified by lead[126].



(48)

B. Conjugated Dienes

A conjugated double bond should be more resistant to hydrogenation than an isolated one, because the conjugation energy is included in the energy balance (the heat of hydrogenation is 227 kJ mol^{-1} for 1,3-pentadiene and 255 kJ mol^{-1} for 1,4-pentadiene). In spite of this, conjugated olefins are hydrogenated more easily[127].

Much experience concerning the hydrogenation of conjugated dienes was obtained with butadiene hydrogenation. On Pt single crystals the reaction was found to be structure sensitive; the activity sequence of different planes (marked with Miller's index) is

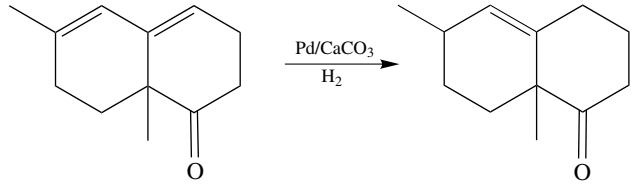
$$(111) < (100) < (110)$$

The $H_2 + D_2$ equilibration reaction was much faster than the diene hydrogenation, so that the rate-limiting step is not the hydrogen dissociation. The Pt behaves as a bifunctional

catalyst, and the hydrogenation and hydrogen exchange reactions do not occur at the same kind of sites. An adsorbed hydrocarbon layer is present on the Pt surface during the hydrogenation. This does not prevent the dissociation of hydrogen but induces geometrical hindrance as well as an electronic effect[128].

In the case of Pd/Al_2O_3 catalysts the morphology of the metal particles is also important because it determines the hydrogenation and isomerization selectivity. On flat metal surfaces isomerization is preferred whereas rough surfaces are more active in hydrogenation[129].

The most disputed question about the hydrogenation of conjugated dienes is whether 1,2- or 1,4-addition takes place as in the following reaction (equation 49)[128].

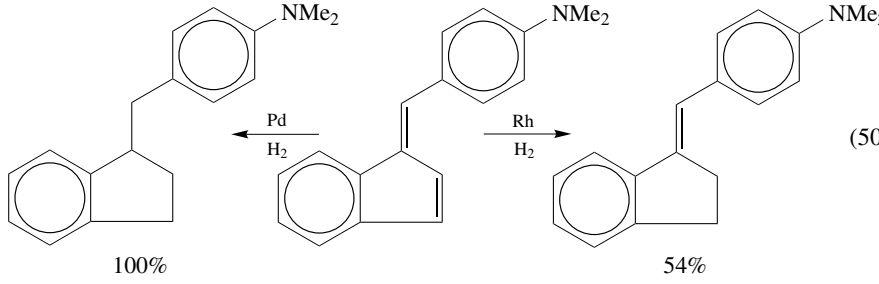


(49)

This is the most dubious in the case of Pd catalysts, which have high activity in isomerization and double-bond migration. From studies of the half hydrogenation and the isomerization of isoprene[130] with Pd, Pt and Ni, the Pd catalyst led to the highest extent of isomerization. From the results of the reduction of isoprene it appears that 1,4-addition as well as 1,2- and 3,4-additions took place, because a significant amount of 2-methyl-2-butene was formed with all catalysts.

Most researchers have found 1,2-addition of hydrogen in C=C hydrogenation of conjugated double bonds[131–134], for example, in the reduction of 1-vinylcyclohexene, 4-methylene-1,2,3-trimethylcyclobutene-3-ol benzoate and some steroid derivatives.

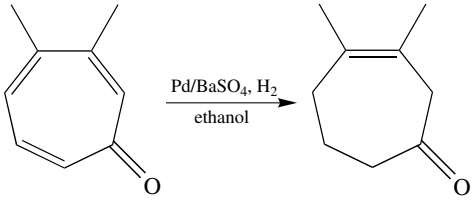
The selectivity of partial hydrogenation depends on the catalyst in the case of a benzylidene indene derivative (equation 50)[135].



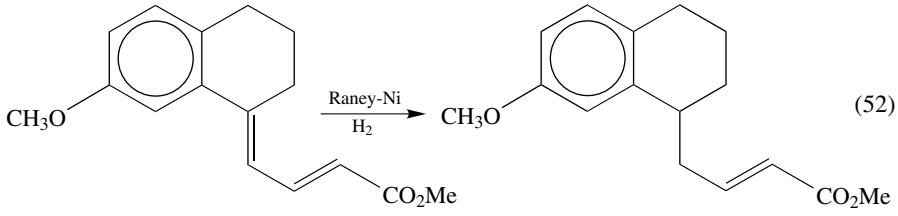
(50)

The reduction of some polyenes is affected by the double bond migration, e.g. when a tetrasubstituted olefin is formed, since it is hydrogenated with difficulty. For example, the reduction of the second double bond was fast, but the reduction ceased after the uptake of two moles of hydrogen (equation 51)[136].

Raney-nickel was found to be selective in the hydrogenation of cyclopentadiene and cyclohexadiene and of their methyl and ethyl derivatives at 0–40 °C and 2–5 bar pressure[137,138]. The skeletal nickel proved to be selective in the semihydrogenation of conjugated polyenic compounds (equation 52)[139].

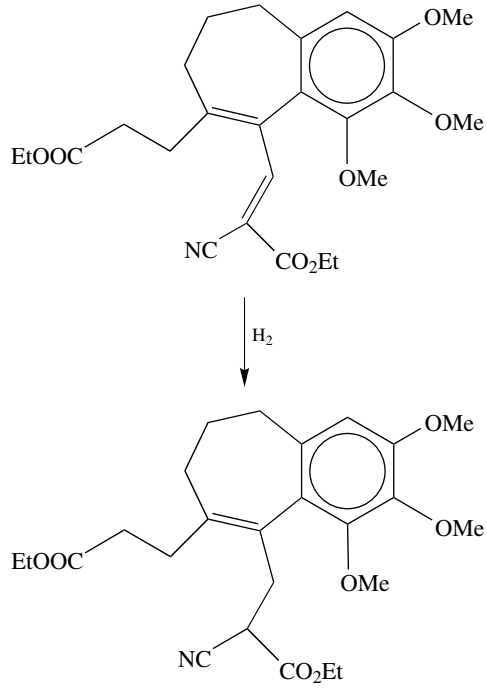


(51)



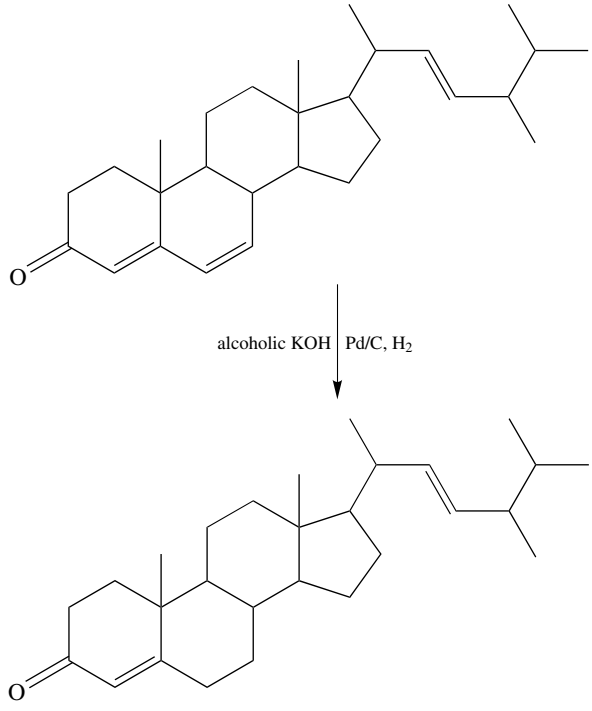
(52)

In the above mentioned reaction, platinum oxide and palladium on barium sulfate showed no perceptible change in the rate of hydrogen uptake. On the other hand, platinum oxide was selective in the hydrogenation of cyclohexa-2,4-diene-1,2-dicarboxylic acid to 1,4,5,6-tetrahydrophthalic acid[140]. A similar result may be the favored reduction of a symmetrical disubstituted double bond over a more hindered trisubstituted bond. The retarding effect of additional substitution is demonstrated in the hydrogenation of a trisubstituted double bond in the presence of a tetrasubstituted double bond (equation 53)[141].



(53)

The selectivity can be increased by addition of alkali (equation 54)[142].

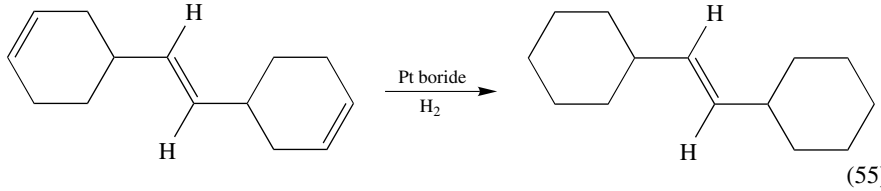


(54)

Another method of increasing the catalyst's selectivity is its poisoning with heavy metals, like lead. This was effective with a Pd catalyst in the hydrogenation of cyclopentadiene, 1,3-cyclohexadiene and cyclooctatriene[143].

C. Isolated Dienes

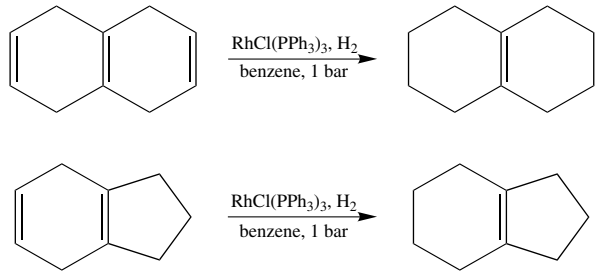
The selectivity in the hydrogenation of isolated double bonds depends on the type of substitution of the unsaturated carbon atoms, as in the reaction in equation 55[144].



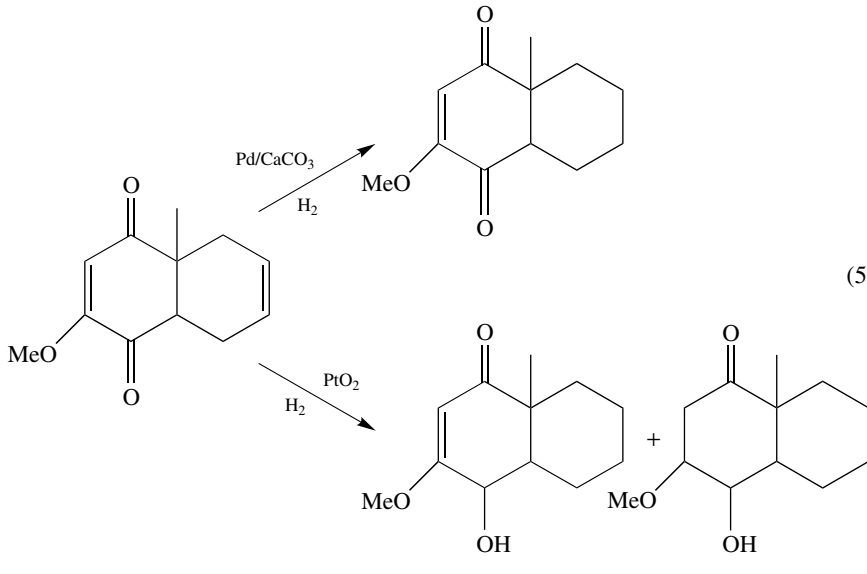
(55)

A similar phenomenon was observed in a homogeneous rhodium complex catalyzed hydrogenation (equation 56)[6].

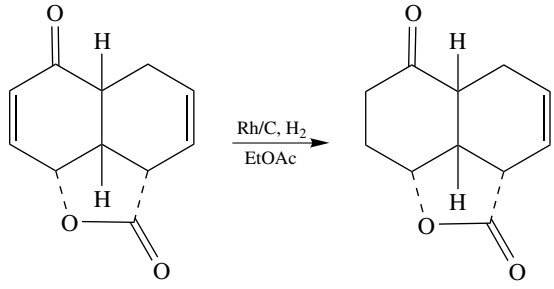
In the case of molecules which have both conjugated and isolated double bonds, the selectivity of the hydrogenation depends on the catalysts and on the nature of the substituents of the unsaturated compound (equations 57 and 58)[145,146].



(56)



(57)

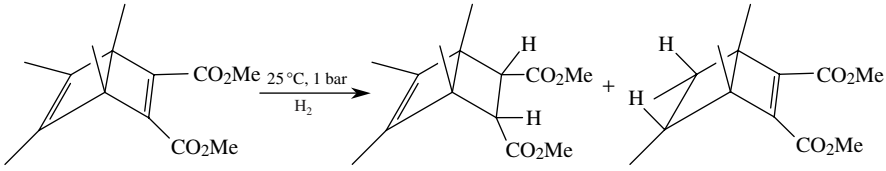


(58)

The selectivity of hydrogenation of dimethyl tetramethylbicyclo[2.2.0]hexa-2,5-diene-5,6-dicarboxylate depends on the catalytically active metal and on the bulk of the ester substituent (equations 59 and 60)[147].

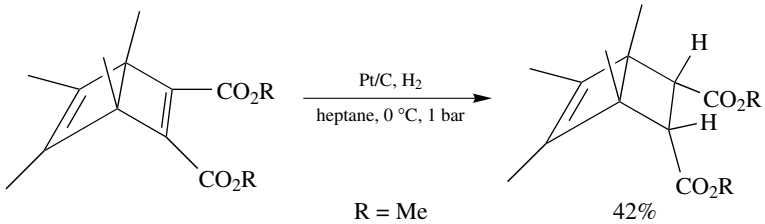
There are other possibilities for selective reduction in the hydrogenation of symmetrically substituted dienes. Raney-nickel afforded 1-alkenes, whereas supported Pd catalysts gave a mixture of 1- and 2-alkenes[148]. A selective reduction of a terminal double bond was carried out in the presence of an endocyclic double bond, which was trisubstituted[149–152].

The ability of Pd to cause isomerization is demonstrated in the reaction of equation 61[153].



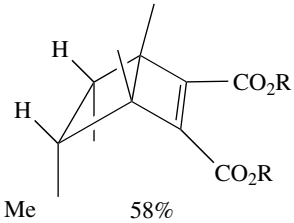
Raney-Ni	100%	0%
Pd/C	85%	15%
Ru/C	66%	34%
Rh/C	52%	48%
Pt/C	47%	53%
Os	32%	68%

(59)



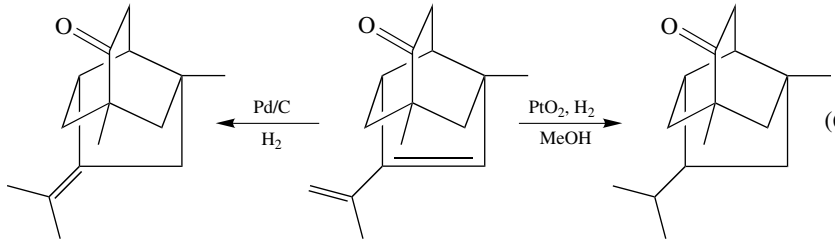
R = Me 42%
R = *t*-Bu 5%

\+



R = Me 58%
R = *t*-Bu 95%

(60)

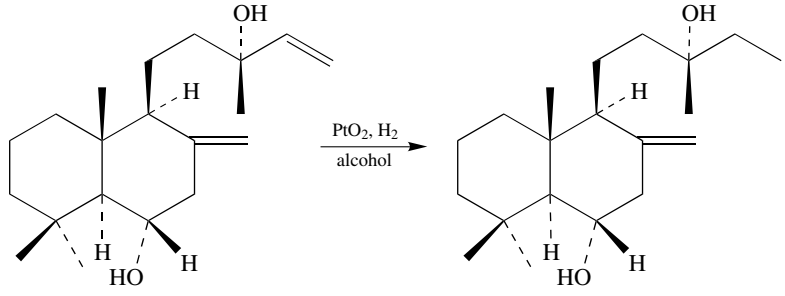


(61)

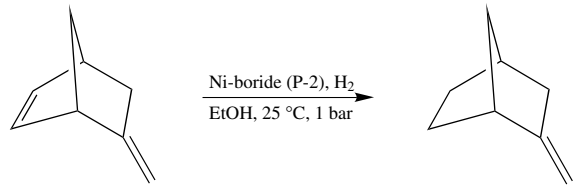
Preferential reduction of a monosubstituted double bond in the presence of an unsymmetrically disubstituted double bond is shown in equation 62[154].

Ring strain can also exert an important influence on the regioselectivity: the hydrogenation of 5-methylenenorbornene over a Ni-boride catalyst (P-2) resulted in preferential

saturation of the strained endocyclic double bond, although the exocyclic double bond seems to be more accessible (equation 63)[63].

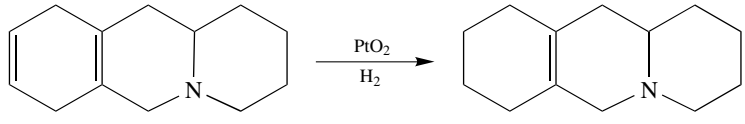


(62)



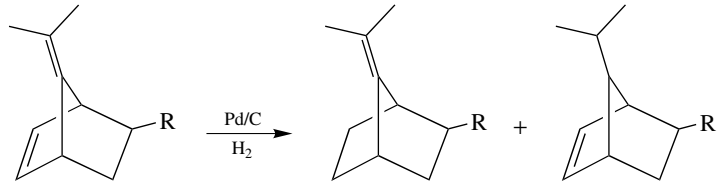
(63)

The hydrogenation of a symmetrically disubstituted double bond is favored over that of a tetrasubstituted one (equation 64)[155–157].



(64)

Selective reduction of dienes may be influenced by the substituents, which can change the substrate orientation during adsorption on the catalyst surface (equation 65)[158]. It has to be mentioned that this effect worked only if low amounts of catalyst were used; at higher amounts the selectivity decreased.

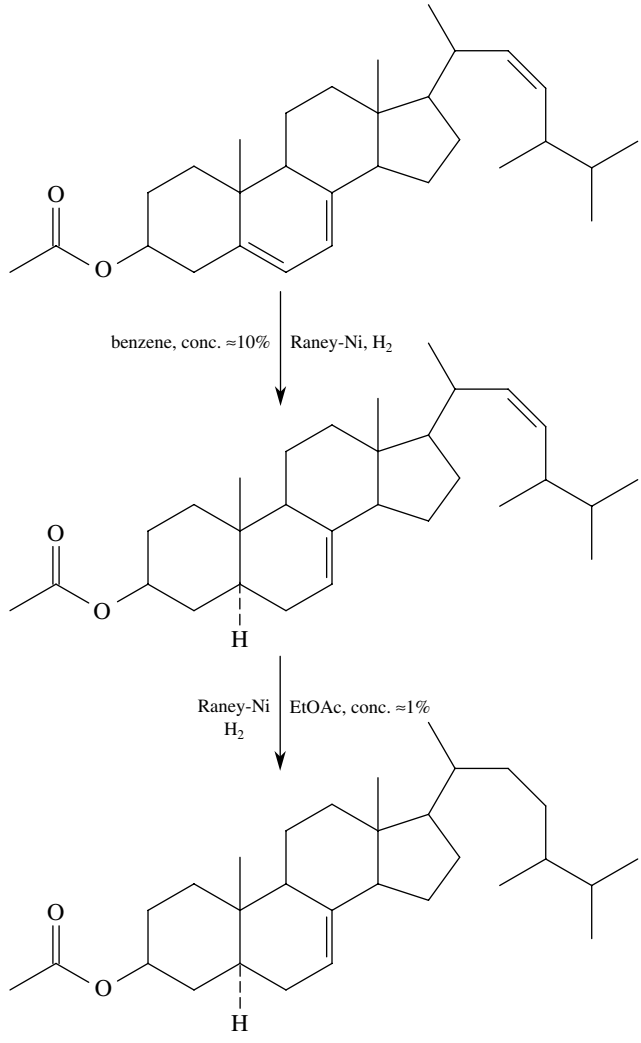


(65)

R = =O	70%	30%
R = –OH	60%	40%
R = –OAc	95%	5%
R = –OTs	>95%	–

The solvent can be an important factor in determining the outcome of hydrogenation as demonstrated by the reduction of a steroid compound (equation 66)[159,160]. At 100 °C

only the saturated compound is produced.



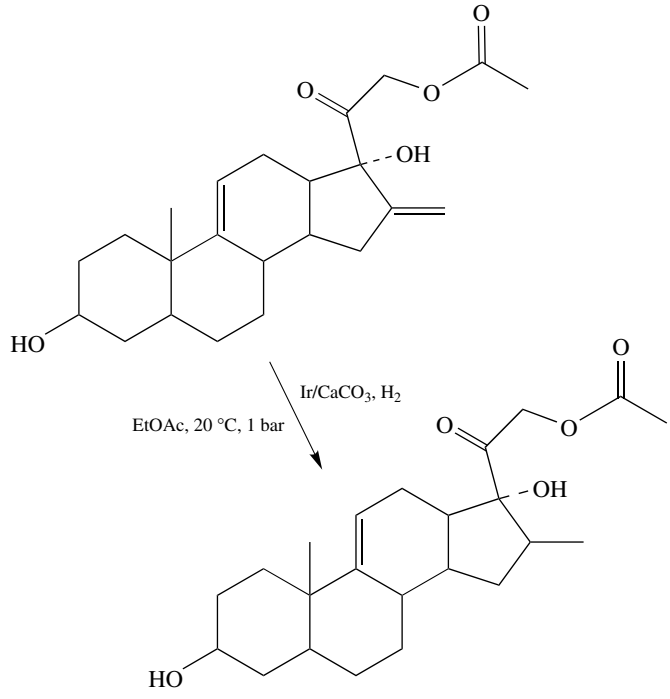
(66)

An iridium catalyst was used in the selective hydrogenation of a steroid compound, where the exocyclic double bond was saturated in the presence of an endocyclic one (equation 67)[161].

D. Polymeric Compounds

Reduction is an important method for polymer modification resulting in a variety of useful elastomers and thermoplastics with unique structures and properties. Reduction also offers a convenient synthetic route to polymers with special monomer sequences, which are inaccessible, difficult or too expensive to prepare by conventional polymerization

methods. The saturated elastomers have good resistance to oxidative and thermal degradation, excellent resistance to oils and fluids at elevated temperatures, low permeability to gases, and better processibility as compared with the unsaturated elastomers[162].



(67)

The aim of the reduction of polymeric compounds is the complete saturation of the substrate, which is different from the usual practice of the hydrogenation of dienes and polyenes, where the incomplete reduction, i.e. a selective reduction, is the main goal.

The reduction can be carried out with stoichiometric reducing agents and by homogeneous or heterogeneous catalytic hydrogenation. A problem in the selectivity in these reactions is the presence of highly coordinating functionalities such as nitrile, carbonyl, amino, hydroxyl, halogen, etc.

The reduction of polymers can be carried out by using a diimide, generated *in situ*. The precursor for diimide can be *p*-toluenesulfonyl hydrazide (TSH), the reaction temperature is between 110–160 °C and the solvents are high boiling aromatic compounds. Possible side-reactions are *cis–trans* isomerization of 1,4-dienes, attachment of hydrazide fragments to the polymer, degradation and cyclization of the polymer.

In the heterogeneous catalytic hydrogenations the polymers, such as the copolymers and homopolymers of styrene, butadiene, isoprene and acrylonitrile, are in solution. The solvents can be cyclohexane, tetrahydrofuran, hexane, acetone, methyl ethyl ketone or methyl isobutyl ketone, the catalytically active metals (Pt, Pd, Ru, Rh, Ni) are supported, the temperature is usually up to 240 °C and the pressure range is from atmospheric to 50 bar. The major advantage of heterogeneous hydrogenation is the easy separation of the catalyst, but the reaction has several disadvantages, such as slow reaction rate, high temperature and pressure, and high catalyst concentration.

The homogeneous hydrogenation catalysts for polymer saturation can be classified into two types: Ziegler-type (Ni, Co, Fe, Ti, Zr based) and noble metal (Rh, Ru, Pd) catalysts.

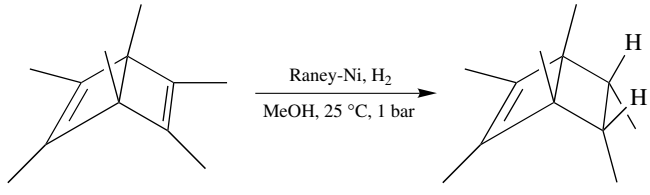
The Ziegler-type catalysts contain also a metal-alkyl, like triethylaluminum. They work usually at moderate temperature and pressure. The most active catalysts for polymer hydrogenation are the noble metal complex catalysts, and they can also be used for reduction of elastomers in the latex phase. The most difficult task is the removal of the catalyst from the reaction mixture. The methods used are based on extraction, adsorption, absorption or on their combination.

The hydrogenated products are nitrile rubber, with good heat resistance, and styrene–butadiene–styrene copolymer, with high tensile strength, better permeability and degradation resistance.

E. Stereoselectivity

In heterogeneous catalytic hydrogenations suprafacial (*cis*) addition of hydrogen would be expected, as the transfer of hydrogen atoms from the catalyst surface to the reactant is usually assumed. However, in some Pt catalyzed reactions antarafacial (*trans*) addition of hydrogen is also observed. The ratio of diastereomeric products formed is determined by the chemisorption equilibrium of the surface intermediates and by the relative rates of hydrogen entrance to the different unsaturated carbon sites. Both effects are influenced by steric factors.

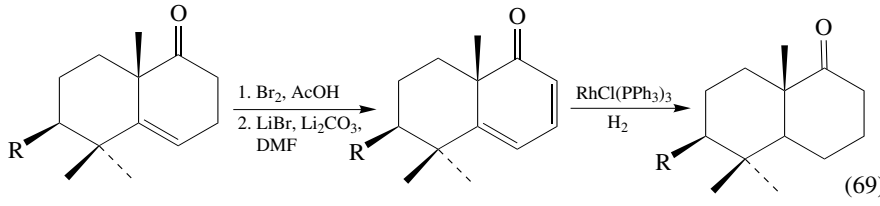
The hydrogenation of hexamethylbicyclo[2.2.0] hexa-2,5-diene over Raney-nickel gives, by *exo* addition, the more strained product. Consequently, it seems that *exo* addition is favored in small bicyclic compounds over the *endo* addition (equation 68)[163].



(68)

α-Hydrogenation of alkenic steroids, which is often observed, plays an important role in many synthetic routes to the steroid skeleton[145,164].

The stereoselective synthesis of tetrahydronaphthalenones was carried out via homogeneous hydrogenation. The reduction at 2 bar hydrogen pressure gave the saturated product in good yield (equation 69)[165].

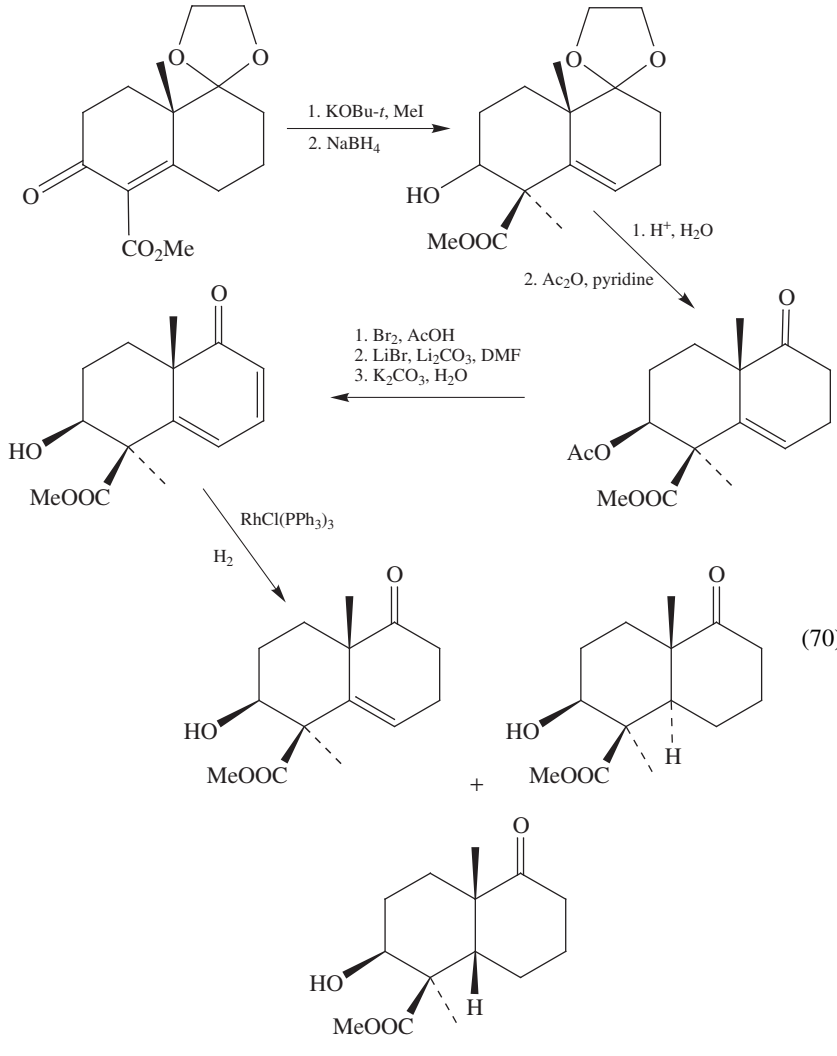


R = H, OAc

(69)

The hydrogenation of the keto ester resulted in the corresponding saturated and half hydrogenated compound, depending on the pressure. Above 5 bar hydrogen pressure the

cis keto ester became a minor product (equation 70)[165].



(70)

Pressure, bar	%	%	%
2	37		63
3.2	62		38
3.9	80		20
4.3	87		13
5	73	<1	27
10.7	70	10	20
16.5	30	30	40

IV. REFERENCES

1. J.-P. Boitiaux, J. Cosyns, M. Derrien and G. Léger, *Hydrocarbon Proc.*, 51 (1985).
2. Kirk-Othmer, *Encyclopedia of Chemical Technology*, Vol. 9, Wiley-Interscience, New York, 1980, p. 813.
3. *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A21, VCH Verlag, Weinheim, 1990, p. 320.
4. B. R. James, *Homogeneous Hydrogenation*, Wiley-Interscience, New York, 1973.
5. F. J. McQuillin, *Homogeneous Hydrogenation in Organic Chemistry*, D. Reidel, Dordrecht, 1976.
6. A. J. Birch and K. A. M. Walker, *Aust. J. Chem*., **24**, 513 (1971).
7. R. E. Ireland and P. Bey, *Org. Synth*., **53**, 63 (1973).
8. R. R. Schrock and J. A. Osborn, *J. Am. Chem. Soc.*, **98**, 2134, 2143, 4450 (1976).
9. J. C. Bailar, *Platinum Met. Rev.*, **15**, 2 (1971); *J. Am. Oil Chem. Soc.*, **47**, 475 (1970).
10. J. Kwiatek, I. L. Mador and J. K. Seyler, *Adv. Chem. Ser.*, **37**, 201 (1963); J. Kwiatek, *Catal. Rev.*, **1**, 37 (1967).
11. M. S. Spencer and D. A. Dowden, U.S. Patent 3,009,969 (1961).
12. A. F. Halasa, U. S. Patent 3,872,072 (1975).
13. G. W. Parshall, *Homogeneous Catalysis*, Wiley-Interscience, New York, 1980, p. 36.
14. G. W. Parshall, *J. Am. Chem. Soc.*, **94**, 8716 (1972).
15. J. Halpern and M. Pribanic, *Inorg. Chem.*, **9**, 2616 (1970).
16. K. Katsuragawa and K. Yoshimitsu, *Jap. Kokai*, **7**, 408, 481 (1974); *Chem. Abstr.*, **81**, 17216 (1974).
17. A. Misomo and I. Ogata, *Bull. Chem. Soc. Jpn.*, **40**, 2718 (1967); U.S. Patent 3,715,405 (1973).
18. L. W. Gosser, U.S. Patent 3,499,050 (1970).
19. J. Tsuji and H. Suzuki, *Chem. Lett.*, 1083 (1977).
20. D. R. Fahey, *J. Org. Chem.*, **38**, 80 (1973).
21. A. D. Shebaldova, V. I. Bystrenina, V. N. Kravtsova and M. L. Khidekel, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2101 (1975); *Chem. Abstr.*, **84**, 16834v (1976).
22. L. W. Gosser, U. S. Patent 3,673,270 (1972).
23. A. Rejvan and M. Cais, *Progress in Coordination Chemistry*, Elsevier, Amsterdom, 1968, p. 32.
24. M. S. Wrighton and M. A. Schröder, *J. Am. Chem. Soc.*, **95**, 5764 (1973).
25. A. Miyake and H. Kondo, *Angew. Chem., Int. Ed. Engl.*, **7**, 631 (1968).
26. B. Heiser, E. A. Broger and Y. Crameri, *Tetrahedron Asym.*, **2**, 51 (1991).
27. H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara and R. Noyori, *J. Am. Chem. Soc.*, **109**, 1956 (1987).
28. M. Sakai, N. Hirano, F. Harada, Y. Sakakibara and N. Uchino, *Bull. Chem. Soc. Jpn.*, **60**, 2923 (1987).
29. I. S. Cho and H. Alper, *Tetrahedron Lett.*, **36**, 5673 (1995).
30. H. Künzer, M. Stahnke, G. Sauer and R. Wiechert, *Tetrahedron Lett.*, **31**, 3859 (1990).
31. D. M. Roundhill, *Adv. Organomet. Chem.*, **13**, 327 (1975).
32. J. W. Herndon and S. U. Turner, *Tetrahedron Lett.*, **30**, 295 (1989).
33. I. Horiuti and M. Polányi, *Trans. Faraday Soc.*, **30**, 1164 (1934).
34. P. B. Wells and G. R. Wilson, *J. Chem. Soc.*, 2442 (1970).
35. G. C. Bond and P. B. Wells, *Adv. Catal.*, **15**, 62 (1964).
36. G. Webb, in *Specialist Periodical Reports: Catalysis* (Eds. C. Kemball and D. A. Dowden), Vol. 2. Chem. Soc., London, 1978, p. 145.
37. J.-P. Boitiaux, J. Cosyns and E. Robert, *Appl. Catal.*, **32**, 145 (1986).
38. J.-P. Boitiaux, J. Cosyns and S. Vasudevan, *Appl. Catal.*, **6**, 41 (1983).
39. V. Ponec and G. C. Bond, *Stud. Surf. Sci. Catal.*, **95**, 500 (1995).
40. B. K. Furlong, J. W. Hightower, T. Y.-L. Chan, A. Sárkány and L. Guczi, *Appl. Catal. A*, **117**, 41 (1994).
41. Ch. Liu, Y. Xu, S. Liao and D. Yu, *Appl. Catal. A*, **172**, 23 (1998).
42. H. Gao, S. Lao, Y. Xu, R. Liu and D. Li, *Catal. Lett.*, **27**, 297 (1994).
43. E. A. Sales, B. Benhamida, V. Caizergues, J.-P. Lagier, F. Fiévet and F. Bozon-Verduraz, *Appl. Catal. A*, **172**, 273 (1998).

44. A. Bahia and J. M. Winterbottom, *J. Chem. Tech. Biotechnol.*, **60**, 305 (1994).
45. A. Sárkány, Z. Schay, G. Stefler, L. Borkó, J. W. Hightower and L. Guczi, *Appl. Catal. A*, **124**, L181 (1995).
46. A. Sárkány, *J. Catal.*, **180**, 149 (1998).
47. W.-J. Wang, M.-H. Qiao, J. Yang, S.-H. Xie and J.-F. Deng, *Appl. Catal. A*, **163**, 101 (1997).
48. A. Behr, N. Döring, S. Durowicz-Heil, B. Ellenberg, Ch. Kozik, Ch. Lohr and H. Schmidke, *Fett Wiss. Technol.*, **95**, 2 (1993).
49. Y. Kitayama, M. Takahashi, H. Sugiyama, T. Kodama and M. Okamura, *J. Am. Oil Chem. Soc.*, **75**, 27 (1998).
50. G. C. Bond and J. C. Rank, *Proc. Int. Congr. Catal. 3rd, 1964*, 2, 1225 (1965).
51. R. H. Hasek, P. G. Gott and J. C. Martin, *J. Org. Chem.*, **29**, 2513 (1964).
52. L. Kh. Freidlin, B. D. Polkovnikov and Y. P. Egorov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 910 (1959); *Chem. Abstr.*, **54**, 1355i (1960).
53. A. C. Cope and H. C. Campbell, *J. Am. Chem. Soc.*, **74**, 179 (1952).
54. Y. Komatsu, Jap. Patent 75 16,325 (1969–1975).
55. R. Bachir, P. Marecot, B. Didillon and J. Barbier, *Appl. Catal. A*, **164**, 313 (1997).
56. W. F. Newhall, *J. Org. Chem.*, **23**, 1274 (1958).
57. K. M. Nicholas, *J. Am. Chem. Soc.*, **97**, 3254 (1975).
58. Y. Imizu, M. Toyofuku, N. Okazaki, H. Hoh and A. Tada, *Stud. Surf. Sci. Catal.*, **90**, 457 (1994).
59. A. Rédey, D. Smrz and W. K. Hall, in *New Frontiers in Catalysis* (Ed. L. Guczi), *Proceedings of the 10th International Congress on Catalysis, 1992, Budapest*, Elsevier, Amsterdam, 1993, p. 2383.
60. Y. Okamoto, H. Kane and T. Imaka, *Catal. Lett.*, **2**, 335 (1989).
61. Y. Okamoto, H. Onimatsu, M. Hori, Y. Inui and T. Imanaka, *Catal. Lett.*, **12**, 239 (1992).
62. V. Amir-Ebrahimi and J. J. Rooney, *J. Mol. Catal. A*, **67**, 339 (1991).
63. C. A. Brown and V. K. Ahuja, *J. Org. Chem.*, **38**, 2226 (1973).
64. J. J. Brunet, P. Gallois and P. Caubere, *J. Org. Chem.*, **45**, 1937 (1980).
65. J. J. Brunet, P. Gallois and P. Caubere, *Tetrahedron Lett.*, 3955 (1977).
66. C. A. Brown, *J. Org. Chem.*, **35**, 1900 (1970).
67. H. C. Brown and C. A. Brown, *Tetrahedron*, *Suppl. 8*, *Part I*, 149 (1966).
68. C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3989 (1966).
69. C. A. Brown, *Chem. Commun.*, 952 (1969).
70. C. A. Brown, *J. Am. Chem. Soc.*, **85**, 1004 (1963).
71. J. J. Brunet, L. Mordenti, B. Loubinoux and P. Caubere, *Tetrahedron Lett.*, 1069 (1977).
72. E. J. Corey, W. L. Mock and D. J. Pasto, *Tetrahedron Lett.*, 347 (1961).
73. S. Hünig, H.-R. Müller and W. Their, *Tetrahedron Lett.*, 353 (1961).
74. D. J. Pasto, in *Comprehensive Organic Synthesis* (Eds. B. M. Frost and I. Fleming), Vol. 8, Pergamon, Oxford, 1991, p. 471.
75. D. J. Pasto and R. T. Taylor, in *Organic Reactions* (Ed. L. A. Paquette), Vol. 40, Wiley, New York, 1991, p. 91.
76. E. E. van Tamelen, R. S. Dewey and R. J. Timmons, *J. Am. Chem. Soc.*, **83**, 3728 (1961).
77. C. E. Miller, *J. Chem. Educ.,* **90**, 254 (1965).
78. S. F. Forner and R. L. Hudson, *J. Chem. Phys.*, **28**, 719 (1958).
79. N. Wiberg, G. Fischer and H. Bachhuber, *Chem. Ber.*, **107**, 1456 (1974).
80. N. Wiberg, G. Fischer and H. Bachhuber, *Angew. Chem.*, *Int. Ed. Engl.*, **15**, 385 (1976).
81. T. Okuyama, K. Toyoshima and T. Fueno, *J. Org. Chem.*, **45**, 1604 (1980).
82. E. W. Garbisch, S. M. Schildrout, D. B. Patterson and C. M. Sprecher, *J. Am. Chem. Soc.*, **87**, 2932 (1965).
83. G. Nagendrappa, S. N. Moorthy and D. Devaprabhakara, *Ind. J. Chem.*, **14B**, 81 (1976).
84. S. Siegel, M. Foreman, R. P. Fischer and S. E. Johnson, *J. Org. Chem.*, **40**, 3599 (1975).
85. D. N. Kursanov, Z. N. Parnes and N. M. Loim, *Synthesis*, 633 (1974).
86. D. J. Pasto, in *Comprehensive Organic Synthesis* (Eds. B. M. Frost and I. Fleming), Vol. 8, Pergamon, Oxford, 1991, p. 486.
87. D. N. Kursanov, Z. N. Parnes, G. I. Bassola, N. M. Loim and V. I. Zdanovich, *Tetrahedron*, **23**, 2235 (1967).
88. F. A. Carey and H. S. Temper, *J. Am. Chem. Soc.*, **90**, 2578 (1968).

89. D. N. Kursanov, V. N. Setkina and Y. D. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1911 (1964); *Chem. Abstr.*, **62**, 2684a (1965).
90. M. P. Doyle and C. C. McOsker, *J. Org. Chem.*, **43**, 693 (1978).
91. Z. N. Parnes, G. I. Bolestova and D. N. Kursanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987 (1972); *Chem. Abstr.*, **78**, 28811z (1973).
92. Z. N. Parnes, G. A. Khotimskaya, Y. I. Lyakhovetsky and P. V. Petrovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1562 (1971); *Chem. Abstr.*, **75**, 109902v (1971).
93. S.-K. Chung, *J. Org. Chem.*, **44**, 1014 (1979).
94. F. Sato, S. Sato and M. Sato, *J. Organomet. Chem.*, **131**, C26 (1977).
95. F. Sato, S. Sato, H. Kodayama and M. Sato, *J. Organomet. Chem.*, **142**, 71 (1977).
96. B. Das, A. Kashinatham and P. Madhusudhan, *Tetrahedron Lett.*, **39**, 677 (1998).
97. S. W. Heinzman and B. Ganem, *J. Am. Chem. Soc.*, **104**, 6801 (1982).
98. T. B. Sim and N. M. Yoon, *Bull. Chem. Soc. Jpn.*, **70**, 1101 (1997).
99. G. W. Watt, *Chem. Rev.*, **46**, 325 (1950).
100. S. Montiel-Smith, L. Quintero-Cortes and J. Sandoval-Ramírez, *Tetrahedron Lett.*, **36**, 8359 (1995).
101. E. A. Hall, G. P. Moss, J. H. P. Utley and B. C. L. Weedon, *Chem. Commun.*, 586 (1976).
102. N. el Murr, R. Riveccie and E. Lavion, *Tetrahedron Lett.*, 3339 (1976).
103. M. A. Fox, K. Din, D. Bixler and W. S. Allen, *J. Org. Chem.*, **44**, 3208 (1979).
104. G. J. Yusen and P. N. Pintaro, *J. Am. Oil Chem. Soc.*, **69**, 399 (1992).
105. P. Gramatica, P. Manito, B. M. Ranzi, A. Delbianco and M. Francavilla, *Experienta*, **38**, 775 (1982).
106. P. Gramatica, P. Manito, D. Monti and G. Speranza, *Tetrahedron*, **43**, 4481 (1987).
107. P. Gramatica, P. Manito, D. Monti and G. Speranza, *Tetrahedron*, **44**, 1299 (1988).
108. P. Ferraboschi, P. Grisenti, R. Casati, A. Fiecchi and E. Santaniello, *J. Chem. Soc., Perkin Trans. 1*, 1743 (1987).
109. F. G. Fischer and O. Wiedemann, *Justus Liebigs Ann. Chem.*, **520**, 52 (1935).
110. S. Kurogochi, S. Tahara and J. Mizutani, *Agric. Biol. Chem.*, **39**, 825 (1975).
111. S. Tahara, S. Kurogochi and M. Kudo, *Agric. Biol. Chem.*, **41**, 1635 (1975).
112. C. R. Kepler, K. P. Hivons, J. J. McNeill and S. B. Tove, *J. Biol. Chem.*, **241**, 1350 (1966).
113. C. R. Kepler and S. B. Tove, *J. Biol. Chem.*, **242**, 5686 (1967).
114. H. Eyssen and A. Verhulst, *Appl. Environ. Microbiol.*, **47**, 39 (1984).
115. A. Verhulst, G. Parmentier, G. Janssen, S. Asselberghs and H. Eyssen, *Appl. Environ. Microbiol.*, **51**, 532 (1986).
116. Y. Noma and S. Nonomura, *Agric. Biol. Chem.*, **38**, 741 (1974).
117. A. Arnone, R. Cardillo, G. Nasini and O. Vaina de Pava, *J. Chem. Soc., Perkin Trans. 1*, 3061 (1990).
118. M. Protiva, A. Capek, J. O. Jilek, B. Kakac and M. Tadra, *Collect. Czech. Chem. Commun.*, **30**, 2236 (1965).
119. U. Naik and S. Mavuinkurve, *Can. J. Microbiol.*, **33**, 658 (1987).
120. Kh. V. Bal'yan, A. A. Petrov, N. A. Borovikova, V. A. Korner and T. V. Yakovleva, *Zh. Obshch. Khim.*, **30**, 3247 (1960); *Chem. Abstr.*, **55**, 19753c (1961).
121. G. Englinton, E. R. H. Jones, G. H. Mansfield and M. C. Whiting, *J. Chem. Soc.*, 3197 (1954).
122. P. D. Gardner and M. Narayana, *J. Org. Chem.*, **26**, 3518 (1961).
123. G. C. Bond and J. Sheridan, *Trans. Faraday Soc.*, **48**, 658 (1952).
124. E. J. Glamkowski, G. Gal, R. Purick, A. J. Davidson and M. Sletzinger, *J. Org. Chem.*, **35**, 3510 (1970).
125. H. Westmijze, J. Meijer and P. Vermeer, *Tetrahedron Lett.*, 2923 (1975).
126. R. Kuhn and H. Fischer, *Chem. Ber.*, **93**, 2285 (1960).
127. G. B. Kistiakowsky, *J. Am. Chem. Soc.*, **60**, 440 (1938); **61**, 1868 (1939).
128. C.-M. Pradier and Y. Berthier, *J. Catal.*, **129**, 356 (1991).
129. J. Götz, M. A. Volpe and R. Touroude, *J. Catal.*, **164**, 369 (1996).
130. I. V. Gostunskaya, N. B. Dobroserdova and B. A. Kazansky, *J. Gen. Chem. USSR (Engl. Transl.)*, **27**, 2458 (1957).
131. G. Ohloff, H. Farnow and G. Schade, *Chem. Ber.*, **89**, 1549 (1956).
132. C. F. Wilcox and D. L. Nealy, *J. Org. Chem.*, **28**, 3446 (1963).
133. C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).

134. G. D. Laubach and K. J. Brunings, *J. Am. Chem. Soc.*, **74**, 705 (1952).
135. C. T. Bahner, D. Brotherton and T. Harmon, *J. Med. Chem.*, **13**, 570 (1970).
136. H. Rapoport, R. H. Allen and M. E. Cisney, *J. Am. Chem. Soc.*, **77**, 670 (1955).
137. T. W. Evans, R. C. Morris and E. C. Shokal, U. S. Patent 2,360,555 (1944).
138. L. Kh. Friedlin and B. D. Polkovnikov, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 691 (1959).
139. G. Stork, *J. Am. Chem. Soc.*, **69**, 2936 (1947).
140. K. Alder and M. Schumaker, *Justus Liebigs Ann. Chem.*, **564**, 96 (1949).
141. J. Martel, E. Toromanoff and C. Huynh, *J. Org. Chem.*, **30**, 1753 (1965).
142. D. A. Shepherd, R. A. Dania, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, J. E. Stafford, R. L. Pedersen and A. C. Ott, *J. Am. Chem. Soc.*, **77**, 1212 (1955).
143. M. Seefelder and W. Raskob, U. S. Patent 3,251,892 (1966).
144. I. N. Nazarov, S. N. Ananchenko and I. V. Torgov, *Zh. Obshch. Khim.*, **26**, 1175 (1956); *Chem. Abstr.*, **50**, 13845a (1956).
145. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).
146. S. K. Roy and D. M. S. Wheeler, *J. Chem. Soc.*, 2155 (1963).
147. F. van Rantwijk, G. J. Timmermans and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **95**, 39 (1976).
148. L. Horner and I. Grohmann, *Justus Liebigs Ann. Chem.*, **670**, 1 (1963).
149. G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 2081 (1948).
150. J. W. ApSimon, P. V. Demaro and J. Lemke, *Can. J. Chem.*, **43**, 2493 (1965).
151. W. Kimel, N. W. Sax, S. Kaiser, G. H. Eichmann, G. O. Chase and A. Ofner, *J. Org. Chem.*, **23**, 153 (1958).
152. R. T. Blickenstaff, *J. Am. Chem. Soc.*, **82**, 3673 (1960).
153. G. A. Schiehser and J. D. White, *J. Org. Chem.*, **45**, 1864 (1970).
154. W. Sandermann and K. Burns, *Chem. Ber.*, **99**, 2835 (1966).
155. S. M. Kupchan, G. R. Flouret and C. A. Matuszak, *J. Org. Chem.*, **31**, 1707 (1966).
156. S. M. Kupchan and C. G. De Grazia, *J. Org. Chem.*, **31**, 1716 (1966).
157. H. H. Inhoffen, R. Jones, H. Krösche and U. Eder, *Justus Liebigs Ann. Chem.*, **694**, 19 (1966).
158. C. H. DePuy and P. R. Story, *J. Am. Chem. Soc.*, **82**, 627 (1960).
159. G. D. Laubach and K. J. Brunings, *J. Am. Chem. Soc.*, **74**, 5929 (1952).
160. P. Bladon, *J. Chem. Soc.*, 2402 (1951).
161. G. J. Gregory, *J. Chem. Soc.*, 2201 (1966).
162. N. K. Singha, S. Bhattacharjee and S. Sivaram, *Rubber Chem. Technol.*, **70**, 309 (1997).
163. H. van Bekkum, F. van Rantwijk, G. van Minnen-Pathnis, J. D. Remijnse and A. van Veen, *Recl. Trav. Chim. Pays-Bas*, **88**, 911 (1969).
164. R. T. Blickenstaff, A. C. Gosh and G. C. Wolf, *Total Synthesis of Steroids*, Academic Press, New York, 1974, p. 20.
165. J. T. A. Reuvers and A. deGroot, *J. Org. Chem.*, **49**, 1110 (1984).

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CHAPTER **13**

Catalysis of Diels–Alder reactions in water and in hydrogen-bonding environments

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I. INTRODUCTION

One of the main questions in chemical synthesis is the choice of solvent. Apart from the fact that it determines the outcome of a reaction, it also creates one of the main sources of pollution, an aspect which is particularly important in industrial processes. Modern chemistry attempts to reduce sources of environmental hazards caused by organic solvents which are typically used in much larger quantities than the solutes. Leakage and evaporation often lead to direct pollution of the environment. For instance, in 1995 the emission of volatile organic compounds in Germany amounted to about 2.1×10^6 tons[1]. Furthermore, halogenated solvents are particularly notorious with respect to their toxic character and limited bio-degradability. For these reasons a lot of research is currently devoted to the development of solvent-free systems[2] or to the replacement of organic solvents by more environmentally-friendly ones[3]. Water may be the prime choice for this purpose because of its non-toxic character, its ubiquitous availability and its price.

A. Water — A Unique Substance

Water is a moderately volatile, highly mobile liquid over a large temperature range with many exceptional characteristics. Compared to simpler liquids with fewer solvent–solvent or solvent–solute interactions, water has certain anomalous thermodynamic properties: a temperature of maximum density in the liquid phase over a wide range of pressures, an unusually high surface tension, a minimum in the isothermal compressibility as a function of temperature and a large heat capacity throughout the liquid range[4]. Most of these properties originate from strong hydrogen bonds between the water molecules and the large dipole moment ($\mu = 1.82$ D; 298 K, bulk water). The large dielectric constant ($\varepsilon = 78.36$ at 298 K) and its solvation power make water an extremely good solvent for many substances. Most salts as well as many covalently bound polar compounds like methanol, acetic acid or acetone are completely soluble in water. Another property is the ability of water molecules to act as efficient hydrogen-bond donors and acceptors[5]. The tendency for hydrogen bonding also leads to other qualities of water which make it unique amongst solvents. These characteristics are partly due to the small size of the water molecule, which enables water to interact efficiently and multi-molecularly with Lewis bases[6]. The relatively high melting and boiling points of water are quite unusual for a chemical compound of such a small molecular mass. The high boiling point and the high enthalpy of evaporation may be considered as disadvantages for organic reactions because removal of the solvent is difficult. On the other hand, the high affinity of water towards some inorganic salts to build up hydrates (like $MgSO_4 \cdot nH_2O$ or $Na_2SO_4 \cdot nH_2O$) partially annihilates this alleged disadvantage. Aqueous reaction mixtures can be extracted with smaller amounts of organic solvents than would be needed if the reaction was conducted in a non-aqueous solvent. Again, this leads to high yields and decreased consumption of environmentally dangerous substances. Another advantage of water leading to simplified reaction conditions is that an inert atmosphere is normally not needed.

The amphoteric character of water (i.e., the ability to act either as an acid or as a base) makes water so special. While this renders the use of water as a solvent in acid- or base-sensitive reactions problematic, the possibility to have the solvent as a reactant in acid- or base-initiated reactions is often desirable. These qualities led chemists to rediscover water as a solvent in organic chemistry. Unfortunately, from a chemical point of view, not all transformations are feasible in aqueous solvent systems. Many reagents decompose when brought into contact with water while many others are insoluble. Consequently, it is not surprising that water has not been a very popular solvent in organic chemistry in the past, but this picture is changing rapidly.

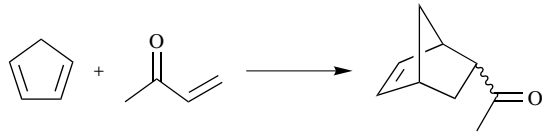
B. Organic Chemistry in Water

Hydrogen-bonding and hydrophobic effects[7] (we will describe these terms later) are prime factors in commonly observed accelerations of pericyclic reactions in water, with[8] and without[9] added co-catalysts. The remarkable efficiency of these catalytic systems with accelerations up to one million-fold[10], increased yields, higher selectivities and their obvious relation with and compatibility to physiological conditions are a clear indication that, for instance, pericyclic reactions are likely also to occur in biosynthesis. Most biochemical processes take place in pure water or in the presence of water, and the diversity of the reactions *in vivo* should prompt chemists to discover the potential of water as the solvent of choice. Biological processes are of exemplary efficiency and biological catalysts, i.e. enzymes, lead to outstanding rate accelerations and very high selectivities. All these biological processes and reactions are carried out in 'aqueous media' and chemists are well advised to investigate the potential of organic synthesis in water.

There are a number of chemical transformations which are not only compatible with aqueous media but actually benefit strongly from the unique characteristics of water. These are demonstrated in Tables 1–3[11].

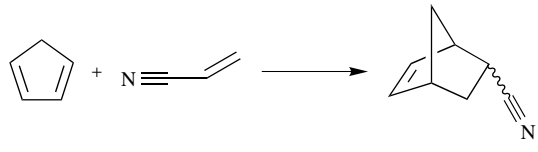
The fact that water often permits, as noted above, a simplified reaction or work-up procedure made 'Organic Chemistry in Water' an active field of research[9,12–14]. This might sound quite surprising due to (a) the limited solubility of non-polar organic molecules in water and (b) the danger of hydrolysis. Nevertheless, many organic reactions can be carried out in water, often with improved results.

TABLE 1. Rate constants for the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone in different solvents



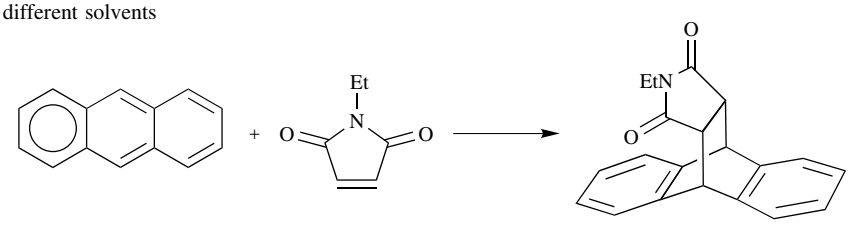
Solvent	$10^5 k(M^{-1}\,s^{-1})$
iso-octane	5.94 ± 0.3
MeOH	75.5
H_2O	4400 ± 70

TABLE 2. Rate constants for the Diels–Alder reaction of cyclopentadiene and acrylonitrile in different solvents



Solvent	$10^5 k(M^{-1}\,s^{-1})$
iso-octane	1.9
MeOH	4.0
H_2O	59.3

TABLE 3. Rate constants for the Diels–Alder reaction of anthracene and *N*-ethylmaleimide in different solvents



Solvent	$10^5 k(M^{-1}\,s^{-1})$
iso-octane	796 ± 71
1-Butanol	666 ± 23
MeOH	344 ± 25
Acetonitrile	107 ± 8
H_2O	22600 ± 700

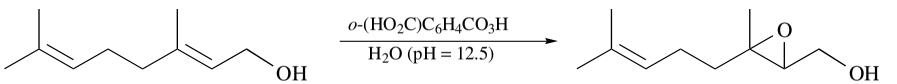
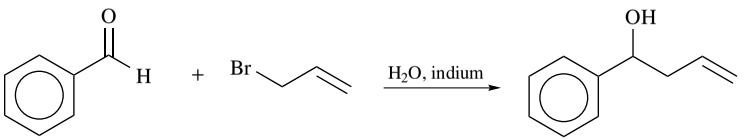
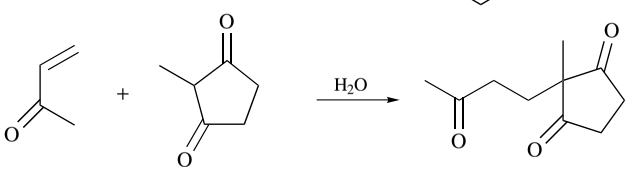
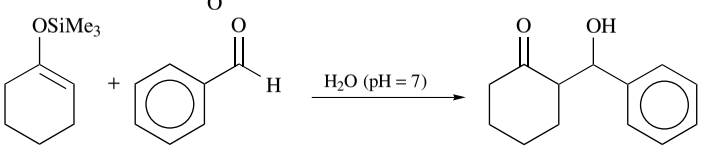
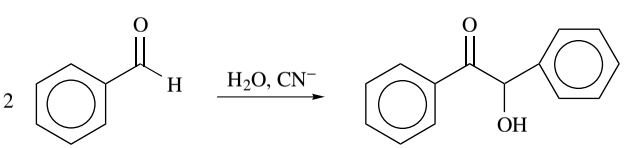
One might suspect that water is disadvantageous for catalytic reactions, because traditional Lewis acid catalysts are expected to be much less effective in the aqueous phase, but we will demonstrate in the following sections that the accelerating effects of Lewis acids and water can be additive. It will be shown that the complexation abilities of water and those of Lewis acids can lead to enhanced reactivities and selectivities, despite their apparent competition.

To date, most standard organic transformations have been carried out in water. Organic peroxide oxidations which convert olefins into epoxides result in improved yields in aqueous media compared with organic solvents (Table 4, entry A)[15–17]. A large number of metal-catalysed hydrogenations[18,19] and metal mediated allylations[20] in aqueous media have been reported (Table 4, entry B). Both 1,2- and 1,4-nucleophilic additions to carbonyl groups can be conducted in aqueous solutions and have been shown to benefit from such media (Table 4, entry C)[21–23]. The aldol condensation is another example where a Lewis acid catalyst is often required in organic solvents but where the reaction occurs readily in pure water (Table 4, entry D)[24–26]. Other nucleophilic transformations like the benzoin condensation (Table 4, entry E)[27], the Mannich (Table 4, entry F)[28], the Prins (Table 4, entry G)[29] and the Wittig–Horner reaction (Table 4, entry H)[30] were realized in aqueous media.

Water can also have a beneficial effect on halogenations (Table 4, entry I)[31,32], polymerizations[33] and photochemical transformations (Table 4, entry J)[34,35]. As mentioned before, a large number of organometallic reactions[18,20] were conducted in water, whereby Lewis acid catalysis is still feasible even in aqueous media[36]. Notoriously solvent-insensitive reactions such as Claisen rearrangements (Table 4, entry K)[37–40], 1,3-dipolar cycloadditions (Table 4, entry L)[41–44] and Diels–Alder (Table 4, entry M)[11,44] reactions can be accelerated dramatically in aqueous media. In the case of the Diels–Alder reaction, accelerations in the order of 12,800 were observed simply by changing the solvent from hexane to water[45].

In this chapter we wish to review the collected evidence for the astonishing effects of water on reactivities and selectivities as exemplified by the Diels–Alder reactions of dienes. Examples of Lewis acid and micellar catalysis in aqueous media are also presented. Finally, the newest computational investigations including solvent effects on Diels–Alder reactions are put forward in order to rationalize some of the remarkable observations.

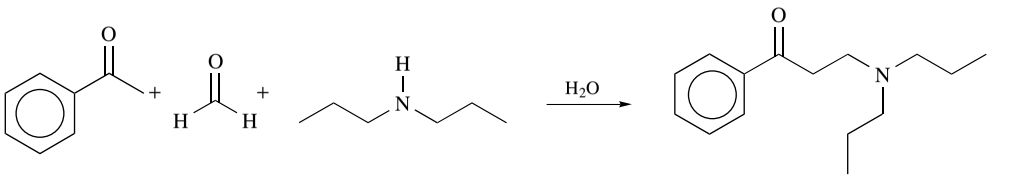
TABLE 4. Examples of organic reactions carried out in water

Entry	Exemplary reaction	Reference
A		16
B		20
C		22
D		24
E		27

(continued overleaf)

TABLE 4. (*Continued*)

F



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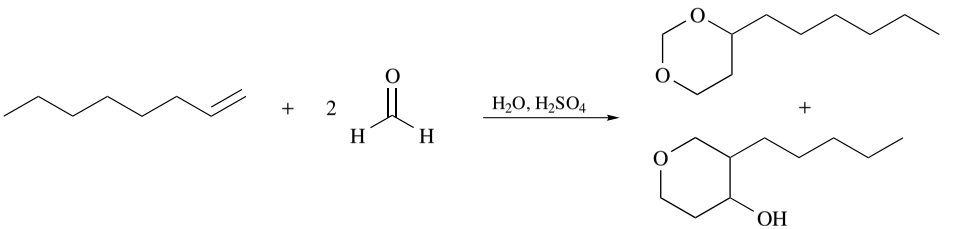

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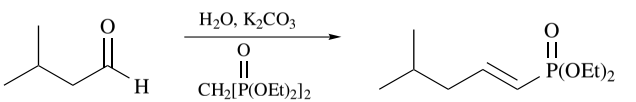

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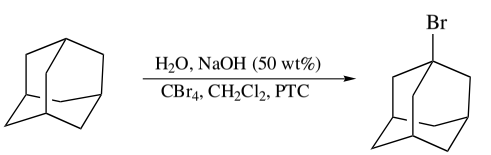

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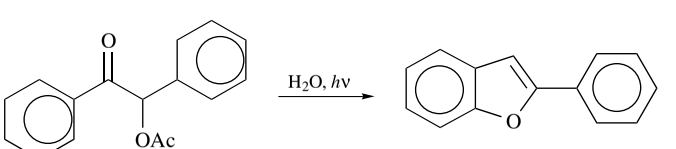

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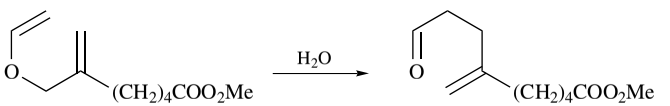
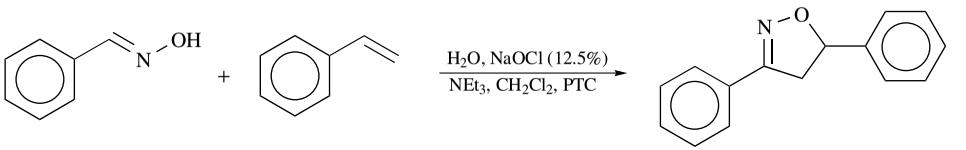
K


O
(CH2)4COO2Me
H2O
O
(CH2)4COO2Me

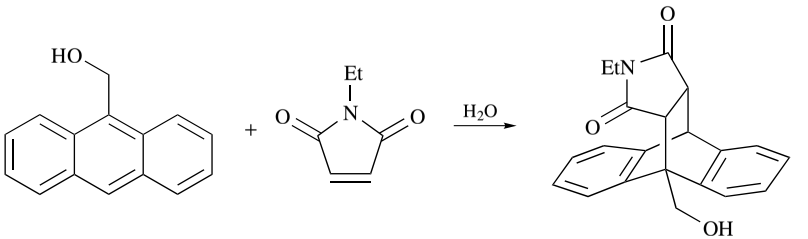
40

L


N
OH
+
H2O, NaOCl (12.5%)
NEt3, CH2Cl2, PTC
N
O

43

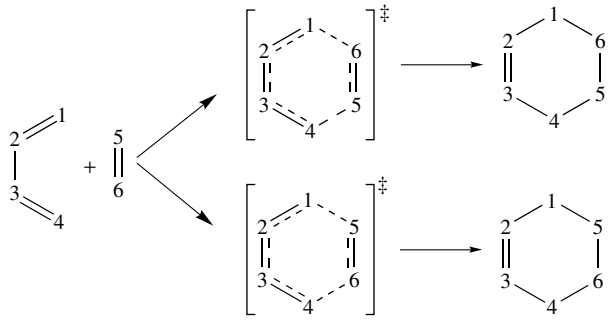
M


HO
+
Et
N
O
O
H2O
O
EtN
O
OH

11

C. The Diels–Alder Reaction

The Diels–Alder reaction is *the* classical method for the synthesis of substituted cyclohexenes. The six-membered ring is typically formed by a [4 + 2]-cycloaddition of a diene and a two-π-electron component which is usually referred to as the dienophile. The Diels–Alder reaction is of outstanding value for the synthetic organic chemist and is the key step in the construction of compounds containing six-membered rings (Scheme 1). Since the reaction is stereospecific in the sense that the conformation of the reacting double bonds is fully retained in the configuration of the product, and because the regioselectivity of the ring closure can be controlled efficiently, the reaction is a formidable tool in synthetic organic chemistry.

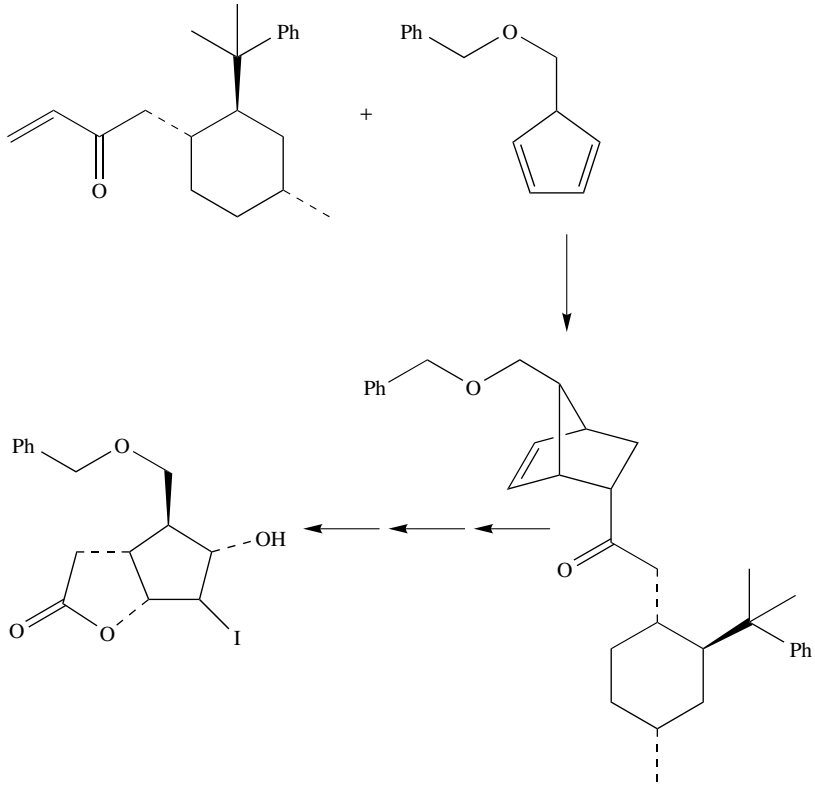


SCHEME 1. Schematic representation of the Diels–Alder reaction. The two possible ring closures together with the two transition states and the resulting regioisomers are presented. The versatility of the reaction is illustrated by the fact that heteroatoms are allowed at any of the positions 1–6 (hetero-Diels–Alder reaction)

The first example of a Diels–Alder reaction, the dimerization of tetrachlorocyclopentadienone, was observed in 1892[46], and was further investigated in the next 20 years[47–49], but it took nearly 30 years until its importance was recognized by chemists in the 1920s. In 1928 the famous paper on the detailed description of synthetic and theoretical aspects of this reaction was published by Otto Diels and Kurt Alder[50], two German chemists. For their ground-breaking work, they ultimately were awarded the Nobel Prize in 1950.

Since the Diels–Alder reaction is both experimentally and theoretically well characterized, we now have a thorough understanding of this important transformation. This allowed one to influence rates and selectivities of this cycloaddition. An illustrative example is the selective synthesis of a key prostaglandine precursor[51] (Scheme 2) in which all stereochemical information derives from the starting materials. Although the general mechanism of Diels–Alder reactions is well understood, it is still uncertain if these reactions occur in biosynthesis. An instructive example is represented by the total synthesis of optically active plagiospirolides **1** and **2** (Scheme 3)[52]. These syntheses were considered to be biomimetic and are indications that Diels–Alder reactions may also occur *in vivo*.

Although there are many natural products **1–4** (Scheme 3 and 4)[52,53] which may formally derive from [4 + 2]-cycloadditions, and although the Diels–Alder (DA) reaction is of great value and is irreplaceable for synthetic chemists, there is no definitive proof for Diels–Alder reactions occurring in biosynthesis[54]. At the same time cell-free extracts, for instance, from the fungus *aleternaria solani*, accelerate Diels–Alder reactions by a factor of 4.1 and reverse the normally observed *endo*-selectivity[55]. Still, there is no

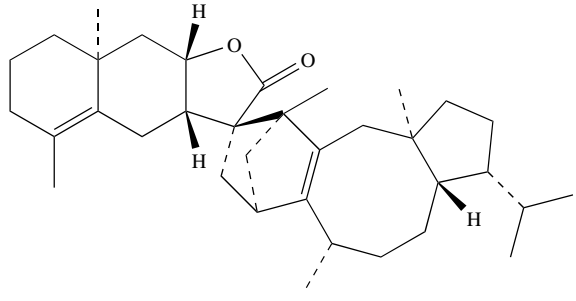


SCHEME 2. The stereoselective Diels–Alder reaction leading to an important iodolactone prostaglandine precursor

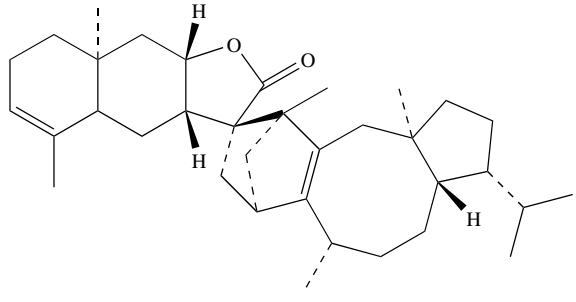
specific 'Diels–Alder-ase' enzyme which would, by analogy to commonly carried out DA reactions, catalyse these transformations at ambient temperatures[56].

The controversy on the existence of *in vivo* Diels–Alder reactions cannot be put to rest here, but the numerous examples of natural products containing cyclohexene groups and the catalytic effectivity of 'biological' surroundings support the idea of *in vivo* Diels–Alder reactions. Apart from cell-free extracts, RNA-based mixtures of metals also show catalytic activity and it was demonstrated that this catalyst system can be quite effective as an artificial Diels–Alder-ase[57]. We will show that water, the prime solvent of biosynthesis, also catalyses [4 + 2]-cycloadditions. Considering that biosyntheses are often of exceptional selectivity, it is clear that understanding biomimetic transformations in water as the solvent is an important goal of modern chemistry. The possibilities offered by and the reasons for Diels–Alder catalysis in water will be the main topic of this chapter.

We will present mechanistic aspects of the Diels–Alder reaction, its selectivity and reactivity in order to explain solvent effects on the one hand, and the effects of Lewis acids on the other. Other catalytic systems like micelles will also be addressed. Some of the explanations may seem trivial or are well-known but, as we will use these in later sections, a clear terminology is desirable.

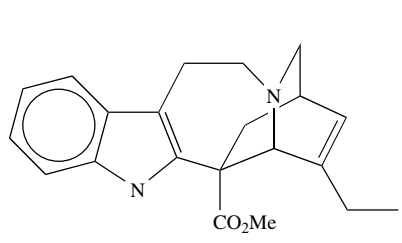


(**1**)

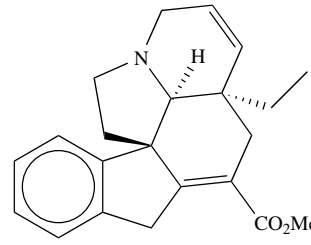


(**2**)

SCHEME 3. Plagiospirolides **1** and **2**, synthesized by Diels–Alder reactions. The natural compounds are suggested to be formed via *in vivo* cycloaddition processes



(**3**)



(**4**)

SCHEME 4. Catharanthine **3** and tabersonine **4**, natural compounds containing a cyclohexene moiety. These may derive from *in vivo* Diels–Alder reactions[53]

The reactivity and selectivity of the Diels–Alder reaction can be understood in terms of Frontier Molecular Orbital (FMO) theory which evolved during studies of the role of orbital symmetry in pericyclic reactions by Woodward and Hoffmann[58] and, independently, by Fukui[59]. FMO theory explains the driving force of a reaction between two compounds by the efficiency with which the molecular orbitals of the two partners overlap. This orbital interaction is maximized when their energy separation is small. FMO theory further states that the two most important interacting orbitals are the Highest Occupied

Molecular Orbital (HOMO) of one component and the Lowest Unoccupied Molecular Orbital (LUMO) of the other. Within the scope of FMO theory, the reactivity of two reaction partners towards each other is described quantitatively by the Klopman–Salem–Fukui relationship (equation 1)[60–62]:

$$\Delta E = -\sum_{ab}(q_a + q_b)\beta_{ab}S_{ab} + \sum_{k<l}\frac{Q_k Q_l}{\varepsilon R_{kl}} + \sum_{r}^{occ.}\sum_{s}^{unocc.} - \sum_{s}^{occ.}\sum_{r}^{unocc.} 2\frac{\left(\sum_{ab} c_{ra}c_{sb}\beta_{ab}\right)^2}{E_r - E_s} \tag{1}$$

where q_a and q_b are electron densities at the atomic orbitals a and b, β and S are the resonance and overlap integral, Q_k and Q_l are the total charges of atoms k and l, ε is the dielectric constant, R_{kl} is the distance between atoms k and l, c_{ra} is the coefficient of atomic orbital a in the molecular orbital r, r and s are the indices of the two interacting molecules and E_r is the energy of the molecular orbital r.

The three terms of this equation simply represent the different energetic aspects of two approaching molecules leading to a reaction. The first part determines the first-order closed-shell repulsion, i.e. the interaction of the occupied orbitals of one reaction partner with those of the other. In general, this first sum is larger than the others but its value is nearly constant for different reaction paths. Hence, the first term is nearly unspecific and does not explain the observed selectivities. Within the scope of FMO theory the first part of the Klopman–Salem–Fukui equation is generally neglected because the theory attempts to explain changes in the reaction rates and selectivities.

The second term determines the electrostatic interactions of the two reacting partners. This part is important in reactions of ions and other charged species, but in the scope of FMO theory this term is usually disregarded. Hence, this limits the general applicability of FMO theory; in reactions of highly charged molecules it may lead to wrong conclusions. In reactions of uncharged molecules with low polarity, neglect of the second term of the Klopman–Salem–Fukui equation is an acceptable approximation.

The interactions of the occupied orbitals of one reactant with the unoccupied orbitals of the other are described by the third term of the Klopman–Salem–Fukui equation. This part is dominant and the most important for uncharged reaction partners. Taking into account that the denominator is minimized in case of a small energy gap between the interacting orbitals, it is clear that the most important interaction is the HOMO–LUMO overlap. With respect to the Diels–Alder reaction, one has to distinguish between two possibilities depending on which HOMO–LUMO pair is under consideration. The reaction can be controlled by the interaction of the HOMO of the electron-rich diene and the LUMO of the electron-poor dienophile (normal electron demand) or by the interaction of the LUMO of an electron-poor diene and the HOMO of an electron-rich dienophile (inverse electron demand; cf Figure 1).

In the case of normal electron demand Diels–Alder reactions, the HOMO–LUMO gap can be diminished by either raising the energy of the HOMO of the diene by introducing electron–donating groups or by lowering the energy of the dienophile LUMO through electron-withdrawing groups. The opposite applies to inverse electron demand Diels–Alder reactions[63].

While the reactivity is determined by the HOMO–LUMO energy separation, the selectivity is dominated by the orbital coefficients[64]. As a consequence, the kinetically controlled regioselectivity of the Diels–Alder ring closure, and thus the formation of the two new σ-bonds (between atoms 1,6 and 4,5 or between atoms 1,5 and 4,6 in Scheme 1), is determined by the FMO coefficients at the terminal carbon atoms of the diene and the dienophile. The FMO predictions boil down to the fact that the formation of σ-bonds between carbon atoms with similar orbital coefficients is preferred. The magnitudes of these coefficients

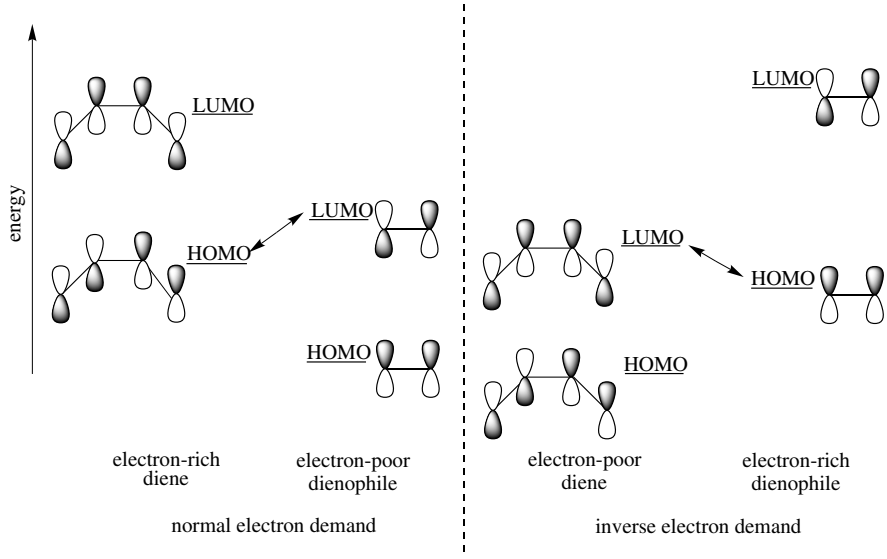


FIGURE 1. The HOMO/LUMO interactions in Diels–Alder reactions with normal and inverse electron demand

can be qualitatively evaluated using resonance theory[65–68], or by high-level quantum chemical computations.

Besides the regioselectivity described in the previous paragraph, there is another type of selectivity arising when substituted dienes and dienophiles form cyclohexene derivatives. While the above-mentioned selectivity determines the ring closure, there are still two different products possible, namely the *endo*- and *exo*-forms, depending on the way the dienophile attacks the diene (Figure 2). The *endo/exo* ratio is kinetically controlled; under normal conditions the *endo*-product is preferred. This preference was studied extensively and is now explained in terms of secondary orbital interactions (Figure 2)[69]. The Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone is an example for a normal electron demand Diels–Alder reaction in which the selectivity is controlled by the diene HOMO and the dienophile LUMO interaction. Considering that only the geometry of the *endo*-transition structure allows for effective secondary orbital interactions, the selectivity of Diels–Alder reactions for the *endo*-product becomes clear. Hence, only the *endo*-transition structure is energetically stabilized and the reaction forming the *endo*-product is accelerated.

The reasons for the *endo*-selectivity of Diels–Alder reactions are only useful for the reactions of dienophiles bearing substituents with lone pairs; without a Lewis basic site no secondary orbital interactions are possible. But even in reactions of pure hydrocarbons the *endo*-selectivity is observed, requiring alternative explanations. For example, the *endo*-preference of the reactions of cyclopropene with substituted butadienes have been rationalized on the basis of a 'special type' of secondary orbital interactions[70]. Apart from secondary orbital interactions which are probably the most important reason for the selectivities of Diels–Alder reactions, recent literature also advocates other interpretations.

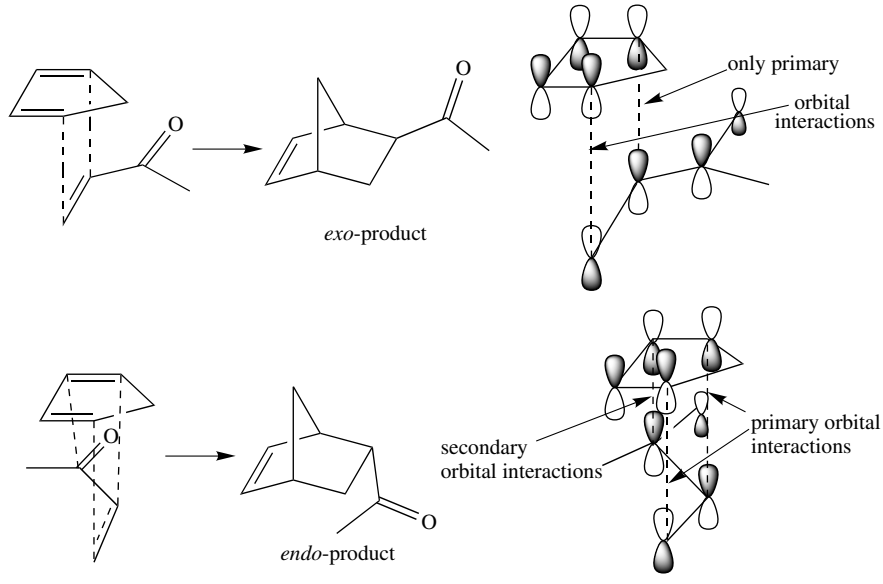
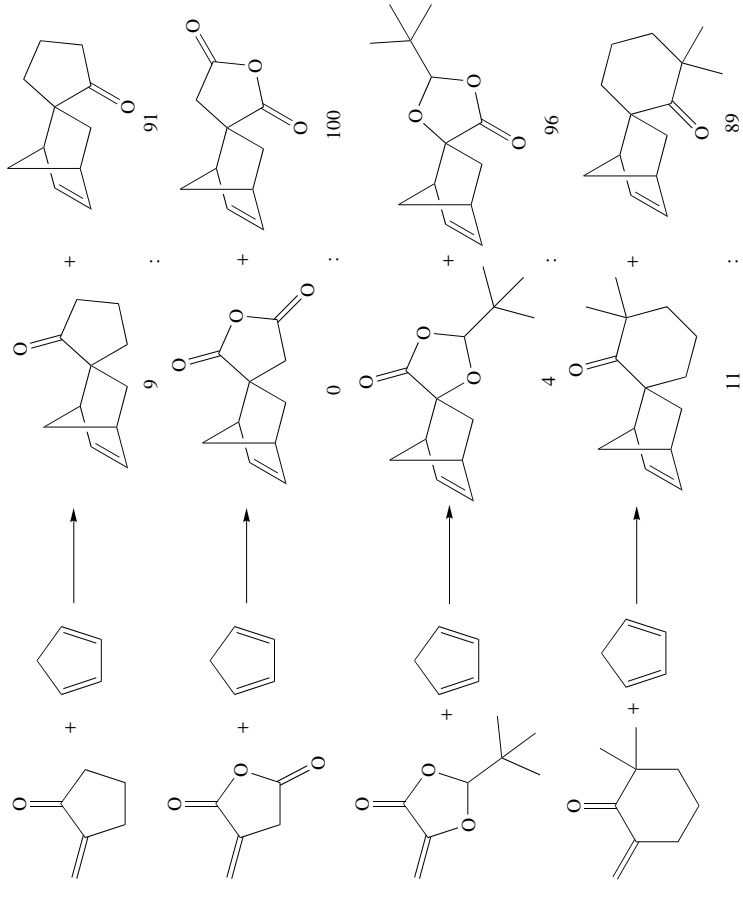


FIGURE 2. The Diels–Alder reaction of cyclopentadiene with methyl vinyl ketone. The selectivity leading to the *endo*-product (*endo*-selectivity of Diels–Alder reactions) is rationalized by secondary orbital interactions in the *endo*-transition state

For instance, steric effects are frequently suggested to be important in determining the selectivity, especially in the reactions of α-substituted dienophiles and in reactions forming the unexpected *exo*-product with high selectivity (Scheme 5)[71,72]. London dispersion interactions have also been considered, and it has been argued that these interactions can sometimes override secondary orbital interactions[73–75].

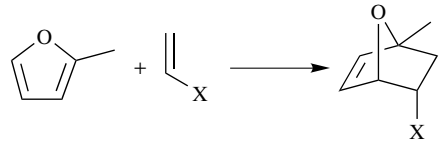
While many observations are well understood, e.g. those dealing with the reaction rate or with the selectivity, there are some factors which cannot be generalized. Many transformations of particular reactants or under unusual reaction conditions led to unexpected results. There are often singular explanations for such reactions but no overall concept. For instance, computations on Diels–Alder transition structures and thermodynamics of retro-Diels–Alder reactions confirmed that the activation volume of these [4 + 2]-cycloadditions is negative[80]. This result, pointing to the compact character of the transition structure, is used to explain the dependence of reactivity and selectivity on internal as well as external pressure[81–83]. These effects are only observed at relatively high external pressures (Table 5).

Another example is the influence of ultrasonic sound treatment. In chlorinated or brominated solvents it leads to extreme rate accelerations and higher selectivities (Table 6)[84]. This observation was explained by the formation of hydrogen halide from the sonolysis of the solvent molecules, followed by protonation of the dienophiles and ordinary acid catalysis. Nevertheless, although there are quite a few aspects of the Diels–Alder reaction which are not totally understood, the general mechanisms leading to selectivities and catalysis are clear.



SCHEME 5. High *exo*-selectivities in the Diels–Alder reaction of α-substituted dienophiles with cyclopentadiene[76–79]

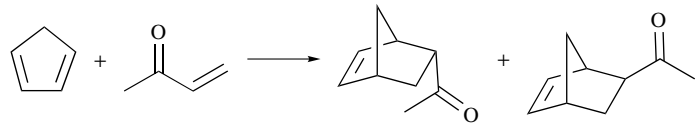
TABLE 5. External pressure dependence on the reaction of 2-methylfuran with several dienophiles[82] (these reactions do not proceed at atmospheric pressure)



Entry	X	Medium	Ratio[a]
1	$COCH_3$	water	3.4
		CH_2Cl_2	4.6
2	$COOCH_3$	water	3.2
		CH_2Cl_2	5.0
3	CN	water	3.1
		CH_2Cl_2	5.3

[a]Reactivity ratio at 3000 vs 1100 bar, respectively.

TABLE 6. Influence of ultrasonic))))) irradiation on the yield and *[endo]/[exo]* product ratio of the reaction of cyclopentadiene with methyl vinyl ketone in various organic solvents[84]



Solvent	Yield (%)[a]		*[endo]/[exo]* ratio[a]	
		)))))		)))))
CH_3OH	17 ± 1	17 ± 2	11.5 ± 0.5	11.5 ± 0.5
$C_6H_5CH_3$	3 ± 1	3 ± 1	5.0 ± 0.3	4.9 ± 0.3
$CHCl_3$	7 ± 1	15 ± 2	7.2 ± 0.4	12.7 ± 0.5
CH_2Cl_2	4 ± 1	18 ± 2	6.7 ± 0.3	15.5 ± 0.5
CH_2Br_2	7 ± 1	58 ± 3	6.5 ± 0.3	19.5 ± 0.6

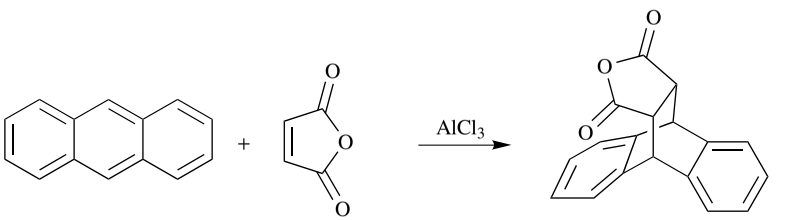
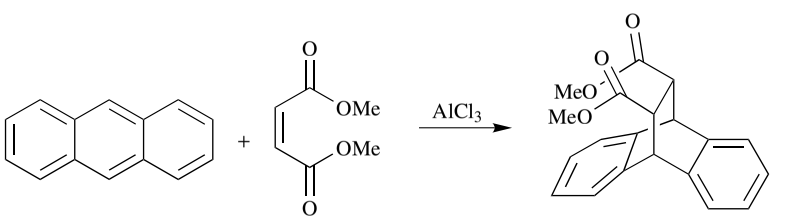
[a]After 1 h at 10 °C.

II. ASPECTS OF CATALYSIS

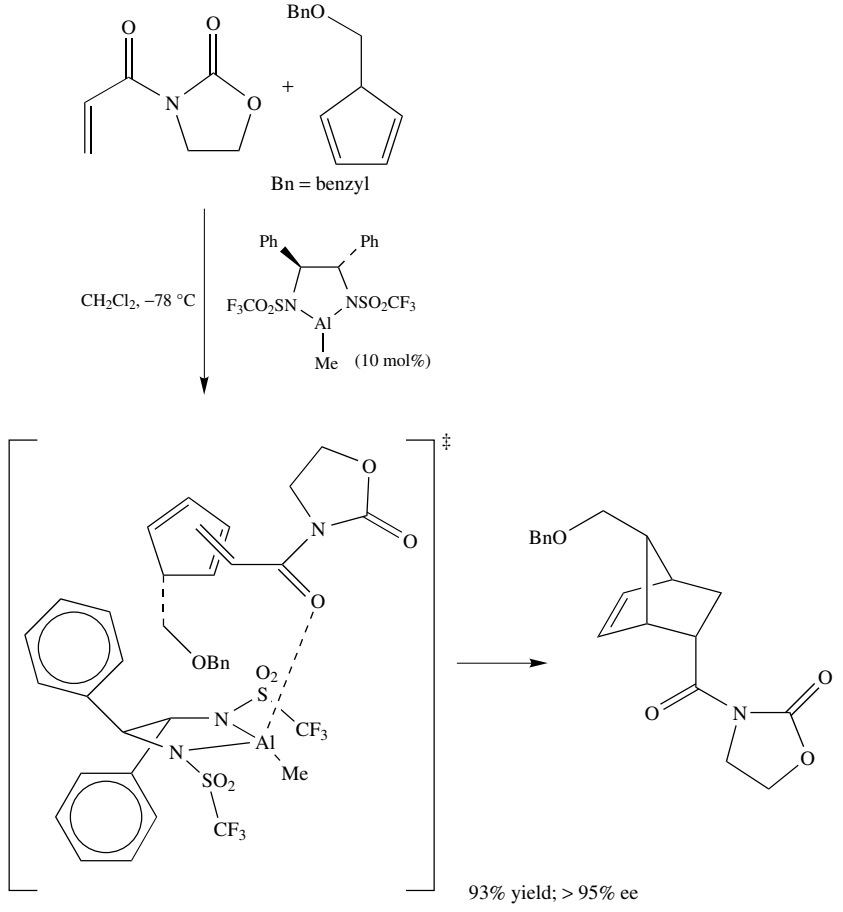
A. Lewis Acids

Uncatalysed Diels–Alder reactions usually have to be carried out at relatively high temperatures (normally around 100 °C)[73], often leading to undesired side reactions and retro-Diels–Alder reactions which are entropically favoured. The Diels–Alder reaction became applicable to sensitive substrates only after it was realized that Lewis acids (e.g. Al_2Cl_6) are catalytically active[56]. As a consequence, Diels–Alder reactions can now be carried out at temperatures down to −100 °C[85]. The use of Lewis acid catalysts made the [4 + 2]-cycloaddition applicable to the enantioselective synthesis of many natural compounds[51,86]. Nowadays, Lewis acid catalysis is the most effective way to accelerate and to stereochemically control Diels–Alder reactions. Rate accelerations of ten-thousand to a million-fold were observed (Table 7, entries A and B).

TABLE 7. Effects of Lewis acid catalysis on the rate of some Diels–Alder reactions

Entry	Reaction	Observation
A		Catalysed reaction completed after 1.5 min. From an extrapolation of the rate curve it was estimated that 4800 h would be required for 95% yield in the uncatalysed reaction
B		Catalysed reaction (CH_2Cl_2, rt) completed after 5 min. In the absence of catalyst the reaction took 3 days (95%) in refluxing dioxane

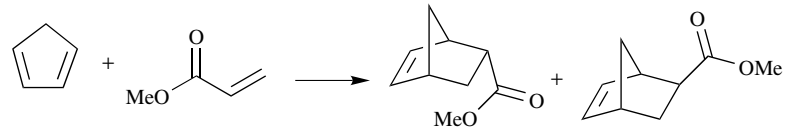
Lewis acid catalysis is not limited to cases in which increased yields or enhanced selectivities are desired. Lewis acids offer also the possibility to induce chiral information leading to enantioselective product formation. The *enantioselective induction* by chiral Lewis acids found widespread application in organic synthesis, especially in the synthesis of natural products with many chiral centres. An enantioselective Diels–Alder reaction is the key step in the synthesis of an iodolactone prostaglandine precursor (Scheme 6).[88]



SCHEME 6. Enantioselective Diels–Alder reaction induced by a chiral aluminium-containing Lewis acid[88]

Furthermore, regioselectivities[89] as well as the diastereofacial selectivities[90,91] may be increased in the presence of Lewis acids (Table 8). For instance, $AlCl_3 \cdot OEt_2$ improves the *endo*-selectivity of the reaction of cyclopentadiene and methyl acrylate from 82% to 98%[87]. The astonishing rate accelerations, the improved yields and higher selectivities make the Lewis acid catalysed Diels–Alder reaction one of the most important organic reactions.

TABLE 8. Rate and selectivity enhancements of Diels–Alder reactions by addition of Lewis acids[56,87]



(5) **(6)**

Entry	Catalyst	Yield (%)	**5**	**6**
1	—	22–51	82	18
2	$BF_3 \cdot OEt_2$	66	97	3
3	$AlCl_3 \cdot OEt_2$	79–91	98	2
4	$SnCl_4$	67–79	95	5
5	$TiCl_4$	80	95	5

Lewis acid catalysis enormously enriches the scope of Diels–Alder reactions, but it is limited to reagents containing Lewis basic sites, i.e. functional groups with lone pairs such as carbonyl, amino, ether or nitro close to the reaction centre. As we have seen in the discussion about the FMO aspects of Lewis acids, the major reason for catalysis is the reduction of the HOMO–LUMO gap. In case of Diels–Alder reactions with normal electron demand, it follows that the coordination of the Lewis acid lowers the LUMO energy of the dienophile. Such interactions are only possible if there is a spatial proximity or an electronic conjugation between the coordinated Lewis basic site and the reaction centre. Fortunately, in nearly every Diels–Alder reaction one of the reagents, mostly the dienophile, meets this requirement.

The Lewis acid activation mechanism can be understood within the scope of FMO theory. Upon coordination to a lone pair at the Lewis basic centre of the dienophile (in the case of a Diels–Alder reaction with normal electron demand), the electron-withdrawing effect of the catalytically active Lewis acids leads to a change of the electron density on the Lewis basic atom and, in turn, of the entire conjugated system. It might be surprising, but the complexation by an electron-withdrawing group does not necessarily lead to a decrease of electron density at the Lewis acidic centre. For instance, while the charge on the carbonyl oxygen of acrolein is calculated to be $-0.52\,e$, the charge on this atom after protonation is $-0.62\,e$. In the case of the acrolein–trifluoroborane complex the charge amounts to $-0.59\,e$[92]. On the other hand, of course, the charge at the reacting carbon–carbon double bond is increased, or rather the atoms become more positive. This change in charge goes hand in hand with a lowering of the orbital energies. The decrease of the HOMO–LUMO energies causes the increased rate of accelerations in Diels–Alder reactions.

The effects of Lewis acids on the stereoselectivities can also be understood in terms of orbital interactions. The variation in charge at the respective basic centre gives rise to a change in the magnitude of the orbital coefficients of the entire interacting molecular orbital. These effects are visualized by the HOMO and LUMO representations of the Lewis acid–base complex of acrolein and trifluoroborane (Figure 3), and in an even more extreme case by the HOMO and LUMO representations of one of the simplest dienophile–Lewis acid complexes: protonated acrolein[92,93].

The change in electron distribution caused by the Lewis acid involves the entire conjugated system. Firstly, the decrease in HOMO and LUMO energies leads to a more efficient

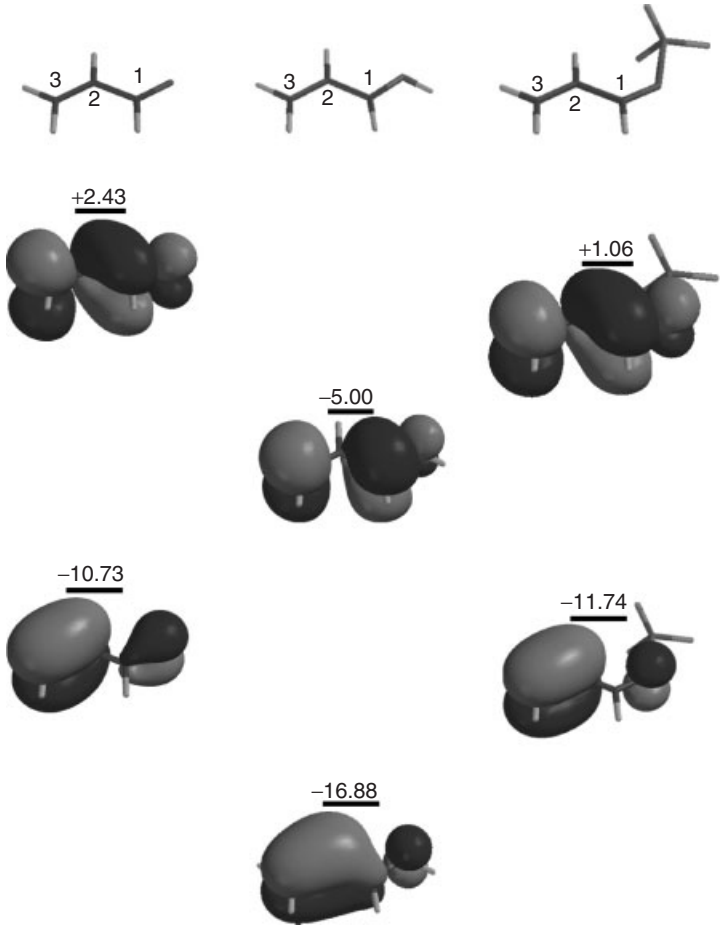
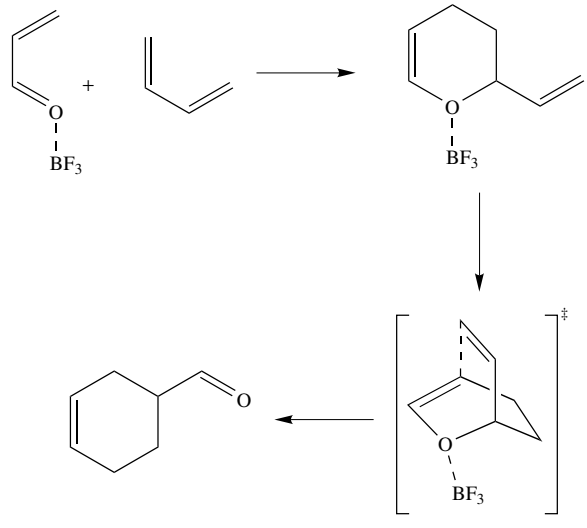


FIGURE 3. Frontier molecular orbital energies (eV) and representations of the coefficients of acrolein, protonated acrolein and the acrolein–trifluoroborane complex[101]. Geometry optimizations were performed at the AM1[102,103] level of theory; orbital energies and electronic distributions were determined at HF/3-21G[104–107]

orbital overlap between the reactants and thus to a rate acceleration. Secondly, the higher polarization at the alkene moiety, reflected in the increased difference of the orbital coefficients at carbons 1 and 2, gives rise to enlarged regioselectivities observed in Lewis acids catalysed Diels–Alder reactions. Thirdly, the increase of the orbital coefficient at the carbonyl carbon 1, in connection with stronger secondary orbital interactions, results in higher *endo/exo* selectivities. The FMO theory serves well to explain the effects of Lewis acids on the reactivities[94–97] and on the stereoselectivities, but there are also other rationalizations. For example, a more compact transition state for the catalysed reaction[93] and conformational changes in the complexed dienophile[98–100] are used as arguments for the increased diastereofacial stereoselectivity.

In the Lewis acid catalysed reactions of α,β-unsaturated carbonyl compounds with dienes, sometimes the products of a [2 + 4]-cycloaddition, where the carbonyl compounds function as heterodienes, were isolated. It was proposed that the intermediate of the [2 + 4]-cycloaddition is formed first in this case, followed by a Cope rearrangement which leads to the 'normal' Diels–Alder product (Scheme 7).



SCHEME 7. Postulated alternative mechanism of a Lewis acid catalysed Diels–Alder reaction[108], the so-called Butadiene + Acrolein Paradigm[109]

Further investigations of this unexpected behaviour showed a complex dependence on the steric demand of the dienophile as well as on the nature of the Lewis acid[110]. Large substituted dienophiles lead to [2 + 4]-cycloaddition, whereas dienophiles with less steric demand follow the normal path of the Diels–Alder reaction. While $BF_3 \cdot OEt_2$ gives the usual Diels–Alder products, Al_2Cl_6 reacts rather unselectively, while BBr_3 leads to hetero-Diels–Alder products. These findings initiated several studies on the stereoselectivities of Lewis acid catalysed Diels–Alder reactions of small α,β-unsaturated carbonyl compounds with butadiene or cyclopentadiene. Since the selectivities of kinetically controlled reactions are directly related to the transition state energies, computations on the transition structures of several Diels–Alder reactions were carried out. These *ab initio* computations supported the experimental findings that both large and electron-demanding substituents favour [2 + 4]-cycloaddition[110–112]. The cycloaddition of a diene and a sterically demanding dienophile mostly leads to the hetero-Diels–Alder product.

During investigations into the dependence on the Lewis acid it was noted that in the case of Al_2Cl_6 the activation energies of the hetero and homonuclear Diels–Alder reactions are rather similar. On the other hand, it was found that for the $BF_3 \cdot OEt_2$ catalysed reaction the [4 + 2]-, and for the BBr_3 catalysed reaction the [2 + 4]-transition structure, is energetically favourable. In cases where the normal Diels–Alder products were obtained, calculations [HF/3-21G geometry optimizations in connection with MP3/6-31G(d) single-point energies] showed that the [2 + 4]-cycloaddition can be followed by a Cope rearrangement leading to the 'normal' Diels–Alder adduct[108]. The computations

suggest that sometimes the Cope rearrangement does not occur and that it should be possible to isolate the [2 + 4] adduct[108]. In a similar way the hetero-Diels–Alder reactions of azadienes[113], sulphur dioxide[114] and nitrosoethylene[115] were investigated in great detail[116]. These examples demonstrate the far-reaching power of computational chemistry methods in elucidating reaction mechanisms.

The Diels–Alder reaction of enantiomerically pure chiral acrylic esters with cyclopentadiene leads to a pair of diastereomers. Their ratio depends strongly on the choice and amount of Lewis acid catalyst (Scheme 8)[117]. While titanium tetrachloride leads preferentially to the (2*R*)-diastereomer with high selectivity, ethyl aluminium dichloride gives the (2*S*)-diastereomer in only 56% de.

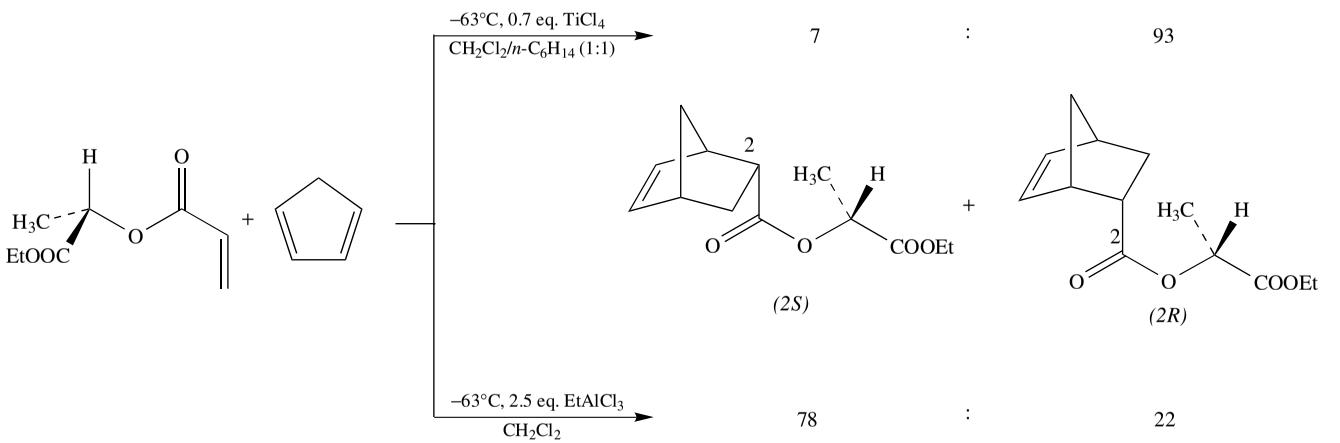
The dependence of the diastereomeric ratio on the choice of Lewis acid can be understood when considering the geometry of the Lewis acid complex. In the case of the titanium tetrachloride catalysed reaction, the interaction of the ester and the catalyst is strongly supported by the first crystal structure observed of the Lewis acid with a chiral dienophile (Figure 4)[118].

The activation of various reactions by Lewis acids is now an everyday practice in synthetic organic chemistry. In contrast, solvent effects on Lewis acid catalysed Diels–Alder reactions have received much less attention. A change in the solvent can affect the association step leading to the transition structure. *Ab initio* calculations on the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone in aqueous media showed that there is a complex of the reactants which also involves one water molecule[119]. In an extreme case solvents can even impede catalysis[120]. The use of inert solvents such as dichloromethane and chloroform for synthetic applications of Lewis acid catalysed Diels–Alder reactions is thus well justified. General solvent effects, in particular those of water, will be discussed in the following section.

B. Solvent Effects on Diels–Alder Reactions

Solvent effects on the reactivities and selectivities of organic reactions are intricate combinations of non-covalent interactions. Generally, these are separated into hydrogen bonding, hydrophobic interactions and electrostatic effects. In a typical approach, a property of a reaction, such as its rate or selectivity, is measured in a number of different solvents. This procedure allows the comparison of solvent properties and their effects on reaction rates as well as selectivities, and other observable parameters. Correlating the characteristics of a particular reaction with one or more solvent parameters reveals which non-covalent interactions are important. The major drawback is, however, that solvent parameters are often not independent. Here also, theoretical models and computer simulations provided valuable additional insights[121]. Both methods, the experimental dissection of the solvent effects and the computational models, have been applied successfully to Diels–Alder reactions. In the following we will attempt to generalize the results of these studies. We will discuss separately the interactions which lead to rate accelerations and increased selectivities.

At first glance the Diels–Alder reaction represents an organic transformation which is relatively insensitive to solvent effects (Table 9). For the dimerization of cyclopentadiene, the second-order rate constants in a broad range of organic solvents are quite similar[5]. The data of Table 9 refer to the special case of a Diels–Alder reaction between two pure hydrocarbons. Usually, Diels–Alder reactions only proceed at an appreciable rate when either the diene or the dienophile is activated by electron-donating or electron-withdrawing



SCHEME 8. Stereodichotomy of the Lewis acid catalysed Diels–Alder reactions of a chiral acrylic ester and cyclopentadiene

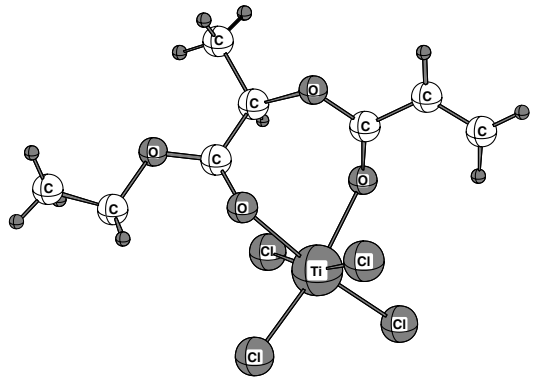


FIGURE 4. The crystal structure of the Lewis acid complex of a chiral dienophile with titanium tetrachloride[118]

substituents which mostly contain heteroatoms. These can interact efficiently with the solvent, resulting in an amplification of the solvent effect on the reaction.

There are numerous attempts to correlate solvent parameters with the reaction rate of Diels–Alder reactions[122]. Examples are the Brownstein Polarity Parameter S[123], the Solvophobicity Parameter Sp[124,125] the $D-\pi$ parameter (based on the solvent effect on the reaction of tetracyanoethylene and diazodiphenylmethane with benzene as the reference solvent)[126] or the Acceptor Number AN[127,128] (a parameter which describes the ability of a solvent to act as an electron pair acceptor)[129]. These examples included either reactions that were next to insensitive to solvent effects (like that in Table 9) or reactions in which the reactants mainly interact with the electron pair on the donor atom of the solvent[130].

These results led to a separation of the observed Diels–Alder reactivities into three categories: (a) increase of the rate constants on increasing the Lewis acid character of the solvent as quantified by the *AN* parameter; this behaviour reflects the interactions between the LUMO of the solvent and the HOMO of the reactants and is similar to Lewis acid catalysis (*vide supra*); (b) reaction retardation by electron donation, as quantified by the $D-\pi$ parameter; the $HOMO_{solvent}-LUMO_{reactant}$ interactions are held responsible for this effect, representing an 'anti-Lewis acid' interaction which increases the HOMO–LUMO gap and hence hampers the reaction; (c) the Diels–Alder reactions show very small solvent effects and are relatively insensitive to specific reactant–solvent interactions, and

TABLE 9. Second-order rate constants k for the dimerization of cyclopentadiene in the gas phase and in several solvents at 25°C[5]

Solvent/state	$k\ M^{-1}\ s^{-1}$
Gas phase	6.9×10^{-7}
Neat	5.6×10^{-7}
CCl_4	7.9×10^{-7}
$PhNO_2$	13×10^{-7}
EtOH	19×10^{-7}

the dimerization of cyclopentadiene is a typical example (Table 9). To our knowledge, pure water or mixtures of water with other solvents were not examined[131].

In studies on Diels–Alder reactions of type (a) in which only organic solvents were used, the rate constants correlate well with the solvent hydrogen-bond donating capacity α[106]. For the methyl acrylate/cyclopentadiene reaction, log k, the logarithm of the rate constant in a number of solvents, correlates linearly with α. In mixtures of water with acetone or 1,4-dioxane, log k gave a linear correlation with the solvophobicity parameter Sp[132]. In studies including mixtures of water and several organic solvents, an empirical combination of Sp and the E_T^N [a normalized E_T (30) parameter] scale[5] allowed the calculation of rate constants leading to excellent agreement with observed rate constants[133,134]. The rates of Diels–Alder reactions in highly viscous media were correlated with solvent density and were ascribed to internal pressure effects[135,136]. These empirical correlations can only be generalized within narrow bounds. It should be noted that analysis of the interplay between a specific organic reaction and the physical properties of the solvents is not easy. Even the effects of apparently simple solvent systems like a 5 M solution of lithium perchlorate in diethyl ether lead to controversy[137–139]. Diels–Alder reactions in such media are accelerated and rationalizations from internal pressure effects[138,140] to Lewis acid catalysis by the lithium cation had been advanced[137,139]. It was suggested that only if Diels–Alder reactions are not sensitive to Lewis acid catalysis, internal pressure and similarly weak effects can explain the very modest accelerations[141]. If there are several catalytic effects, Lewis acid catalysis is most effective. Combining Lewis acid catalysis with the use of water as a solvent seems therefore a worthwhile undertaking. The results available to date will be presented in the following.

Solvents and additives can influence Diels–Alder reactions through a multitude of different interactions, of which the contributions to the overall rate depend uniquely on the particular solvent–diene–dienophile combination. Attempts to build a general picture are limited to the most extensively studied type (a) Diels–Alder reactions. These Diels–Alder reactions are dominated by hydrogen-bonding and solvophobic interactions. This observation predicts a very special role of water as a solvent for type (a) Diels–Alder reactions.

The influence of the solvent on the regioselectivity is perfectly described by FMO theory[142]. As mentioned above, the regioselectivity is determined by orbital coefficients on the terminal carbons of the diene and dienophile which, in turn, are determined by the electronic substituent effects. These can be modified by electron donation or electron withdrawal by the solvent or additives like Lewis acids.

Changing the electron distribution through the solvent can be achieved efficiently by hydrogen bonding. This has become apparent from multiparameter analyses of the solvent effects on the regioselectivities, which revealed a dominant contribution of the hydrogen-bond donating character of the solvent[143]. Apart from that, solvent effects on the *endo/exo* ratio of Diels–Alder reactions were interpreted in terms of different polarities of the individual Lewis acid–base complexes involved[144]. In general, the *endo*-transition structure is of higher polarity than the *exo*-transition structure because the dipole moments in the *endo*-complex of the diene and dienophile are aligned, whereas in the latter they are pointing in opposite directions (Figure 5).

This explains the experimentally confirmed predictions that polar solvents attenuate the *endo*-preference, while non-polar solvents increase the *endo*-selectivity of Diels–Alder reactions. The strong correlation between the polarity of the solvent and the *endo/exo* ratios in the Diels–Alder reaction led to the empirical polarity scale $\Omega = \log(endo/exo)$ using the reaction of cyclopentadiene with methyl acrylate as the standard[144]. The importance of solvent polarity has also been discerned on the basis of experimental[142] and theoretical investigations[145]. Dependence on the polarizability was also noted[146].

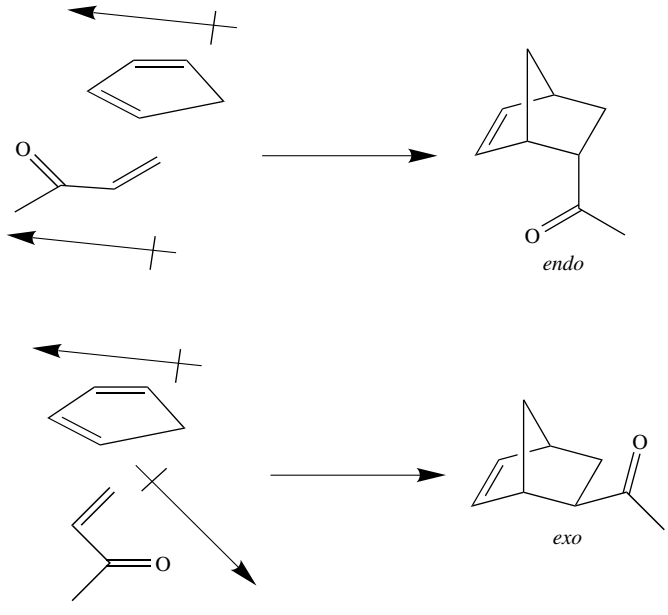


FIGURE 5. The different transition structure polarities, as indicated by the dipole arrows, of the Diels–Alder reaction

In summary, the interactions responsible for the typical solvent effects on Diels–Alder reactions are comparable to those of Lewis acids. The rate acceleration, the increase of regioselectivity and the higher *endo/exo* selectivity on changing the solvent may be explained by the FMO theory.

C. Hydrogen Bonding

1. Water

The classical description of a hydrogen bond begins with a pair of closed-shell molecules, both in their electronic ground state[147]. The interactions between a molecule AH containing a positively polarized hydrogen atom and another molecule containing a negatively polarized heteroatom X with at least one electron lone pair, mostly oxygen, nitrogen or fluorine, are summarized as *hydrogen bonding*. AH and X are not necessarily different molecules; intermolecular and intramolecular hydrogen bonds are also possible. Although in most cases AH and X are uncharged, one of the most important contributions to hydrogen bonding is electrostatics. The lone pair of the acceptor atom is 'pulled' towards the bridging proton to form a non-covalent bond. The strength of these hydrogen bonds reaches from 2 kcal mol^{-1} up to 15 kcal mol^{-1} for strongly hydrogen-bonded complexes like the ammonia–hydrogen fluoride complex[148]. The water dimer, which lies in between, will be used to describe the various components leading to hydrogen bonding. With the help of the Morokuma–Kitaura schemes[149,150] it is possible, at least approximately[151], to separate the different interactions (Table 10). This energy separation shows that the electrostatic interaction E_{ES} between the monomers is the most important. The other terms, the exchange energy E_{EX}, the stabilization by polarization E_{PL} and the charge transfer

TABLE 10. Morokuma–Kitaura component analysis of the SCF interaction energy of the water dimer[a]

Morokuma–Kitaura component	Energy
E_{ES}	−7.5
E_{EX}	4.3
E_{PL}	−0.5
E_{CT}	−1.8
E_{MIX}	−0.1
ΔE	−5.6

[a] All values in kcal mol^{-1}[150].

energy E_{CT}, are normally less important. All remaining effects are collected in the last 'mixing' term, E_{MIX}.

The component analysis demonstrates the importance of the electrostatic attraction for the stability of the water dimer, but it also emphasizes the significance of other interactions. In hydrogen-bonded complexes of molecules which are more easily polarizable than water, the polarization and the charge transfer energies may constitute a larger fraction of the total complexation energy. Hydrogen bonding is intimately involved in the structures and properties of water in its various phases, and of molecules in aqueous solution. In addition to the traditional role of the hydrogen bond as a structural element in large molecules such as proteins and nucleic acids[152], a cooperative array of such bonds appears to be vital to the function of many enzymes[153]. There are some indications that hydrogen bonds play an even more important role in biological electron transfer across long distances than much stronger covalent bonds[154]. The principles of hydrogen-bond formation have been taken as a means to design new materials capable of self-assembly into well-ordered crystal structures[155], for molecular recognition of organic molecules[156] and for organic analogs of zeolites with supramolecular cavities and continuous channels[157]. Hydrogen bonding opens an avenue to stereocontrol of certain reactions[158] and for understanding the structures of monolayers[159]. The most obvious effects of hydrogen bonding are the anomalous thermodynamic properties of water, which mostly derive directly from the unique molecular structure of liquid water and ice (Figure 6). Strong hydrogen bonds between the water molecules produce relatively stable clusters even in the liquid state. These lead to the high heat capacity, the large enthalpies of evaporation and solidification and the high surface tension of water. The water–water interactions can be influenced by solutes as well as by suspensed agents. This can lead to the unique solvent effects observed in organic transformations carried out in water or aqueous solutions.

Studies of such solvent effects on type (a) Diels–Alder reactions revealed that the reactivity was primarily determined by two solvent parameters: hydrogen-bond donating capacity and solvophobicity[161]. The interactions of water with the activating group of the dienophile in normal electron demand Diels–Alder reactions via hydrogen bonding strongly influence the reaction rate[45,162]. The correlation with the hydrogen-bond donating capacity strongly suggests that in water, a hydrogen-bond donating solvent *par excellence*, the Diels–Alder reaction benefits not only from hydrophobic but also from hydrogen-bonding interactions. Several computations, including *ab initio* calculations and Monte Carlo simulations, as well as NMR studies showed that water is able to build up strong hydrogen bonds to Lewis-basic functional groups of organic compounds[119,121,163].

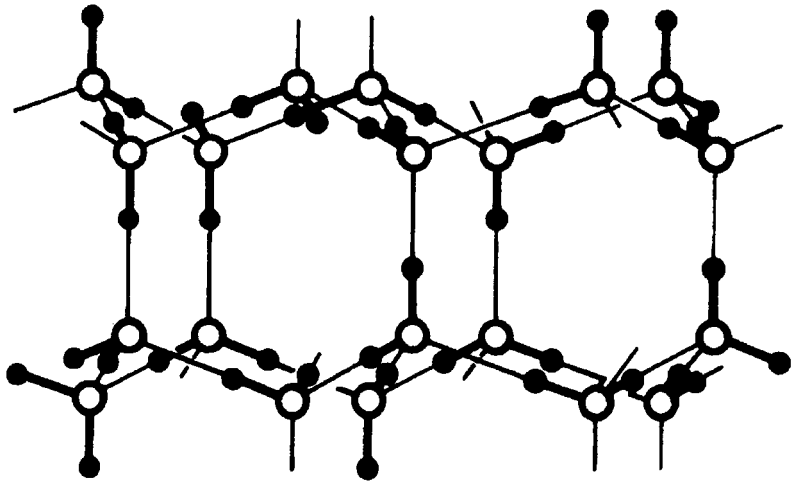


FIGURE 6. The crystal structure of water, dominated by hydrogen bonds[160]

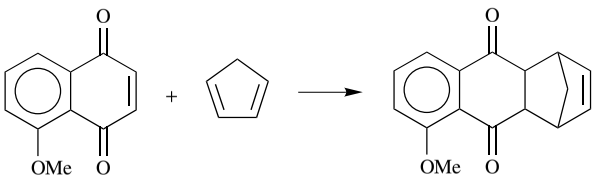
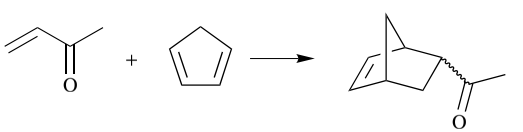
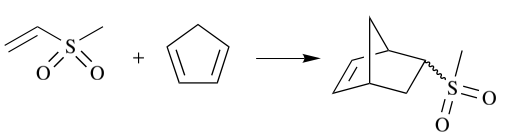
The interactions of hydrogen-bond donors and carbonyl groups are of particular interest, as these interactions often lead to effective H-bonding[164,165]. Furthermore, the small size of the water molecules allows efficient interaction with hydrogen-bond acceptors by forming more hydrogen bonds than in the case of larger protic organic solvents. This notion is supported by detailed kinetic studies on a number of carefully selected Diels–Alder reactions which showed that hydrogen bonds strengthen the electron-withdrawing capacity of the carbonyl functionality and thereby decrease the HOMO–LUMO gap between diene and dienophile.

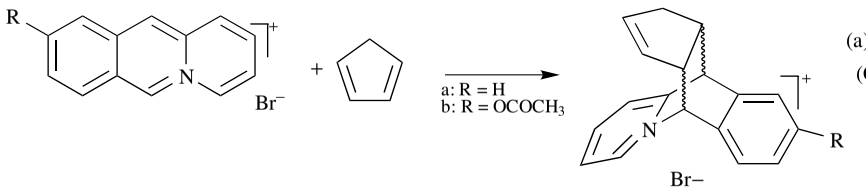
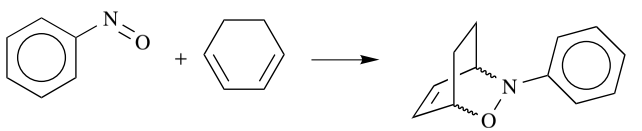
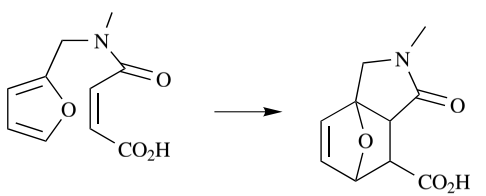
By comparison of the reaction of cyclopentadiene with a carbonyl (Table 11, entry B) and a sulphonyl-containing substrate (Table 11, entry C), the effects of hydrogen bonding on the reaction rates were examined. The presence of the sulphur atom results in less effective hydrogen bonding and, in turn, in a smaller rate acceleration. The lower sensitivity of the sulphonyl compound in comparison with the carbonyl compound is demonstrated by a much less pronounced water-induced acceleration. Further proof for the importance of hydrogen-bonding interactions comes from the observation that the strong hydrogen-bond donor HFP also leads to impressive rate enhancements (Table 11, entries A, C, D, F)[169] and that in case of weak hydrogen-bond acceptors the rate accelerations in water are somewhat smaller (Table 11, entry E)[166].

2. Hydrogen-bonding additives

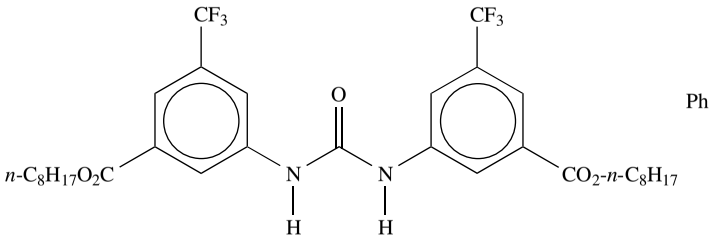
In an extension of these conclusions hydrogen-bonding additives can be of particularly great value in non-hydrogen-bonding solvents. Specific catalysts (Scheme 9, **7–10**) are hydrogen-bond donors, which lead to rate accelerations and selectivity enhancements[170]. Only very few examples of non-aqueous hydrogen-bond donors in organic synthesis are known, but they open new avenues for developing such catalytic systems, perhaps to ultimately replace sometimes harmful Lewis acids.

TABLE 11. Relative rate constants of selected Diels–Alder reactions in water compared with organic solvents of different hydrogen-bond donor capacities

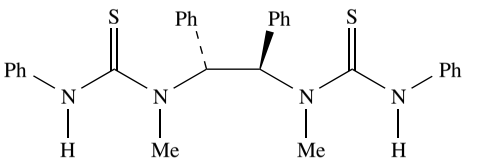
Entry	Reaction	Aprotic	EtOH	HFP[a]	H_2O	Reference
A		1 (hexane)	28.0	4320	12800	45
B		1 (CH_3CN)	4.79	100	290	45
C		1 (CH_3CN)	2.49	22.6	71.0	45 162

D		(a)	1 (CH$_3$CN)	1.69	—	8.95	162
		(b)	—	1	—	102	166
E			1 (toluene)	1.14	5.49	44.3	167
F			1 (hexane)	1.90	—	153	168

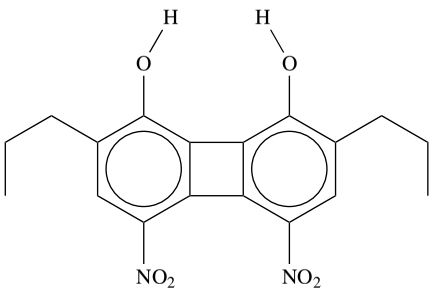
[a] 1,1,1,3,3,3-Hexafluoro-2-propanol.



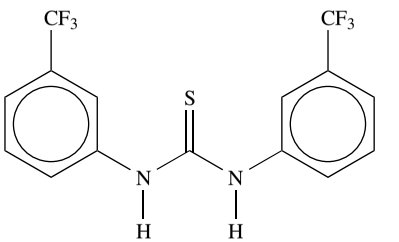
(7)



(8)



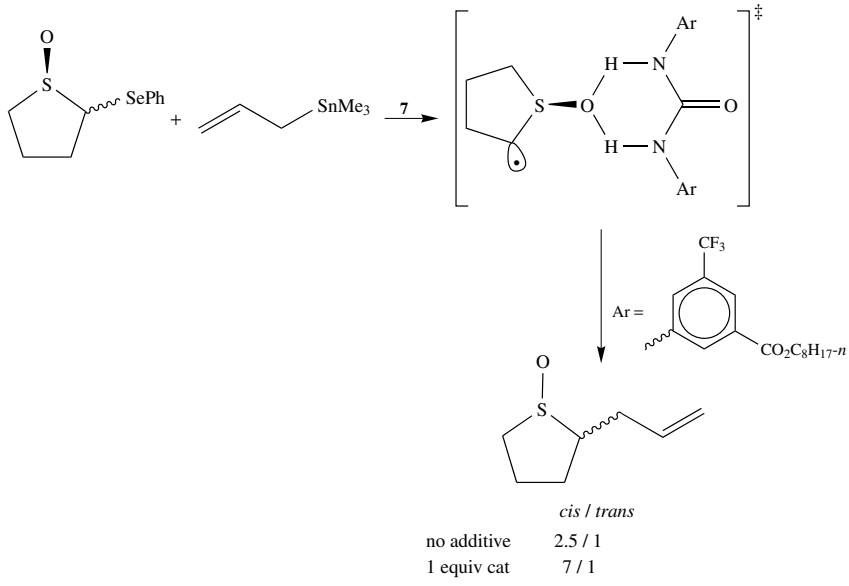
(9)



(10)

SCHEME 9. Catalytically active hydrogen-bond donors

Hydrogen-bond donors have the ability to enhance the selectivities and rates of organic reactions. Examples of catalytic active hydrogen-bond donor additives are urea derivatives, thiourea derivatives (Scheme 10, Tables 12 and 13) as well as diols (Table 14). The urea derivative **7** (Scheme 9) increases the stereoselectivity in radical allylation reactions of several sulphoxides (Scheme 10)[171]. The modest increase in selectivity was comparable to the effects exerted by protic solvents (such as CF_3CH_2OH) or traditional Lewis acids like $ZnBr_2$[172]. It was mentioned that the major component of the catalytic effect may be the steric shielding of one face of the intermediate radical by the complex-bound urea derivative.



	cis / *trans*
no additive	2.5 / 1
1 equiv cat	7 / 1

SCHEME 10. Catalysis of a radical allylation by the urea derivative **7**[171,172]. The enhanced *cis/trans*-selectivity is caused by the steric shielding in the transition structure

TABLE 12. The asymmetric reduction of prochiral ketones under catalysis of chiral urea derivative **8**[173] (in all reactions 5% catalyst was used)

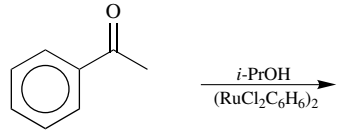
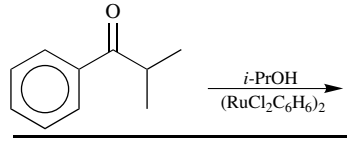
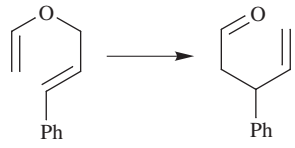
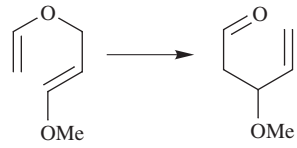
Reaction	Time	Yield(%)	ee(%)
	3 h	85	87 (S)
	9 h	98	87 (S)
	3 h	30	94 (S)
	17 h	92	94 (S)

TABLE 13. Acceleration of Claisen rearrangements by substituted diphenylurea **7**.[174]

Reaction	equiv cat	k_{rel}[a]
	none	1
	0.2	1.7
	0.5	3.1
	1.0	4.2
	none	1
	0.1	2.7
	0.4	5.0
	1.0	22.4

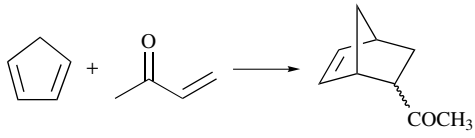
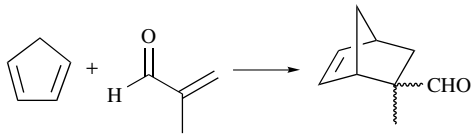
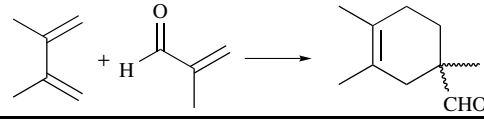
[a]Relative first-order rate constants compared with the uncatalysed reaction.

Apart from enhanced stereoselectivities, rate accelerations by hydrogen-bonding interactions were also observed. Examples of noticeable rate accelerations are Claisen rearrangements catalysed by a substituted diphenylurea **7** (Scheme 9, Table 13)[174]. Apart from changing the *cis/trans* ratio (Scheme 10), stereoselective induction by chiral hydrogen-bond donors is also possible. A chiral thiourea catalyst **8** (Scheme 9) for the asymmetric reduction of prochiral ketones and aldehydes yields up to 87% enantiomeric excess (with an overall yield of 98% after 9 h; Table 12). In this reaction a direct coordination of the hydrogen-bond donor to the Lewis-basic carbonyl group of the prochiral ketones is, however, rather unlikely, as the ruthenium centre of the reactant is much more Lewis-acidic. A complex of urea catalyst and metal centre sounds more reasonable. An important advantage of the urea catalyst in comparison with other compounds like the diol **9** (Scheme 9) is that the chemistry of nitrogen-containing organic compounds offers wider possibilities, and the search as well as evaluation of new kinds of chiral ligands is still a topical issue[173].

The strong dependence of the reaction rate on the catalyst concentration relative to control experiments in which the amino-hydrogen atoms of **7** were substituted by methyl groups demonstrate that hydrogen bonding represents the major interaction responsible for the observed accelerations. Diels–Alder reactions are also accelerated by hydrogen-bond *donors*. It was shown that a biphenylenediol **9** is able to catalyse [4 + 2]-cycloadditions of cyclopentadiene, 2,3-dimethylbutadiene and other simple dienes with various α,β-unsaturated carbonyl compounds (Table 14)[175].

There are very few examples of crystal structures exhibiting chelate-like dihydrogen bonds, in which the hydrogen bond donors and acceptors are different molecules[176]. The geometry of the initial complex between the biphenylenediol and the carbonyl compounds leading to Diels–Alder catalysis is suggested by an X-ray structure of a hydrogen-bonded adduct of the catalyst and a trimethyl pyranone (Figure 7)[177,178]. This structure was used as a binding motive for the transition structure of the catalysed reaction.

TABLE 14. Some Diels–Alder reactions catalysed by the biphenylenediol catalyst (cat) **9**[175]

Reaction	Conditions	Product formation (%)	
		without cat	with cat
	23 °C, 10 min	3	90
	55 °C, 2 h	16	97
	55 °C, 48 h	5	60

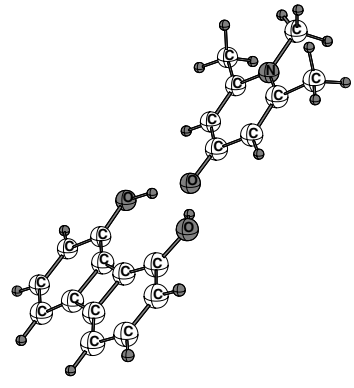


FIGURE 7. Crystal structure of the bidendate hydrogen-bonded complex of 1,2,6-trimethyl-4-pyridone and 1,8-biphenylenediol[177]

Most hydrogen-bond-containing crystal structures are homomolecular, i.e. both the hydrogen-bond accepting and donating functionality exist in the same molecule. Examples of such co-crystals are urea and thiourea derivatives as well as non-cyclic imides[156,179,180].

The effectivity of ureas and thioureas as catalysts and the possibility to catalyse Diels–Alder reactions leads to the assumption that thioureas also should be active catalysts for the [4 + 2]-cycloaddition. A thiourea should be a more active nitrogen-containing

catalyst for the Diels–Alder reaction than a urea derivative. The higher acidity of the thiourea (urea: $pK_a = 26.9$, thiourea: $pK_a = 21.0$)[181] most likely leads to more stable hydrogen-bonded complexes. The *m*-trifluorotolyl group is an ideal substituent because it increases the acidity and, in turn, the hydrogen-bond donor activity of the N–H bonds. Further advantages of a *m*-trifluorotolyl-substituted thiourea are, in comparison with the respective urea derivative, the better solubility and the cheap and safe preparation. Finally, the sulphur atom is a much weaker hydrogen-bond acceptor, which leads to less self-association of the catalyst and to a higher concentration of free catalyst. Hence, the substituted diphenylurea **10** offers the possibility to catalyse the Diels–Alder reaction by a nitrogen-containing organic compound. As expected, the thiourea **10** is catalytically active in Diels–Alder reactions, even in solvents which are donors themselves. The results of this investigation are summarized in Table 15[182].

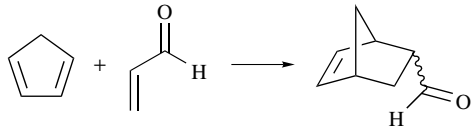
As expected, the reaction is fastest in water due to its hydrogen-bonding ability and high dielectric constant. Addition of 1 mol% of the thiourea catalyst **10** increases the yields after 1 h in cyclohexane and chloroform by about 60%; a 40 mol% catalyst doubles the yield. A sizeable catalytic effect of the *m*-trifluoromethyl-substituted thiourea was also found in water. Explanations for the surprising fact that this hydrogen-bond donor is catalytically active even in a highly competitive solvent such as water will be given in Section III.D.3.

In the previous part we showed that hydrogen bonding may lead to rate accelerations and increased selectivities. The effects of pure hydrogen bonding of suitable additives is most evident in non-polar solvents, because of the competition of H-bond accepting solvents and the reactants. Water exhibits some other solvent effects derived from its special properties, as discussed below.

D. Hydrophobicity

Apart from hydrogen bonding, the unique position of water amongst solvents derives from an intriguing phenomenon observed in this solvent: hydrophobicity[7]. This rather complex property is governed by the limited ability of water to dissolve non-polar molecules and is considered to be important in the folding of proteins, enzyme–substrate interactions, the formation of biological membranes, the aggregation of amphiphilic molecules into supramolecular structures (e.g. micelles and vesicles), in molecular recognition phenomena[183] and surface forces[184]. The interactions appearing with the introduction of a non-polar solute into water can be reduced to two distinct processes: *hydrophobic*

TABLE 15. Dependence of the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone on the solvent and the catalyst concentration using thiourea **10**

Reaction	Solvent	Mol% cat	Conversion[a]
	cyclohexane	none	18
	cyclohexane	1	30
	chloroform	none	31
	chloroform	1	52
	chloroform	40	65
	water	none	74
	water	1	85

[a] After one hour, in %.

hydration and *hydrophobic interaction*, which are often summarized as *hydrophobicity*. This term should not detract from the fact that the overall interactions between water and a hydrophobic substance are *attractive*.

The *hydrophobic hydration* denotes the way in which non-polar solutes affect the organization of the water molecules in their immediate vicinity. Investigations on the transfer of non-polar molecules from the gas phase into a solvent showed that the temperature dependence of the thermodynamic data (ΔH_t°, ΔG_t°, ΔS_t°) of this process are characteristic for a particular solvent[184]. This pattern indicates that the enthalpy and entropy changes upon solvation of small non-polar compounds (from hydrogen to cyclohexane) in aqueous media are dominated by the properties of water. This led to the concept that to a first approximation the effects of solvation depend only on the nature of the solvent[185]. Classical studies on this topic state that the water molecules around a non-polar solute show increased quasi-solid structuring[186–188]. Already in the early days of these studies the importance of hydrophobic effects in protein folding was stressed[189].

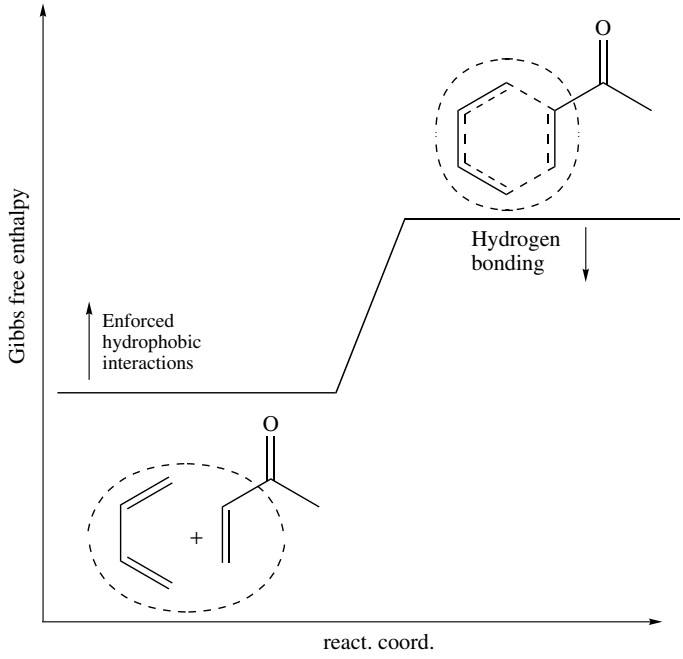
With more detailed information from computer simulations, on the hydrophobic hydration shells the ideas about hydrophobic hydration gradually changed. It became apparent that the hydrogen bonds in the hydrophobic hydration shell are not[190], or only to a minor extent[191], stronger than in normal water. These results are confirmed experimentally through neutron scattering[192–194] and X-ray studies (EXAFS)[195]. These studies revealed that the water molecules in the hydrophobic hydration shell remain essentially fully hydrogen-bonded. For each water molecule in contact with the non-polar solute one O–H bond is oriented parallel to the non-polar surface; the other bonds point into bulk water.

In summary, it is evident that water is able to accommodate non-polar solutes without sacrificing a significant number of its hydrogen bonds. Hence, the water molecules in the first solvation shell are engaged in hydrogen bonds with their neighbours, leading to a tangential orientation with respect to the non-polar surface. Due to this arrangement, the water molecules around a non-polar solute suffer an entropic penalty, which is most likely a consequence of the reduction of the number of hydrogen bonds.

The *hydrophobic interaction* describes the tendency of non-polar molecules or parts thereof to agglomerate in aqueous media[7]. In the traditional view, hydrophobic interactions are assumed to originate from the release of water molecules from the hydrophobic hydration shells when non-polar solutes approach each other. Although the concepts about the structure of the hydrophobic hydration shell are constantly modified, this view is essentially unaltered. Nevertheless, one has to consider that the reorganization of water molecules around a non-polar solute is essential to solvation, i.e. if the water did not have to be reorganized and be forced to form a hydrophobic hydration shell, hydrogen bonds would have to be sacrified upon dissolving the solute, so that the solubility of non-polar compounds in water would be even smaller. It follows that the formation of a hydrophobic hydration shell opposes the aggregation of the solute. Hence, hydrophobic interactions are entropy driven. The only difference between aggregation under hydrophobic interaction control and a normal phase separation is the fact that the separation process is arrested in an intermediate stage because efficient interactions between the polar headgroups of the detergent and the surrounding water molecules prevent the aggregates from forming still larger structures[196].

Hydrophobic interactions appear when a non-polar compound is transported into aqueous media. They include the following steps: separating the non-polar molecule from its non-polar surrounding, filling up this empty space in the non-polar medium with water, cavity formation accounting for the interactions between water and the non-polar molecules, and reorganizing the water molecules around the non-polar solute.

In summary, the effects of water which lead to rate accelerations of Diels–Alder reactions can be explained by a combination of hydrophobic interactions and hydrogen bonding. Firstly, the enforced hydrophobic interactions lead to an increase in the Gibbs free enthalpy of the starting material. Secondly, hydrogen bonding leads to a stabilization of the transition structure. These two effects are the most important reasons for the observed rate accelerations of Diels–Alder reactions in water and aqueous solutions (Scheme 11). The big difference between water and ordinary organic solvents is the molecular origin of the hydrophobic interaction which is entropy driven in pure water at room temperature and results primarily from the strong water–water interactions.



SCHEME 11. The reasons for the acceleration of Diels–Alder reactions in water

In 1948 the effects of water on the reactivity of a Diels–Alder reaction were examined for the first time. A change in the *endo/exo* selectivity in the reaction of furan and maleic acid (Table 16, entry A) was noticed[197]. Twenty-five years later the first rate acceleration in a [4 + 2]-cycloaddition was reported (Table 16, entry B)[198]. Still, it was not until the work of Breslow that it became common knowledge that water was a unique medium for Diels–Alder reactions[11].

Further investigations showed that these accelerations in water are a general phenomenon; Table 11 contains another selection from the multitude of Diels–Alder reactions in aqueous media. Note that the rate enhancements induced by water can amount to a factor of 12,800 compared to organic solvents (Table 11, entry A). A detailed study on solvent effects in an exemplary Diels–Alder reaction is presented in Table 17[162]. It was demonstrated that the solvent enhancements depend on the dienophile and, more strongly, on the solvent.

TABLE 16. Historical experiments concerning the observed rate accelerations and selectivities of Diels–Alder reactions in different solvents

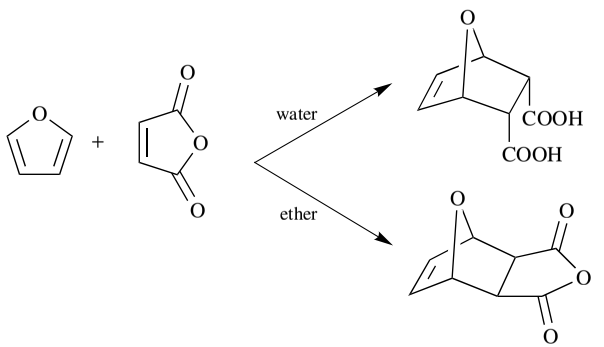
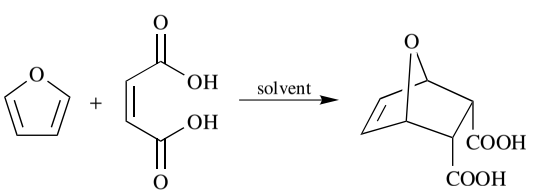
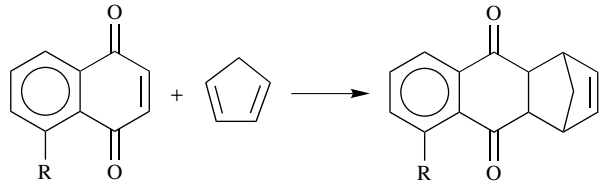
Entry	Reaction		Reference
A			197
B		*yields after* 5 *days* (rt) D_2O: 55% CD_3OD: 33% DMSO-d_6: 10%	198

TABLE 17. Second-order rate constants $10^3 k_2(M^{-1}\,s^{-1})$ for the Diels–Alder reaction of **11a–e** with cyclopentadiene in different solvents at 25 °C[162]

(11)(a) R = NO_2
(b) R = $COCH_3$
(c) R = H
(d) R = CH_3
(e) R = OCH_3



Solvent	**11a**	**11b**	**11c**	**11d**	**11e**
n-Hexane	21.2	5.37	1.08	0.509	0.435
Acetonitrile	92.2	21.6	6.28	5.35	3.90
Ethanol	158	45.0	10.0	12.2	
1-Propanol	228		19.6		
2-Propanol		64.9		13.2	14.8
TFE[a]	3520	867	438	291	326
HFP[b]	13100	3080	1690	988	1880
Water	25000	8870	4950	3690	5560

[a] 1,1,1-Trifluorethanol.
[b] 1,1,1,3,3,3-Hexafluoro-2-propanol.

These rate accelerations were explained in terms of hydrophobicity[11]. The influences of a solute on the internal structure of the solvent are summarized in the terms 'chaotropic' and 'anti-chaotropic'. Chaotropic agents are compounds (mostly salts) which destroy the ordered structure of liquid water by forming hydrogen bonds; anti-chaotropic agents are compounds which stabilize the ordered structure of water[199]. By demonstrating that cycloadditions can further be accelerated by adding 'anti-chaotropic' salts such as lithium chloride ('chaotropic' salts like guanidinium chloride lead to retardation)[200,201], it was shown that it must be hydrophobic effects which cause these changes in reactivity[12].

There are numerous alternative explanations for the observed Diels–Alder reactions in water. It was suggested that catalysis with amphiphilic compounds may be due to micellar catalysis[202–205]. This notion inspired some authors to raise aggregation phenomena as general explanations for the aqueous acceleration of Diels–Alder reactions[206–208]. Other studies suggest that 'hydrophobic packing'[200,201,209] and 'aggregation'[12] induce pre-association of the reactants. Although it is likely that the lifetime of such encounter complexes of non-polar molecules in water exceeds that in organic solvents, this pre-association is unlikely to be strong enough to be held responsible for the observed rate effects; this is supported by kinetic measurements for an intramolecular Diels–Alder reaction (Table 11, entry F). Despite the fact that the diene and the dienophile are already associated, water is still capable of accelerating the reaction by a factor of 153 compared with *n*-hexane[168].

Other authors have repeatedly invoked the 'internal pressure' of water as an explanation for the rate enhancement of Diels–Alder reactions in water[138,210,211]. These studies were inspired by the large effects of external pressure on the rates of cycloadditions[80,212,213]. However, the internal pressure $p_i = (\delta E/\delta V)_T$[214,215] of water is very low (due to the open and relatively flexible hydrogen-bond network of water, a small change in volume of the solvent does not require much energy)[5] and does not seem to offer a good explanation for the effect of water on Diels–Alder reactions. The cohesive energy density $ced = (\Delta H_{vap} - RT)/V_M$ of water is another term used to explain solvent effects in

Diels–Alder reactions. This term describes how much energy is needed for evaporation of the solvent per unit of volume[168,216] and represents a measure of the internal water–water interactions. In contrast to the internal pressure, the *ced* of water is extremely high due to the large number of hydrogen bonds per unit volume. Since solvation and cavity formation lead to the rupture of solvent–solvent interactions, the *ced* essentially quantifies solvophobicity and hydrophobicity, and has been used successfully for describing solvent effects on Diels–Alder reactions[217]. These studies stress the importance of hydrophobic interactions. The significance of these and the relative unimportance of internal pressure is further supported by the observation that Diels–Alder reactions in water are less accelerated by pressure than those in organic solvents, which is in line with the notion that pressure diminishes hydrophobic interactions.

III. REACTIONS IN WATER

A. Reactivity

The reasons for the observed rate accelerations of Diels–Alder reactions in aqueous media were elucidated mainly by quantum chemical methods. In one of the first studies, the energy lowering of the transition structure by water complexation was revealed by Monte Carlo simulations[119]. Going down from the transition structure to the reactants as well as to the product, the minimum energy reaction path (MERP) of the Diels–Alder reaction of methyl vinyl ketone with cyclopentadiene in the gas phase was determined by means of *ab initio* computations. The resulting structures along the MERP were then 'solvated' employing three solvents (water, methanol and propane)[163]. Two main conclusions followed from this study. Firstly, the change in the total dipole moment along the MERP is significant; the dipole moments for methyl vinyl ketone, the transition structure and the product are 3.06, 3.44 and 2.98 D, respectively. As a consequence, the transition structure interacts more strongly with the solvents than the reactants or the product. Secondly, this finding is also supported by the computed relative energy changes. The predicted stabilization of the transition structure in water relative to propane of 4.2 kcal mol^{-1} compares well with the observed rate data, which gave a 3.8 kcal mol^{-1} lowering of the Gibbs free enthalpy of activation in water relative to *iso*-octane[11]. The difference in Gibbs enthalpy of solvation of the initial state and the product amounted to 1.1 kcal mol^{-1} in favour of the product. This estimate is in excellent agreement with the difference in Gibbs enthalpy, derived from experiments, of the transfer from the gas phase to water between initial and product state for the Diels–Alder reaction of ethene with butadiene ($\Delta\Delta G_t = 1.5$ kcal mol^{-1}) and with isoprene ($\Delta\Delta G_t = 1.3$ kcal mol^{-1})[119]. Further analysis showed that, although the number of hydrogen bonds to the carbonyl oxygen remains around 2–2.5 during the reaction, the strength of each bond is 1–2 kcal mol^{-1} greater at the transition structure. This reflects the sensitivity of hydrogen bonding to small charge variations[218]. The main consequence is that the aqueous acceleration of the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone contains a significant non-hydrophobic component which derives from enhanced polarization of the transition structure due to stronger hydrogen bonds at the carbonyl oxygen.

Analogous studies on the dimerization of cyclopentadiene in water revealed a stabilization of the transition structure relative to the initial structure as a result of a difference in solvation of 1.7 kcal mol^{-1}[119]. Unfortunately, at least to our knowledge, reliable experimental data for this process are not available. Recently, in a similar approach[219], the Gibbs enthalpies of hydration of the Diels–Alder reaction of cyclopentadiene with isoprene and methyl vinyl ketone were determined. Surprisingly, it was observed that water stabilized the transition structure of the cyclopentadiene + isoprene reaction more than that of the

cyclopentadiene + methyl vinyl ketone reaction (4.6 vs 3.5 kcal mol^{-1}) relative to the initial state. This trend opposes the experimental data collected in Table 11, which seem to indicate that the aqueous acceleration diminishes when the hydrogen-bonding interactions become less effective. The authors attributed the transition structure stabilization in the non-hydrogen bonding case to hydrophobic effects. However, these calculations suggest that the magnitude of the hydrophobic effect on Diels–Alder reactions in aqueous solution depends on the nature of the diene and the dienophile.

B. Effects on Selectivity

Three years after the first notion of the large effects of water on the rate of the Diels–Alder reactions[11], the same authors demonstrated that the *endo/exo* selectivity is also increased in water[44]. Studying the influence of salting-in and salting-out agents[220], the authors pinpointed hydrophobic effects as the most important contributors to the enhanced *endo/exo* selectivities[209] because hydrophobic effects are assumed to stabilize the more compact *endo*-transition structure more than the *exo*-transition structure. This difference in compactness of both structures is evident from the well-known smaller activation volume of the *endo*-cycloaddition (*vide supra*)[212]. Additionally, the high polarity of water significantly enhances the *endo/exo* selectivity[210].

Likewise, in the reactions of amphiphile-like reactants in aqueous solutions one finds an increased preference for the *endo*-adduct. This was attributed to 'orientational effects' within the micelles that are presumed to be present in the reaction mixtures[202]. Although the existence of some type of aggregates cannot be excluded under these conditions, other studies have clearly demonstrated that micelle formation is not the reason for the improved selectivities[221]. In contrast, it was shown that micellar aggregates tend to diminish the preference for the *endo*-adduct[44]. Studies dealing with solvent effects on the *endo/exo* selectivity of Diels–Alder reactions revealed the importance of hydrogen bonding in addition to the already mentioned solvophobic interactions and polarity effects. These findings are supported by computer simulations[222] and by the analogy to Lewis acid catalysis which is known to enhance the *endo/exo* ratio dramatically (*vide supra*).

In conclusion, the special influence of water on the *endo/exo* selectivity stems from the fact that all effects favouring the *endo*-adduct are combined in this solvent: (1) strong hydrogen bonding, (2) polarity and (3) hydrophobicity. Water also increases the diastereofacial-[143,161,223] and the regioselectivity[223,224] of Diels–Alder reactions. Mechanistic investigations on the reaction between cyclopentadiene and methyl acrylate emphasized the importance of hydrogen-bond donor characteristics and polarity[143,161,225].

C. Additives

In the last paragraphs we presented evidence for the rate accelerations of Diels–Alder reactions in pure water. In the following we will discuss further rate accelerations and stereoselectivity enhancements by additives[11]. Chaotropic salts or salting-out agents lower the solubility of non-polar compounds in water mainly by preventing solute cavity formation. Anti-chaotropic or salting-in agents are involved in direct solvation of the solute[226,227]. The resulting increased solubility leads to decreased hydrophobic interactions[12]. In general, salt effects on Diels–Alder reactions correlate strongly with the size of the anion of the salt[228]. The origins of the rate accelerations caused by salt effects were investigated for the reaction of *cis*-dicyanoethene with cyclopentadiene under lithium chloride catalysis[229]. It was found that the modest decrease in Gibbs enthalpy of activation results from a dramatic decrease in the activation enthalpy that is almost completely

compensated by an increase in the activation entropy. This trend can be ascribed to the reduced ability of aqueous lithium chloride solutions to form hydrophobic hydration shells. Consequently, hydrophobic interactions become larger and enthalpy driven.

The addition of alcohols, especially in small amounts, also changes the reaction rates[162,216]. It was suggested that the alcohol molecules disturb the hydrophobic hydration shell leading to enhanced hydrophobic interactions[168]. At higher co-solvent concentrations direct alcohol–reagent contacts are suggested to occur and the rate constant decreases sharply until the value found for the pure alcohol is reached[168]. The increased hydrophobic interactions are supported by a good correlation between the solubility of the reagents in alcohol–water mixtures and the rate constant. From this relation the change in solvent-accessible surface between the initial state and the activated complex in the dimerization of cyclopentadiene and in the reaction of 9-(hydroxymethyl)anthracene with *N*-methylmaleimide in alcohol–water mixtures was estimated[230]. It was concluded that solvation effects on hydrophobic surfaces in the transition structures are similar to those of normal molecules, at least in these reactions. Besides these additives, the effects of salt solutions in ethanol[208] and of the addition of sugars on aqueous Diels–Alder reactions[231] were also the topics of several investigations.

While widespread investigations on rate accelerations in Diels–Alder reactions by additives were highly successful, the effect of these additives on the selectivities of [4 + 2]-cycloadditions in water has not received much attention. Scattered reports on this aspect point to an increase in *endo/exo* selectivity by additives, due to an increase in the hydrophobic interactions[209].

In a Lewis acid catalysed Diels–Alder reaction, the first step is coordination of the catalyst to a Lewis basic site of one of the reactants, e.g. to the carbonyl oxygen of the dienophile. The most common solvents for these protocols are inert non-polar liquids such as dichloromethane or benzene. Protic solvents, and water in particular, are avoided because of their strong interactions with the catalyst. Other catalysed organic reactions, such as hydroformylations, on the other hand are not problematic and they are carried out industrially in water. This apparent paradox results from the difference in hardness of the reactants and the catalyst.

According to the hard and soft acids and bases (HSAB) principle, developed by Pearson in 1963[232,233], Lewis acids and Lewis bases are divided into two groups: hard and soft. Pearson correlated the hardness of acids and bases with their polarizability, whereby soft acids and bases are large and easily polarizable, and *vice versa*. A selected list of Lewis acids ordered according to their hardness in aqueous solution is presented in Table 18. The HSAB principle predicts strong association of 'like' partners. Hard acid–soft base complexes mainly result from electrostatic interactions, while soft acid–soft base complexes are dominated by covalent interactions.

The described difference between hard–hard and soft–soft interactions is also supported by thermodynamic analysis. In water, hard–hard interactions are usually endothermic and occur only as a result of a gain in entropy, originating from a liberation of water molecules from the hydration shells of the Lewis acid and the ligand. In contrast, soft–soft interactions are mainly enthalpic in origin and are characterized by a negative change in entropy[234].

Several alternative attempts were made to quantify Lewis-type interactions[235,236]. Following the HSAB principle, the applicability of a one-parameter Lewis acidity scale will inevitably be restricted to a narrow range of structurally related Lewis bases; addition of parameters results in more general relationships[237–239]. The quantitative prediction of the gas-phase stabilities of Lewis acid–Lewis base complexes is still difficult. Hence the interpretation, not to mention the prediction, of solvent effects on Lewis acid–Lewis base interactions is often speculative.

TABLE 18. Classification of the hardness in aqueous solution of some selected Lewis acids according to the HSAB principle[232]

Hard	Borderline	Soft
H^+	Fe^{2+}	Cu^+
Fe^{3+}	Ni^{2+}	Hg^+
Co^{3+}	Cu^{2+}	Cd^+
Al^{3+}	Zn^{2+}	
La^{3+}		

The most effective Lewis acid catalysts for Diels–Alder reactions are 'hard' cations. Not surprisingly, they coordinate to hard nuclei of the reacting system, typically to oxygen atoms. Consequently, 'hard' solvents such as water are likely to affect these interactions significantly. Solvents are able to affect Lewis acid–Lewis base equilibria through a number of non-covalent interactions. First, the solvent can act itself as a Lewis base by coordinating to the catalyst. Aprotic and non-polar solvents coordinate relatively weakly to catalysts, whereas polar solvents exhibit much stronger interactions. Water with its high polarity, its large chemical hardness and its effective hydrogen-bonding activity is, as a bulk liquid, one of the strongest Lewis basic solvents. The interactions between catalysts and solvents have to be disrupted before the Diels–Alder reactants can coordinate to the added Lewis acid[240]. Furthermore, steric interactions between the coordinated reactant and solvent molecules are important in determining the stability of the complex[241]. Consequently, catalysis by Lewis acids in strongly coordinating solvents is likely to be less effective.

The second important solvent effect on Lewis acid–Lewis base equilibria concerns the interactions with the Lewis base. Since water is also a good electron-pair acceptor[129], Lewis-type interactions are competitive. This often seriously hampers the efficiency of Lewis acid catalysis in water. Thirdly, the intermolecular association of a solvent affects the Lewis acid–base equilibrium[242]. Upon complexation, one or more solvent molecules that were initially coordinated to the Lewis acid or the Lewis base are liberated into the bulk liquid phase, which is an entropically favourable process. This effect is more pronounced in aprotic than in protic solvents which usually have higher cohesive energy densities. The unfavourable entropy changes in protic solvents are somewhat counterbalanced by the formation of new hydrogen bonds in the bulk liquid.

Finally, the solvent also interacts with Lewis acid and Lewis base sites that are not directly involved in mutual coordination, thereby altering the electronic properties of the complex. For example, delocalization of charges onto the surrounding solvent molecules causes ions in solution to be softer than in gas phase[241]. Again, water is particularly effective in this respect because it can act as an efficient electron-pair acceptor and donor.

In summary, water appears as an extremely unsuitable solvent for coordination of hard Lewis acids to hard Lewis bases, as it strongly solvates both species and hinders their interaction. Hence, catalysis of Diels–Alder reactions in water is expected to be difficult due to the relative inefficiency of the interactions between the Diels–Alder reactants and the Lewis acid catalyst. On the other hand, the high stereoselectivities and yields observed in biosyntheses, with water as *the* solvent, indicate that these rationalizations cannot entirely be true. As a matter of fact, we will demonstrate in the following that Lewis acid catalysis in water is not only possible, but also allows for effective as well as environmentally friendly reaction conditions.

The appreciable rate effects in water are generally overpowered by the large accelerations found for Lewis acid catalysis in normal electron demand Diels–Alder

reactions[120,199,243]. In analogy to the hydrogen-bonding effect, Lewis acids can decrease the HOMO–LUMO gap between the diene and the dienophile and thereby increase the reaction rate. Taking into consideration the effects of water and Lewis acids on the Diels–Alder reaction, one may ask what would be the result of a combination of these two effects. If they are additive, will huge accelerations follow? How does water affect the Lewis acid catalysis and what is the influence of the Lewis acid on the enforced hydrophobic interactions and hydrogen bonding? These and related questions are addressed below.

D. Catalysis

1. General aspects

The demand for environmentally friendly chemistry and its widespread applicability have made water an increasingly popular solvent for organic transformations[13]. Mixtures of water and other solvents such as tetrahydrofuran are now commonly employed for a number of organic transformations[244]. For instance, the Lewis acid catalysed aldol reaction of silyl enol ethers, commonly known as the Mukaiyama aldol reaction, which was firstly reported in the early seventies, can be carried out in such media[245]. With titanium tetrachloride as the catalyst this reaction proceeds regioselectively in high yields, but the reaction has to be carried out strictly under non-aqueous conditions in order to prevent decomposition of the catalyst and hydrolysis of the silyl enol ethers. In the absence of the catalyst it was observed that water had a beneficial influence on this process (Table 4, entry D)[25]. Nevertheless, the yields in the uncatalysed version were still unsatisfactory. Improved results were obtained with water-tolerant Lewis acids. The first reported example for Lewis acid catalysis in aqueous media is the hydroxymethylation of silyl enol ethers with commercial formaldehyde solution using lanthanide triflates[246]. In the meantime, the influence of several lanthanide triflates in cross-aldol reactions of various aldehydes was examined[247–249]. The reactions were most effectively carried out in 1 : 9 mixtures of water and tetrahydrofuran with 5–10% $Yb(OTf)_3$, which can be reused after completion of the reaction (Table 19, entry A). Although the realization of this reaction is quite simple, the choice of the solvent is crucial (Table 20).

While the yields are rather poor in pure organic solvents, the reaction is best carried out in an organic solvent containing 10–20% water. Higher percentages of water decrease again the yields of aldol products which was attributed to the competitive hydrolysis of the silyl enol ether. Besides the catalysis of the Mukaiyama aldol reaction by lanthanide triflates, allylation reactions also benefit from the presence of water. The synthesis of homoallylic alcohols via a Lewis acid catalysed reaction of organometallic reagents with a carbonyl compound in organic media has been reported many times (Table 19, entry B)[250]. This reaction can also be carried out in aqueous mixtures of tetrahydrofuran, ethanol or acetonitrile catalysed by $Sc(OTf)_3$ and $Yb(OTf)_3$[251]. The catalysts in these reactions can be recovered without loss of activity[248].

Furthermore, the use of a Lewis acid promoter leads to increased stereoselectivities (Table 19, entry C)[252,254]. Compared to the aprotic reaction, where allyl silane was used instead of allyl bromide and indium chloride, an almost complete reversal of the diastereoselectivity was found. It was demonstrated recently that the Lewis acid catalysed allylation reaction can be carried out efficiently without any organic solvent in saturated ammonium chloride solution[255]. Finally, Lewis acid catalysed Mannich reactions can be carried out conveniently in mixtures of organic solvents and water. However, the exact role of the Lewis acid catalyst has not been clarified (Table 19, entry D)[253]. The same reaction can be carried out in pure water with catalysis by indium trichloride[256].

TABLE 19. Lewis acid catalysed organic transformations in aqueous media

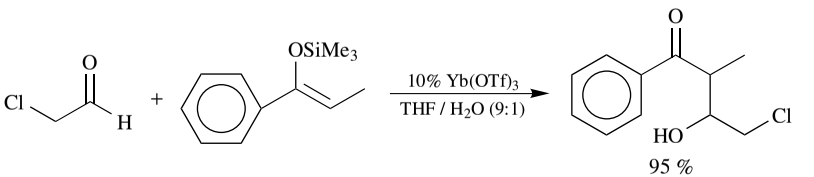
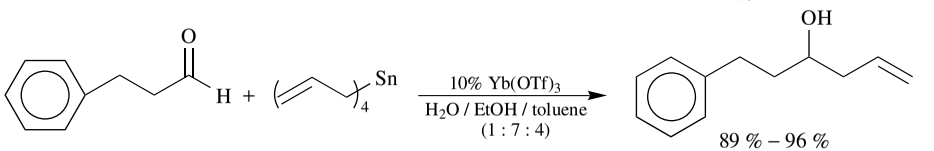
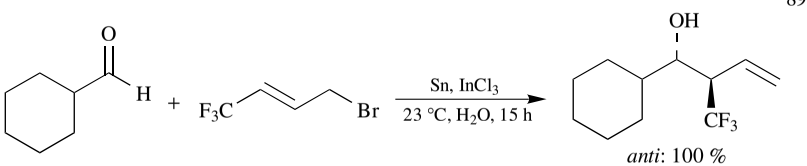
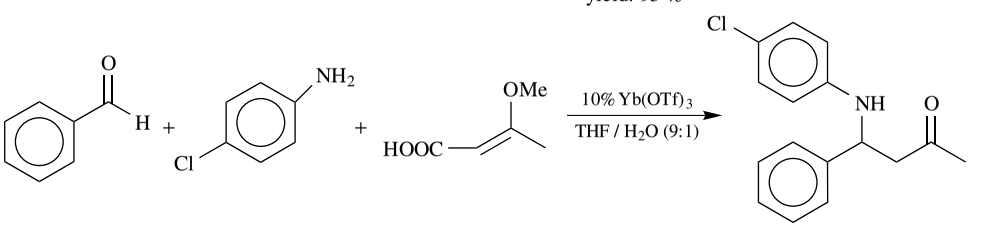
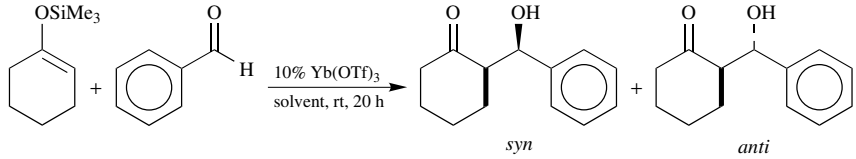
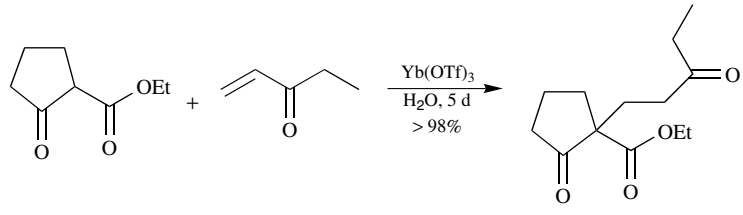
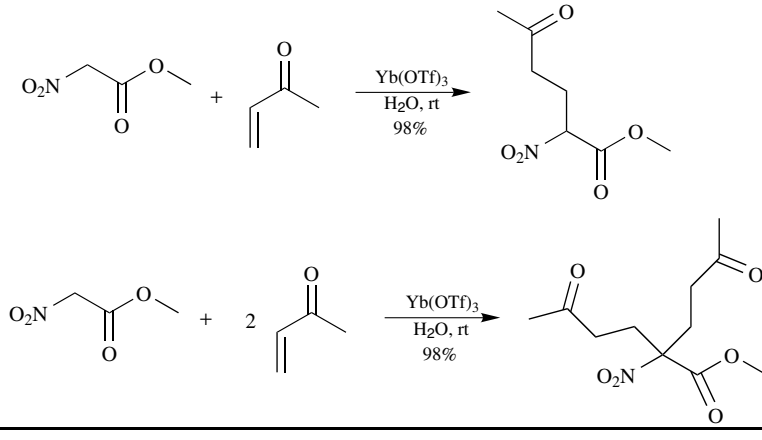
Entry	Reaction	Reference
A	 95 %	247
B	 89 % – 96 %	248
C	 *anti*: 100 % yield: 95 %	252
D		253

TABLE 20. Effects of solvent on cross-aldol reactions[249]



Solvent	Yield(%)	[*syn*]/[*anti*]
CH_2Cl_2	10	—
THF	10	—
CH_2CN	5	—
DMF	56	73/27
H_2O–THF (1 : 4)	91	73/27

TABLE 21. Lewis acid catalysed reactions in pure water

Entry	Reaction	Reference
A		257
B		258

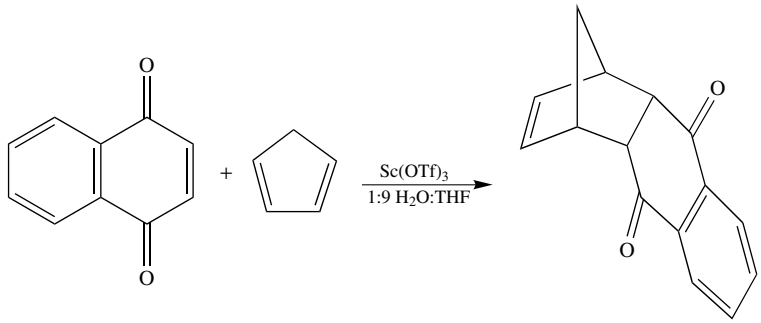
There are only few examples of organic reactions catalysed effectively by Lewis acids which can be carried out in pure water without any organic co-solvent. While water can be used successfully for the uncatalysed Michael addition of 1,3-diketones (Table 4, entry D)[22], the corresponding reaction of β-ketoesters does not give satisfactory results. On the other hand, the $Yb(OTf)_3$ catalysed Michael reaction of various β-ketoesters (Table 21, entry A)[257] and α-nitroesters (Table 21, entry B)[258] takes place.

Besides these, the metal-ion catalysed hydrolyses of carboxylate esters[259–262], phosphate esters[263–268], amides[262,269–273] and nitriles[274–277] in water were studied extensively. Although the exact mechanism of these reactions is not clear, it was noted that the most important role of the catalyst is coordination of a hydroxide ion which acts as the nucleophile[277]. Furthermore, the activation of the substrate through coordination to the Lewis acidic metal centre also plays a role in the catalysis but it depends strongly on the substrate; for monodentate reagents, this interaction is not very efficient[278,279].

In summary, only a limited number of mechanistic studies of Lewis acid catalysed reactions in water have been published. Most of these studies make use of a lanthanide ion whose coordination to a carbonyl group is assumed. It was noted that in aqueous solutions donor groups containing neutral oxygen or nitrogen atoms generally bind *only* when they are included in multidentate ligands with at least one or two other groups with negatively charged oxygens[280]. Hence, instead of direct Lewis acid catalysis, the beneficial effect might well be indirect. Solutions of Lewis acids in water are modestly acidic, which indicates the simultaneous presence of lanthanide-ion coordinated hydroxide ions as well as hydronium ions. Clearly, detailed mechanistic studies are required to identify the mechanisms of Lewis acid catalysis in aqueous solutions.

2. Diels–Alder reactions

In the preceding paragraphs the advantages of water in uncatalysed Diels–Alder reactions were outlined. An important question is whether these advantages can be transferred to Lewis acid catalysed reactions as well. Since the majority of Diels–Alder reactants are likely to have a negligible tendency to interact with Lewis acid catalysts in water, this issue was addressed only recently. The first step was the development of water-tolerant catalytic systems for [4 + 2]-cycloadditions, and there are now a few examples of Lewis acid catalysed Diels–Alder reactions that not only tolerate the presence of small amounts of water[281–284] but even benefit from it[285]. An example of a Lewis acid catalysed Diels–Alder reaction carried out in water:THF mixture is presented in Scheme 12[286].

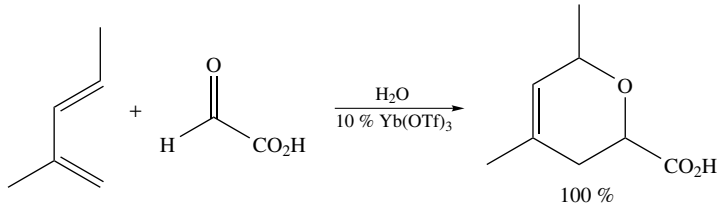


yield: 93%; [*endo*]/[*exo*] = 100/0

SCHEME 12. A water-tolerant Lewis acid catalysed Diels–Alder reaction[286]

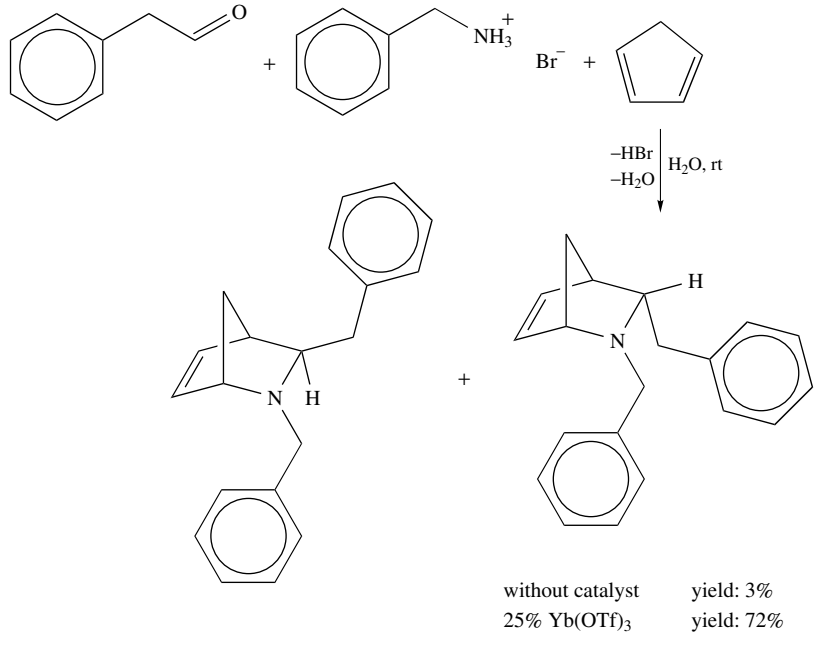
Unfortunately, a comparison with the uncatalysed reaction was not carried out in that particular study. The first comparison between a catalysed and an uncatalysed Diels–Alder reaction was published only in 1994[287]. Within the scope of this investigation several

lanthanide triflates or chlorides were used as catalysts, and their effectivities were checked by comparison with the uncatalysed reactions in aqueous media. While in the presence of ytterbium triflate a quantitative reaction was observed, pure water only gave 55% yield (Scheme 13)[287]. Other lanthanide(III) triflates were also catalytically active.



SCHEME 13. A Lewis acid catalysed hetero-Diels–Alder reaction in aqueous solution

Another example of the use of Lewis acids in organic reactions in water is the lanthanide(III) triflate catalysed aza-Diels–Alder reaction, exemplified in Scheme 14. In this reaction the hetero-dienophile is formed *in situ* from a primary ammonium hydrochloride and a carbonyl compound followed by the actual Diels–Alder reaction[288,289]. This type of reaction proceeds readily in aqueous media[290–296], and a dramatic increase in the yield upon addition of lanthanide triflates was observed[288,289]. The exact role of the catalyst, however, is not entirely clear. Although it was suggested that the catalyst binds to the dienophile, other mechanisms, such as simple proton catalysis, are also plausible. Moreover, these reactions are further complicated since they are often heterogeneous.

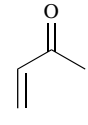
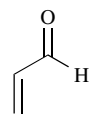
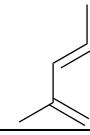
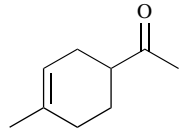
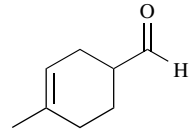
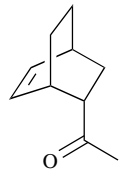
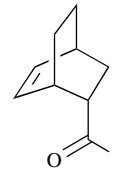
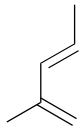
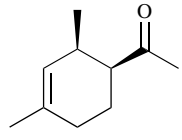
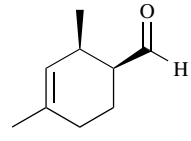
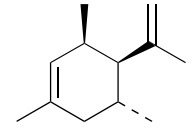


SCHEME 14. Lanthanide(III) triflate catalysed aza-Diels–Alder reaction in water[288]

The reverse reaction is catalysed by copper sulphate in an ethanol/water (50 : 50) mixture[297,298]. Indium(III) chloride catalysis of Diels–Alder reactions was also reported, but the effects were poor and comparison to uncatalysed reactions was made only in a few cases[299,300]. A very versatile Lewis acid catalyst for such reactions is methylrhenium trioxide (MTO)[300]. This catalyst can be used without a solvent, in pure organic solvents like chloroform and even in pure water. While the catalyst is active in the latter two solvents (Table 22), it gives the best results in water (Table 23).

Considering that the activity of a Lewis acid depends strongly on the stability of the acid–base complex and that the complexation is notoriously hampered by chemically 'hard' solvents like water, it is clear that reactions of bidentate dienophiles can be catalysed very efficiently[36]. Prototypical are the derivatives of 3-phenyl-1-(2-pyridyl)-2-propen-1-ones (*vide infra*). Their Diels–Alder reactions (Table 24) clearly show that the accelerating solvent effect of water is still present in the Lewis acid catalysed reactions, and that the Lewis acid activity is not necessarily hindered by the solvent[301]. While

TABLE 22. MTO-catalysed Diels–Alder reactions in water (A) and in chloroform (B)[a] with yields and [*endo*]/[*exo*] ratios

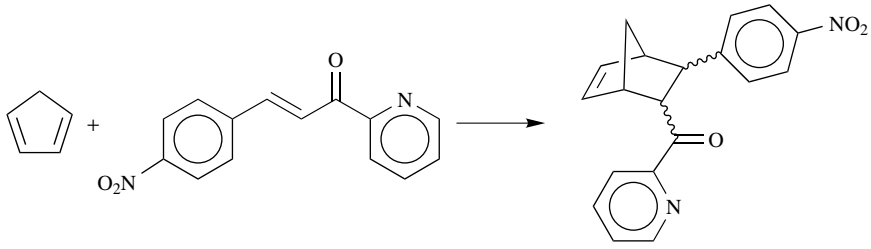
			
	 A: 2.5 h, 90% [> 99 : <1] B: 18 h, 90% [> 99 : <1]	 2.5 h, 91% [> 99 : <1] 18 h, 90% [> 99 : <1]	
	 A: 16 h, 91% [> 99 : <1] B: 4 d, 94% [>> 99 : <<1]	 16 h, 90% [>> 99 : <<1] 4 d, 90% [> 99 : <1]	
	 A: 4 h, 90% [> 99 : <1] B: 12 h, 94% [98 : 2]	 16 h, 90% [>> 99 : <<1] 4 d, 94% [>> 99 : <<1]	 10 h, 90% [95 : 5] 7 d, 90% [80 : 20]

[a]Major products, yields and *endo/exo* ratios are given[300].

TABLE 23. Additive effects of MTO and water

Conditions	*endo/exo* rate	$t_{1/2}$ (min)
neat	3.15 : 1	45
1% MTO	15.4 : 1	20
water	20 : 1	25
water, 1% MTO	>99 : 1	14

TABLE 24. Second-order rate constants ($M^{-1}\,s^{-1}$) for the Diels–Alder reaction of 3(4-nitrophenyl)-1-(2-pyridyl)-2-propen-1-one in different media at 25 °C



Entry	Solvent	$10^5 k$	
		Uncatalysed	With 10 mM Cu^{2+}
1	MeCN	1.32	
2	EtOH	3.83	7.69×10^4
3	H_2O	402	3.25×10^5

copper(II) nitrate turned out to be the catalyst of highest effectivity, the nitrates of Co^{2+}, Ni^{2+} and Zn^{2+} were good promoters as well.

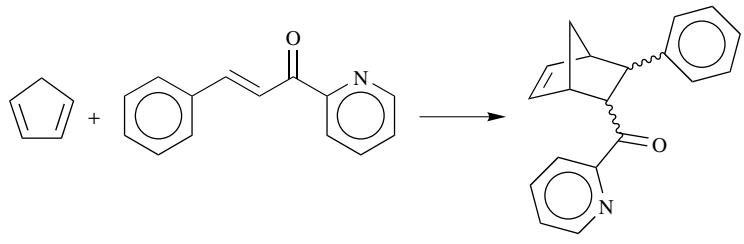
In order to exclude simple proton catalysis, this study also examined the catalytic activity of Brønsted acids. It was noted that a 10 mM solution of hydrochloric acid has only a small catalytic effect (second-order rate constant $k_2 = 7.62 \times 10^{-2} M^{-1}\,s^{-1}$; compare Table 24). Another dienophile derivative also showed changes in rate (Table 25) and in the *endo/exo* selectivity (Table 26)[302]. A dramatic acceleration and an increase in the selectivity in 1,1,1-trifluoroethanol was observed in the presence of Cu^{2+} (Table 25).

In this paragraph it was demonstrated that Lewis acid catalysis can be extended to aqueous media. Although water is likely to alter the complexation step, the use of Lewis acids is not restricted to organic solvents. Most importantly, the advantageous effects of Lewis acid catalysis and water are often additive. Since the development of catalytic systems which are water-tolerant or even benefit from the presence of water is still in its infancy, these results are highly promising and open new avenues for future research.

3. Non-Lewis acid catalysis

Besides metal containing Lewis acids, non-metal additives have also found application in catalysis. These studies are quite pertinent to the development of artificial enzyme-like catalysts. As there is a large number of Lewis basic sites in living systems able to be involved in hydrogen bonds, the analysis of the catalytic activity of hydrogen bonding additives would give some indication as to the existence of Diels–Alder reactions

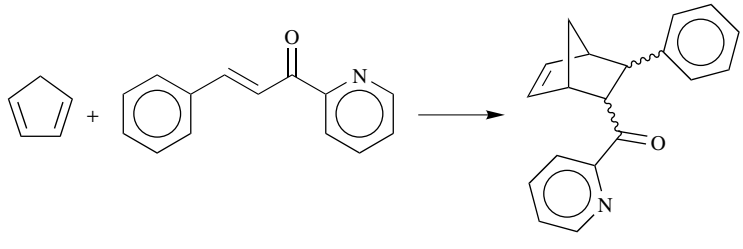
TABLE 25. Relative second-order rate constants $k(M^{-1}\,s^{-1})$ for the Diels–Alder reaction shown below in different media at 25 °C[302]



Entry	Solvent	Uncatalysed	With 10 mM Cu^{2+}
1	MeCN	1	158.000
2	EtOH	2.7	54.900
3	H_2O	287	691.000
4	CF_3CH_2OH	482	1.110.000[a]

[a]Only 0.1 mM catalyst was used.

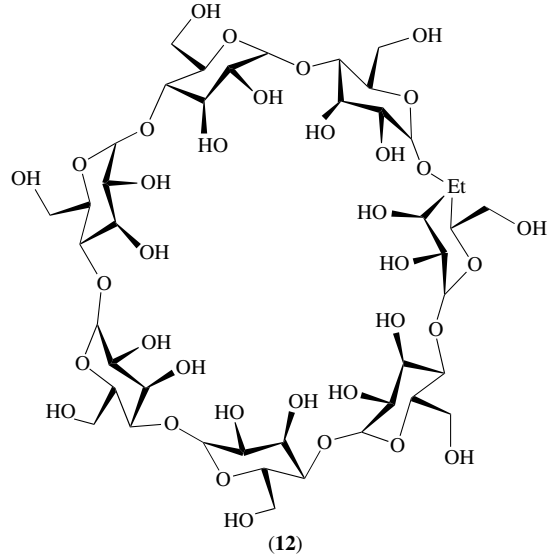
TABLE 26. *Endo/exo* selectivities for the reaction below in the absence and presence of a Cu(II) catalyst[302]



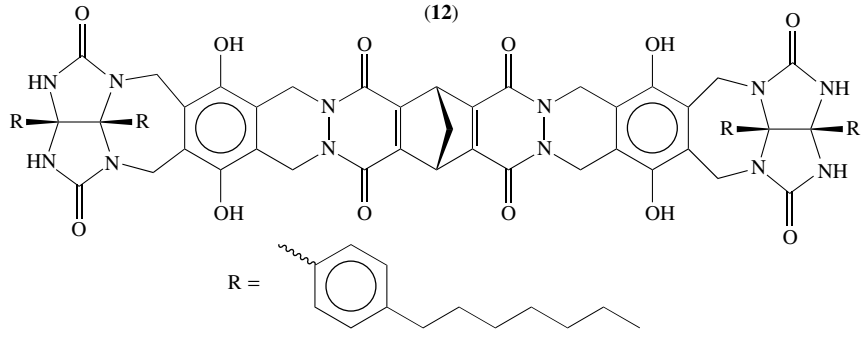
Entry	Solvent	Uncatalysed	With 10 mM Cu^{2+}
1	MeCN	67/33	94/6
2	EtOH	77/23	96/4
3	H_2O	84/16	93/7

in biosynthesis[55]. Catalytic non-metal additives like cyclodextrins (**12** in Scheme 15)[221], large organic compounds (**13a** in Scheme 15)[303] which dimerize to *self-assembled molecular capsules* (**13b** in Scheme 15) and other catalytically active macrocycles (**14** in Scheme 15)[124] are able to form micelles. The general interactions of such additives with the reactants will be discussed in the following.

Surfactant molecules (also called amphiphiles or detergents) combine a polar or ionic head and a non-polar tail within the same molecule. The non-polar part, which is typically made up of one or more alkyl chains, causes these compounds to be sparingly soluble in water, whereas the polar or ionic part interacts strongly with water. Upon increasing the concentration of the amphiphilic compound in water, the solubility limit will be reached at a certain point and phase separation will set in. Due to the efficient interactions between the polar headgroups and the surrounding water molecules, a complete phase separation is usually unfavourable. Instead, the process halts in an intermediate stage

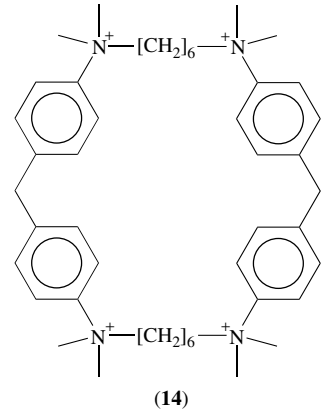


(**12**)



(**13a**)

(**13b**)



(**14**)

SCHEME 15. Catalytically active encapsulating species

with concomitant formation of aggregates of amphiphilic material, wherein the non-polar parts stick together and are shielded from water, with the headgroups located in the outer regions of the aggregate. A multitude of different aggregates can be formed this way[304]. The morphology of these assemblies is mainly determined by the shape of the individual surfactant molecules. The formation of micelles sets in after a certain critical concentration of surfactant, the critical micelle concentration, has been reached. Beyond this, the concentration of monomeric surfactant molecules will result in an increase in the number of micelles, while the concentration of monomeric surfactant remains almost constant[305].

Micelles are extremely dynamic aggregates. Ultrasonic, temperature and pressure jump techniques have been employed to study various equilibrium constants. Rates of uptake of monomers into micellar aggregates are close to diffusion-controlled[306]. The residence times of the individual surfactant molecules in the aggregate are typically in the order of 1–10 microseconds[307], whereas the lifetime of the micellar entity is about 1–100 miliseconds[307]. Factors that lower the critical micelle concentration usually increase the lifetimes of the micelles as well as the residence times of the surfactant molecules in the micelle. Due to these dynamics, the size and shape of micelles are subject to appreciable structural fluctuations.

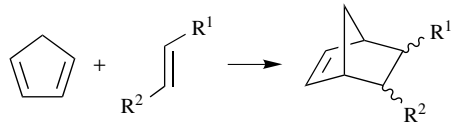
One of the most important characteristics of micelles is their ability to enclose all kinds of substances. Capture of these compounds in micelles is generally driven by hydrophobic, electrostatic and hydrogen-bonding interactions. The dynamics of solubilization into micelles are similar to those observed for entrance and exit of individual surfactant molecules, but the micelle-bound substrate will experience a reaction environment different from bulk water, leading to kinetic medium effects[308]. Hence, micelles are able to catalyse or inhibit reactions. The catalytic effect on unimolecular reactions can be attributed exclusively to the local medium effect. For more complicated bimolecular or higher-order reactions, the rate of the reaction is affected by an additional parameter: the local concentrations of the reacting species in or at the micelle.

On the basis of the pronounced non-polar character of the majority of Diels–Alder reactants, efficient micellar catalysis of their reaction might be anticipated. The first time a micellar catalysed Diels–Alder reaction was mentioned, not the micelle itself, '*but some type of micellar catalysis, resulting in mutual binding of reactants*' was suggested to be responsible for the observed rate accelerations[202]. Further investigations on the catalytic activity of micelles showed that several species which are able to form micelles in aqueous solution lead to higher yields in intramolecular Diels–Alder reactions[206]. In detailed studies of the effects of β-cyclodextrin **12** on the rates of Diels–Alder reactions[124,221] it became clear that the influence of cyclodextrin micelles can lead either to inhibition or to acceleration (Table 27).

The results in Table 27 were explained by the changes in hydrophobicity of the dienophile. For optimum catalytic effects a discrete range of hydrophobicity and polarity is required. While an increase in hydrophilicity of polar dienophiles (Table 27, entries 1–3) leads to smaller rate enhancements, the larger hydrophobic alkoxy group on less polar dienophiles (Table 27, entries 5–8) leads to smaller catalytic activities of the cyclodextrin[125]. Quite similar are the effects of **13a**, but the investigation of its catalytic activity is much less extensive[303].

Comparable to the influence of such structural well-defined macrocycles, cell-free extracts[55] as well as antibodies[309,310] also show strong catalytic effects. Hence, the use of organic compounds, which are able to form micelles, being active in water and easy to handle could lead to new insights and unexpected results for catalytic Diels–Alder

TABLE 27. Rate constants $k(M^{-1}\,s^{-1})$ for Diels–Alder reactions of cyclopentadiene with several dienophiles in methanol, water and a β-cyclodextrin **12** water solution [125]



Entry	Dienophile		Methanol	Water	β-Cyclodextrin–water[a]
	R^1	R^2			
1	COOEt	COOEt	1.37	148	9270
2	COOH	COOEt	1.51	47.2	1490
3	COOH	COOH	1.24	24.1	172
4	COOH	$CO_2C_6H_{11}$-*c*	1.03	31.8	177
5	H	COOMe	0.031	238	235
6	H	COOEt	0.031	225	121
7	H	COOPr	0.031	135	23.9
8	H	COOBu	0.031	100.3	38

[a][β-cyclodextrine] $= 9 \times 10^{-3}$ mol l^{-1}.

reactions. A first step in this direction was taken recently by a combination of Lewis acid and micellar catalysis in water[10]. The Lewis acid Cu(II) dodecyl sulphate (0.01 mol%), a micelle-forming compound, accelerated the Diels–Alder reaction depicted in Table 24 by a factor of 1,800,000 in water, relative to the uncatalysed reaction in acetonitrile.

IV. CONCLUSIONS

The present chapter aims at introducing the reader to the emerging field of organic synthesis in water as exemplified by the well-known Diels–Alder reaction. As this transformation is exceptionally well understood mechanistically and highly valuable for building complex structures, it lends itself to examining and probing the effects of aqueous media and other factors which influence the reactivities and selectivities.

Most notably, virtually all Diels–Alder reactions are accelerated in aqueous media. This observation is due to a complex array of intricate interactions comprised of hydrogen bonding, hydrophobicity and others of lesser significance. Hydrogen-bonding interactions, mostly with lone pairs of the reactants, lead, in analogy to Lewis acid catalysis, to a reduction in the HOMO–LUMO energy separation. However, this effect is much less pronounced than for Lewis acids, so that the enormous accelerations of up to 12,800-fold cannot be explained solely by cooperative hydrogen bonding in water. Additives which are able to deliver specific 'isolated' hydrogen bonds such as diols or ureas are less effective (accelerations of 6–8-fold in water vs 3–4-fold with the respective additives in chloroform). This supports the notion that hydrophobicity is also an important factor, a conclusion which is also amplified by the rate accelerations observed in cyclodextrins, micelles and other supramolecular aggregates.

A striking result is that the beneficial effects on the rates and selectivities are often additive, i.e. Lewis acid catalysis is possible even in water! Again, this may be understood in terms of an interplay between the strong donor–acceptor interactions of the, for instance, metal atom of a Lewis acid on the one hand, and the cavity-forming ability of water, which brings the reactions partners in close proximity, on the other.

As a consequence of these findings, *in vivo* Diels–Alder reactions may occur and may be catalysed by formation of various kinds of hydrogen bonds. This casts some doubt on the long-standing search for a specific 'Diels–Alder-ase' which has not yet been identified.

In summary, we hope to have demonstrated that aqueous media for organic reactions, specifically the Diels–Alder reaction, are neither a curiosity only applicable to 'unusual' transformations nor are they a limitation for catalysis. It is more than likely that the potential of water as an environmentally friendly and safe solvent will be used more effectively in the future for a large number of different reactions.

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VI. REFERENCES

1. D. Lenoir and J. O. Metzger, *Nachr. Chem. Tech. Lab.*, **47**, 291 (1999).
2. J. O. Metzger, *Angew. Chem., Int. Ed. Engl.*, **37**, 2975 (1998); *Angew. Chem.*, **110**, 3145 (1998).
3. C.-J. Li and T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997.
4. K. A. T. Silverstein, A. D. J. Haymet and K. A. Dill, *J. Am. Chem. Soc.*, **120**, 3166 (1998).
5. C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 2nd edn., VCH, Cambridge, 1990.
6. M. A. McCarrick, Y.-D. Wu and K. N. Houk, *J. Org. Chem.*, **58**, 3330 (1993).
7. W. Blokzijl and J. B. F. N. Engberts, *Angew. Chem., Int. Ed. Engl.*, **32**, 1545 (1993); *Angew. Chem.*, **105**, 1610 (1993).
8. S. Otto, F. Bertoncin and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **120**, 4238 (1998).
9. C.-J. Li, *Chem. Rev.*, **93**, 2023 (1993).
10. S. Otto, J. B. F. N. Engberts and J. C. T. Kwak, *J. Am. Chem. Soc.*, **120**, 9517 (1998).
11. D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, **102**, 7816 (1980).
12. R. Breslow, *Acc. Chem. Res.*, **24**, 159 (1991).
13. P. A. Grieco, *Aldrichim. Acta*, **24**, 59 (1991).
14. A. Lubineau, J. Augé and Y. Queneau, *Synthesis*, 741 (1994).
15. F. Fringuelli, R. Germani, F. Pizzo and G. Savelli, *Tetrahedron Lett.*, **30**, 1427 (1989).
16. F. Fringuelli, F. Pizzo and R. Germani, *Synlett*, 475 (1991).
17. F. Fringuelli, R. Germani, F. Pizzo, F. Santinelli and G. Savelli, *J. Org. Chem.*, **57**, 1198 (1992).
18. W. A. Herrmann and C. W. Kohlpaintner, *Angew. Chem., Int. Ed. Engl.*, **32**, 1524 (1993); *Angew. Chem.*, **105**, 1588 (1993).
19. M. Grosselin and C. Mercier, *J. Mol. Catal.*, **63**, L25 (1990).
20. T. H. Chan, C. J. Li, M. C. Lee and Z. Y. Wei, *Can. J. Chem.*, **72**, 1181 (1994).
21. A. Lubineau and J. Augé, *Tetrahedron Lett.*, **33**, 8073 (1992).
22. U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, **10**, 496 (1971); *Angew. Chem.*, **83**, 492 (1971).
23. C. Larpent and H. Patin, *Tetrahedron*, **44**, 6107 (1988).
24. A. Lubineau, *J. Org. Chem.*, **51**, 2142 (1986).
25. A. Lubineau and E. Meyer, *Tetrahedron*, **44**, 6065 (1988).
26. T. H. Chan, C. J. Li and Z. Y. Wei, *J. Chem. Soc., Chem Commun.*, 505 (1990).
27. E. T. Kool and R. Breslow, *J. Am. Chem. Soc.*, **110**, 1596 (1988).
28. V. Tychopoulos and J. H. P. Tyman, *Synth. Commun.*, **16**, 1401 (1986).
29. D. R. Adams and S. P. Bhatnagar, *Synthesis*, 661 (1977).

30. M. Rambaud, A. D. Vecchio and J. Villieras, *Synth. Commun.*, **14**, 833 (1984).
31. P. R. Schreiner, O. Lauenstein, I. V. Kolomitsyn, S. Nadi and A. A. Fokin, *Angew. Chem., Int. Ed. Engl.*, **37**, 1895 (1998); *Angew. Chem.,* **110**, 1993 (1998).
32. H. Shaw, H. D. Perlmutter, C. Gu, S. D. Arco and T. O. Quibuyen, *J. Org. Chem.*, **62**, 236 (1997).
33. Y. Yamamoto, S. Shiraki and D. Gao, *J. Chem. Soc., Perkin Trans. 2*, 1119 (1993).
34. V. Ramamurthy, *Tetrahedron*, **42**, 5753 (1986).
35. N. R. Bantu, T. G. Kotch and A. J. Lees, *Tetrahedron Lett.*, **34**, 2039 (1993).
36. J. B. F. N. Engberts, B. L. Feringa, E. Keller and S. Otto, *Recl. Trav. Chim. Pays-Bas*, **115**, 457 (1996).
37. J. J. Gajewski, J. Jurayj, D. R. Kimbrough, M. E. Gande, B. Ganem and B. K. Carpenter, *J. Am. Chem. Soc.*, **109**, 1170 (1987).
38. S. D. Copley and J. R. Knowles, *J. Am. Chem. Soc.*, **109**, 5008 (1987).
39. E. Brandes, P. A. Grieco and J. J. Gajewski, *J. Org. Chem.*, **54**, 515 (1989).
40. P. A. Grieco, E. B. Brandes, S. McCann and J. D. Clark, *J. Org. Chem.*, **54**, 5849 (1989).
41. C. Grundmann and R. Richter, *J. Org. Chem.*, **32**, 2308 (1967).
42. C. Grundmann and S. K. Datta, *J. Org. Chem.*, **34**, 2016 (1969).
43. G. A. Lee, *Synthesis*, 508 (1982).
44. R. Breslow, U. Maitra and D. Rideout, *Tetrahedron Lett.*, **24**, 1901 (1983).
45. S. Otto, W. Blokzijl and J. B. F. N. Engberts, *J. Org. Chem.*, **59**, 5372 (1994).
46. T. Zincke and H. Günther, *Justus Liebigs Ann. Chem.*, **272**, 243 (1892).
47. T. Zincke, *Justus Liebigs Ann. Chem.*, **296**, 135 (1897).
48. T. Zincke and K. H. Meyer, *Justus Liebigs Ann. Chem.*, **367**, 1 (1909).
49. T. Zincke and W. Pfaffendorf, *Justus Liebigs Ann. Chem.*, **394**, 3 (1912).
50. O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 98 (1928).
51. E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, **97**, 6908 (1975).
52. N. Kato, X. Wu, H. Nishikawa, K. Nakanishi and H. Takeshita, *J. Chem. Soc., Perkin Trans. 1*, 1047 (1994).
53. U. Pindur and G. H. Schneider, *Chem. Commun.*, 409 (1995).
54. S. Laschat, *Angew. Chem., Int. Ed. Engl.*, **35**, 289 (1996); *Angew. Chem.*, **108**, 313 (1996).
55. H. Oikawa, K. Katayama, Y. Suzuki and A. Ichihara, *J. Chem. Soc., Chem. Commun.*, 1321 (1995).
56. P. Yates and P. Eaton, *J. Am. Chem. Soc.*, **82**, 4436 (1960).
57. T. M. Tarasow, S. L. Tarasow and B. E. Eaton, *Nature*, **389**, 54 (1997).
58. R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969); *Angew. Chem.*, **81**, 797 (1969).
59. K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971).
60. G. Klopman, *J. Am. Chem. Soc.*, **90**, 223 (1968).
61. L. Salem, *J. Am. Chem. Soc.*, **90**, 543 (1968).
62. L. Salem, *J. Am. Chem. Soc.*, **90**, 553 (1968).
63. K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973).
64. M. Sodupe, R. Rios, V. Branchadell, T. Nicholas, A. Oliva and J. J. Dannenberg, *J. Am. Chem. Soc.*, **119**, 4232 (1997).
65. G. W. Wheland, *Resonance in Organic Chemistry*, Wiley, New York, 1955.
66. A. F. Voter and W. A. Goddard III, *Chem. Phys.*, **57**, 253 (1981).
67. F. W. Bodrowicz and W. A. Goddard III, in *Modern Theoretical Chemistry, Methods of Electronic Structure Theory* (Ed. H. F. Schaefer III), Plenum Press, New York, 1977.
68. O. Exner, *J. Org. Chem.*, **53**, 1810 (1988).
69. R. B. Woodward and T. J. Katz, *Tetrahedron*, **15**, 70 (1959).
70. Y. Apeloig and E. Matzner, *J. Am. Chem. Soc*, **117**, 5375 (1995).
71. F. Fotiadu, F. Michael and G. Buono, *Tetrahedron Lett.*, **31**, 4863 (1990).
72. M. Kakushima, *Can. J. Chem.*, **57**, 2564 (1979).
73. Y. Kobuke, T. Fueno and J. Furukawa, *J. Am. Chem. Soc.*, **92**, 6548 (1970).
74. Y. Kobuke, T. Sugimoto, J. Furukawa and T. Fueno, *J. Am. Chem. Soc.*, **94**, 3633 (1972).
75. E. T. McBee, M. J. Keogh, R. P. Levek and E. P. Wesseler, *J. Org. Chem.*, **38**, 632 (1973).
76. R. R. Sauers and T. R. Henderson, *J. Org. Chem.*, **39**, 1850 (1974).
77. R. K. Hill and T. V. vanAuken, *J. Org. Chem.*, **23**, 626 (1958).
78. J. Mattay, J. Mertes and G. Maas, *Chem. Ber.*, **122**, 327 (1989).

79. C. J. Northcott and Z. Valenta, *Can. J. Chem.*, **65**, 1917 (1987).
80. M. K. Diedrich and F.-G. Klärner, *J. Am. Chem. Soc.*, **120**, 6212 (1998).
81. K. N. Houk and L. J. Luskus, *J. Am. Chem. Soc.*, **93**, 4606 (1971).
82. G. Jenner, *Tetrahedron Lett.*, **35**, 1189 (1994).
83. M. Ciobanu and K. Matsumoto, *Justus Liebigs Ann. Chem./Recueil*, 623 (1997).
84. T. P. Caulier and J. Reisse, *J. Org. Chem.*, **61**, 2547 (1996).
85. D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem Soc.*, **110**, 1238 (1988).
86. E. Lattmann, J. Coombs and H. M. R. Hoffmann, *Synthesis*, 171 (1996).
87. J. Sauer and J. Kredel, *Tetrahedron Lett.*, 731 (1966).
88. E. J. Corey, N. Imai and S. Pikul, *Tetrahedron Lett.*, **32**, 7517 (1991).
89. T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 1121 (1966).
90. H. M. Walborsky, L. Barush and T. C. Davies, *Tetrahedron*, **19**, 2333 (1963).
91. L. M. Tolbert and M. B. Ali, *J. Am. Chem. Soc.*, **106**, 3806 (1984).
92. RHF/3-21G results; charges and orbitals were computed utilizing natural bond orbital (NBO) analyses.
93. K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc*, **95**, 4094 (1973).
94. K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975).
95. K. N. Houk, *Top. Curr. Chem.*, **79**, 1 (1979).
96. R. Sustmann and W. Sicking, *Tetrahedron*, **48**, 10293 (1992).
97. J. Sauer and R. Sustmann, *Angew. Chem.*, **19**, 779 (1980).
98. M. D. Rozeboom, I.-M. Tegmo-Larsson and K. N. Houk, *J. Org. Chem.*, **46**, 2338 (1981).
99. A. Venturini, J. Joglar, S. Fustero and J. Gonzáles, *J. Org. Chem.*, **62**, 3919 (1997).
100. A. Sbai, V. Branchadell, R. M. Ortuno and A. Oliva, *J. Org. Chem.*, **62**, 3049 (1997).
101. *Spartan Version 5.0*, Wavefunction, Inc., Irvine, 1998.
102. M. J. S. Dewar, E. V. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
103. A. Holder, 'AM1', in *Encyclopedia of Computational Chemistry* (Eds. P. v. R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer III and P. R. Schreiner), Wiley, Chichester, 1998, pp. 8–11.
104. J. A. Pople, *Trans. Faraday Soc.*, **49**, 1375 (1953).
105. J. A. Pople and R. K. Nesbet, *J. Chem. Phys.*, **22**, 571 (1954).
106. P. M. W. Gill, *'Density Functional Theory, HF and the Self-consistent Field'*, in *Encyclopedia of Computational Chemistry* (Eds. P. v. R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer III and P. R. Schreiner), Wiley, Chichester, 1998, pp. 678–689.
107. W. J. Pietro, M. M. Frankl, W. J. Hehre, D. J. DeFrees, J. A. Pople and J. S. Binkley, *J. Am. Chem. Soc.*, **104**, 5039 (1982).
108. S. Yamabe, T. Dai and T. Minato, *J. Am. Chem. Soc.*, **117**, 10994 (1995).
109. J. I. Garciá, V. Martinez-Merino, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, **120**, 2415 (1998).
110. W.-M. Dai, C. W. Lau, S. H. Chung and Y.-D. Wu, *J. Org. Chem.*, **60**, 8128 (1995).
111. J. I. Garciá, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, **118**, 11680 (1996).
112. D. M. Birney and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 4127 (1990).
113. M. E. Trân Huu Dau, J.-P. Flament, J.-M. Lefour, C. Riche and D. S. Grierson, *Tetrahedron Lett.*, **33**, 2343 (1992).
114. D. Suárez, J. Gonzáles, T. L. Sordo and J. A. Sordo, *J. Org. Chem.*, **59**, 8058 (1994).
115. B. S. Jursic and Z. Zdravkovski, *J. Org. Chem*, **60**, 3163 (1995).
116. B. S. Jursic and Z. Zdravkovski, *J. Phys. Org. Chem.*, **7**, 641 (1994).
117. T. Poll, G. Helmchen and B. Bauer, *Tetrahedron Lett.*, **25**, 2191 (1984).
118. (a) T. Poll, J. O. Metter and G. Helmchen, *Angew. Chem., Int. Ed. Engl.*, **14**, 112 (1985); *Angew. Chem.*, **97**, 116 (1985).
(b) The atomic coordinates are available, on request, from the Cambridge Crystallographic Data Center. The Refcode of this structure is CUZXIE.
119. J. F. Blake and W. L. Jorgensen, *J. Am. Chem. Soc.*, **113**, 7430 (1991).
120. V. D. Kiselev and A. I. Konovalov, *Russ. Chem. Rev.*, **58**, 383 (1989).
121. W. L. Jorgensen, J. F. Blake, D. Lim and D. L. Severance, *J. Chem. Soc., Faraday Trans.*, **90**, 1727 (1994).
122. C. Cativiela, J. I. Garciá, J. A. Mayoral and L. Salvatella, *Chem. Soc. Rev.*, 209 (1996).

123. B. von Blankenburg, H. Fiedler, M. Hampel, H. Hauthal, G. Just, K. Kahlert, J. Korn, K.-H. Müller, W. Pritzkow, Y. Reinhold, E. Sauer, D. Schnurpfeil and G. Zimmermann, *J. Prakt. Chem.*, **316**, 804 (1974).
124. H.-J. Schneider and N. K. Sangwan, *J. Chem. Soc., Chem. Commun.*, 1787 (1986).
125. N. K. Sangwan and H.-J. Schneider, *J. Chem. Soc., Perkin Trans. 2*, 1223 (1989).
126. T. Oshima, S. Arikata and T. Nagai, *J. Chem. Res. (S)*, 204 (1981).
127. G. Desimoni, G. Faita, P. Righetty, N. Tornaletti and M. Visigalli, *J. Chem. Soc., Perkin Trans. 2*, 437 (1989).
128. M. Burdisso, G. Desimoni, G. Faita, P. Righetti and G. Tacconi, *J. Chem. Soc., Perkin Trans. 2*, 845 (1989).
129. U. Mayer, V. Gutmann and W. Gerger, *Monatsh. Chem.*, **106**, 1235 (1975).
130. G. Desimoni, G. Faita, P. P. Righetti and L. Toma, *Tetrahedron*, **46**, 7951 (1990).
131. A. Corsico Coda, G. Desimoni, G. Faita, P. Righetti and G. Tacconi, *Tetrahedron*, **45**, 775 (1989).
132. C. Cativiela, J. A. Mayoral, A. Avenoza, J. M. Peregrina and M. A. Roy, *J. Phys. Org. Chem.*, **3**, 414 (1990).
133. C. Cativiela, J. I. Garciá, J. A. Mayoral, A. Avenoza, J. M. Peregrina and M. A. Roy, *J. Phys. Org. Chem.*, **4**, 48 (1991).
134. M. F. Ruiz-Lopez, X. Assfeld, J. I. Garciá, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, **115**, 8780 (1993).
135. R. A. Firestone and M. A. Vitale, *J. Org. Chem.*, **46**, 2160 (1981).
136. R. A. Firestone and S. G. Saffar, *J. Org. Chem.*, **48**, 4783 (1983).
137. M. A. Forman and W. P. Dailey, *J. Am. Chem. Soc.*, **113**, 2761 (1991).
138. P. A. Grieco, J. J. Nunes and M. D. Gaul, *J. Am. Chem. Soc.*, **112**, 4595 (1990).
139. G. Jenner and R. B. Salem, *Tetrahedron*, **53**, 4637 (1997).
140. A. Kumar, *J. Org. Chem.*, **59**, 4612 (1994).
141. G. Faita and P. Righetti, *Tetrahedron*, **51**, 9091 (1995).
142. J. M. Mellor and C. F. Webb, *J. Chem. Soc., Perkin Trans. 2*, 26 (1974).
143. C. Cativiela, J. I. Garciá, J. Gil, R. M. Martinez, J. A. Mayoral, L. Salvatella, J. S. Urieta, A. M. Mainar and M. H. Abraham, *J. Chem. Soc., Perkin Trans. 2*, 653 (1997).
144. J. A. Berson, Z. Hamlet and W. A. Mueller, *J. Am. Chem. Soc.*, **84**, 297 (1962).
145. T. Karcher, W. Sicking, J. Sauer and R. Sustmann, *Tetrahedron Lett.*, **33**, 8027 (1992).
146. K. Nakagawa, Y. Ishii and M. Ogawa, *Tetrahedron*, **32**, 1427 (1976).
147. W. M. Latimer and W. H. Rodebush, *J. Am. Chem. Soc.*, **42**, 1419 (1920).
148. Z. Latajka and S. Scheiner, *J. Chem. Phys.*, **81**, 4014 (1984).
149. K. Morokuma and K. Kitaura, in *Molecular Interactions* (Eds. H. Ratajczak and W. J. Orville-Thomas), Wiley, New York, 1980, pp. 21–87.
150. K. Morokuma and K. Kitaura, in *Chemical Applications of Atomic and Molecular Electrostatic Potentials* (Eds. P. Politzer and D. G. Truhlar), Plenum Press, New York, 1980, pp. 215–242.
151. R. F. Frey and E. R. Davidson, *J. Chem. Phys.*, **90**, 5555 (1989).
152. G. P. Dado and S. H. Gellman, *J. Am. Chem. Soc.*, **116**, 1054 (1994).
153. L. L. Kiefer, S. A. Paterno and C. A. Fierke, *J. Am. Chem. Soc.*, **117**, 6831 (1995).
154. P. J. F. deRege, S. A. Williams and M. J. Therien, *Science*, **269**, 1409 (1995).
155. J. C. MacDonald and G. M. Whitesides, *Chem. Rev.*, **94**, 2383 (1994).
156. M. C. Etter, *Acc. Chem. Res.*, **23**, 120 (1990).
157. K. Endo, T. Sawaki, M. Koyanagi, K. Kobayashi, H. Masuda and Y. Aoyama, *J. Am. Chem. Soc.*, **117**, 8341 (1995).
158. S. Hanessian, H. Yang and R. Schaum, *J. Am. Chem. Soc.*, **118**, 2507 (1996).
159. I. Engquist, M. Lestelius and B. Liedberg, *J. Phys. Chem.*, **99**, 14198 (1995).
160. M. L. Huggins, *Angew. Chem., Int. Ed. Engl.*, **10**, 147 (1971); *Angew. Chem.*, **83**, 163 (1971).
161. C. Cativiela, J. I. Garciá, J. A. Mayoral, A. J. Royo, X. Assfeld, L. Salvatella and M. F. Ruiz-Lopez, *J. Phys. Org. Chem.*, **5**, 230 (1992).
162. J. B. F. N. Engberts, *Pure Appl. Chem.*, **67**, 823 (1995).
163. (a) J. F. Blake, D. Lim and W. L. Jorgensen, *J. Org. Chem.*, **59**, 803 (1994).
(b) C. J. Cramer and D. G. Trahlar, *J. Am. Chem. Soc.*, **116**, 3892 (1994).
164. T. R. Ramelot, C.-H. Hu, J. E. Fowler, B. J. DeLeeuw and H. F. Schaefer III, *J. Chem. Phys.*, **100,** 4347 (1994).
165. P. Bobadova-Parvanova and B. Galabov, *J. Phys. Chem. A*, **102**, 1815 (1998).

166. G. K. van der Wel, J. W. Wijnen and J. B. F. N. Engberts, *J. Org. Chem.*, **61**, 9001 (1996).
167. J. W. Wijnen and J. B. F. N. Engberts, *Justus Liebigs Ann. Chem./Recueil*, 1085 (1997).
168. W. Blokzijl, M. J. Blandamer and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **113**, 4241 (1991).
169. J. W. Wijnen and J. B. F. N. Engberts, *J. Org. Chem.*, **62**, 2039 (1997).
170. P. Gamez, B. Dunjic, F. Fache and M. Lemaire, *J. Chem. Soc., Chem. Commun.*, 1417 (1994).
171. D. P. Curran and L. H. Kuo, *J. Org. Chem.*, **59**, 3259 (1994).
172. P. Renaud, N. Moufid, L. H. Kuo and D. P. Curran, *J. Org. Chem.*, **59**, 3547 (1994).
173. F. Touchard, P. Gamez, F. Fache and M. Lemaire, *Tetrahedron Lett.*, **38**, 2275 (1997).
174. D. P. Curran and L. H. Kuo, *Tetrahedron Lett.*, **36**, 6647 (1995).
175. T. R. Kelly, P. Meghani and V. S. Ekkundi, *Tetrahedron Lett.*, **31**, 3381 (1990).
176. P. Murray-Rust and J. P. Glusker, *J. Am. Chem. Soc.*, **106**, 1018 (1984).
177. (a) J. Hine, K. Ahn, J. C. Gallucci and S.-M. Linden, *J. Am. Chem. Soc.*, **106**, 7980 (1984). (b) The atomic coordinates are available, on request, from the Cambridge Crystallographic Data Center. The Refcode of this structure is COXLAC.
178. J. Hine and K. Ahn, *J. Org. Chem.*, **52**, 2083 (1987).
179. M. C. Etter, *J. Phys. Chem.*, **95**, 4601 (1991).
180. M. C. Etter and S. M. Reutzel, *J. Am. Chem. Soc.*, **113**, 2586 (1991).
181. E. Fan, S. A. V. Arman, S. Kincaid and A. D. Hamilton, *J. Am. Chem. Soc.*, **115**, 369 (1993).
182. P. R. Schreiner and A. Wittkopp, manuscript in preparation.
183. D. A. Stauffer, R. E. Barrans and D. A. Dougherty, *J. Org. Chem.*, **55**, 2762 (1990).
184. Y.-H. Tsao, D. F. Evans and H. Wennerström, *Science*, **262**, 547 (1993).
185. J. A. Butler, *Trans. Faraday Soc.*, **33**, 229 (1937).
186. M. H. Abraham, *J. Am. Chem. Soc.*, **104**, 2085 (1982).
187. H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945).
188. D. N. Glew, *J. Phys. Chem.*, **66**, 605 (1962).
189. W. Kauzmann, *Adv. Protein Chem.*, **14**, 1 (1959).
190. R. L. Mancera, *J. Chem. Soc., Faraday Trans.*, **92**, 2547 (1996).
191. J. T. Slusher and P. T. Cummings, *J. Phys. Chem.*, **101**, 3818 (1997).
192. J. L. Finney, *Faraday Discuss.*, **103**, 1 (1996).
193. R. D. Broadbent and G. W. Neilson, *J. Chem. Phys.*, **100**, 7543 (1994).
194. P. H. K. de Jong, J. E. Wilson, G. W. Neilson and A. D. Buckingham, *Mol. Phys.*, **91**, 99 (1997).
195. A. Filipponi, D. T. Bowron, C. Lobban and J. L. Finney, *Phys. Rev. Lett.*, **79**, 1293 (1997).
196. S. Lüdemann, R. Abseher, H. Schreiber and O. Steinhauser, *J. Am. Chem. Soc.*, **119**, 4206 (1997).
197. R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).
198. T. A. Eggelte, H. de Koning and H. O. Huisman, *Tetrahedron*, **29**, 2491 (1973).
199. U. Pindur, G. Lutz and C. Otto, *Chem. Rev.*, **93**, 741 (1993).
200. R. Breslow and T. Guo, *J. Am. Chem. Soc.*, **110**, 5613 (1988).
201. R. Breslow and C. J. Rizzo, *J. Am. Chem. Soc*, **113**, 4340 (1991).
202. P. A. Grieco, P. Garner and H. Zhen-min, *Tetrahedron Lett.*, **24**, 1897 (1983).
203. P. A. Grieco, K. Yoshida and P. Garner, *J. Org. Chem.*, **48**, 3137 (1983).
204. P. A. Grieco, P. Garner and H. Zhen-min, *Tetrahedron Lett.*, **25**, 5715 (1984).
205. K. Yoshida and P. A. Grieco, *Chem. Lett.*, 155 (1985).
206. D. D. Sternbach and D. M. Rossana, *J. Am. Chem. Soc.,* **104**, 5853 (1982).
207. T. Dunams, W. Hoekstra, M. Pentaleri and D. Liotta, *Tetrahedron Lett.*, **29**, 3745 (1988).
208. C. K. Pai and M. B. Smith, *J. Org. Chem.*, **60**, 3731 (1995).
209. R. Breslow and U. Maitra, *Tetrahedron Lett.*, **25**, 1239 (1984).
210. A. Lubineau and Y. Queneau, *J. Org. Chem.*, **52**, 1001 (1987).
211. A. Kumar, *J. Org. Chem.*, **59**, 230 (1994).
212. T. Asano and W. J. Le Noble, *Chem. Rev.*, **78**, 407 (1978).
213. R. van Eldik, T. Asano and W. J. Le Noble, *Chem. Rev.*, **89**, 549 (1989).
214. M. R. J. Dack, *J. Chem. Educ.*, **51**, 231 (1974).
215. M. R. J. Dack, *Chem. Soc. Rev.*, **4**, 211 (1975).
216. W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **114**, 5440 (1992).
217. J. J. Gajewski, *J. Org. Chem.*, **57**, 5500 (1992).
218. R. W. Zwanzig, *J. Chem. Phys.*, **22**, 1420 (1954).
219. T. R. Furlani and J. Gao, *J. Org. Chem.*, **61**, 5492 (1996).

220. H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, **30**, 1306 (1991); *Angew. Chem.*, **103**, 1335 (1991).
221. H. Schneider and N. K. Sangwan, *Angew. Chem., Int. Ed. Engl.*, **26**, 896 (1987); *Angew. Chem.*, **99**, 924 (1987).
222. I. Schlachter, J. Mattay, J. Suer, U. Höweler, G. Würthwein and E.-U. Würthwein, *Tetrahedron*, **53**, 119 (1997).
223. A. Lubineau, J. Augé and N. Lubin, *J. Chem. Soc., Perkin Trans. 1*, 3011 (1990).
224. S. Arseniyadis, R. Rodriquez, D. V. Yashunsky, J. Camara and G. Ourisson, *Tetrahedron Lett.*, **35**, 4843 (1994).
225. X. Assfeld, M. F. Ruiz-Lopez, J. I. Garciá, J. A. Mayoral and L. Salvatella, *J. Chem. Soc., Chem. Commun.*, 1371 (1995).
226. R. Breslow and T. Guo, *Proc. Natl. Acad. Sci. U.S.A.*, **87**, 167 (1990).
227. R. Breslow and S. Halfon, *Proc. Natl. Acad. Sci. U.S.A.*, **89**, 6916 (1992).
228. C. J. Rizzo, *J. Org. Chem.*, **57**, 6382 (1992).
229. I. Hunt and C. D. Johnson, *J. Chem. Soc., Perkin Trans. 2*, 1051 (1991).
230. R. Breslow and Z. Zhu, *J. Am. Chem. Soc.*, **117**, 9923 (1995).
231. A. Lubineau, H. Bienaymé, Y. Queneau and M.-C. Scherrmann, *New J. Chem.*, **18**, 279 (1994).
232. R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963).
233. R. G. Pearson, *Coord. Chem. Rev.*, **100**, 403 (1990).
234. S. Ahrland, *Helv. Chim. Acta*, **50**, 306 (1967).
235. P. Lazlo and M. Teston, *J. Am. Chem. Soc.*, **112**, 8750 (1990).
236. Y.-R. Luo and S. W. Benson, *Inorg. Chem.*, **30**, 1676 (1991).
237. R. S. Drago and B. B. Wayland, *J. Am. Chem. Soc*, **87**, 3571 (1965).
238. R. S. Drago, *J. Chem. Educ.*, **51**, 300 (1974).
239. R. S. Drago, L. B. Parr and C. S. Chamberlain, *J. Am. Chem. Soc.*, **99**, 3203 (1977).
240. Y. Marcus, *J. Solution Chem.*, **13**, 599 (1984).
241. R. D. Hancock and A. E. Martell, *Adv. Inorg. Chem.*, **42**, 89 (1995).
242. I. Persson, *Pure Appl. Chem.*, **58**, 1153 (1986).
243. H. B. Kagan and O. Riant, *Chem. Rev.*, **92**, 1007 (1992).
244. S. Kobayashi, *Eur. J. Org. Chem.*, 15 (1999).
245. T. Mukaiyama, K. Narasaka and K. Banno, *Chem. Lett.*, 1011 (1973).
246. S. Kobayashi, *Chem. Lett.*, 2087 (1991).
247. S. Kobayashi and I. Hachiya, *Tetrahedron Lett.*, **33**, 1625 (1992).
248. S. Kobayashi, I. Hachiya and Y. Yamanoi, *Bull. Chem. Soc. Jpn.*, **67**, 2342 (1994).
249. S. Kobayashi and T. Hachiya, *J. Org. Chem.*, **59**, 3590 (1994).
250. Y. Yamamoto and N. Asao, *Chem. Rev.*, **93**, 2207 (1993).
251. I. Hachiya and S. Kobayashi, *J. Org. Chem.*, **58**, 6958 (1993).
252. T. Loh and X. Li, *Angew. Chem.*, **109**, 980 (1997).
253. S. Kobayashi and H. J. Ishitani, *J. Chem. Soc., Chem. Commun.*, 1379 (1995).
254. T. Loh and X. Li, *Chem. Commun.*, 1929 (1996).
255. T.-P. Loh, G.-Q. Cao and J. Pei, *Tetrahedron Lett.*, **39**, 1453 (1998).
256. T.-P. Loh and L.-L. Wei, *Tetrahedron Lett.*, **39**, 323 (1998).
257. E. Keller and B. L. Feringa, *Tetrahedron Lett.*, **37**, 1879 (1996).
258. E. Keller and B. L. Feringa, *Synlett*, 842 (1997).
259. R. J. Angelici and J. W. Allison, *Inorg. Chem.*, **10**, 2238 (1971).
260. R. Nakon, P. R. Rechani and R. J. Angelici, *J. Am. Chem. Soc.*, **96**, 2117 (1974).
261. J. Chin and M. Banaszczyk, *J. Am. Chem. Soc.*, **111**, 2724 (1989).
262. M. A. Mortellaro, T. J. Bleisch, B. F. Duerr, M. S. Kang, H. Huang and A. W. Czarnik, *J. Org. Chem.*, **60**, 7238 (1995).
263. A. Tsubouchi and T. C. Bruice, *J. Am. Chem. Soc.*, **116**, 11614 (1994).
264. A. Tsubouchi and T. C. Bruice, *J. Am. Chem. Soc.*, **117**, 7399 (1995).
265. H. Schneider, J. Rammo and R. Hettich, *Angew. Chem., Int. Ed. Engl.*, **32**, 1716 (1993); *Angew. Chem.*, **105**, 1773 (1993).
266. B. Linkletter and J. Chin, *Angew. Chem., Int. Ed. Engl.*, **34**, 472 (1995); *Angew. Chem.*, **107**, 529 (1995).
267. K. G. Ragunathan and H. Schneider, *Angew. Chem., Int. Ed. Engl.*, **35**, 1219 (1996); *Angew. Chem.*, **108**, 1314 (1996).
268. K. Bracken, R. A. Moss and K. G. Ragunathan, *J. Am. Chem. Soc.*, **119**, 9323 (1997).

269. J. von Westrenen, J. A. Peters and H. van Bekkum, *Inorg. Chim. Acta*, **181**, 223 (1991).
270. D. A. Buckingham, J. M. Harrowfield and A. M. Sargeson, *J. Am. Chem. Soc.*, **96**, 1726 (1974).
271. J. T. Groves and J. R. R. Chambers, *J. Am. Chem. Soc.*, **106**, 630 (1984).
272. A. Schepartz and R. Breslow, *J. Am. Chem. Soc.*, **109**, 1814 (1987).
273. L. Zhu and N. M. Kostic, *Inorg. Chem.*, **31**, 3994 (1992).
274. R. L. de la Vega, R. W. J. Ellis and W. L. Purcell, *Inorg. Chim. Acta*, **68**, 97 (1983).
275. C. M. Jensen and W. C. Trogler, *J. Am. Chem. Soc.*, **108**, 723 (1986).
276. (a) J. Chin and J. H. Kim, *Angew. Chem., Int. Ed. Engl.*, **29**, 523 (1990).
(b) J. Chin and J. H. Kim, *Angew. Chem.*, **102**, 580 (1990).
277. J. H. Kim, J. Britten and J. Chin, *J. Am. Chem. Soc.*, **115**, 3618 (1993).
278. J. Chin, *Acc. Chem. Res.*, **24**, 145 (1991).
279. J. Suh, *Acc. Chem. Res.*, **25**, 273 (1992).
280. F. S. Richardson, *Chem. Rev.*, **82**, 541 (1982).
281. W. Odenkirk, A. L. Rheingold and B. Bosnich, *J. Am. Chem. Soc.*, **114**, 6392 (1992).
282. W. Odenkirk and B. Bosnich, *J. Chem. Soc., Chem. Commun.*, 1181 (1995).
283. T. K. Hollis, N. P. Robinson and B. Bosnich, *J. Am. Chem. Soc.*, **114**, 5464 (1992).
284. K. Ishihara, N. Hanaki, M. Funashi, M. Miyata and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **68**, 1721 (1995).
285. K. Mikami, O. Kotera, Y. Motoyama and H. Sakagushi, *Synlett*, 975 (1995).
286. S. Kobayashi, I. Hachiya, M. Araki and H. Ishitani, *Tetrahedron Lett.*, **34**, 3755 (1993).
287. A. Lubineau, J. Augé, E. Grand and N. Lubin, *Tetrahedron*, **50**, 10265 (1994).
288. L. Yu, D. Chen and P. G. Wang, *Tetrahedron Lett.*, **37**, 2169 (1996).
289. L. Yu, J. Li, J. Ramirez, D. Chen and P. G. Wang, *J. Org. Chem.*, **62**, 903 (1997).
290. P. A. Grieco and S. D. Larsen, *J. Org. Chem.*, **51**, 3553 (1986).
291. P. A. Grieco, S. D. Larsen and W. F. Fobare, *Tetrahedron Lett.*, **27**, 1975 (1986).
292. H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, **27**, 274 (1988); *Angew. Chem.*, **100**, 307 (1988).
293. H. Waldmann, *Justus Liebigs Ann. Chem.*, 231 (1989).
294. H. Waldmann and M. Dräger, *Justus Liebigs Ann. Chem.*, 681 (1990).
295. H. Waldmann and M. Braun, *Justus Liebigs Ann. Chem.*, 1045 (1991).
296. H. Waldmann, *Synthesis*, 535 (1994).
297. P. A. Grieco, D. T. Parker, W. F. Fobare and R. Ruckle, *J. Am. Chem. Soc.*, **109**, 5859 (1987).
298. P. A. Grieco and J. D. Clark, *J. Org. Chem.*, **55**, 2271 (1990).
299. T. Loh, J. Pei and M. Lin, *Chem. Commun.*, 2315 (1996).
300. Z. Zhu and J. H. Espenson, *J. Am. Chem. Soc.*, **119**, 3507 (1997).
301. S. Otto and J. B. F. N. Engberts, *Tetrahedron Lett.*, **36**, 2645 (1995).
302. S. Otto, F. Bertoncin and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **118**, 7702 (1996).
303. J. Kang, G. Hilmersson, J. Santamaria and J. Rebek, *J. Am. Chem. Soc.*, **120**, 7389 (1998).
304. T. Kunitake, *Angew. Chem., Int. Ed. Engl.*, **31**, 709 (1992); *Angew. Chem.*, **104**, 692 (1992).
305. B. Lindmann and H. Wennerström, *Top. Curr. Chem.*, **87**, 1 (1980).
306. P. J. Sams, E. Wyn-Jones and J. Rassing, *Chem. Phys. Lett.*, **13**, 233 (1972).
307. J. K. Thomas, F. Gieser and M. Wong, *Ber. Bunsenges. Phys. Chem.*, **82**, 937 (1978).
308. W. H. Noordman, W. Blokzijl and J. B. F. N. Engberts, *J. Org. Chem.*, **58**, 7111 (1993).
309. D. Hilvert, K. W. Hill, K. D. Nared and M.-T. M. Auditor, *J. Am. Chem. Soc.*, **111**, 9261 (1989).
310. A. C. Braisted and P. G. Schultz, *J. Am. Chem. Soc.*, **112**, 7430 (1990).

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