Supplement A

The chemistry of

double-bonded functional groups

Volume 2

Part 2

THE CHEMISTRY OF FUNCTIONAL GROUPS

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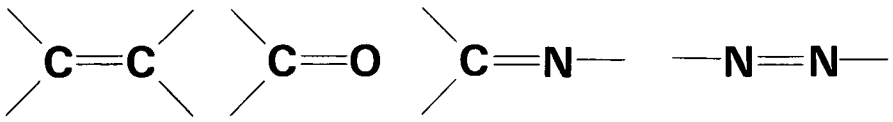

Supplement A
The chemistry of
double-bonded functional groups

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Edited by

SAUL PATAI

The Hebrew University, Jerusalem

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Foreword

The first supplementary volume in The Chemistry of Functional Groups series was published in 1976. This included thirteen chapters in the form of essay-reviews complementing the original main volumes in the series on C=C, C=O, C=N and N=N double bonds. As then, in the present second Supplement A2, several of the authors were asked to write 'integrative' chapters, i.e. chapters which give a unified and comparative treatment of several double-bonded functional groups together. It is a great satisfaction to the Editor, that this aim has been achieved and indeed more than half of the chapters in the book are such 'integrative' ones, concentrated in the first part of the volume.

Other chapters deal with special subjects which for various reasons have not been treated in the original volumes or in Supplement A. Unfortunately, several chapters which were planned did not materialize. We hope that these omissions will be filled in future volumes of the Series, together with the presentation of novel developments in the various subjects at present being actively studied.

The literature coverage in most chapters is up to about the end of 1987 and in some cases even to the middle of 1988.

Jerusalem
March 1989

SAUL PATAI

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 Editor set himself 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 or 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 author 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 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 and F). 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.

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

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 me invaluable aid. My sincere thanks are due to all of them, especially to Professor Zvi Rappoport, who for many years shares the work and responsibility of the editing of this Series.

The Hebrew University
Jerusalem, ISRAEL

SAUL PATAI

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
All	allyl
An	anisyl
Ar	aryl
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
CNDO	complete neglect of differential overlap
Cp	η^5-cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
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	ferrocene
FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_5)
Hex	hexyl(C_6H_{11})
c-Hex	cyclohexyl(C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital

i-	iso
Ip	ionization potential
IR	infrared
ICR	ion cyclotron resonance
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
MNDO	modified neglect of diatomic overlap
MS	mass spectrum
n	normal
Naph	naphthyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
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
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TMEDA	tetramethylethylene diamine
Tol	tolyl(MeC_6H_4)
Tos	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, pp. 305–322, will also be used in their unabbreviated forms, both in the text and in structures.

We are sorry for any inconvenience to our readers. However, the rapidly rising costs of production make it absolutely necessary to use every means to reduce expenses—otherwise the whole existence of our Series would be in jeopardy.

The Chemistry of Double-bonded Functional Groups
Edited by S. Patai

CHAPTER **13**

Carbonylation of main-group organometallic compounds

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I. INTRODUCTION

Carbonylation is a very general term, usually employed in a non-specific manner to denote a reaction in which carbon monoxide is introduced into an organic molecule. This may be achieved by a conceptually simple 'direct' process, such as the conversion of an ether into a carboxylic acid ester via the 'insertion' of carbon monoxide into the ethereal carbon–oxygen bond[1].

The most widely studied reactions are the insertions of carbon monoxide into transition metal compounds and worldwide extensive research has produced a deep understanding of the structural[2,3], mechanistic[3b,4,5] and important industrial applications[6–8] of the usually catalytic processes involved. The matter has been the subject of several reviews in the past ten years[9–13], and it has also been partially reviewed in recent volumes of this series[1,14].

Although the reaction of carbon monoxide with some main group metal organometallic compounds has been studied for many years, recently important advances on the subject have been made. Acyl derivatives of lithium, magnesium, zinc, aluminium, i.e. those metals whose alkyls and aryls are potent nucleophilic reagents, are of prime interest. The potential importance of nucleophilic acylation is to provide a more direct route to valuable products such as aldehydes, ketones, amides, α-hydroxyketones, α-diketones, β-hydroxyketones, etc. The obvious problem with these systems is the competition by side-reactions owing to the high reactivity of the reagents with the substrates as well as with the products and the instability of the active metal acyl compounds. This concern has been previously voiced in reviews dealing with nucleophilic acylation[14–16].

The low stability of alkyl, aryl and acyl derivatives of most of these metals interferes with structural determinations as well as with detailed mechanistic studies by conventional techniques. Nevertheless, extensive research carried out at present, dealing with many and varied reactions that these systems can undergo, is stimulating the development of new methods to obtain structural and chemical bonding information and has also opened extensive vistas of research for theoretical chemists as well as for those interested in new routes of synthesis of organic and organometallic compounds.

This chapter deals mainly with the wide applications of these reactions in synthesis and the advantage of using the appropriate organometallic compound to carry out a specific transformation. For these reasons, tables showing the products and the yields of the most relevant reactions are included. In addition, within the limitation of the space available, a short description of the state of knowledge regarding structures, chemical bonding and mechanistic considerations is also given.

To our knowledge, the carbonylation of main group organometallic compounds has not been reviewed before, although the reactions of some organometallic reagents described here have been included in two recent general reviews on organic synthesis via carbonylation of organometallic reagents[17,18]. Several major books have contributed enormously to the use of carbon monoxide[8,9,20,21] as well as of organometallics in synthesis[21–24] and the reader is referred to them for a detailed approach to this subject.

Literature coverage extends up to the close of 1987, but several relevant publications accessible to us after this date have also been included.

II. INSERTION OF CARBON MONOXIDE INTO C—M BONDS

A. Structural Studies of Reagents and Intermediates

The reagent that would be formed formally by the insertion of carbon monoxide into a carbon–metal bond would have the general formula **2** (equation 1).

Acyl metals of type **2** are commonly isolated in the carbon monoxide migration

(1)

reactions of the organometal carbonyls of transition metals and their structures have been widely studied[1-3,25]. These acyl-transition metal reagents are commonly stable and their structures have been determined by X-ray diffraction studies. However, when M is a main group metal they are not stable enough to be studied in the solid state, in many cases even in solution their instability prevents structural determinations by conventional techniques.

Valuable information can be obtained from the structural studies of the reagents, **1**, for which in many cases X-ray structures have been recently determined at low temperatures[26-30]. These, combined with structural studies of acyl-d or f metals could help in understanding the bonding situation in pathway represented by equation 1 and in the further reactions of intermediate **2**. Schleyer and coworkers have recently reviewed studies on the crystal structures of organolithium compounds[31] and also the organometallic structures of the heavier alkali metals[32]. Structural reports on other organometallic compounds have also been reviewed in a previous volume of this series[33].

Reagents **1** are commonly used in solution, and in the case of the most widely used and versatile reagents, the organolithium compounds, there is abundant evidence that they exist as aggregates[26,34-37]. It is now well known (as will be shown in the following sections) that the reactivity, the regio- and stereoselectivity of the organometallic reactions are widely affected by the effects of temperature, concentration, solvent and traces of 'impurities'. These features are of great synthetic importance as can be easily grasped by examining the yields in most of the tables in this chapter.

The usually complex and fast reactions observed have so far limited the number of kinetic investigations. In a few cases, partial kinetic orders with respect to the organometallic substrate have been determined[38]. In the case of organolithium compounds, they have been interpreted in terms of an initial rapid dissociation of aggregated organolithium into monomer, which is considered to be the predominantly reactive species[39]. Such an interpretation has been supported by the observed change in reaction order upon dilution, e.g. the order of butyllithium changes from approximately 0.33 to 1 in its reaction in THF, as the concentration is lowered from 100 to 1.5 mM[40]. Nevertheless, it has been recently shown that no direct evidence for monomeric butyllithium in THF could be found at concentrations down to 100 μM[37]. It has also been shown that aggregation plays an important role in the reactions with electrophiles[41] and a rapid-injection NMR (ri-NMR) study of butyllithium aggregates in THF show that the dimer and even the tetramer react directly with benzaldehyde[42]. Aggregation is then very important in many of the organometallic reagents that we will consider and, in this respect, the coordinated metal will resemble the organo transition-metal complexes which, because of their stability, were much more extensively studied.

The effect of solvent is also very important in organic synthesis and the degree of solvation of aggregates is germane to any mechanistic study. It has been shown by colligative as well as by spectroscopic methods that the degree of association diminishes when passing from hydrocarbon to ethereal solvents. The usually hexameric alkyllithiums change to tetrameric aggregates and some ether molecules are associated to the oligomer[30,39]. Direct determination of the degree of solvation in aggregates is, in principle, available from spin-lattice relaxation data for solute and solvent nuclei, although, in practice, a number of assumptions must be made[43]. This approach has been applied to lithium phenolate in pyridine. The observation of a biphasic temperature dependence of chemical shifts which is independent of concentration may be taken as evidence of an equilibrium between differently solvated species having the same degree of

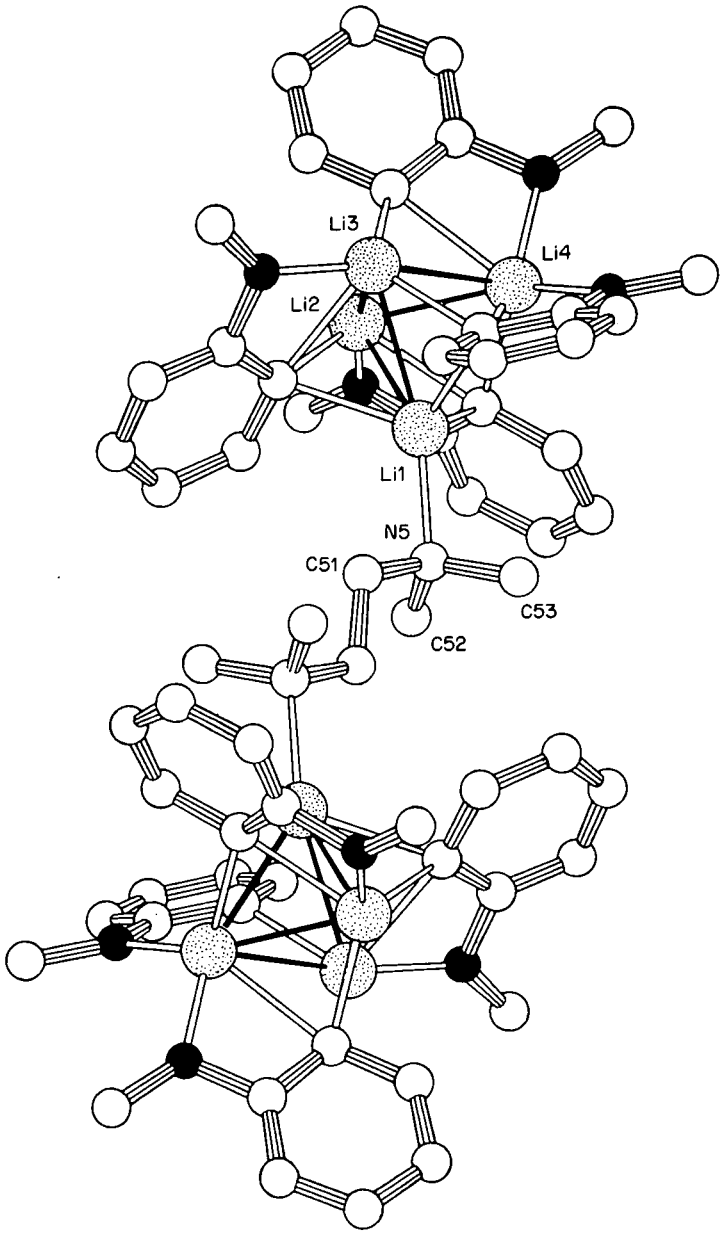


FIGURE 1. Perspective view of the complete complex, involving two centrosymmetrically related tetrameric aggregates of lithiomethoxybenzene bridged by a TMEDA ligand (of which the atom numbering is shown). For clarity the hydrogen atoms have been omitted, and the lithium atoms are indicated by the large speckled spheres with atom numbers. Reprinted with permission from *J. Organomet. Chem.*, **339**, 12 (1988).

aggregation, particularly if the equilibrium involves a substantial (80–160 $J mol^{-1}$) deg^{-1}) entropy change[44].

It will be shown in subsequent sections that the addition of some donor bases to the system also has a very relevant effect in some cases. It has been shown by X-ray studies that amine molecules also become incorporated in the crystal cell unit. Figure 1 shows the crystal structure of [1-lithio-2-methoxybenzene]$_8$·TMEDA[45a]. It can be observed that the structure consists of two tetrameric aggregates of 1-lithio-2-methoxybenzene linked together by a TMEDA ligand, which possesses a centre of inversion in the middle of the C—C bond. In the tetrameric cluster, the twelve C—Li bonds and four O—Li bonds should be sufficient for coordinative saturation (the lithium atom in organolithium compounds is often tetracoordinate), and therefore participation of one N donor atom of TMEDA must result in five coordination at one of the Li atoms. As is seen from Figure 1, Li(4) possesses five contacts (3 C—Li and 2 O—Li), but two of the C—Li contacts are rather long and therefore Li(4) must be regarded as three-coordinate[45a]. Some other pertinent structures gathered by Seebach and coworkers[45b] are shown in Figure 2.

Careful ^{13}C NMR studies carried out in donor solvent (R_2O, R_3N) mixtures have shown that similar aggregates are found in solution[45]. Seebach and coworkers[45] have

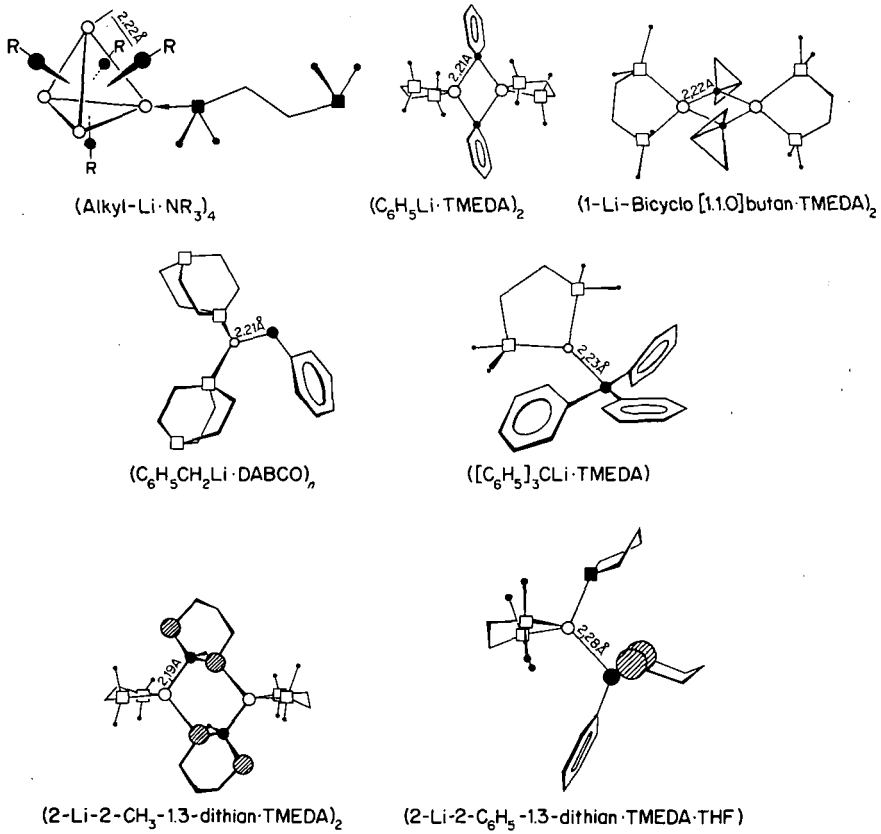


FIGURE 2. ·CH_3 and CH_2 groups on N or O atoms, ● C atom on Li, ○ lithium, ◍ S atom, □ N atom, ■ O atom, DABCO-diazabicyclooctane, TMEDA-tetramethylethylene diamine. Reproduced with permission from *Helv. Chim. Acta.*, **66**, 308 (1983).

summarized some of their surprising observations as well as their interpretations and consequences: (a) Butyllithium solutions in THF, THF/TMEDA and dimethyl ether contain increasing amounts of dimer upon cooling, the equilibrium (tetramer·4 THF) + THF ⇄ 2(dimer·4 THF) being shifted to the right; thus different species are present at low temperatures, with the accompanying changes in reactivity. (b) Mixed higher aggregates are formed upon addition of butyllithium to bicyclobutyllithium; these are broken up to dimers upon addition of TMEDA. (c) The solid state, the calculated gas phase and the solution species of phenyllithium all have dimeric structures, and so do vinyl and cyclopropyl lithium derivatives; the ^{13}C deshielding observed upon replacement of H by Li on sp^2 and sp carbon atoms is related to a polarization of the π electrons. (d) The spectra of halo-lithium carbenoids show three striking features as compared to the C, H compound which might be the consequence of a reduced degree of hybridization of the carbenoid carbon atom[45].

Finally, it has also been observed that the presence of lithium alkoxides, due to oxygen contamination, sometimes has important synthetic consequences.

Lithium oxide, another common contaminant in this type of compound, may also be incorporated into the 'cluster'. In fact, when 2,6-dimethoxyphenyllithium was crystallized from ether and its structure studied by X-ray diffraction, the data indicated additional atoms not belonging to solvent molecules[46]. In spite of the careful synthesis carried out under dry argon atmosphere, the authors conclude that one unit of Li_2O has been included in the hexamer. The crystal structure of the Li_2O complex of 2,6-dimethyoxyphenyllithium, $(C_8H_9O_2Li)_6Li_2O$[46], demonstrates that all lithium atoms of the six formula units of the complex are combined together with the Li_2O to form a long cluster, Li_8O, in the centre of the molecules. This cluster is composed of two Li_4 pyramids, each of which is connected to the oxygen atom via its Li_3 base in such a way that the oxygen atom has a nearly octahedral coordination with very short Li–O distances[46].

By ri-NMR it has been recently established that butyllithium, which exists in THF mainly as a tetramer, exists in equilibrium with a dimer and the presence of lithium butoxide, due to oxygen contamination, leads to successive replacement of alkyl groups in the tetrameric structure by alkoxide ligands[37].

It will be shown in Sections II.C.2 and III.C.2 that addition of organocopper compounds, or even the addition of copper salts, has important synthetic consequences. (Organolithium cuprates as well as organo-copper/Grignard mixtures are useful reagents in organic synthesis.) It would then be desirable to have some information on the structural implications of this type of co-reagent. Bau and coworker[47] have recently reported the first structural characterization of a transition-metal cluster complex containing magnesium, Cu_4MgPh_6, and its lithium analogue, $[Cu_4LiPh_6]^-$. A plot of the Cu_4MgPh_6 cluster is shown in Figure 3. This compound represents, according to the authors[47], the first example of a transition-metal cluster complex containing a magnesium atom (or any member of the magnesium family) structurally characterized. Note that, unlike $[Cu_4LiPh_6]^-$ (Figure 4), Cu_4MgPh_6 contains a solvent molecule as a ligand (to Mg). This may be due to the fact that, whereas in the other compound the axial atoms (Cu or Li) are roughly coplanar with the plane of the three ipso carbon atoms, in Cu_4MgPh_6 the Mg atom is displaced 0.4 Å away from it, making it more 'exposed' to coordination by ether, with the reactivity consequences. It has been also suggested that, at least for phenylating reagents, the basic trigonal-bipyramidal structure may in fact be one of the dominant species (perhaps the thermodynamically most stable entity) in phenyllithium-cuprate solutions. Nevertheless, perhaps what may be taking place in solution is an equilibrium between $[MPh_2]^-$ monomers (presumably linear) and $[M_3M'_2Ph_6]^-$ (i.e. $3[MPh_2]^- + 2[M']^+ \rightleftarrows [M_3M'_2Ph_6]^-$), with the latter perhaps being the predominant species[47].

It could be useful from a synthetic point of view to mention briefly the novel 1,2-

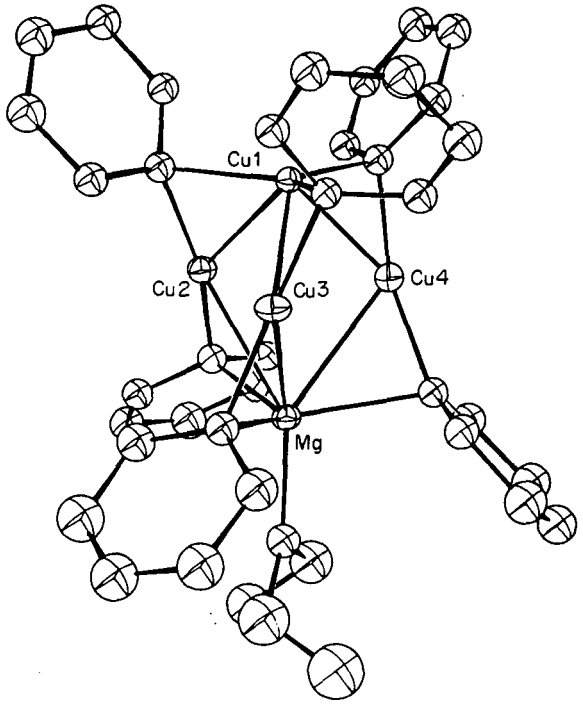


FIGURE 3. Molecular plot of $Cu_4MgPh_6 \cdot Et_2O$. Reprinted with permission from *J. Am. Chem. Soc.*, **107**, 1682 (1985). Copyright (1985) American Chemical Society.

migration reactions recently observed in compounds containing main group metals such as aluminium, zinc and magnesium. Negishi and Akiyoshi[48] presented experimental data which suggest that the 1,2-migration reactions of organo main group metals (equation 2) are much more widespread than previously available data indicated (Table 1).

$$L_nMR \xrightarrow[2.\ H_2O]{1.\ LiCH(Cl)SiMe_2Ph} RCH_2SiMe_2Ph \qquad (2)$$

R = Me, Pr or *t*-Bu; ML_n = Al-, Mg-, Zn- or Cd-containing group

Typically, addition of the organometal to $LiCH(Cl)SiMe_2Ph$ at $-78\,^{\circ}C$ (generated *in situ* by treating $ClCH_2SiMe_2Ph$ and TMEDA in THF with *sec*-butyllithium in cyclohexane)[48] followed by warming the mixture at 23 °C for the indicated reaction times, afforded the corresponding RCH_2SiMe_2Ph in the yields shown in Table 1. Organometals containing Al, Mg, Zn, Cd are readily hydrolyzed to produce organic products. This would make the synthetic significance of their 1,2-migration reactions quite distinct from those of organoboranes, opening a new area of 1,2-migration reactions of organo main group metals.

As mentioned before, the first intermediate formed in these reactions, compound **2**, is too unstable to be isolated for structural determinations, but studies on related complexes have been recently carried out in order to gain some information by analogy. Although in equation 1 the insertion reaction is written as if occurring by a classical polar mechanism, Nudelman and coworkers[49] have recently demonstrated that, at least in the

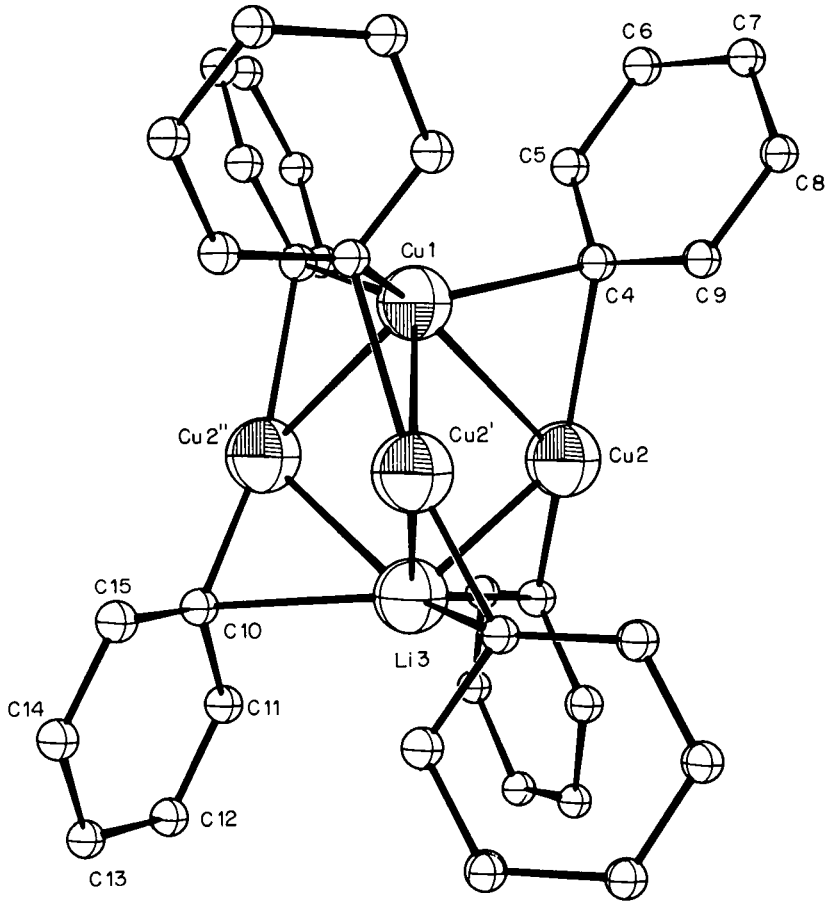


FIGURE 4. Molecular plot of the $[Cu_4LiPh_6]^-$ anion. Reprinted with permission from *J. Am. Chem. Soc.*, **107**, 1682 (1985). Copyright (1985) American Chemical Society.

reaction of phenyllithium with carbon monoxide, radical anions are formed in high concentration.

Most of the reported studies concerned with the structure of radical anions in solution have been based on either UV-visible or ESR spectrophotometric techniques[50]. Both methods are applicable to very dilute solutions of radical anions but, as will be shown in the subsequent sections, the structure and reactivity of radical anions is concentration dependent.

Screttas and Screttas[51–55] have recently published most interesting investigations on the structure of ketyl anions in solution at concentrations comparable to those of the preparative reactions. They have found that the aromatic ketyl anions $(Ph_2C=O)^{\dot{-}}\ M^+$ (M = Li, Na), $(Fl{=}O)^{\dot{-}}\ M^+$ (Fl=O = fluorenone, M = Li, Na, K), $(1\text{-naphthyl-COPh})^{\dot{-}}\ M^+$ (M = Li, K) and $2\text{-naphthyl-COPh})^{\dot{-}}\ Li^+$ produce paramagnetic solvent shifts of both the α and β proton bands of THF, which are proportional to the radical anion concentration, in the range 0.2–0.9 M (see below for wider ranges). The two molar paramagnetic solvent shifts, referred to the two bands of THF solvent, $\Delta\nu^{\alpha}_{m}$ and $\Delta\nu^{\beta}_{m}$, are

TABLE 1. 1,2-Migration reactions of organometals containing aluminium and other main group metals with $LiCH(Cl)SiMe_2Ph$[a]. Reprinted with permission from *J. Am. Chem. Soc.*, **110**, 646 (1988). Copyright (1988) American Chemical Society

Organometals	Products	Time (h)	Yield[b] (%)
i-Bu_3Al	*i*-$BuCH_2SiMe_2Ph$	6	80(62)
i-Bu_2AlCl	*i*-$BuCH_2SiMe_2Ph$	48	5
Pr_3Al	*n*-$PrCH_2SiMe_2Ph$	6	77(53)
Me_3Al	$MeCH_2SiMe_2Ph$	6	83
(*E*)-HeptCH=	(*E*)-*n*-HeptCH=		
	$CHSiMe_2Ph$	1	85(65)
$CHAl(Bu\text{-}i)_2$[c]	and *i*-$BuCH_2SiMe_2Ph$		9
i-Bu_2AlPh[d]	$PhCH_2SiMe_2Ph$	6	48
	and *i*-$BuCH_2SiMe_2Ph$		31
Bu_2Mg[e]	*n*-$BuCH_2SiMe_2Ph$	0.5	72
Bu_2Zn[e]	*n*-$BuCH_2SiMe_2Ph$	0.5	61
BuZnCl[e]	*n*-$BuCH_2SiMe_2Ph$	24	10
Bu_2Cd[e]	*n*-$BuCH_2SiMe_2Ph$	1	55

[a]Unless otherwise mentioned, all reactions were carried out under the standard conditions reported in the text.
[b]By GLC based on an organometal. The numbers in parentheses are isolated yield.
[c]Prepared by the reaction of DIBAH with 1-octyne.
[d]Prepared by the reaction of *i*-Bu_2AlCl with 1 equiv of PhLi.
[e]Prepared by the reaction of the corresponding metal dichloride with BuLi.

not equal, as they should be if the observed shifts were arising from bulk paramagnetic effects[51]. The difference between the two molar shifts has been accounted for on the basis of Fermi contact interactions. Examination of the cation dependence of the molar paramagnetic solvent shifts leads to the conclusion that the microscopic interactions between the odd electron of the anion and the solvent molecules are transmitted through the mediation of the cation. Other synthetically important conclusions drawn from the studies are that benzophenone and fluorenone ketyl anions do not tend to undergo disproportionation at high concentrations. Using potassium benzophenone it was also proved that the addition of 18-crown-6 as a co-solvent does not produce a 'naked anion' by complexing with the potassium cation as was usually assumed[51]. It appears that in the presence of this co-solvent a fraction of the paramagnetic species undergoes some transformation to a diamagnetic species.

It has been shown that the effect of solvents, and added co-solvents, exerts a marked influence on the structure of the reagents and this affects the mechanism and product distribution of the carbonylation reactions (see the following sections). In order to gain information about the influence on the structure of intermediates, Doctorovich and Nudelman[56] have studied the effect of radical concentration and of added benzene on the ^{13}C NMR of $Ph_2CO^{\cdot-}$ Li^+ in THF solution. As observed before by Screttas and Screttas[51], the bandwidths of the α and β C of the THF are proportional to the radical concentration, [I], in the range 0.2–1 M, but, as is shown in Figure 5, the plot of the bandwidth of the C_α deviates from the straight line at [I] > 1.2 M. Something similar is observed for the bandwidth of C_β but to a lesser extent. This result was confirmed with different starting materials and is interpreted as a measure of the amount of solvent molecules affected by each radical anion molecule (a sort of solvation shell). Calculations give a value of around 10 molecules of THF for each radical anion.

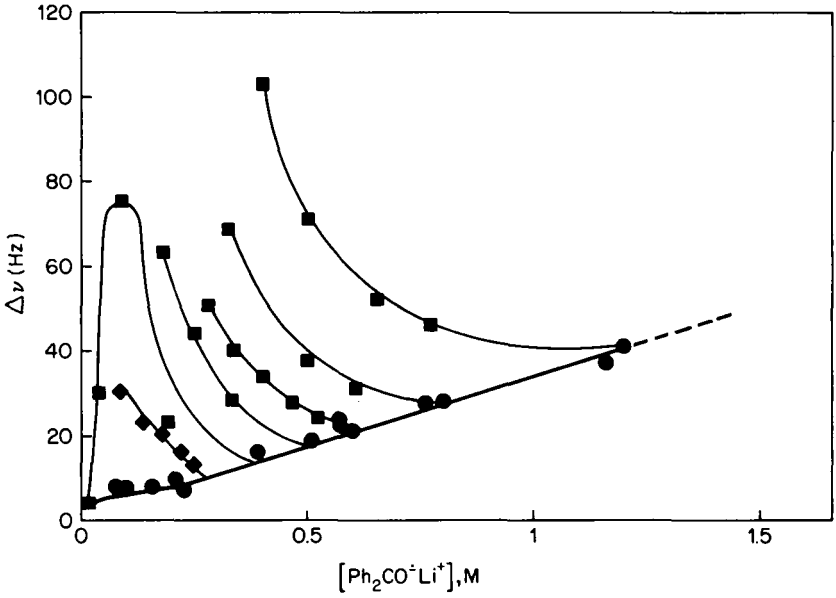


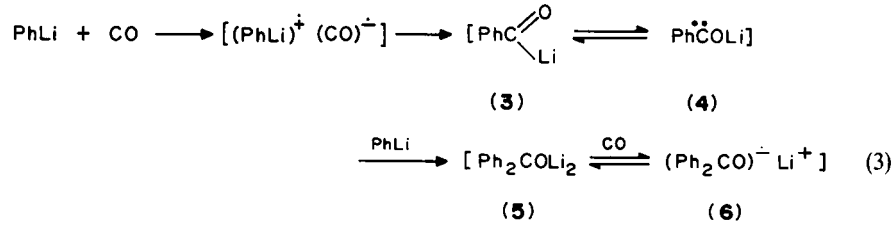
FIGURE 5. Bandwidth ($\Delta\nu$, Hz) of the ^{13}C NMR of the THF C_α signal in the presence of lithium benzophenone ketyl ($Ph_2CO^{\cdot-}Li^+$): ● pure THF (straight + broken line), ■ dilution with various amounts of benzene.

Although lithium benzophenone ketyl is known to be diamagnetic in benzene, dilution of the THF solution with benzene results in a spectacular increase in the bandwidth. Curves lines in Figure 5 show the increase in paramagnetism with respect to dilution with benzene: the bandwidth increases upon dilution with benzene up to a certain value of radical anion concentration, after which the bandwidth diminishes on further benzene additions, to reach the value of the pure THF at a certain benzene content in the solvent, and becoming diamagnetic in solutions of high benzene: THF ratios. These results were confirmed with different starting concentrations of the radical anion as shown in Figure 5. Once the maximum point of the curves is reached, the deep blue solutions (λ_{max} 593 nm) change to a clear greenish colour (no absorption in the visible region) indicating the gradual shift to diamagnetic species. All these results are indicative of a strong increase in the paramagnetism of the solutions due to the effect of benzene, in spite of the fact that the substrate is diamagnetic in pure benzene. This effect was found to be proportional to the benzene content and dependent only on the lithium benzophenone ketyl concentration[35]. These THF and THF–benzene solutions are stable for several days at room temperature. On the other hand, in the case of more crowded radical anions such as lithium phenyltrityl ketyl, Screttas and Screttas[53] found that disproportionation to the dianion and the neutral ketone occurs in a short time.

Very little is as yet known about the mechanism of formation of the radical anion in the insertion reactions, and about the mechanism of the electron transfer from the anion to the substrate. Possibly a step toward understanding this mechanism could be the elucidation of the mechanism of interaction between the radical anion and the ethereal solvent molecules in which the reactions are usually carried out. Screttas and Screttas[54] found that the rate of attenuation of the two molar paramagnetic shifts of both carbons of THF, as expressed by $\Delta\delta^{\alpha}_{m}/\Delta\delta^{\beta}_{m}$, is cation dependent. This ratio, which is independent of

the state of aggregation of the radical anion, may provide evidence that the amount of spin transferred to solvent nuclei is cation dependent. A mechanism for spin density transfer is proposed, and requires ternary complexing among the anion, the cation and the solvent molecules, and (at least) partial covalency in the bonding between the anion and cation. Spin density transfer is supposed to take place by a σ delocalization mechanism through covalent bonds. The same mechanism is proposed also for the electron transfer from anion to substrate. The mechanism of spin density transfer to solvent should include the following two steps: (1) transfer from anion to metal and (2) transfer from metal to solvent molecules. The Screttas and Screttas[54] mechanism of electron transfer is analogous to the 'inner-sphere' electron transfer mechanism of Taube[57], but here the metal provides orbitals of proper symmetry in order to delocalize the electron from the anion to the coordinated-to-cation substrate. As a support for the mechanism, the authors found evidence for hyperfine interactions between radical anions and alkyl halides, which proves that the substrates develop some covalency with the cation. The phenomenon is also cation dependent[54].

The intermediation of paramagnetic species in the carbon monoxide insertion into phenyllithium has been recently proved by Nudelman and collaborators[49] using ^{13}C NMR and ESR spectroscopy. The reaction of solid phenyllithium with carbon monoxide was run at 110 °C and ^{13}C NMR studies were carried out on the reddish purple residue dissolved in THF. A change of colour (which turned to blue) was observed upon dilution with THF which is consistent with the existence in the reaction mixture of species which are diamagnetic and are stabilized in the paramagnetic form(s) by interaction with the oxygenated solvent. (The electronegative oxygen in ketyls can attain coordination numbers as high as 6[58].) It was observed in different runs that the reaction mixtures produce a marked increase in the bandwidth of the THF C_α and C_β (as well as a certain shift of the signals). By comparison with the results observed with $Ph_2CO^{\cdot-}\ Li^+$ (Figure 5), the concentration of paramagnetic species in the reaction mixture could be calculated. It was found that it is in the range of concentration of the starting material, indicating that anion radicals are real intermediates in the reaction and not just artifacts produced in negligible side-reactions. The reactions of phenyllithium with carbon monoxide should then be reformulated as in equation 3.



(3)

The first acyllithium intermediate, **3**, exhibits some carbene character, **4**, with the second intermediate being an equilibrium between the lithium benzophenone dianion, **5**, and the lithium benzophenone ketyl, **6**. EPR studies on the reaction mixture (Figure 6a) demonstrate that not only the benzophenone ketyl **6** is formed (Figure 6b), but other radical anions could be present as well. A complete identification of the paramagnetic species present in this reaction is in progress.

Closely related to the bonding situations found in the several steps of this type of reaction is the recently published study of McGarrity and coworkers[37] on the reaction of butyllithium with benzaldehyde followed by the ri-NMR method. When benzaldehyde is injected into a large excess of butyllithium in THF at − 85 °C the reaction is over in less than 50 ms (Figure 7a). In contrast, the reaction can be readily followed when

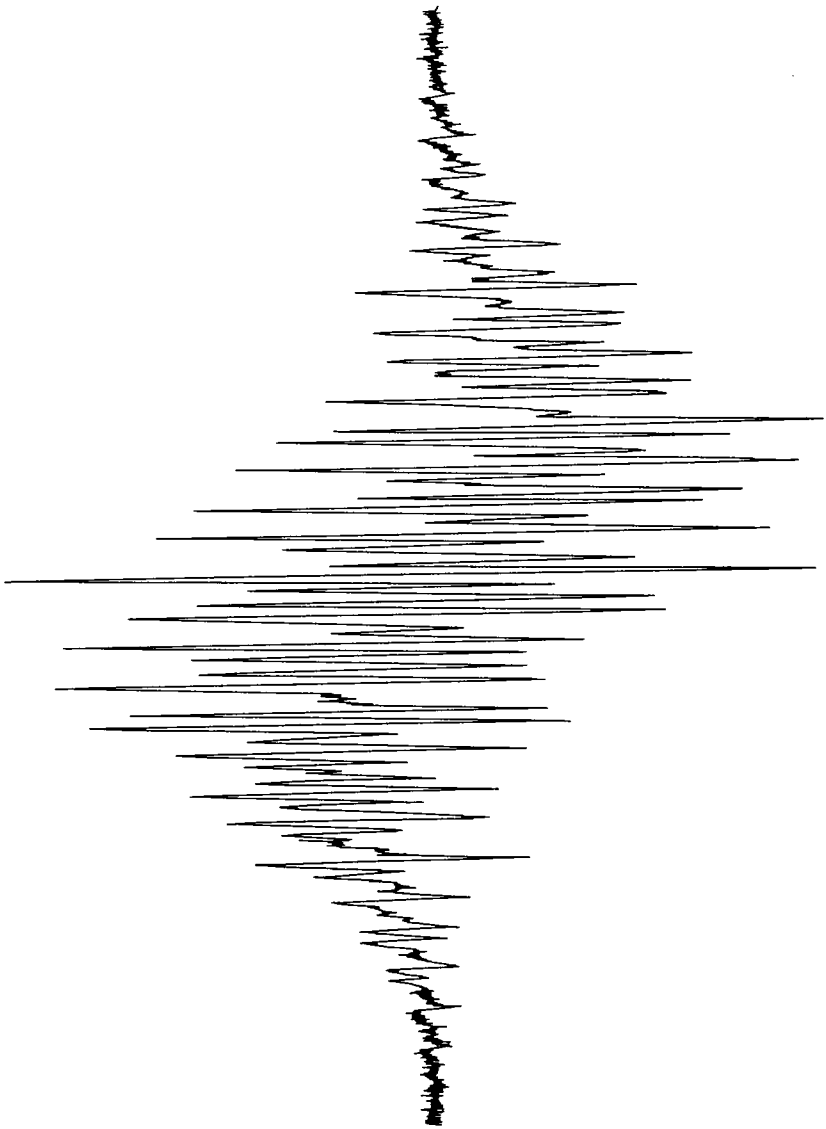


FIGURE 6a. ESR spectrum of the reaction mixture of phenyllithium with carbon monoxide in THF.

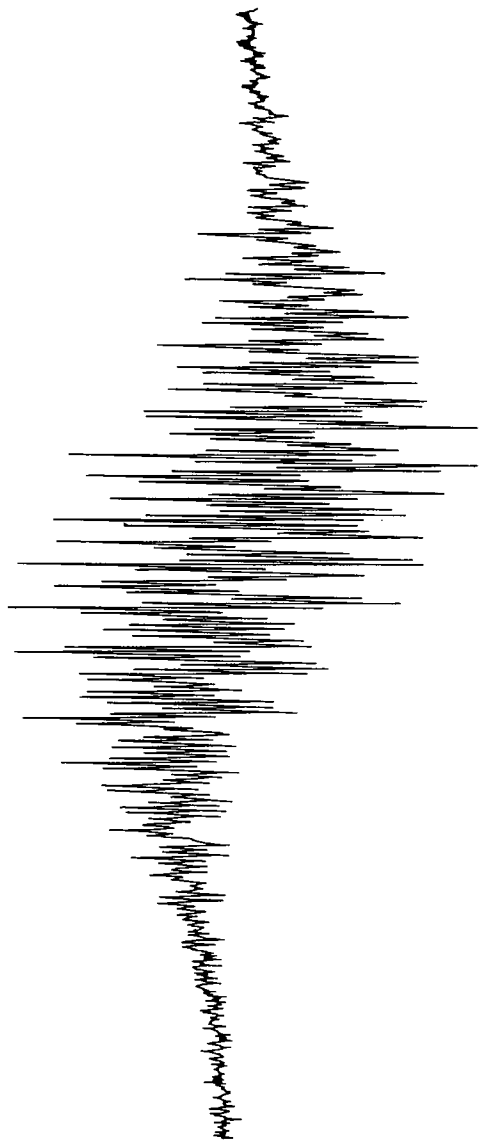


FIGURE 6b. ESR spectrum of $(Ph_2CO)^{\cdot-}$ Li^+ in THF.

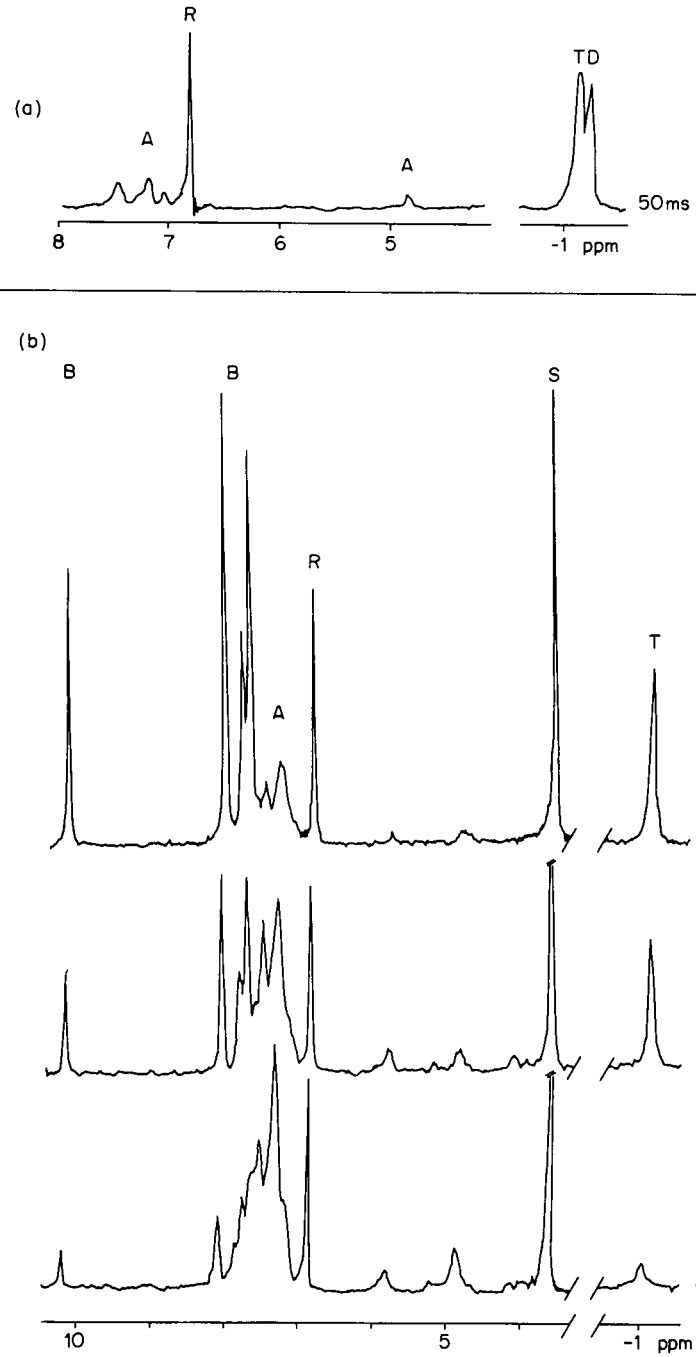
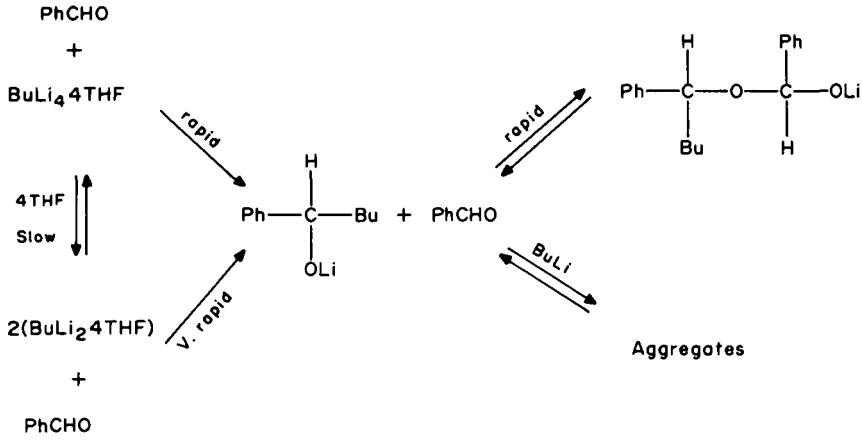


FIGURE 7. RINMR spectra following the injection (a) of benzaldehyde (14 mM) into butyllithium (81 mM) in THF-d_8 and (b) of butyllithium in toluene-d_8 (48 mM) into benzaldehyde (64 mM) in THF-d_8 at -85 °C. Reprinted with permission from *J. Am. Chem. Soc.*, **107**, 1813 (1985). Copyright (1985) American Chemical Society.

butyllithium in toluene-d_8 is injected into benzaldehyde in THF-d_8. (Figure 7b). Furthermore, no butyllithium dimer is visible during the course of the reaction. Obviously, under these conditions the dimer is consumed as rapidly as it is formed from higher oligomers. It can be observed that during the reaction not only are the alcoholate aromatic resonances poorly defined, but also other aliphatic resonances emerge rapidly at δ 5.74, 5.13 and 4.09 and then subside to leave the normal alcoholate methine resonances at 4.79. A further curious feature of the reaction emerges by examination of the concentration–time profiles of the reagents: the tetramer decreases more rapidly than can be accounted for by its dissociation into dimer. Therefore, the tetramer must also react directly with benzaldehyde[37]. However, the aldehyde apparently undergoes a further reaction, as its concentration not only decreases more rapidly than that of butyllithium but also goes through a minimum before attaining its final value.

McGarrity and coworkers[37] rationalize both the additional transient peaks and the anomalous variation in benzaldehyde concentration by the reaction sequence outlined in Scheme 1.



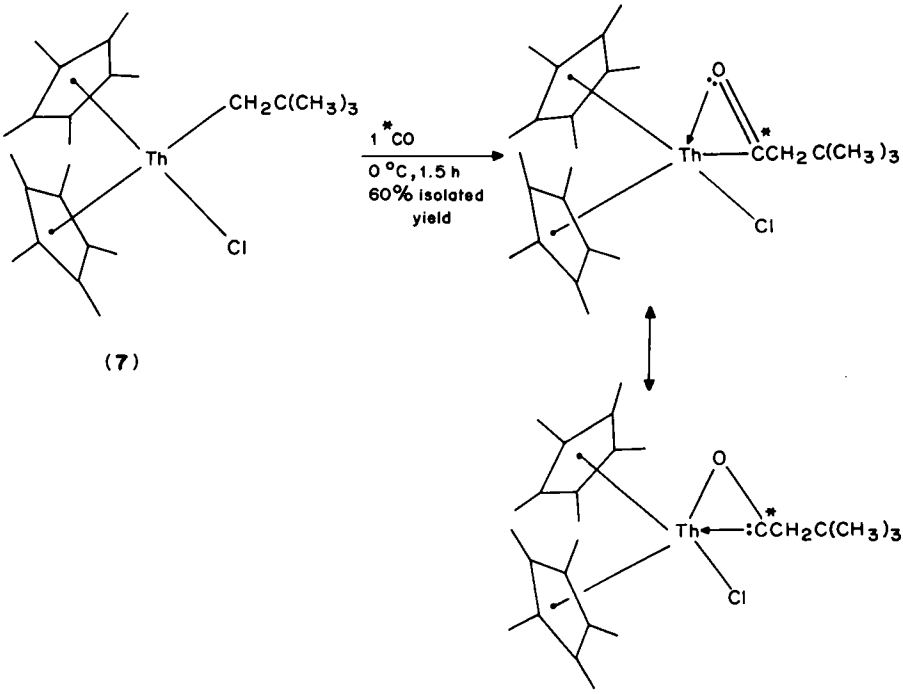
SCHEME 1

The alcoholate initially formed adds reversibly onto benzaldehyde to give a hemiacetal salt. Nucleophilic addition of the alcoholate can apparently compete only with that of the tetramer, as whenever excess dimer is present no side-reaction is evident. The ri-NMR studies indicate that the alcoholate is initially formed in a more reactive, non-equilibrated state. McGarrity and coworkers[37] have been able to identify peaks which are characteristic of this 'nascent' lithium 1-phenylpentanolate, and it is this 'nascent' product which partakes in side-reactions in competition with tetrameric butyllithium. The recognition of non-equilibrated species with enhanced reactivity is a significant outcome of these experiments, and its likelihood of formation in the related reactions discussed in the following sections should not be overlooked.

It has been shown that the solvents, and added co-solvents, have strong influence on the structure of the reagents. It has been recently reported by Screttas and Screttas[55] that the addition of metal alkoxides also affects the solubility, stability and the structure of radical anions in hydrocarbon media. In fact, solutions of $Ph_2C{=}O^{\cdot-}M^+$ (M = Li, Na) which are feebly paramagnetic in toluene show a marked increase of paramagnestism of dilution with $LiOCH_2CH_2OEt$ (from 15% to 73% of the reducing electrons being

unpaired, for M = Li)[55]. The radical anion is likely an intermediate in the carbonylation reaction of phenyllithium[49] and the formation of mixed alkoxide–ketyl clusters should affect the mechanism and product distribution in the reaction. Gunther and collaborators[59] have recently described the high utility of modern NMR spectroscopy, in particular the two-dimensional techniques, for the better characterization of aggregates and complexes, and the expectations that even more detailed information about structure and reactivity of organolithium compounds can be obtained in the near future.

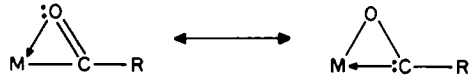
Although the acyl metal intermediates discussed in this chapter are too unstable to allow X-ray structural determinations by the currently available techniques, valuable information can be obtained by the more stable transition-metal dihaptoacyls. By carbonylation of neopentyl bis(pentamethylcyclopentadienyl)thorium chloride, **7**, in toluene, Marks and coworkers[60] prepared the insertion product **8**, as pale yellow plates from pentane (equation 4).



(7)

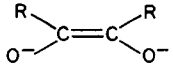
(8) (a) $^{*}C = {}^{12}C$
(b) $^{*}C = {}^{13}C$ (4)

The molecular structure of **8** was determined by single-crystal X-ray diffraction techniques and the thorium coordination geometry (Figure 8) is the familiar pseudo-tetrahedral arrangement. Especially noteworthy is the dihaptoacyl ligation: Th–O is 0.07 Å shorter than Th–C(acyl) and only slightly longer than the Th–O single-bond distance in complexed thorium enediolates. The metal–C–O angle in **8** is significantly small, while the metal–C_α–C_1 angle is larger than expected for a dihaptoacyl structure. All these features are in accord with an oxycarbene character of **8** (equation 5).



(5)

The intermediacy of a carbene-like dihaptoacyl activated by the actinide coordination environment had been proposed before in the rapid formation of enediolate (**9**) complexes obtained by carbonylation of $M[\eta^5\text{-}(CH_3)_5C_5]_2R_2$ compounds (M = Th, U; R = alkyl).



(**9**)

It is very significant that coupling products like **9** have been also isolated by Nudelman and coworkers[61,62] in the carbonylation of aryllithium compounds (see Section II.C.1) indicating that the aroyl intermediates in those reactions should also have a *carbene-like* structure, as proposed (Equation 3).

Particularly interesting is the irreversible reaction of **8** with excess CO (0.66 atm) in toluene to yield the dark purple product **10** (equation 6). The molecular structure of **10** was determined by single-crystal diffraction techniques and it was found that a *coupling*

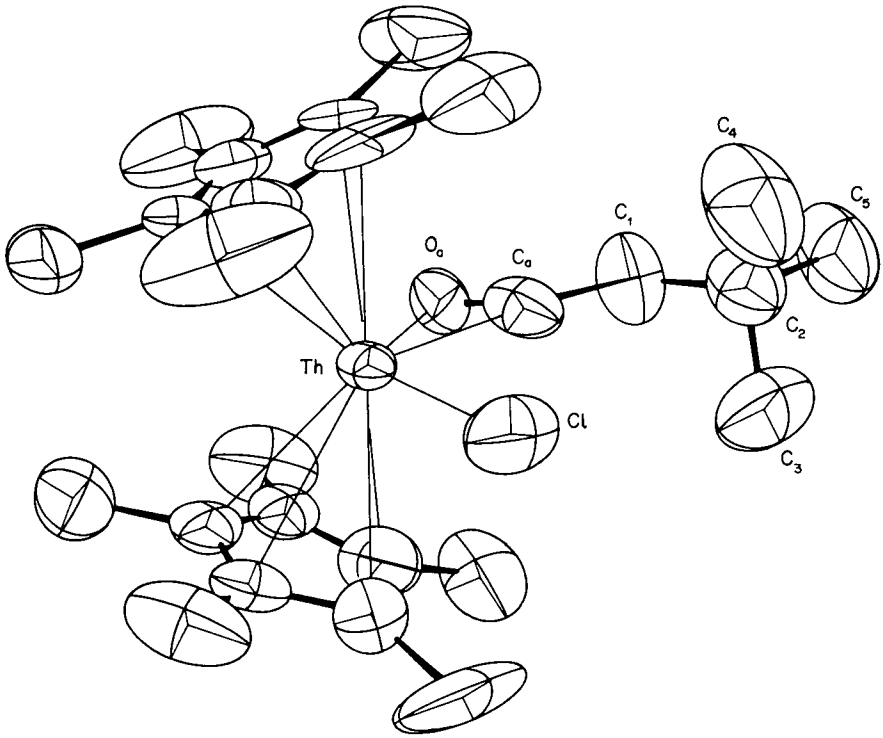
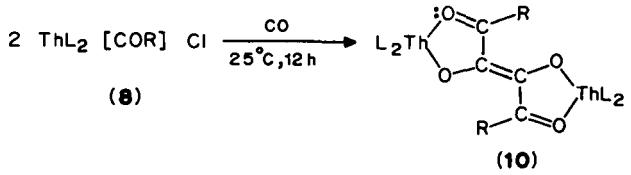


FIGURE 8. ORTEP drawing for $Th((CH_3)_5C_5)_2(\eta^2\text{-}COCH_2C(CH_3)_3)Cl$. Reprinted with permission from *J. Am. Chem. Soc.*, **102**, 5394 (1980). Copyright (1980) American Chemical Society.

of four CO functionalities has occurred to produce a centrosymmetric dimer with a unique, bridging enedione diolate ligand **10** (equation 6).



(8) (10) (6)

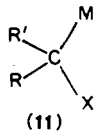
At present, the most plausible pathway from **8** to **10** appears to involve the addition of CO to the coordinated carbene and further coupling. Compounds arising from a double carbonylation of organolithium compounds have also been isolated in the reaction of phenyllithium with carbon monoxide[61] (see Section II.C.1).

B. Theoretical Studies

Due to the high instability and reactivity of the carbonyl anions, R—C̄=O, little is known experimentally about their energies, geometries or electronic structures. Nevertheless, because of their practical importance in organic synthesis, they were the subject of serious theoretical calculations, most of them by Schleyer's group[63]. Recent theoretical developments make it possible to optimize geometries and to use more sophisticated basis sets and computational levels to provide reasonably accurate structures and energies both for the anions[64,65] and for the corresponding organometallic species[66–68]. Such geometry optimization led to the discovery of rather remarkable non-tetrahedral bridged structures[66] and also revealed that the energies of standard geometry forms[63] were often not representative[69].

A commonly cited work on the calculated thermodynamic stability of carbonyl anions is Schleyer's[64] molecular orbital examination. Schleyer used the semiempirical MNDO[70] method for the study of large carbanions and MNDO and '*ab initio*' (the Gaussian 76 series of programs were initially employed)[71] for the smaller anions. Since diffuse orbitals are needed for proper '*ab initio*' descriptions of carbanions[72], they augmented the standard 4-31G basis by a set of diffuse s and p valence orbitals on all first-row atoms[73]. Although the geometries and energies of most of the smaller anions were then improved by further calculations, most of the proton affinities calculated by that time agreed fairly well with the experimental values. Nevertheless, the thermodynamical instability of these species was clear and consistent with the current thinking that 'carbonyl anions are inaccessible as practical synthetic intermediates'[64].

Since early computational studies[63b] had been concerned with the possible involvement of d orbitals in the bonding, Schleyer's group[67] then examined the importance of second-row d orbitals on the structures and stabilities of α-heterosubstituted organolithium and organosodium compounds of the type **11** and **12**. They found that the d-orbital effects do not contribute significantly to the stabilization energies of second-row-substituted carbanions, although the geometries are improved significantly. They also found that the polarizability of such atoms and/or the availability of low-lying σ^* orbitals are more important than the d-orbital effects.



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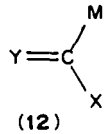
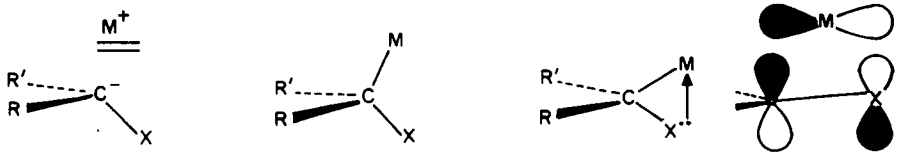


(12)

Substituent effects on anion stabilities in solution depend on the nature of the species involved. They might exist as 'solvent separated ion pairs' (**13**) or as 'contact ion pairs' with more covalent character (**14**). In that case, coordination of the metal to the lone pairs of the substituents, X, can occur and an 'extra stabilization' expected. The bridging between the M and the heteroatom may arise either from Coulombic attraction $M^{\delta+}$ and $X^{\delta-}$, as represented by **15**, or from a covalent interaction of the high-lying HOMO of the carbanion and a low-lying vacant p orbital of the metal, as shown in **16**. Therefore, the nature of the metal as well as the nature of the substituent should influence the structure and stability of these species[67].



(13) (14) (15) (16)

For compounds where X = NH_2, OH, F, Cl Schleyer[67] found that the bridged structures are more stable than the unbridged isomers. Thus, bridged $LiCH_2OH$ is about 14 kcal mol^{-1} lower in energy than the unbridged *anti* isomer; in contrast, the *anti* hydroxymethyl anion is about 6 kcal mol^{-1} more stable than the *syn* conformation. The geometrical parameters are indicated in Figure 9. The role of the metal in stabilizing the carbanion is shown by a difference of 9 kcal mol^{-1}. Also, in the case of $NaCH_2OH$ the bridge structure is preferred. The thermodynamic consequences of bridging are negligible, however, and the hydroxy group actually stabilizes $NaCH_2OH$ slightly less than it stabilizes $^-CH_2OH$. This observation can be generalized to other cases studied and the results can be summarized as follows[67]:

(1) The tendency for bridging interaction between the metal and the α heteroatom follows the order of stabilities of the corresponding M^+XH_n complexes. Li^+ bridges more effectively than Na^+; presumably this trend will continue down the periodic table with K^+, Rb^+ and Cs^+, larger and more ionic cations.

(2) The second-row heteroatoms show little tendency to bridge with either Li or Na, α-NR_2, OR and F-substituted organolithiums are strongly stabilized by bridging. These compounds are 5–10 kcal mol^{-1} more stable than the anions and as much as 20 kcal mol^{-1} more stable than the unbridged conformations. Dipolar interactions also favor the *syn* conformations.

(3) Hyperconjugative and polarization stabilization by SiH_3, PH_2 and SH are effectively eliminated in the corresponding organolithium and organosodium compounds. Only a small residual stabilization of the organometallic remains.

Figure 10 summarizes the energetic results pictorially. The extra stabilization of bridged organolithium compounds (X = NH_2, OH, F) and the greatly diminished stabilization of $LiCH_2X$ and $NaCH_2X$ when X = SiH_3, PH_2 and SH are quite obvious. The $NaCH_2X$ species have the same relative energies as the free anion for first-row X substituents; for the second-row groups, the order of stabilities is the same as that for $LiCH_2X$.

Since, as was shown earlier in solution the organometallics are aggregated, the stabilities of anionic species in solution should follow an order intermediate between those calculated for the free anions and for the organometallics, since the anion is never free. The calculations on monomers overestimate the tightness of association of the metal cation to the anion.

Schleyer and coworkers[68] have recently published an extensive calculation of the

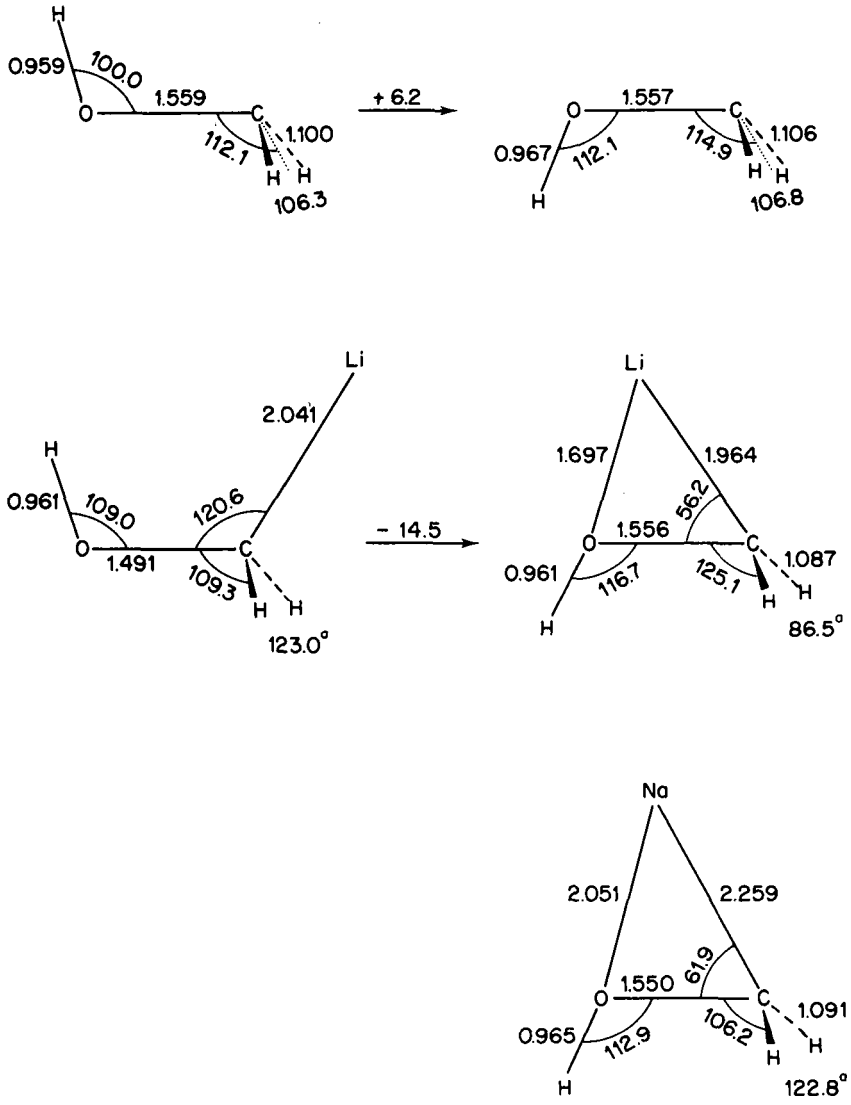


FIGURE 9. Geometries of oxygen compounds. Reprinted with permission from *J. Am. Chem. Soc.*, **106**, 6469 (1984). Copyright (1984) American Chemical Society.

structures and energies of main group metal formyl complexes which completes this subject and extends the conclusion to other main group metal complexes.

On the basis of previous experimental evidence (see Sections II.A. and II.C) the formyl moiety, **17**, was assumed to be in equilibrium with an alkoxy-carbene structure. Since formyl and acyl anions have adjacent carbon and oxygen lone pairs available for coordination, either η^2 or η^1 coordination to metal is possible (**18** and **19**, respectively).

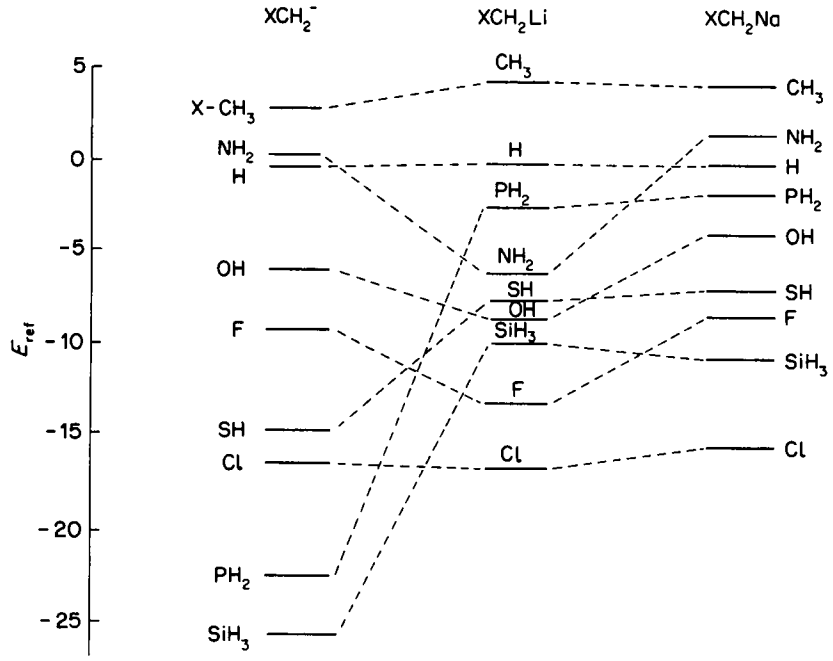
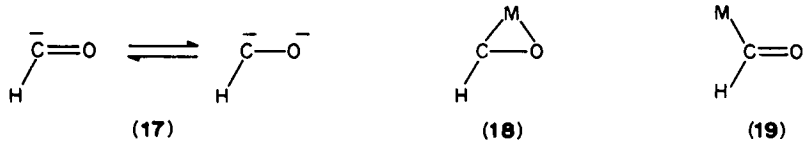


FIGURE 10. Comparison of stabilization energies of substituted methyl anions and their corresponding organosodium and organolithium compounds. Reprinted with permission from *J. Am. Chem. Soc.*, **109**, 2555 (1987). Copyright (1987). American Chemical Society.

For the smallest system, the lithium formyl complex, an extensive study was undertaken to check the performance of basis sets for geometries and relative energies and correlation energies; and in this case two additional structures were considered: a CO molecule attached to lithium hydride by C or O coordination, (structures **20** and **21** respectively); **20** is a model for a simple metal carbonyl, **21** for a hypothetical 'isocarbonyl' complex.



(20) (21)

Calculations were performed with a wide variety of basis sets: diffuse sp orbitals on carbon and oxygen and d functions on all non-hydrogen atoms were added (6-31G basis sets) as well as inclusion of correlation corrections in some cases. All calculated structures were found to be planar except formylborane and formylalane which had C_s symmetry and hydrogens on both sides of the mirror plane. Examination of the O–C–M angles and

TABLE 2. Geometries of formaldehyde and formyl–metal complexes at various levels[a]. Reprinted with permission from *J. Am. Chem. Soc.*, **109**, 2555 (1987). Copyright (1987) American Chemical Society

		3-21 + G	3-21 G*	6-31 G*
H_2CO		1.207[b]	1.182	1.184
BeH, η^2	CO	1.291[b]	1.254	1.249
	CBe	1.742	1.686	1.673
	OBe	1.592	1.752	1.582
	OCBe	61.2	63.4	63.6
	[BeH][c]		4.18	
	[O][d]		9.26	
BeH, η^1	CO	1.233[b]		1.207
	CBe	1.741		1.738
	OBe	2.526		2.471
	OCBe	115.2		112.9
BH_2perp, η^1	CO	1.221[b]	1.198	1.197
	CB	1.576	1.587	1.591
	OB	2.446	2.342	2.425
	OCB	121.4	113.7	120.2
	[BH_2][c]		6.42	
	[O][d]		9.26	
BH_2 plan, η^1	CO	1.230		1.197
	CB	1.601		1.611
	OB	2.482		2.457
	OCB	121.9		121.4
Na, η^2	CO	1.288	1.237	1.239
	CNa	2.256	2.180	2.243
	ONa	2.046	2.090	2.165
	OCNa	63.8	69.2	70.3
	[Na][c]		10.10	
	[O][d]		9.33	
MgH, η^2	CO	1.296	1.251	1.247
	CMg	2.140	2.078	1.074
	OMg	1.973	1.957	1.995
	OCMg	64.7	66.8	68.8
	[Mg][c]		12.12	
	[O][d]		9.33	
AlH_2 perp, η^2	CO	1.290	1.249	1.243
	CAl	2.039	1.973	1.956
	OAl	1.930	1.876	1.913
	OCAl	66.5	66.9	69.4
	[AlH_2][c]		14.14	
	[O][d]		9.33	
AlH_2 perp, η^1	CO	1.240		
	CAl	2.044		
	OAl	2.820		
	OCAl	116.2		
AlH_2 plan, η^1	CO	1.236		1.201
	CAl	2.048		2.030
	OAl	2.885		2.825
	OCAl	121.0		119.7

[a]Distances in angstroms, angles in degrees.
[b]3-21 G optimization.
[c]Electron population on the metal fragment including hydrogens.
[d]Electron population on oxygen.

oxygen–metal distances (Tables 2 and 3) suggests that LiCHO, HBeCHO, NaCHO, HMgCHO and H_2AlCHO adopt η^2 coordination[68]. All of these structures are quite similar. The long C=O distances (1.24–1.25 Å; 1.18 Å in H_2CO at the same level of theory) indicate a significant perturbation of the carbonyl group. As a test, formyllithium was optimized with correlation corrections at the MP2/6-31G* level. In Table 3, it can be seen that correlation has rather minor effects, although the C=O bond length is somewhat lengthened compared to the Hartree–Fock structures. All of the η^2 coordinated metals carry large positive charges (*ca* +0.85); the interaction with the negatively charged oxygen provides electrostatic stabilization.

Inherent in the η^2 structures are extremely small O–C–M angles (*ca* 65°); this restricts the covalent overlap between the metal and carbon. These calculated structures parallel those in crystal structures of η^2 acyl–metal complexes. Fachinetti and collaborators[74] have reported O–C–M angles of 78.6° and C=O bond lengths of 1.21 Å with their acyl–zirconium complexes, which is fairly close, taking into account that zirconium is much larger than any of the metals studied.

Optimization of formylborane led to a η^1 coordinated structure, **19**, with the normal carbonyl bond length, 1.20 Å, which characterizes all of the η^1 species. The moderate positive charge on the borane fragment (+0.58) implies a strong covalent contribution to the carbon–boron bond resulting from the small electronegativity difference between these elements[68].

Another important feature has been deduced from calculations: in the η^2 formyl complexes, the carbonyl bonds are rather long (*ca* 1.25 Å) and the oxygen carries a large

TABLE 3. Geometries of LiCHO isomers at various levels[a]. Reprinted with permission from *J. Am. Chem. Soc.*, **109**, 2556 (1987). Copyright (1987) American Chemical Society

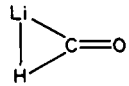
			3-21G	3-21G*	6-31G*	6-31+G*	MP2/6-3G*
LiCHO, η^2	2	CO	1.280	1.246	1.243	1.244	1.277
		CLi	1.938	1.895	1.902	1.907	1.891
		OLi	1.746	1.762	1.782	1.774	1.835
		OCLi	61.8	64.1	65.1	64.5	67.6
		CH	1.098		1.104	1.104	1.114
		OCH	113.4		112.8	112.6	112.4
		[Li]		2.12[b]	2.12[c]		
		[O]		9.28[b]	8.87[c]		
OC–LiH	4	CO	1.121		1.107	1.107	
		CLi	2.267		2.339	2.327	
		LiH	1.641		1.643	1.639	
CO–LiH	5	CO	1.138		1.119	1.119	
		OLi	1.928		2.042	2.027	
		LiH	1.654		1.641	1.638	
(LiH)(CO)	6	CO	1.208		1.191	1.192	
		CLi	1.927		1.947	1.930	
		OCLi	166.5		163.7	167.1	
		CH	1.240		1.209	1.215	
		OCH	113.6		112.4	111.8	
		LiH	2.101		2.180	2.115	

[a]Distances in angstroms, angles in degrees.
[b]Integrated electron population on lithium and oxygen at 3-21G*.
[c]Natural population on lithium and oxygen at 6-31G*.

negative charge (*ca* − 1.3), therefore, there appears to be a contribution from an alkoxy-carbene resonance form, **17**, in the formyl ligand. This conclusion, achieved by theoretical calculations, agrees satisfactorily with the experimental results obtained in 1981[62] in the reactions of PhLi/CO, where a contribution of the carbene form of the benzoyl lithium intermediate was proposed to explain the stereospecific formation of the diacetate of the *cis* enol of benzoin[60] (see Section II.C.1). Examination of the population effects in the π MOs shows that much of the increase in the oxygen electron density of the formyl–metal complex (e.g. 1.73 electrons in HBeCHO) is the result of a π-bond polarization which indicates that the formyl anion in these complexes has significant alkoxy-carbene character.

By limiting lithium to a basis set that contains only a 1s shell, the lithium can be forced to interact completely ionically. This drastic change in basis sets results in only small changes in geometry. Thus, the η^2 geometry is indeed given by a totally ionic model. Previous work[75–77] indicates that the carbon–lithium bond in general is largely ionic. Since the other η^2 formyl–metal complexes have structures and electron distributions similar to formyllithium, their carbon–metal bonds are also expected to be dominated by ionic interactions[73].

Recently, Koga and Morokuma[78,79] have investigated theoretically the CO insertion into transition metal–carbon bonds. Some EHT studies of transition metal and actinide acyl complexes[80,81] have also been published. Schleyer and coworkers[68] have studied the mechanism of the simplest system, namely the LiH/CO reaction, at high levels. They found that lithium hydride and carbon monoxide first form a complex. Of the two possibilities, lithium attached to oxygen or to carbon, in linear geometries calculation with a larger basis set shows that HLi—OC, **20**, is slightly more stable than HLi—CO, **21**, and also is the global minimum at the Hartree–Fock level. This result had also been anticipated by Nudelman and Vitale[60] in the mechanism proposed in 1983 for the carbon monoxide activation in the reaction of phenyllithium with carbon monoxide. Because of the known change in the CO dipole moment direction at correlated levels[82], inclusion of electron correlation corrections reverses the relative stability of the two linear complexes. Nevertheless, both isomers, and also formyllithium, LiCHO, are very close in energy[68].



(22)

The transition structure **22** has been located on the route from HLi—CO to formyllithium, LiCHO, and the best theoretical estimate of the activation energy is about 19 kcal mol^{-1}[68]. This relatively small value in the gas phase indicates that LiCHO can clearly serve as a catalyst or intermediate for further reactions, especially in solution where solvation or aggregation effects may reduce the overall energy. The relative energies of the other formyl systems can be assessed by means of equations 7 and 8. Equation 7 gives the energy involved by inserting CO into the MH bond. Equation 8 evaluates the stabilization energy of the metal ligands bound to the formyl with respect to CH_3M as a standard.

$$MH + CO = MCHO \tag{7}$$

$$CH_3M + HCHO = MCHO + CH_4 \tag{8}$$

Only the formation of the η^2 coordinated species has favorable energies in equation 7, and lithium is by far the best. This may be due to the small radius of the lithium cation

resulting in a very effective electrostatic interaction with the oxygen of the carbonyl group. Most of the reaction energies for both equations 7 and 8 are within the 0 to $\pm 5\,kcal\,mol^{-1}$ range[68].

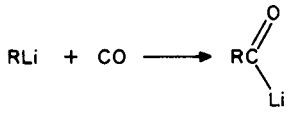
Another important conclusion of potentially practical significance has been deduced from the calculations. Since they show that the overall reaction for the system LiH—CO is almost thermoneutral, the authors conclude that 'these findings may encourage attempts to isolate derivatives of such lithium–carbonyl species'[68].

It has been shown that η^2 coordination is characteristic even of wholly ionic bonding, and hence it can be expected to apply to any metal carbonyl with some ionic character. Thus, the η^2 coordination seems to be more important than may have been appreciated in the past[68].

C. Carbonylation Reactions

1. Organolithium compounds

The carbon monoxide insertion into the C—Li bonds of organolithium compounds, to give the powerful nucleophilic acylating agent, the acyl lithium intermediate **23** (equation 9), has been sought by many group since early times. Nevertheless, it was not until the present decade that this reagent could be trapped.



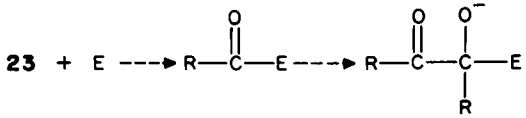
(9)

(23)

The first report of a reaction between an organolithium compound and carbon monoxide was by Wittig[83], who in 1949 reported in a review (without details) that phenyllithium reacts with carbon monoxide to give α,α-diphenylacetophenone, **24**. The formation of this product is not straightforward as was demonstrated by Jutzi and Schroeder[84] 30 years later. It was suggested that this unexpected product was formed by the reaction course shown in Scheme 2.

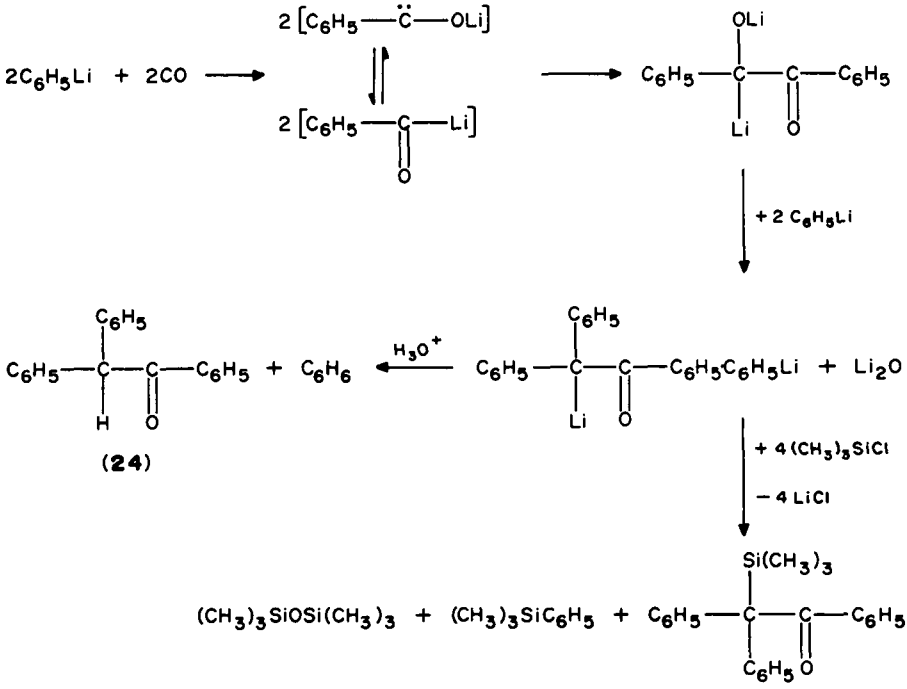
Jutzi and Schroeder[84] isolated compound **24** in 86% yield upon hydrolysis of the reaction mixture, but silylation of the reaction mixture prior to hydrolysis gave the analogous silylated product (Scheme 2), in only a 15% yield. This finding shows only one of the many intriguing results observed in the complex reaction 9.

One important and obvious problem with the process shown in equation 9 is that the formerly formed acyllithium reagent **23** is expected to be highly reactive. The general complication shown in equation 10 is overshadowed by the inherent instability of the lithium carbonyl anion, **23**. The high energy of these intermediates is manifested in their propensity to undergo secondary reactions, as has been frequently voiced[14–16]. Reaction of the acyllithium reagent with unreacted organolithium compound to give the organic dianion (equation 11) or coupling of two molecules of intermediate **23** to produce the dimeric intermediate (equation 12) are just two of the many complications that have been observed in the reactions generally shown by equation 9.

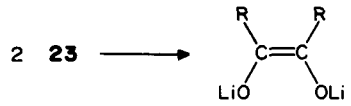


(10)

(11)



SCHEME 2



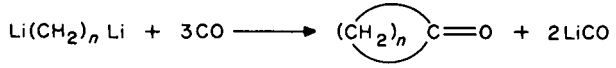
(12)

Thus, in contrast to the solution stability of most alkyllithiums and aryllithiums[39], stable solutions of acyllithiums apparently cannot be prepared and it can be expected that the reactions with this reagent will not be 'clean' and that undesired reactions of the reagent would lower the yield of the desired product unless special ways to prevent these reactions are designed.

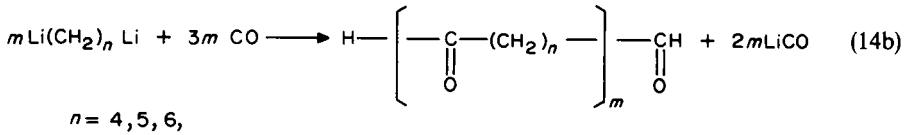
Prior to the work by Jutzi and Schroeder, Ryang and Tsutsumi[85] reported the preparation of symmetrical ketones by the reaction of alkyl- and aryllithium reagents with carbon monoxide in ethyl ether or petroleum ether at − 78 °C. The yields of ketones ranged from 28% (diamyl ketone) to 55% (benzophenone). The reaction was written as in equation 13: it was assumed that carbon monoxide attacked organolithium compounds nucleophilically and abstracted the lithium as lithium carbonyl, producing symmetrical ketones, but no mechanistic studies were carried out.

(13)

The reaction was then applied to organic dilithium compounds to produce polyketones and cyclic ketones (equation 14)[86]. High dilutions favour the formation of the cyclopentanone: thus 0.1 mol of tetramethylenedilithium in 200 ml of diethyl ether is reported to be converted into cyclopentanone (2.5%) and into the polyketone (56%); higher dilution (0.025 mol in 400 ml ethyl ether) changes the yields to 40 and 16%, respectively[86].



(14a)



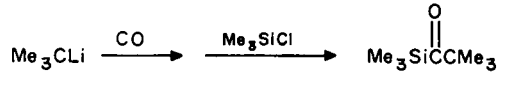
(14b)

$n = 4, 5, 6,$

Nevertheless, further attempts by Whitesides and coworkers[87] to reproduce the isolation of benzophenone in the reported yield[85] from the reaction of phenyllithium and carbon monoxide in diethyl ether at $-70\,^{\circ}C$ were unsuccessful, and, benzophenone was obtained in 26% yield only[87].

Jutzi and Schroeder[84] studied also the reaction of butyllithium with carbon monoxide and the results were similar to those outlined for the phenyllithium reaction in Scheme 2. Hydrolysis of the reaction mixture gave 51% of $(C_4H_9)_2CHC(O)C_4H_9$. Addition of the reaction mixture to trimethylsilyl chloride in ethyl ether gave, after reflux, the silylated product: $(C_4H_9)_2C(SiMe_3)C(O)C_4H_9$ (37%). An almost quantitative yield of the ketone **24** was achieved almost 10 years later by Nudelman and Vitale[88] by the heterogeneous reaction of solid phenyllithium and carbon monoxide at high temperature (110 °C).

Jutzi and Schroeder[84] carried out an experiment of some significance with *t*-butyllithium. When a hexane solution of this reagent was carbonylated, at room temperature, a vigorous reaction occurred to give a dark-red solution. When this solution was added to trimethylchlorosilane in ethyl ether/THF, the acylation product was obtained in 15% yield (equation 15).



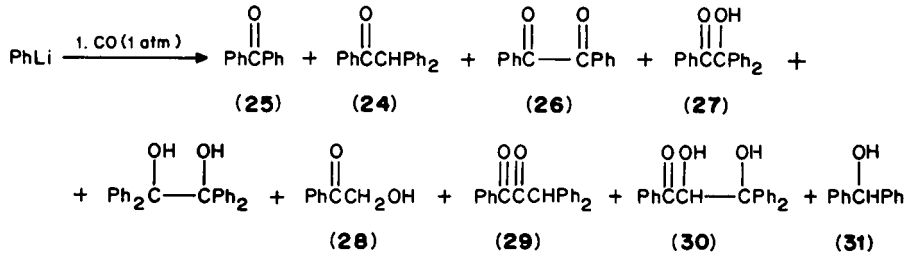
(15)

Although the pivaloylsilane yield was low, the fact that any quantity at all of this material was obtained is interesting and significant: this is the first report of the formation of the expected acylation product in a reaction of an RLi + CO-derived reagent. Apparently, the important steric hindrance around the acyllithium moiety prevents its further reaction with the starting *t*-butyllithium or with the trimethylacyllithium first formed.

A landmark in the investigation of the reaction of organolithium reagents with carbon monoxide[89] was the detailed, thorough study by Whitesides and collaborators[87] of the PhLi/CO interaction.

The reaction carried out in diethyl ether solution at $-78\,^{\circ}C$ and 1 atm carbon monoxide pressure is over in *ca* 6 h, while at 0 °C it is complete in 3–4 h. A careful identification of the reaction products led to: benzophenone (**25**), α,α-diphenylacetophenone (**24**), benzil (**26**), α,α-diphenyl-α-hydroxyacetophenone (**27**), α-hydroxy-

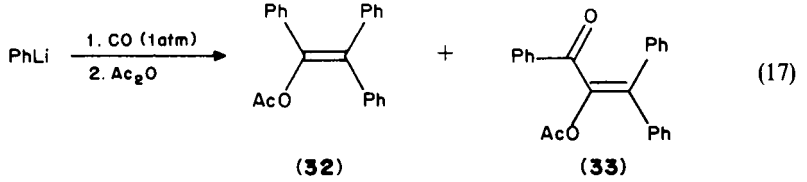
acetophenone (**28**), 1,3,3-triphenyl-1,2-propanedione (**29**), 1,3,3-triphenyl-2,3-dihydroxy-1-propanone (**30**) and benzhydrol (**31**) (equation 16).



(16)

Phenyllithium prepared by the reaction of bromobenzene with lithium metal gives a completely homogeneous reaction with carbon monoxide, while the reagent prepared by transmetallation of diphenylmercury(II) with lithium metal or by metal–halogen exchange between butyllithium and iodobenzene gives heterogeneous reactions in the latter stages; nevertheless, in all cases the product distribution was similar.

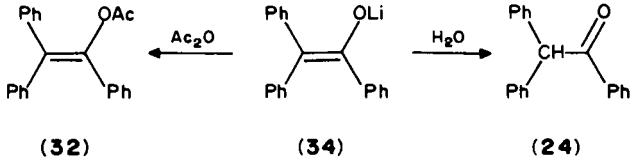
When reaction mixtures were quenched with acetic anhydride before hydrolysis, only two major products were isolated: 1-acetoxy-1,2,2-triphenylethylene (**32**) and 1-benzoyl-1-acetoxy-2,2-diphenylethylene (**33**) (equation 17). The combined yields of these materials is approximately 50–60%: **32** dominates at room temperature, **33** at low temperature[87].



(17)

The absence of triphenylcarbinol as a product indicates that benzophenone does not appear in the reaction mixture until phenyllithium has been completely consumed. This conclusion was strengthened by treating the reaction mixture with lithium aluminium hydride prior to hydrolysis; the amount of benzophenone observed after hydrolysis was nearly the same as observed in the absence of lithium aluminium hydride. Any benzophenone present before hydrolysis would have been reduced to benzhydrol by $LiAlH_4$.

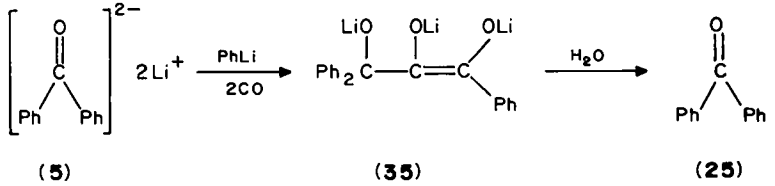
Since **32** replaces **24** in room temperature reaction mixtures quenched with acetic anhydride, the immediate precursor of **24** before hydrolysis is probably the corresponding lithium enolate **34** (equation 18).



(18)

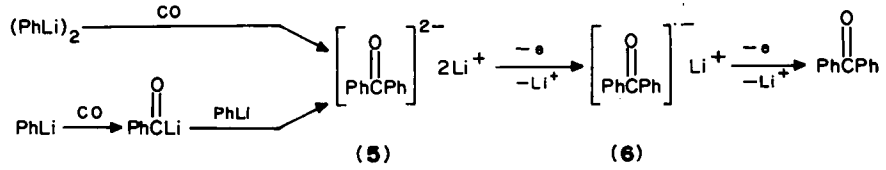
Similarly, the observation that **25**, **28** and **29** are replaced by **33** on acetic anhydride

treatment of product mixtures obtained at low temperature suggests that these materials share a common precursor. Isolation of compound **30** and determination of the product yields of the reaction of phenyllithium with carbon monoxide by isotopic dilution techniques led to the conclusion that part of the yield of benzophenone obtained by GLPC comes from partial decomposition of **30** to **25** in the GLPC injection port[87] (equation 19).



(5) (35) (25) (19)

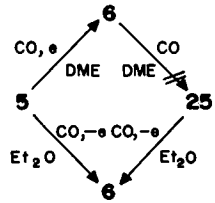
Two pathways have been proposed for the formation of benzophenone: carbon monoxide insertion into a phenyllithium dimer would yield the dilithium benzophenone dianion (**5**); alternatively, carbon monoxide insertion into phenyllithium monomer could yield a transitory benzoyl species which could be converted into **5** by reaction with a second molecule of phenyllithium (the state of aggregation of phenyllithium under the conditions of the experiments was unknown by that time)[87] (equation 20).



(5) (6) (20)

It has been shown by UV spectroscopic studies[87] that both intermediates, **5** and **6**, are observed in the reaction of phenyllithium with carbon monoxide; intermediate **5** is formed mainly when carbon monoxide is added to a large excess of phenyllithium.

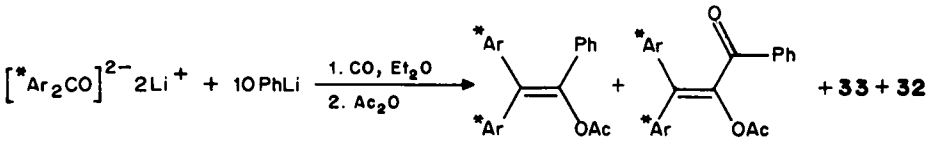
Carbon monoxide is an effective one-electron oxidant toward a variety of aromatic radical ions and dianions and it has been demonstrated that it is also capable of oxidizing **5** and **6** to benzophenone in diethyl ether[87]. The observation of approximately equal yields of benzophenone and benzhydrol, characteristic of **6**, after reaction and hydrolysis of either **5** or **6** with carbon monoxide in DME contrasts with the detection of benzophenone alone after reaction and hydrolysis of these substances in diethyl ether[87] (equation 21).



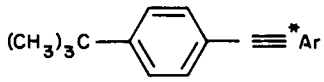
(21)

It was possible to establish by labelling experiments that the benzophenone moiety of **5** was incorporated into both high- and low-temperature products on reaction with phenyllithium and carbon monoxide (equation 22). The labelling experiments were run

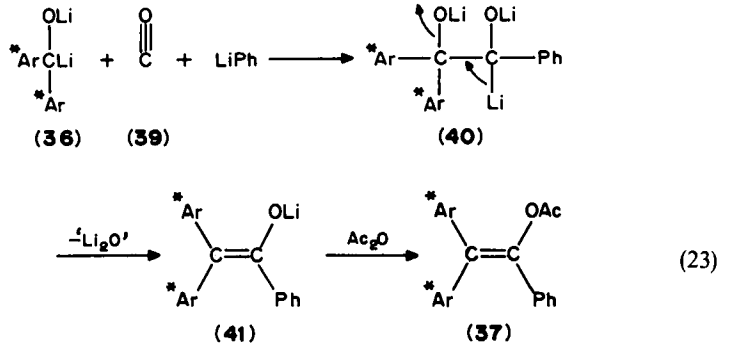
with 4,4'-di-*tert*-butylbenzophenone (**36**) as the labelled benzophenone, for practical reasons.



(**36**) (**37**) (**38**) (22)



The proposed reaction sequence for the transformation of **36** to **37** involves nucleophilic addition of the lithium benzophenone dianion to the initially formed benzoyllithium, or nucleophilic reaction of phenyllithium with an adduct of **5** and carbon monoxide (**39**) to form intermediate **40**. Elimination of the elements of lithium oxide from **40** yield the lithium enolate of **37**, intermediate **41**, (equation 23).

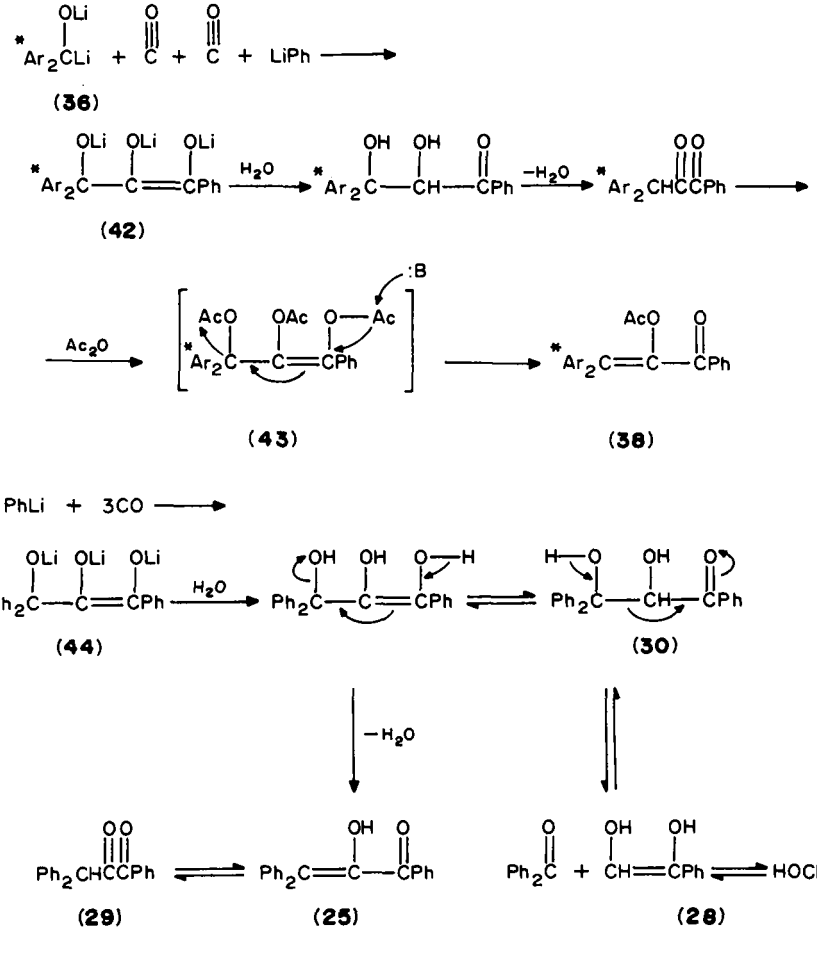


(**36**) (**39**) (**40**) (**41**) (**37**) (23)

The mechanism for conversion of the diarylmethylene moiety of **36** to **38** is clearly more complex that for the transformation of **36** to **37**. Combination of 1 equivalent of dianion **36**, 2 equivalent of carbon monoxide and 1 equivalent of phenyllithium in a process analogous to that required to form **40** would generate the trianion **42**, the labelled analogue of **44**. Acylation of this substance with acetic anhydride, followed by loss of the oxygen originally present in **36** would in turn yield **38** (equation 24). The postulation of **38** as an intermediate is immediately compatible with the formation of compounds **25**, **28**, **29** and **30** as hydrolysis products from the reaction of phenyllithium and carbon monoxide by protonation, dehydration and reverse aldol reaction starting from the unlabeled analog of trianion **42**, intermediate **44** (equation 25).

Thus, examination of products derived from reaction of the labelled dilithium diaryl ketone dianion **36** with phenyllithium and carbon monoxide fully supports the hypothesis that lithium benzophenone **5** is an intermediate in the reaction of phenyllithium and carbon monoxide and provides a unifying mechanistic rationalization for most of the products of this reaction based on conversion of **5** to intermediates having structures **34** and **44**.

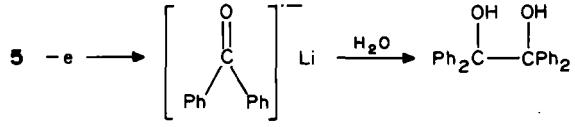
Benzil (**26**) and benzpinacol are the sole isolated products of the reaction of phenyllithium and carbon monoxide that are not easily generated from **34** or **44**;



(24)

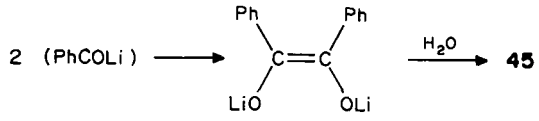
(25)

dimerization of the lithium benzophenone ketyl is the suggested route for the formation of benzpinacol (equation 26).



(26)

Although a two-electron oxidation of the 'dimeric' acyllithium **44a** was tentatively suggested[90] for the formation of benzil, benzoin (**45**) was then identified as the reaction product instead of benzil (both have the same retention time in several columns used in Reference 87)[61b]. Benzoin (**45**) was then shown to be directly formed by hydrolysis of **44a** (equation 27)[90].



(27)

(44a)

In summary, the spectroscopic and labelling experiments allow the conclusion that the dilithium benzophenone dianion is formed in the early stages of the reaction between phenyllithium and carbon monoxide and that its diarylmethylene moiety is effectively incorporated into products. Examination of the influence of temperature and reaction mixture composition on the distribution of products indicates that at least two related processes compete in these reactions. One, taking place at room temperature, converts 3 equivalents of phenyllithium and 2 equivalent of carbon monoxide to the lithium enolate of α,α-diphenylacetophenone (**24**); a second, dominating at −78 °C, involves 3 equivalents of phenyllithium and 3 equivalents of carbon monoxide and generates the trilithium trianion **44**. The products of the reaction, isolated after quenching with water or acetic anhydride, are derived in straightforward ways from **34** and **44**[87]. The derivation of certain of the minor products is still speculative. It could be established, however, that the concentration of intermediate **5** is never high and that its subsequent reactions with carbon monoxide and phenyllithium (or benzoyllithium, whichever is actually involved) are faster than its formation. The factors influencing the partitioning of intermediates between the reaction paths so far identified have not been established.

The most important mechanistic question still unresolved by that time was the importance of benzoyllithium in the reaction; it was not possible to decide whether or not benzoyllithium was involved in the transformations[87].

The illustrated complexity of the reaction as well as the unsuccessful previous attempts to develop a useful active metal acyl reagent led a reviewer on the subject to conclude in 1976: 'the acyl anion *per se* remains for the most part an untamed and elusive chemical creature'[16]. This remains so in the current thinking about direct nucleophilic acylation and stimulates the developing of 'masked acyl anion synthons or equivalents'. These 'acyl anion equivalent' procedures have been applied to problems of organic synthesis with good advantage (a recent compilation[91] listed some 60 acyl equivalents or synthons), but they represent rather costly detours in the preparation of the desired product.

As reported in Section II.B Schleyer's[64] first studies of the thermodynamic stability of acyl anions by means of MO calculations summed up the then current state of affairs. Recent calculations[68], however, were more encouraging and indeed useful syntheses based on direct carbonylations of organolithium reagents started to be reported in this decade.

A careful examination of the different variables that influence the product distribution led Nudelman and Vitale[88] to conditions that produced a quantitative conversion of phenyllithium into α,α-diphenylacetophenone, **24**. The reaction is highly sensitive to variations in temperature, solvents, method of preparation (transmetallation, metal–halogen exchange and direct metallation were tested), concentration and state (solid or in solution) of the reagent as well as to carbon monoxide pressure and speed of stirring. Increasing the temperature favours the formation of **24** and a quantitative conversion into α,α-diphenylacetophenone is achieved by using crystals of phenyllithium prepared by metal–halogen exchange from butyllithium and performing the heterogeneous reaction at 1 atm carbon monoxide pressure and 110 °C, without stirring.

Another useful synthetic application based on PhLi/CO was developed by the above-mentioned authors and reported in the same year[92]. This was based on quasi-kinetic determinations of the rate of formation of the different products (see below) and on the

observed solvent and temperature effects. Taking advantage of the increased rate of carbonylation in a polar solvent such as THF, the reaction could be carried out in the presence of an alkyl bromide at −78 °C, without considerable alkylation of the phenyllithium reagent occurring (equation 28).

$$PhLi + RBr \rightarrow PhR + LiBr \tag{28}$$

Useful diarylalkylcarbinols can be synthesized by this method in good yields by using the appropriate alkyl bromide. Benzoin (**45**) is obtained as a by-product (equation 29) but conditions can be adjusted to increase the yield of diarylalkylcarbinol, **46**, at the expense of benzoin.

$$PhLi + RBr + CO \rightarrow Ph_2RCOH + \underset{(46)}{45} \tag{29}$$

It is shown in Table 4 that the diphenylalkylcarbinol yields are high when primary alkyl bromides are used. Several conclusions can be drawn from the results: (a) Steric effects at the site of reaction notably diminish the amount of diphenylalkylcarbinols formed, increase the amount of benzoin and produce diphenyl alkyl ethers as observed for the reactions of *i*-propyl and *t*-butyl bromide (entries 4 and 5). (b) On the other hand, the yields of diarylalkylcarbinols obtained from *i*-butyl and 3-phenylpropyl bromide show that branching of the alkyl chain far from the reaction site does not affect the main reaction (entries 3 and 8). (c) When chains coming from branching at the reaction site are constrained in a cycle, reduction in the steric effects leads to a good yield of the main product (entry 7). (d) The length of the alkyl chain is also important: when the chain is longer than eight carbon atoms, yields become lower owing to the reduced solubility of the alkyl bromide (entry 6). Other reported results (not shown in Table 4) are: (e) The reaction is very sensitive to the ratio between phenyllithium and alkyl bromide concentrations; the optimum ratio observed is 1/3 (a higher ratio yields more secondary products and a lower one leads to Wurtz coupling products). (f) The concentration of the organolithium reagent itself is also important: on increasing the concentration of the phenyllithium (at a constant ratio) the amount of benzoin formed is also increased.

The following reaction sequence (equations 30–32) was proposed:

$$PhLi + CO \rightarrow PhC(O)Li \tag{30}$$

TABLE 4. Preparation of diarylalkylcarbinols[a]. Reproduced with permission from *J. Organomet. Chem.*, **332**, 10 (1987)

	BrR	Ar_2COHR	ArCOCHOHAr	Others
1.	n-C_3H_7Br	74	21	—
2.	n-C_4H_9Br	80	15	—
3.	*i*-C_4H_9Br	71	16	—
4.	*i*-C_3H_7Br	28	42	14[b]
5.	*t*-C_4H_9Br	20	38	22[c]
6.	n-$C_{12}H_{25}Br$	50	29	—
7.	cyclo-C_6H_5Br	70	18	—
8.	1-Br-3-phenylpropane	78	14	—
9.	n-C_4H_9Br	62	12	10[d]

[a] Yields represent percent conversion, in all cases compounds were identified by spectroscopic methods and confirmed by independent synthesis, in all but the last reaction Ar = Ph, in the last one Ar = *o*-$OCH_3C_6H_4$.
[b] 1, 1-Diphenyl-2-methyl-n-propyl-i-propyl ether.
[c] 1, 1-Diphenyl-2-methyl-n-propyl-*t*-butyl ether.
[d] Anisol.

$$PhC(O)Li + RBr \rightarrow \underset{(47)}{PhC(O)R} \tag{31}$$

$$47 + PhLi \rightarrow Ph_2C(OLi)R \tag{32}$$

The benzoyllithium initially formed reacts with the alkyl bromide producing the asymmetric ketone **47**. Subsequently the unreacted organolithium reagent adds further to the electrophilic CO group in **47**, producing the final product.

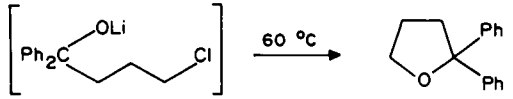
This is a fine balance of different rates of the several reactions that can occur, as shown by the following results: (a) If the reaction is carried out in the presence of an alkyl chloride instead of alkyl bromide, no diphenylalkylcarbinol is obtained but instead a mixture of the products usually found in the reaction of phenyllithium with carbon monoxide under the reaction conditions in the absence of the alkyl chloride. (b) If the reaction is carried out in the presence of an alkyl iodide, only coupling products are obtained (reaction 28 faster than reaction 30).

The lack of reactivity of alkyl chlorides under the reaction conditions can be used constructively for the synthesis of functionalized diarylalkylcarbinols, which are useful synthetic intermediates. Thus the reaction PhLi/CO carried out in the presence of 3-chlorobromopropane produces 3-chloropropyl-diphenylcarbinol **48** in 50% unoptimized yield (equation 33). This compound is an intermediate for the preparation of amino alcohols of known pharmacological activity. Thus, upon treatment of **48** with piperidine (equation 34), 1,1-diphenyl-4-piperidylbutanol (**49**, an anesthetic) is obtained; *cis*-2,6-dimethyl-α,α-diphenylpiperidinebutanol (antiarrhythmic) was prepared in a similar way. This one-step method (equation 33) for the preparation of **48** gives better yields than the previously reported several-step synthesis[93,94].

$$PhLi + BrCH_2CH_2CH_2Cl + CO \longrightarrow \underset{(48)}{Ph_2C(OH)(CH_2)_3Cl} + \mathbf{45} \tag{33}$$

$$Ph_2C(OH)-(CH_2)_3Cl + C_5H_{10}NH \rightarrow \underset{(49)}{Ph_2C(OH)-(CH_2)_3NC_5H_{10}} \tag{34}$$

The reaction was easily extended to the production of 1,1-diphenyltetrahydrofuran. Thus, by heating the reaction mixture of equation 33, before work-up, an intermolecular Williamson reaction takes place, producing the cyclization product **50** (equation 35) in 50% unoptimized yield.



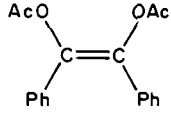
(50) (35)

Another important feature of this reaction is the trapping of the benzoyllithium intermediate which resolves the mechanistic question shown by equation 20. The intermediate **51** could, in principle, be formed by the reaction of the dilithium benzophenone dianion with the alkyl bromide (equation 36), however, this reaction does

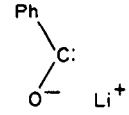
not occur under the reaction conditions. This, together with the fact that not even traces of products derived from subsequent reactions of the dilithium benzophenone dianion (compounds **24**, **25**, **27**, **31**) were found, indicates that the only route for the formation of intermediate **51** is the initial reaction of the benzoyllithium with the alkyl bromide (equation 31)[61].

$$[Ph_2COLi_2] + RBr \not\rightarrow Ph_2C(OLi)R \qquad (36)$$
$$(51)$$

The only by-product isolated from the reaction PhLi/CO/RBr is benzoin, **45**, which is an additional proof of the existence of benzoyllithium (**3** ⇄ **4**) as a real intermediate. **45** comes from dimerization of (**3** ⇄ **4**), as was shown by quenching the reaction mixture with acetic anhydride[61]. In fact, although **45** could, in principle, be envisaged as a condensation of a benzoyllithium molecule with the resulting acyl anion of another molecule, the isolation of the diacetate of the (100%) *cis* enol of benzoin, **52**, indicates that **4** and not **3** is the real precursor of **45**. The stereospecificity of the reaction (only the *cis* isomer is obtained, excludes the equilibrium **44** ⇄ **3**.



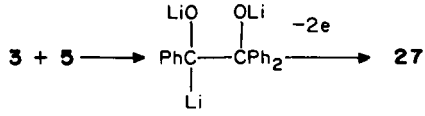
(52)



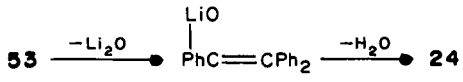
(4) (37)

Nudelman and Vitale[61] propose that trapping of intermediate **44a** suggests the intermediation of a carbene of anionic structure **4**. There is relevant evidence for the nucleophilic character of an anionic carbene[95] and stable acyl–polycarbonyl–metallic compounds of transition metals have been demonstrated to have a carbene structure ESR studies of arylmethylenes have shown that such species have a diradical planar triplet structure[96,97]. Assuming **4** is also in its triplet state, its dimerization could occur in the plane of the molecule; approach of both molecules in a cisoid transition state would allow each lithium atom to coordinate with both oxygens simultaneously. This would explain the absolute stereospecificity of the coupling reaction and affords a useful method for the stereospecific synthesis of the diacetate of enol systems.

The other products formed in the acetic anhydride quenching prove that intermediates **53** and **54** are the real precursors of **24** and **27** (equations 38 and 39)[61].



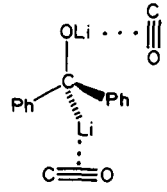
(53) (38)



(54) (39)

Although a substantial part of benzophenone was shown to come from partial decomposition of the intermediate **35** in the GLPC injection port[61], in the present

reaction conditions the isolated yield of benzophenone was very similar to that obtained by GLPC determinations[61]. Furthermore, the overall yield of products accounts for the total fate of phenyllithium and the reaction carried out in the presence of lithium hydride did not show change in the product mixture. Formation of benzophenone is then assumed to arise from oxidation of intermediate **5**. Some obvious oxidation pathways were tested and failed to gain experimental support. It was proposed that **5** is not free in the reaction media but coordinated to two carbon monoxide molecules through the lithium atoms, **55**. The work-up procedure should favour the elimination of the elements of lithium carbonyl, producing the oxidation product[61].



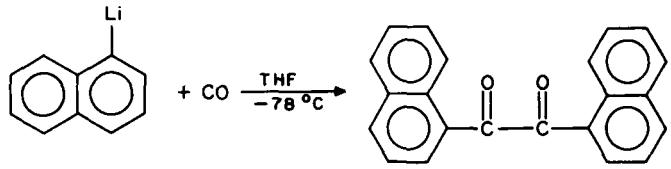
(55)

Indirect signs of such coordination are the following: (a) in the reaction of *o*-anisyllithium (in which the lithium atoms are intramolecularly coordinated with the *ortho*-methoxy groups) *o,o*-dianisylketone and *o,o'*-dianisylcarbinol are obtained in comparable yields (33 and 32% respectively; equation 40), and (b) the effect of donor bases: when the reaction is performed in the presence of DABCO or TMEDA a five-fold decrease in the rate of reaction is observed, although it is known that these amines usually increase the reactivity of organolithium reagents by coordination to the metal atom[39]. This last result could furthermore indicate that the first step in the whole reaction is the coordination of the lithium atom, and subsequent attack on the carbanion producing a four-centre cyclic transition state (**56**) and further rearrangement to give the benzoyllithium.

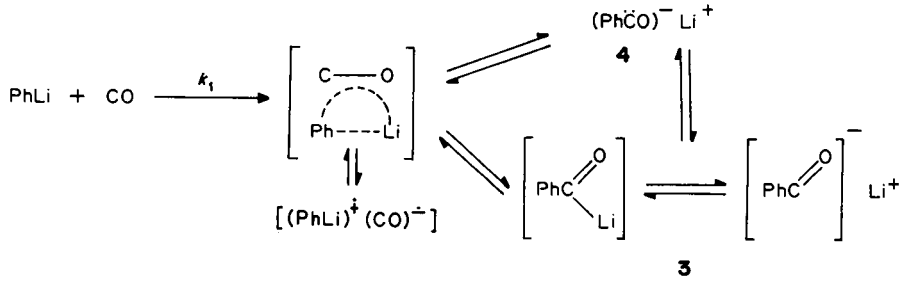
$$\begin{array}{l} \qquad\qquad\quad O \\ \qquad\qquad\quad \| \\ AnLi + CO \rightarrow AnCAn + An_2CHOH \\ An = o\text{-}MeOC_6H_4 \qquad 33\% \qquad\quad 32\% \end{array} \tag{40}$$

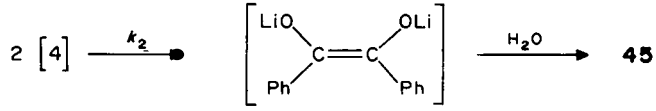
The abundant experimental evidence accumulated on this reaction supports the proposal of Scheme 3 for the several main paths observed in the reaction of phenyllithium with carbon monoxide[61].

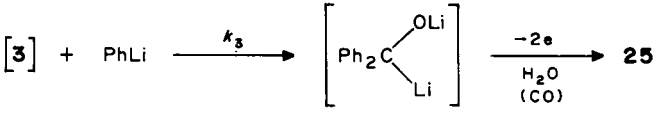
The finding of conditions that prevent further reaction of the acyllithium with the starting organolithium reagent allowed Nudelman and Outumuro[62] to employ the synthetic utilization of this chemistry for the preparation of 1,2-dicarbonyl compounds. Thus, the reaction of naphtyllithium with 1 atm carbon monoxide in THF at $-78\,^{\circ}C$ led to a 96% conversion into the corresponding diketone (equation 41), and 2,6-dimethylphenyllithium was 95% converted into 2,6-dimethylbenzil (equation 42 and Table 5).



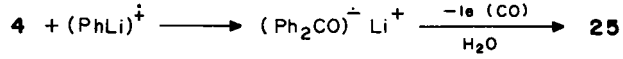
(41)

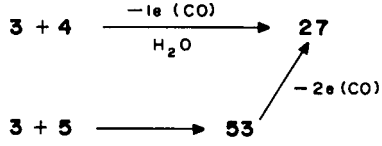

PhLi + CO
k_1
C—O
Ph----Li
$[(PhLi)^{\dagger}(CO)^{\dot{-}}]$
$(PhC\dot{O})^{-}$ Li^{+}
4
PhC
O
Li
Li^{+}
3

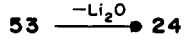

2 [4]
k_2
LiO
OLi
C=C
Ph
Ph
H_2O
45


[3] + PhLi
k_3
Ph_2C
OLi
Li
−2e
H_2O
(CO)
25

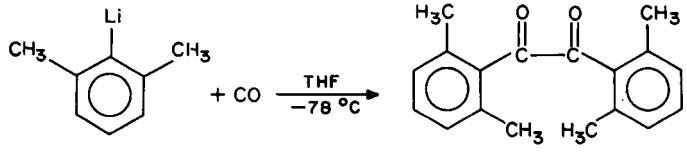
5


4 + $(PhLi)^{\dagger}$
$(Ph_2CO)^{\dot{-}}$ Li^{+}
−1e (CO)
H_2O
25


3 + 4
−1e (CO)
H_2O
27
3 + 5
53
−2e (CO)


53
$-Li_2O$
24

SCHEME 3


Li
CH_3
CH_3
+ CO
THF
−78 °C
H_3C
O
O
CH_3
C
C
CH_3
H_3C

(42)

TABLE 5a. Yields from reaction of 1-naphthyllithium with carbon monoxide[a]. Reproduced with permission from *J. Org. Chem.*, **47**, 4347 (1982)

Temp. (°C)	THF		$(C_2H_5)_2O$		$CH_2(OCH_3)_2$		n-C_6H_{14}	
	2a	3a	2a	3a	2a	3a	2a	3a
−78	22.7	71.2[b]	32.7	58.2	32.9	61.1		
0	17.0	74.9	57.2	34.7	55.0	40.0	< 1	< 1
25	12.2	82.7	55.3	37.7	47.6	45.3	< 1	< 1

[a]The reported yields represent percent conversion.
[b]96.1% in HMPT/THF (20:80, v/v).

TABLE 5b. Yields from reaction of (2,6-dimethylphenyl)lithium with carbon monoxide[a]. Reproduced with permission from *J. Org. Chem.*, **47**, 4347 (1982)

Temp. (°C)	THF		$(C_2H_5)_2O$		$CH_2(OCH_3)_2$	
	2b	3b	2b	3b	2b	3b
−78	< 1	96.4	18.3	75.7	17.1	74.4
0		96.1	31.0	62.8	28.3	64.7
25		97.5	33.2	61.6	30.5	63.8

[a]The reported yields represent percent conversion.

Again, the diacetate of the *cis* enol of the corresponding acyloins were synthesized with absolute stereospecificity by quenching the reactions with acetic anhydride. Special care is needed in these cases to prevent the easy hydrolysis of the diacetates and further spontaneous oxidation to the 1,2-dicarbonyl derivatives[61].

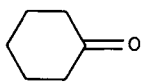
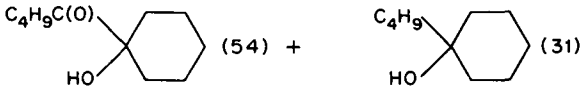
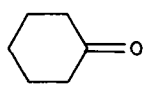
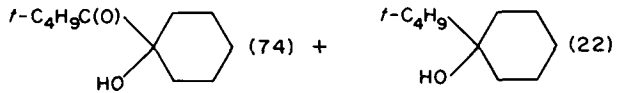
A very important methodology for the direct nucleophilic acylation of aldehydes[98], of esters[98,99], of lactones[100] and of some alkyl silanes[101] in good yields has been recently developed by Seyferth's group using alkyl lithium reagents. The key of the method is the very slow carbonylation of the alkyllithium reagent at very low temperature and trapping of the acyllithium intermediate by '*in situ*' reaction with an electrophile.

Using a 2:1 stoichiometry and a reaction temperature of −110 °C Seyferth and coworkers[99] could effect the acylation of ketones in moderate to excellent yield (Table 6). The competition of the ketone for the alkyllithium, even when the ketone was in 100% excess, was not serious except for the more reactive ketones (e.g. cyclohexanone in Table 6). The yields of the ketone-derived by-product, RR'R"COH, were very low. However, the acylation of an aliphatic, somewhat hindered aldehyde, Me_3CCHO, with C_4H_9Li/CO was only minimally successful when this procedure was used. The yield of the acylation product was only 17%, while that of the undesired alkylation product was 50%[99]. But a further improvement in the yield of the acylation product was achieved using a 1:1 reactant stoichiometry (see below).

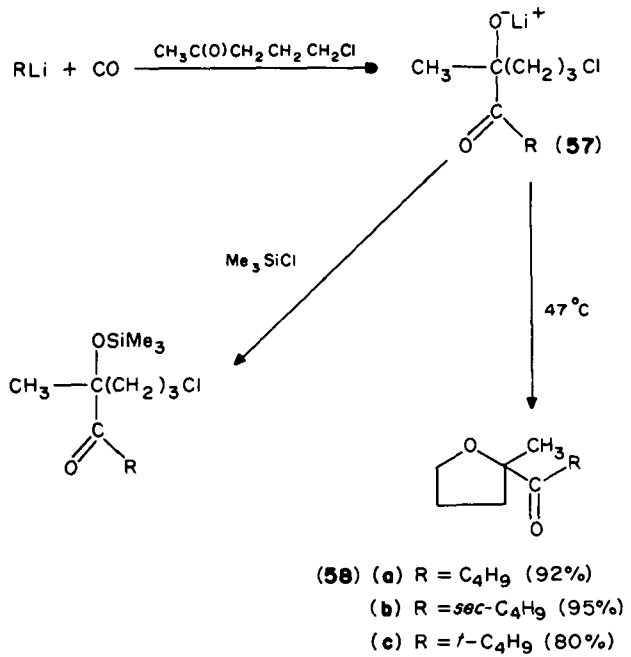
As shown before with the reaction of PhLi/CO/RBr[62] (equation 35), also in this case nucleophilic ketone acylation can be used to construct ring systems if a suitable leaving group is in a remote part of the molecule. Scheme 4 shows one such example[100]. The intermediate adduct **57** could be trapped at low temperature with Me_3SiCl, but heating to somewhat above room temperature caused the ring closure to take place, giving **58**.

TABLE 6. Nucleophilic acylation of ketones. Reproduced with permission from *Isr. J. Chem.*, **24**, 171 (1984)

$$RLi + R'R''CO \xrightarrow[-110\,^{\circ}C]{CO} \xrightarrow{H_3O^+} RC(=O)-CR'R''(OH)$$

RLi	Ketone	Product (% yield)
C_4H_9Li	$CH_3C(O)C_2H_5$	$C_4H_9C(O)C(OH)(CH_3)(C_2H_5)$(71) + $C_4H_9C(OH)(CH_3)(C_2H_5)$(13)
C_4H_9Li	$CH_3C(O)CH(CH_3)_2$	$C_4H_9C(O)C(OH)(CH_3)(CH(CH_3)_2)$(92) + $C_4H_9C(OH)(CH_3)(CH(CH_3)_2)$(5)
C_4H_9Li	$CH_3C(O)C(CH_3)_3$	$C_4H_9C(O)C(OH)(CH_3)(C(CH_3)_3)$(90) + $C_4H_9C(OH)(CH_3)(C(CH_3)_3)$(2)
C_4H_9Li	$(C_2H_5)_2CO$	$C_4H_9C(O)C(OH)(C_2H_5)_2$(67) + $C_4H_9C(OH)(C_2H_5)_2$(4)
C_4H_9Li	$C_6H_5C(O)CH_3$[a]	$C_4H_9C(O)C(OSi(CH_3)_3)_3(CH_3)(C_6H_5)$(43) + $(CH_3)_3SiO(C_6H_5)C{=}CH_2$(50)
C_4H_9Li		
sec-C_4H_9Li	$CH_3C(O)CMe_3$	*sec*-$C_4H_9C(O)C(OH)(CH_3)(C(CH_3)_3)$(55)
t-C_4H_9Li		
iso-PrLi	$CH_3C(O)C(CH_3)_3$	*iso*-$PrC(O)C(OH)(CH_3)(C(CH_3)_3)$(70)
t-C_4H_9Li	$CH_3C(O)C_2H_5$	*t*-$C_4H_9C(O)C(OH)(CH_3)(C_2H_5)$(59) + *t*-$C_4H_9C(OH)(CH_3)(C_2H_5)$(23)

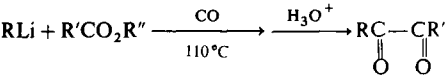
[a]Reaction mixture quenched with Me_3SiCl.



SCHEME 4

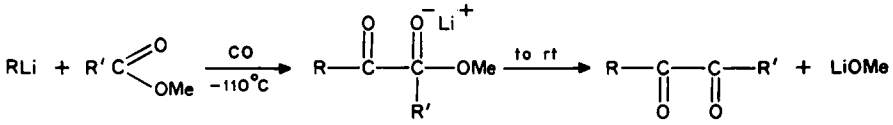
The acylation of esters (equation 43) proceeded in good yield under these conditions (Table 7) and this reaction is an excellent, general synthesis of symmetrical and unsymmetrical α-diketones (which are useful intermediates in organic synthesis)[89]. The preparation can be carried out at − 78 °C, but with some loss in yield and an increase in

TABLE 7. Nucleophilic acylation of esters. Reproduced with permission from *Isr. J. Chem.*, **24**, 172 (1984)



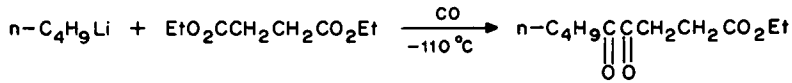
RLi	Ester	Product (% yield)
C_4H_9Li	$CH_3CO_2CH_3$	$C_4H_9C(O)C(O)CH_3$ (71)
C_4H_9Li	$C_2H_5CO_2CH_3$	$C_4H_9C(O)C(O)C_2H_5$ (67)
C_4H_9Li	n-$C_3H_7CO_2CH_3$	$C_4H_9C(O)C(O)C_3H_7$-n (66)
C_4H_9Li	$(CH_3)_3CCO_2CH_3$	$C_4H_9C(O)C(O)C(CH_3)_3$ (80)
C_4H_9Li	n-$C_5H_{11}CO_2C_2H_5$	$C_4H_9C(O)C(O)C_5H_{11}$-n (79)
C_4H_9Li	$C_6H_5CO_2CH_3$	$C_4H_9C(O)C(O)C_6H_5$ (68)
sec-C_4H_9Li	$(CH_3)_3CCO_2CH_3$	*sec*-$C_4H_9C(O)C(O)C(CH_3)_3$ (66)
tert-C_4H_9Li	$(CH_3)_3CCO_2CH_3$	*tert*-$C_4H_9C(O)C(O)C(CH_3)_3$ (69)

the yield of by-products compared to the same reaction carried out at $-110\,^{\circ}C$[89].



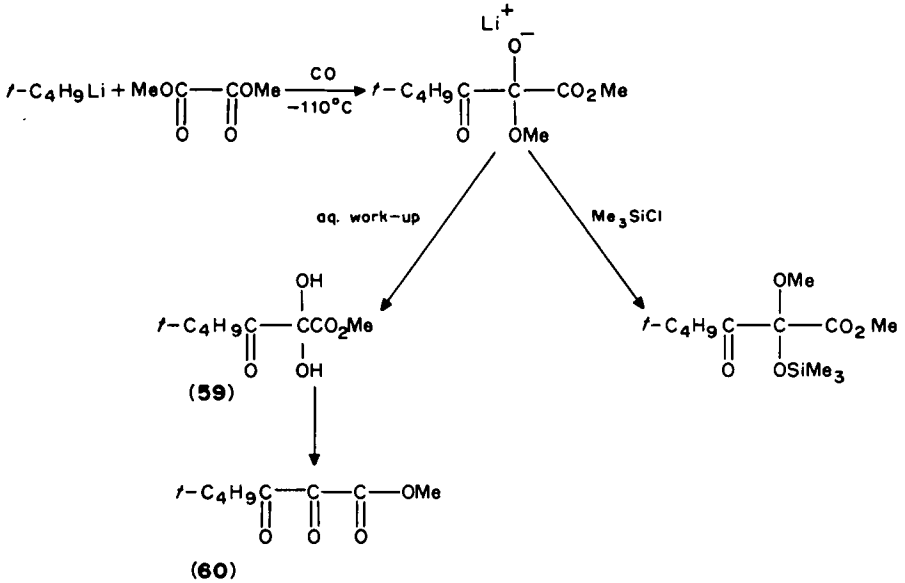
(43)

The reactions with diesters also have been examined (equation 44 and Scheme 5). The hydrate **59**, a white, crystalline solid, initially formed, can be converted thermally to **60**, a yellow liquid which is very hygroscopic, exposure to moisture sufficing to convert it to **59** again [89].



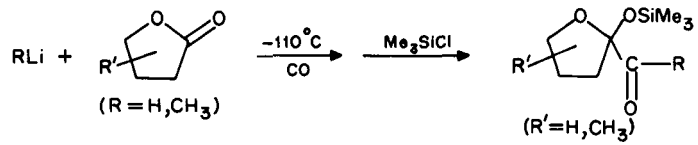
63%

(44)



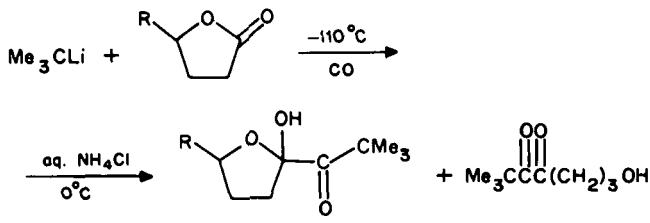
SCHEME 5

Lactones are cyclic esters and these also may be acylated via '*in situ*' RLi/CO reactions. The reactions with five-membered ring lactones were found to proceed readily without ring opening to give 2-acyl-2-trimethylsiloxytetrahydrofurans in good yield (equation 45). In the case of γ-valerolactone, two isomers were observed in the products from each acyllithium reagent.



(45)

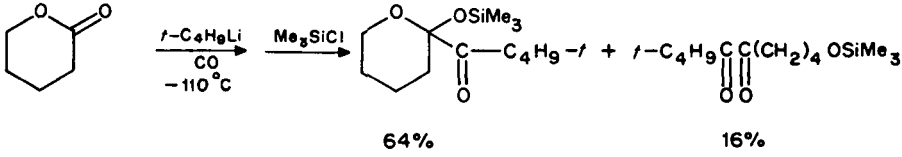
Attempts to prepare 3-hydroxypropyl-α-diketones by the '*in situ*' nucleophilic acylation of lactones followed by hydrolysis of the reaction mixture gave a mixture of cyclic and acyclic products (equation 46).



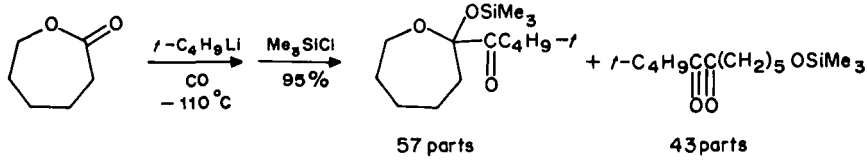
(61)

(46)

Lactones of other ring sizes also could be acylated. A reaction of β-butyrolactone and the *t*-C_4H_9Li/CO reagent at −110 °C gave the α-acyloxetane **61** in 31% yield. Mixtures of cyclic and acyclic products were obtained with six- and seven-membered ring lactones (equations 47 and 48).



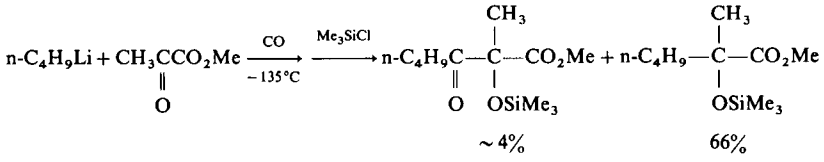
(47)



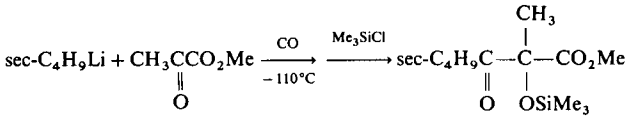
(48)

In the case of all substrates—ketones, aldehydes and esters—Seyferth's group[89] achieved marked improvement by using a 1:1 RLi/organic electrophile stoichiometry, and when the temperature was lowered to −135 °C. The yields of the desired acylated products increased significantly and a concomitant decrease in the amount of undesirable by-products was realized. The most dramatic improvements were observed in the acylation of pivalaldehyde, these changes transforming the reaction from one that was essentially useless to one of synthetic potential[89]. Thus, the yield of the acylation product with BuLi/CO in a 1:1 stoichiometry at −135 °C was increased to 62%, while that of the alkylation product dropped to 18%. Similar reactions with *sec*-BuLi/CO and *t*-BuLi/CO

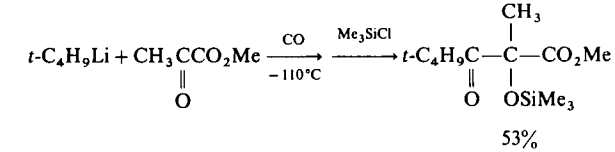
with Me_3CCHO (1:1 at $-135\,^{\circ}C$) proceeded almost quantitatively [86% yield of $MeEtCHC(O)CH(OH)CMe_3$; 90% yield of $Me_3CC(O)CH(OH)CMe_3$] and no alkylation products were formed[89]. However, these changes in stoichiometry and reaction temperature were not effective in all cases, e.g. benzaldehyde could not be acylated with the '*in situ*' BuLi/CO system. Also, in the case of unhindered aliphatic aldehydes as well as in the case of a highly reactive ketone an unsuccessful acylation with butyllithium was observed although good results were obtained with *sec*- and *tert*-butyllithium/CO (equations 49–51).



(49)



(50)

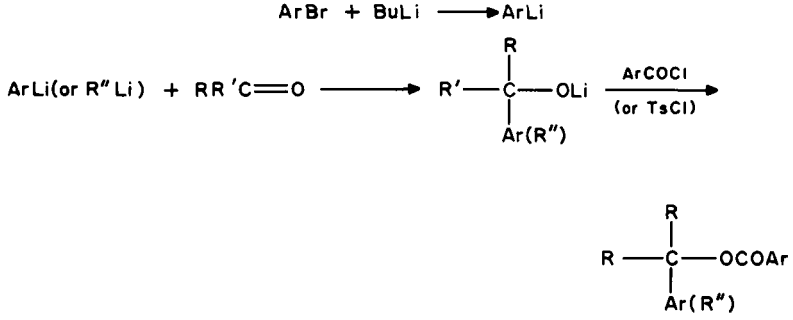


(51)

Improved acylation product yields were also obtained with ketones: in the case of cyclohexanone, using a 1:1 stoichiometry, the yield of the acylation product, 1-pentanoylcyclohexanol, increased to 66%, while the undesired alkylation product, 1-butylcyclohexanol, dropped to 15%. Further improvement was realized when the 1:1 reaction was carried out at $-135\,^{\circ}C$: the acylation product yield rose to 73% while that of the alkylation product dropped to 9%[89]. The very reactive cyclopentanone could be acylated in this system in a 82% yield. Similar improvements were observed in the acylation of esters.

Thus, for most organic carbonyl compounds the optimum conditions for nucleophilic acylation using '*in situ*' generated acyllithium reagents involve 1:1 RLi/organic substrate stoichiometry and a reaction temperature of $-135\,^{\circ}C$. This is especially important in the case of *n*-butyllithium. Side-reactions such as RLi addition to the carbonyl function and enolization are minimized when an excess of the organic electrophile is avoided and when the temperature is lowered to $-135\,^{\circ}C$. Under these conditions the reactions are much cleaner and the acylation product yields are high[89]. It is of importance to note that such reactions may be carried out on a larger, preparative scale and further scale-up should be possible[89].

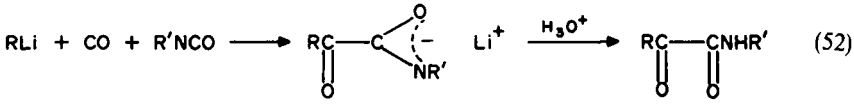
Closely related to the intermediates shown above is the one-pot preparation of tertiary alkyl carboxylates and sulfonates from ketones recently developed by Kuo and Liu[102]. Aryllithium reagents are generated '*in situ*' by the reaction of aryl bromides with butyllithium in THF–hexane (4:1) at −100 °C and a THF solution of the ketone is added to form a tertiary lithium alcoholate, which is then, without isolation, esterified with an appropriate acyl chloride or sulfonyl chloride to give the desired carboxylate or the sulfonate ester (Scheme 6).



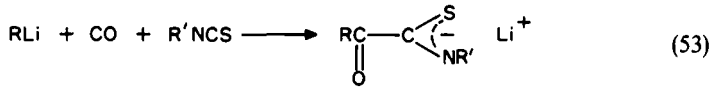
SCHEME 6

It is worth mentioning that the previous treatment of the organolithium reagent with titanium(IV) chloride results in quantitative formation of a $RTiCl_3$ non-basic reagent which reacts chemo- and stereoselectively with carbonyl compounds[103]. This procedure makes possible selective addition to ketones in the presence of such a functionality as nitro, cyano and ester groups.

Seyferth and coworkers[104] also investigated the reaction of various heterocumulenes with the low-temperature, '*in situ*' RLi/CO systems. Isocyanates were acylated in good yield (equation 52)[105].



The ambident intermediate formed in equation 52, was protonated on nitrogen as shown, but was silylated on oxygen giving, in the case of the *t*-BuLi/CO/C_2H_5NCO system, γ-BuC(O)C(OSiMe$_3$)=NC_2H_5 in 60% yield. Results are summarized in Table 8. In the case of butyllithium some side-reactions were observed, although α-oxoamides were produced in reasonable yields. Isothiocyanates reacted in similar fashion to give α-oxothioamides upon protonation of the ambident anion formed, **62** (equation 53; Table 9)[104].



Carbodiimides also underwent direct nucleophilic acylation under these conditions (equation 54)[106,107]. This reaction is more limited in scope (Table 10). It was not observed

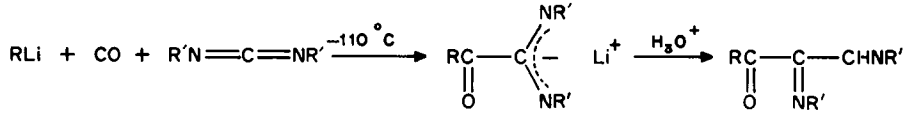
TABLE 8. Nucleophilic acylation of isocyanates. Reproduced with permission from *Nova Acta Leopold.*, **59**, 335 (1985)

R in RLi	R′ in R′NCO	RC(=O)C(=O)NHR′ (% Yield)
t-Bu	Me	84
t-Bu	Et	84
t-Bu	*i*-Pr	86
t-Bu	*n*-Bu	76
t-Bu	*t*-Bu	52
t-Bu	Ph	78
sec-Bu	n-Bu	75
Sec-Bu	Ph	70
n-Bu	Et	41
n-Bu	n-Bu	43
n-Bu	*i*-Pr	61
n-Bu	*t*-Bu	58

TABLE 9. Nucleophilic acylation of alkyl isothiocyanates. Reproduced with permission from *Nova Acta Leopold.*, **59**, 335 (1985)

R in RLi	R′ in R′NCS	Reaction temp. (°C)	RC(=O)C(=S)NHR′ (% yield)
t-Bu	Me	−110	72
t-Bu	Et	−110	71
t-Bu	*i*-Pr	−110	70
t-Bu	n-Bu	−110	80
sec-Bu	Et	−110	73
sec-Bu	n-Bu	−110	85
n-Bu	Me	−135	70
n-Bu	Et	−135	84
n-Bu	*i*-Pr	−135	71
n-Bu	n-Bu	−135	68

to occur in the *n*-BuLi/CO/R′N=C=NR′ systems; also more hindered carbodiimides (R″ = *i*-Pr, *t*-Bu) were unreactive.



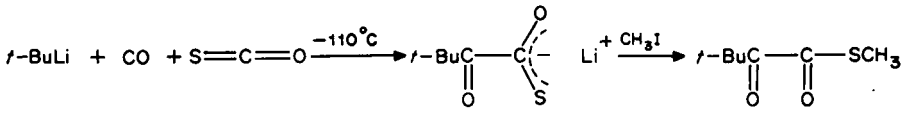
(54)

Carbonyl sulfide and carbon disulfide reactions with '*in situ*' RLi/CO systems were also examined briefly. Nucleophilic acylation of COS proved to be possible (equation 55), but in the case of CS_2 the expected products were not obtained (involving an unknown CS elimination)[107].

TABLE 10. Direct nucleophilic acylation of carbodiimides. Reproduced with permission from *Nova Acta Leopold.*, **59**, 335 (1985)

R in RLi	R′ in R′N=C=NR′	Product (% Yield)[a]
t-C_4H_9	C_2H_5	*t*-$C_4H_9C(=O)NHC_2H_5$ (66) NC_2H_5
t-C_4H_9	n-C_3H_7	*t*-$C_4H_9C(=O)NHC_3H_7$-n (75) NC_3H_7-n
t-C_4H_9	$CH_2CH{=}CH_2$	*t*-$C_4H_9C(=O)NHCH_2CH{=}CH_2$ (83) $NCH_2CH{=}CH_2$
sec-C_4H_9	C_2H_5	*sec*-$C_4H_9C(=O)NHC_2H_5$ (66) NC_2H_5
sec-C_4H_9	n-C_3H_7	*sec*-$C_4H_9C(=O)NHC_3H_7$-n (72) NC_3H_7-n

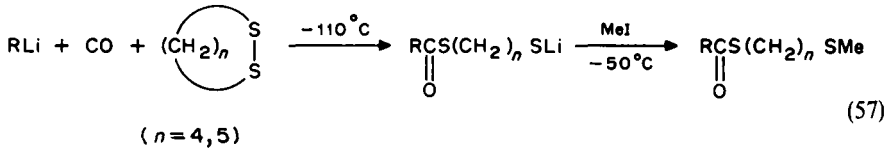
[a]Obtained on hydrolytic work-up.



(55)

Seyferth and Hui[108] also studied reactions of the RLi/CO reagent with organic disulfides (equation 56). In these reactions only half of the alkyl moiety remains in the product, but the reaction is of more potential interest when applied to cyclic disulfides (equation 57).

(56)



(57)

The results obtained with simple aryllithium/CO systems by the method of Seyferth and coworkers[109] were encouraging. Application of the low temperature, *in situ* procedure to phenyllithium using esters and ketones as organic substrates resulted only in phenylation. No benzoylated products were obtained yet.

Since good results in the acylation of aryllithium were obtained by the method of Nudelman and collaborators[61,62,88,90,92,110] both methods are complementary for the direct nucleophilic acylation of organolithium compounds.

TABLE 11. Preparation of γ-halodiphenylalkylcarbinols or cyclic ethers[a]. Reproduced with permission from *J. Organomet. Chem.*, **332**, 13 (1987)

$X(CH_2)_nY$	46[b]	45
$Br(CH_2)_3Br$	50	—
$Br(CH_2)_3Cl$	48	43
$Br(CH_2)_4Br$	77	21
$Br(CH_2)_5Br$	80	20
$Br(CH_2)_6Br$	79	19
$Br(CH_2)_3Br$	50[c]	—
$Br(CH_2)_4Br$	80[c]	—

[a] Yields represent percent conversion.
[b] $R = (CH_2)_nY$.
[c] Yield of cyclic ether $Ph_2C\langle O\rangle(CH_2)_n$

A further examination of the scope of the reaction system PhLi/CO/RBr and its application to the synthesis of useful intermediates have been recently published by Nudelman and coworkers[110]. The reactivity of dihalo-substituted alkanes has been examined and it was found that only one bromine atom becomes substituted giving the corresponding haloalkyldiphenylcarbinol in good yield (equation 58 and Table 11); the only by-product is benzoin.

$$PhLi + Br(CH_2)_nBr + CO \longrightarrow Ph_2C(OLi)(CH_2)_nBr + PhC(O)CH(OLi)Ph \quad (58)$$

This reaction may be easily extended to produce cyclic ethers in a one-pot synthesis. Thus, the reaction of phenyllithium and the dihalo-substituted alkane with carbon monoxide is carried out as described, but the reaction mixture is not quenched with water. Instead, the solvent is distilled off by heating at 60 °C (equation 59). From the residue the cyclic ether can be isolated in good yields (Table 11). Optimum yields are obtained for $n = 3$–5; the yield of cyclic ether decreases when the length of the alkyl chain increases.

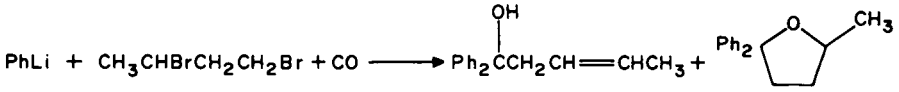
$$PhLi + Br(CH_2)_nCl + CO \xrightarrow[(2)\ \Delta]{(1)\ -78^\circ C} (CH_2)_n\langle O\rangle CPh_2 \quad (59)$$

If the alkyl bromide is branched at the reaction site, an intermolecular Williamson reaction takes place (equation 60) as a competitive reaction with those leading to the diarylalkylcarbinol and benzoin. These ethers are usually difficult to prepare by other methods and efforts are concentrated to develop the present method for its preparation in a more convenient yield[110].

$$PhLi + (CH_3)_3CBr + CO \longrightarrow Ph_2C(CO(CH_3)_3)C(CH_3)_3 + \mathbf{45} \quad (60)$$

The yield of diarylalkylcarbinols obtained from secondary and tertiary alkyl bromides were lower than those with primary alkyl bromides (see Table 4) suggesting that the reaction is faster with primary alkyl bromides or that parallel reactions compete with the main one in the case of secondary and tertiary alkyl bromides. That the first of both

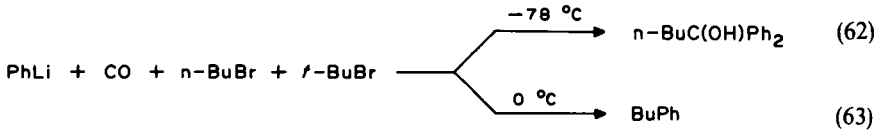
alternatives is true was proved by the following competition experiments: (a) The reaction of 1,3-dibromobutane yields 1,1-diphenylpent-3-enol and 2,2-diphenyl-5-methyltetrahydrofuran (equation 61) as the only alkyl substituted compounds. (b) When



(61)

the reaction was carried out in the presence of equimolar amounts on *n*-butyl and *t*-butyl bromides, only diphenylbutylcarbinol was produced as the main product. Points (a) and (b) indicate the higher reactivity of primary when compared with secondary or tertiary bromides.

This observation has been recently confirmed by competitive experiments carried out by Nudelman and Amorin[111]. When phenyllithium in THF is allowed to react with carbon monoxide in the presence of n- and *t*-butylbromide, only reaction with the *n*-alkyl is observed. As is shown in equations 62 and 63, the reaction product is very sensitive to the temperature of the reaction: carbonylation is observed at $-78\,^{\circ}C$ while just aryl–alkyl coupling occurs at $0\,^{\circ}C$.



(62)

(63)

These results indicate that the carbonylation reaction has a smaller energy of activation than the coupling reaction, for the linear alkyls. On the other hand, when the reaction is carried out at $0\,^{\circ}C$ in the presence of each alkyl halide separately (not shown), the expected coupling product is obtained with *n*-butyl bromide, but *t*-butyl bromide produces carbonylation products besides the coupling product, *t*-BuPh.

Without ruling out a polar mechanism, all the above results, together with the observation of paramagnetic species in the reaction PhLi/CO[49], suggest the existence of electron transfer mechanisms in these reactions.

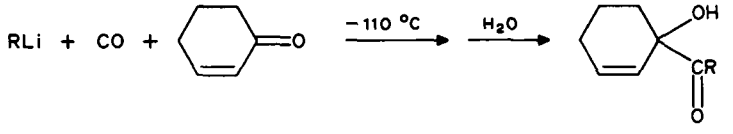
No evidence has been reported for electron transfer in equations 31 and 32, but equation 32 is the addition of an organolithium reagent to a ketone, and it has been recently demonstrated that it occurs by an electron transfer mechanism[112].

2. *Organocuprates*

Although copper is not a main group element, the carbonylation of organocuprates is included in this chapter since the recently developed carbonylation of organolithiumcuprates[113] is an excellent complement of the above described carbonylations of organolithium compounds.

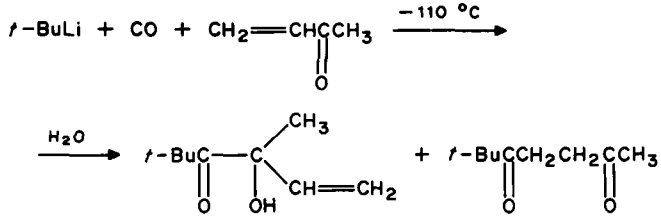
Thus, with α,β-unsaturated ketones the RLi/CO reactions lead almost completely to 1,2-acylations (equations 64a and 64b). However, with those ketones, usually the desired process is conjugate (1,4) acylation to give the 1,4-dicarbonyl compounds, which are very useful in organic synthesis.

To effect 1,4-acylation of α,β-unsaturated carbonyl compounds acylcuprates were developed as a general class of new and useful synthetic reagents[113]. Various types of organocopper species are also known to effect the 1,4-alkylation of α,β-unsaturated carbonyl compounds[114]. Seyferth and Hui[113] used first the so-called 'higher order cuprates'[115], soluble reagents of stoichiometry $R_2(CN)CuLi_2$, formed by addition of two



(64a)

(R = n-Bu, 60%; t-Bu, 80%)



(64b)

molar equivalents of RLi to one CuCN. These (R = n-Bu, *sec*-Bu, *t*-Bu) react with carbon monoxide at −110 °C in the 4:4:1 THF/Et_2O/pentane solvent system to give a carbonylation product which is relatively stable at −110 °C[104]. In this method the preformed, cold (−78 °C) $R_2(CN)CuLi_2$ solution is added slowly to the solvent at

TABLE 12. Direct nucleophilic acylation of α, β-unsaturated carbonyl compounds with acylcuprate reagents $R_2(CN)CuLi_2$. Reprinted with permission from *J. Am. Chem. Soc.*, **107**, 4552 (1985). Copyright (1985) American Chemical Society

R	α,β-Unsaturated carbonyl compd.	Product[a] (% yield)[f]
n-C_4H_9	2-cyclohexenone	3-pentanoylcyclohexanone (86)
	2-cyclopentenone	3-pentanoylcyclopentanone (89)
	CH_2=CHC(O)CH_3	*n*-C_4H_9C(O)CH_2CH_2C(O)CH_3 (66)
	CH_2=CHC(O)C_2H_5	*n*-C_4H_9C(O)CH_2CH_2C(O)C_2H_5 (75)
	C_2H_5CH=CHCHO[b]	*n*-C_4H_9C(O)CH(C_2H_5)CH_2CHO (63)
	n-C_3H_7CH=CHCHO	*n*-C_4H_9C(O)CH(*n*-C_3H_7)CH_2CHO (70)
sec-C_4H_9	2-cyclohexenone	3-(2-methylbutanoyl)cyclohexanone (75)
	CH_2=CHC(O)CH_3	*sec*-C_4H_9C(O)CH_2CH_2C(O)CH_3 (78)
	C_2H_5CH=CHCHO	*sec*-C_4H_9C(O)CH(C_2H_5)CH_2CHO (76)
i-C_4H_9	2-cyclohexenone	3-pivaloylcyclohexanone (78)
	2-cyclopentenone	3-pivaloylcyclopentanone (82)
	CH_2=CHC(O)CH_3	*t*-C_4H_9C(O)CH_2CH_2C(O)CH_3[c] (66)
	CH_2=CHC(O)C_2H_5	*t*-C_4H_9C(O)CH_2CH_2C(O)C_2H_5[d] (64)
	CH_3CH=CHCHO	*t*-C_4H_9C(O)CH(CH_3)CH_2CHO[e] (52)
	C_2H_5CH=CHCHO	*t*-C_4H_9C(O)CH(C_2H_5)CH_2CHO (72)
	n-C_3H_7CH=CHCHO	*t*-C_4H_9C(O)CH(*n*-C_3H_7)CH_2CHO (64)

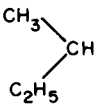
[a] All new compounds were characterized by C/H analysis (± 0.4%) and IR and ^{1}H NMR spectroscopy.
[b] The reaction mixture was treated with the NH_4OH/NH_4Cl mixture at −40 °C and the organic layer was washed with 0.1 N HCl and water.
[c] *t*-$C_4H_9CH_2CH_2C(O)CH_3$ by-product in 14% yield.
[d] *t*-$C_4H_9CH_2CH_2C(O)C_2H_5$ by-ptoduct in 24% yield.
[e] *t*-$C_4H_9CH(CH_3)CH_2CHO$ by-product in 19% yield.
[f] Yields based on utilization of one of the R groups of the $R_2(CN)CuLi_2$ reagent.

$-110\,°C$ which is being kept saturated with a constant stream of carbon monoxide. Addition to these $R_2(CN)CuLi_2/CO$ solutions of various α,β-unsaturated ketones and aldehydes gave the results shown in Table 12[104]. Only 1,4-addition occurred in these reactions and the product yields are good. In the reactions of the t-$Bu_2(CN)CuLi_2/CO$ system with some of the more reactive α,β-unsaturated substrates *ca* 20–25% 1,4-addition of the t-Bu groups [rather than t-BuC(O)] occurred as well.

This methodology, based in a 1:1 $R_2(CN)CuLi_2/\alpha,\beta$-unsaturated substrate ratio, wastes one-half of the organic groups charged. A useful improvement was *recently* achieved by using the carbonylation of 1:1 reagents of the type 'R(CN)CuLi'[116]. In a typical preparation (method I) a hexane solution of t-butyllithium was added to CuCN in THF at $-78\,°C$, and the resulting yellow suspension was allowed to warm to $0\,°C$ until dissolved and then cooled again to $-78\,°C$. Carbon monoxide was bubbled, the α,β-unsaturated ketone added and maintained at $0\,°C$ under CO. In an alternate procedure (method II) the t-Bu(CN)CuLi reagent solution was cannulated into a 4:4:1 THF, Et_2O, pentane mixture at $-110\,°C$ which was kept saturated with a stream of CO for 2 h. The α,β-unsaturated substrate then was added. This procedure was especially useful in the 1,4-acylation of the more reactive α,β-unsaturated electrophiles whose reactions in method I gave 1,4-alkylated by-products, e.g. crotonaldehyde, methylvinyl ketone and 5,6-dihydro-2H-pyran-2-one (Table 13).

The *sec*-Bu(CN)CuLi reagent is less stable. Best results were obtained using method II.

TABLE 13. Direct nucleophilic 1,4-acylation of α,β-unsaturated substrates. Reproduced with permission from *Tetrahedron Lett.*, **27**, 1473 (1986)

Reagent, R(CN)CuLi R =	α,β-Unsaturated substrate	Method (see text)	Product (% yield)
Me_3C	Cyclohexen-2-one	I[a]	3-Pivaloylcyclohexanone 94)
	$CH_2{=}CHC(O)CH_3$	I[b]	$Me_3CC(O)CH_2CH_2C(O)CH_3$ (68)[c]
	$CH_3CH{=}CHC(O)Et$	I[a]	$Me_3CC(O)CH(CH_3)CH_2C(O)Et$ (93)
	$PhCH{=}CHC(O)CH_3$	I[b]	$Me_3CC(O)CH(Ph)CH_2C(O)CH_3$ (88)
	$EtCH{=}CHCHO$	I[b]	$Me_3CC(O)CH(Et)CH_2CHO$ (72)
	$CH_3CH{=}CHCO_2CH_3$	I[d]	$Me_3CC(O)CH(CH_3)CH_2CO_2CH_3$ (72)
	5,6-Dihydro-2*H*-pyran-2-one	II[e]	4-Pivaloyl-δ-valerolactone (81)[f]
	$CH_3CH{=}CHCHO$	II[e]	$Me_3CC(O)CH(CH_3)CH_2CHO$ (71)
	$CH_2{=}CHC(O)CH_3$	II[e]	$Me_3CC(O)CH_2CH_2C(O)CH_3$ (86)
	Cyclohexen-2-one	I[g]	3-(2-Methylbutanoyl)cyclohexanone (80)
	Cyclohexen-2-one	II	3-(2-Methylbutanoyl)cyclohexanone (94)
	$CH_3CH{=}CHC(O)Et$	I[g]	$MeEtCHC(O)CH(CH_3)CH_2C(O)Et$ (75)
	$CH_3CH{=}CHC(O)Et$	II	$MeEtCHC(O)CH(CH_3)CH_2C(O)Et$ (99)
	$PhCH{=}CHC(O)CH_3$	II	$MeEtCHC(O)CH(Ph)CH_2C(O)CH_3$ (91)
	$EtCH{=}CHCHO$	II	$MeEtCHC(O)CH(Et)CH_2CHO$ (73)

[a] α,β Compound added at $0\,°C$.
[b] α,β Compound added at $-20\,°C$.
[c] $Me_3CCH_2CH_2C(O)CH_3$ (14%) by-product.
[d] 4 molar equiv. of ester used; reaction at $-20\,°C$ (1 h) and room temp. (1 h).
[e] Carbonylation at $-110\,°C$ for 2 h.
[f] 4-t-butyl-δ-valerolactone (11%) by-product.
[g] α,β Compound added at $-78\,°C$.

Excellent yields of 1,4-diketones were thus obtained (Table 13) and the yield of the 1,4-ketoaldehydes prepared was good. In order to effect direct nucleophilic 1,4-acylation of α,β-unsaturated ketones and aldehydes with a primary acyl cuprate, the less efficient n-$R_2(CN)CuLi_2/CO$ procedure[113] must be used.

The apparent stability of the R(CN)CuLi/CO reagents studied by Seyferth and Hui[116] decrease in the order R = *t*-Bu > *sec*-Bu > n-Bu. At one extreme the pivaloylcuprate appears to be stable up to room temperature. At the other extreme, the n-Bu(CN)CuLi/CO reagent is, apparently, not formed at all. A possible explanation of these observations[116] is that the carbonylation is a reversible process (equation 65) and thus the α,β-unsaturated substrate has the option of reacting with either **62** or **63**. When R is a bulky secondary or tertiary alkyl group, reaction of the electrophile with **62** is

$$\underset{\textbf{(62)}}{R(CN)CuLi} + CO \rightleftharpoons \underset{\textbf{(63)}}{RC(O)(CN)CuLi} \tag{65}$$

hindered and reaction with the less bulky **63** is favoured. When R is not bulky, as in the case of R = n-Bu then reaction with **62** is preferred. This is an explanation in terms of kinetic factors and the authors are seeking information on the position of the postulated equilibrium in equation 65 by means of ^1H and ^{13}C NMR studies[116].

Grignard reagent-derived cyanocuprates, e.g. *t*-Bu(CN)CuMgCl, *t*-$Bu_2(CN)Cu(MgCl)_2$ and *n*-$Bu_2(CN)Cu(MgCl)_2$, also may be carbonylated at $-110\,^\circ C$ using similar experimental procedures[104]. The *t*-butyl reagents are especially effective. For instance, in the reactions of their carbonylation products with $CH_3CH{=}CHC(O)CH_3$ the yields of *t*-$BuC(O)CH(CH_3)CH_2C(O)CH_3$ obtained were 81% and 95%, respectively[104].

As Seyferth[104] stated: 'a good beginning has been made in the development of direct nucleophilic acylation as a useful new procedure in organic synthesis. However, much remains to be done'.

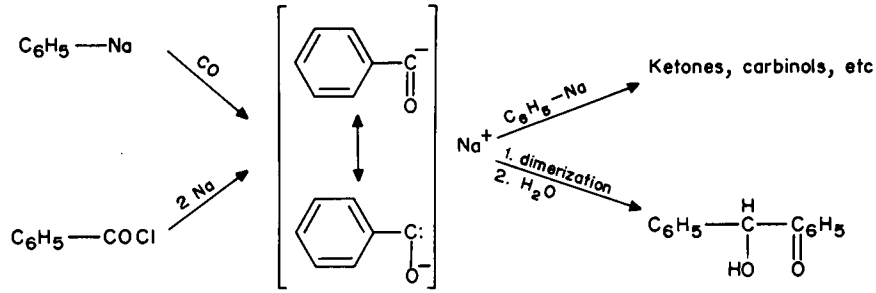
3. *Organosodium and organopotassium compounds*

Organosodium and organopotassium compounds are closely related in their reactivities toward carbon monoxide. The properties and reactions of this type of compound have been reviewed[118]. In accordance with experimental results and pK_a studies[24,119,120] the difference in acidity are rather small and the following order of basic strengths for organosodium and organopotassium compounds can be derived:

$$\text{alkyl} - M > \text{aryl} - M > \text{benzyl} - M > Ph_3C - M$$

Two of the most widely used methods for preparing organolithiums, that is, oxidative metallation and metal–halogen exchange, are not well suited for the preparation of other organoalkali metals due to highly competitive Wurtz coupling. Only aryl derivatives of sodium and potassium are suitably prepared by oxidative metallation. At present, metal–hydrogen exchange reactions and transmetallation reactions represent some of the most commonly employed routes to organosodiums and organopotassiums[24].

By prolonged treatment of phenylsodium suspensions with carbon monoxide Schlubach[121] obtained a mixture of benzophenone, triphenylmethanol and benzoic acid. The reaction was assumed to proceed through an acyl anion intermediate **64**. A mechanism involving the same anion **64** has been postulated to explain the formation of acyloins in the reaction of aryl–sodium complexes with acid chlorides[122] (equation 66).



(64) (66)

Similarly to what has been proposed for the acyl anions formed in the carbonylations of organolithium compounds, the lower resonance structure predicts the properties of a nucleophilic carbene for the acyl anion **64**[123]; however, its existence could not be proved since results showed that it does not add onto olefins or acetylene derivatives[118]. In the light of recent results observed with organolithium compounds (Section II.C.1), it is highly probable that the acyl anion **64** does not exist free in the reaction mixture, since it could not be trapped by the above-mentioned reactions.

Detellier and coworkers[126] have recently determined the mechanism of complexation and decomplexation of sodium cation complexes with dibenzo-24-crown-8 and dibenzo-18-crown-6 in aprotic solvents. In other reactions of these compounds it has been found that complexing the sodium atom with crown ethers increases the reactivity of the 'naked' carbanion, but the effect on the carbonylation has not been examine yet.

Free triphenylmethylsodium does not react with carbon monoxide[124], but does form a dark-coloured adduct with it in the presence of triphenylborane[125]. The structure of the complex has not been completely elucidated.

Until now the carbonylation of organosodium and organopotassium compounds seems to be of little synthetic value. The most common route to alkylsodiums and alkylpotassiums is the oxidative–reductive metallation reaction of alkylmercurials with sodium or potassium (equation 67)[24], but organomercurial carbonylations have been found to be synthetically useful by themselves (see Section II.C.6).

$$Bu_2Hg + Na\ (excess) \xrightarrow{\text{ligroin}} 2BuNa + Na(Hg) \qquad (67)$$

Furthermore, alkylpotassiums react to a considerable extent, even with petroleum ether, within a few hours at room temperature. Since the carbon monoxide absorption is usually slow and requires elevated temperatures, this additional difficulty seriously limits the synthetic usefulness of alkylpotassiums.

Nevertheless, some special organopotassium salts exhibit peculiar and synthetically valuable reactivity with carbon monoxide. An interesting carbonylation reaction of potassium alkoxides has been recently reported[127] (see Section IV.A.2).

The reactions of the very useful disodium tetracarbonylferrate reagent, $Na_2Fe(CO)_4$, have been sometimes referred to as carbonylations of organosodium compounds. The preparation and use of this versatile compound has been reviewed by Collman[128]. The reagent shows a wide scope of synthetic applications for the synthetic of several compounds, such as ketones, aldehydes, etc., and in a sense the $Na_2Fe(CO)_4$ can be considered a transition-metal analogue of a Grignard reagent. The mechanism of the reaction has also been studied[128]; since the organic radical is bonded to the iron atom forming a $RFe(CO)_4$ anionic complex, the reaction cannot be considered a carbonylation

of the carbon–sodium bond and therefore it will be not discussed in this chapter. Something similar applies to the carbonylations of alkyl halides catalyzed by $NaCo(CO)_4$[9].

4. Organomagnesium reagents

Vinay[129] in 1908 reported his observation of the carbon monoxide uptake by organomagnesium reagents. Since that date, the reaction has been studied in detail by many workers using a variety of reaction conditions and catalysts. Nevertheless, until recently, the reaction could not be considered of high synthetic value: the nature of the products seems to depend on the nature of the starting materials, the yields of the desired product are not very high and usually side-reactions make it difficult to isolate the required product.

The main products obtained in this reaction are ketones, ketoins and products obtained from Grignard reagent radical coupling.

Alkyl Grignard reagents slowly absorb carbon monoxide; high temperatures and pressures had to be used and a complex mixture of products resulted[130]. At 150 °C and 100 atm R_2CHOH and the corresponding alkenes and ketoins are the main reaction products[131]. Thus, butylmagnesium bromide gives 4-nonene as the major product (equation 68).

$$C_4H_9MgBr \xrightarrow{CO,\ 150\text{–}250\ atm} \underset{65\%}{C_4H_9CH{=}CHC_3H_7} \tag{68}$$

The formation of olefins with one carbon atom more than provided by the two alkyl groups of the starting primary alkylmagnesium halide has been found to be a general reaction[131,132]. Thus, 3-heptene is obtained in 55% yield by the reaction of propylmagnesium chloride with carbon monoxide under 80 atm pressure at 120 °C for 2 h[132].

Good results have been reported for the reaction of phenylmagnesium bromide with carbon monoxide which at 100 atm pressure and 75–85 °C, produces benzoin (65%), besides biphenyl (2%) and benzil (4%)[131]. However, under similar conditions α-naphthylmagnesium bromide yields only binaphthyl (68%) and no naphthoin could be isolated[131].

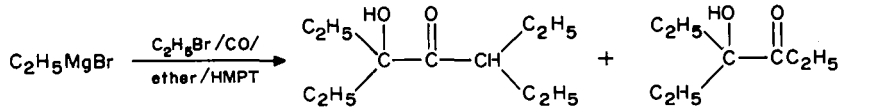
The effect of addition of various additives has been studied[133–135] and much improved results have been observed in some cases. Thus, it has been observed that the addition of HMPA to the solvent of ethereal alkylmagnesium halides enhances the rate of carbonylation: with one mole of HMPA per mole of Grignard reagent, the system readily absorbs carbon monoxide even at room temperature and atmospheric pressure[135]. Using an autoclave (30 atm) the reaction is often complete within one minute. Primary alkylmagnesium halides yield the corresponding acyldialkylmethane as the major product (equation 69). Isolation is achieved without difficulty, as there are little or no carbonylated side-products. Comparable results were obtained for alkyl chlorides. Hence, the present reaction constitutes a simple, one-step procedure for the preparation of acyldialkylmethanes from primary alkyl derivatives.

$$RMgX \xrightarrow{CO,\ 40\ atm,\ 25\,^{\circ}C} R_2CHC(=O)R \tag{69}$$

$R = C_7H_{15}$	(35%)
$R = C_3H_7$	(56%)
$R = C_2H_5$	(36%)

With tertiary alkyl derivatives (R = *t*-butyl, *t*-pentyl) the corresponding dialkyl ketones are produced without formation of side-products of comparable volatility whereas the secondary alkyl derivatives lead to product mixtures containing alkenes, ketoins and acyldialkylmethanes[135].

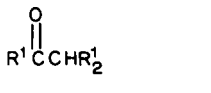
Carbonylation of ethylmagnesium bromide in diethyl ether/HMPA in the presence of an additional amount of ethyl bromide gives a mixture of hydroxyketones[136]. The uptake of CO by the Grignard reagent is speeded up considerably in the presence of HMPA and is often completed within 1–5 min at room temperature and 35 atm (equation 70).



54% 10% (70)

Carbonylation in neat HMPA has also been studied[137]. Although the reaction is very rapid a large number of products is formed (**65–69**). It appears that 0.7–1 equiv of HMPA is about the right proportion from a synthetic point of view, and product composition appears to depend on the method of preparation of the Grignard solution.

From a mechanistic point of view it is important that carbonylation of phenylmagnesium bromide, at low temperature and leading to 5% conversion after 21 h, afforded after



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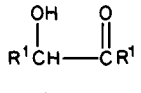

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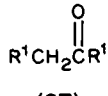
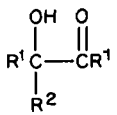


(67)

(a) R^1 = Me
(b) $R^1 = R^2$ = Et, R^3 = Me
(c) R^1 = Pr^n
(d) R^1 = Bu^n, R^2 = Et, R^3 = Me
(e) $R^1 = R^2 = Bu^n$, $R^3 = Pr^n$
(f) R^1 = n-C_7H_{15}
(g) R^1 = Cl[CH_2]4
(h) R^1 = Pr^i
(k) R^1 = Bu^n
(l) R^1 = Bu^t
(m) R^1 = *t*-C_5H_{11}
(n) R^1 = Ph
(p) R^1 = $PhCH_2$



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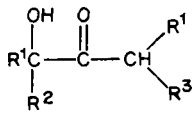
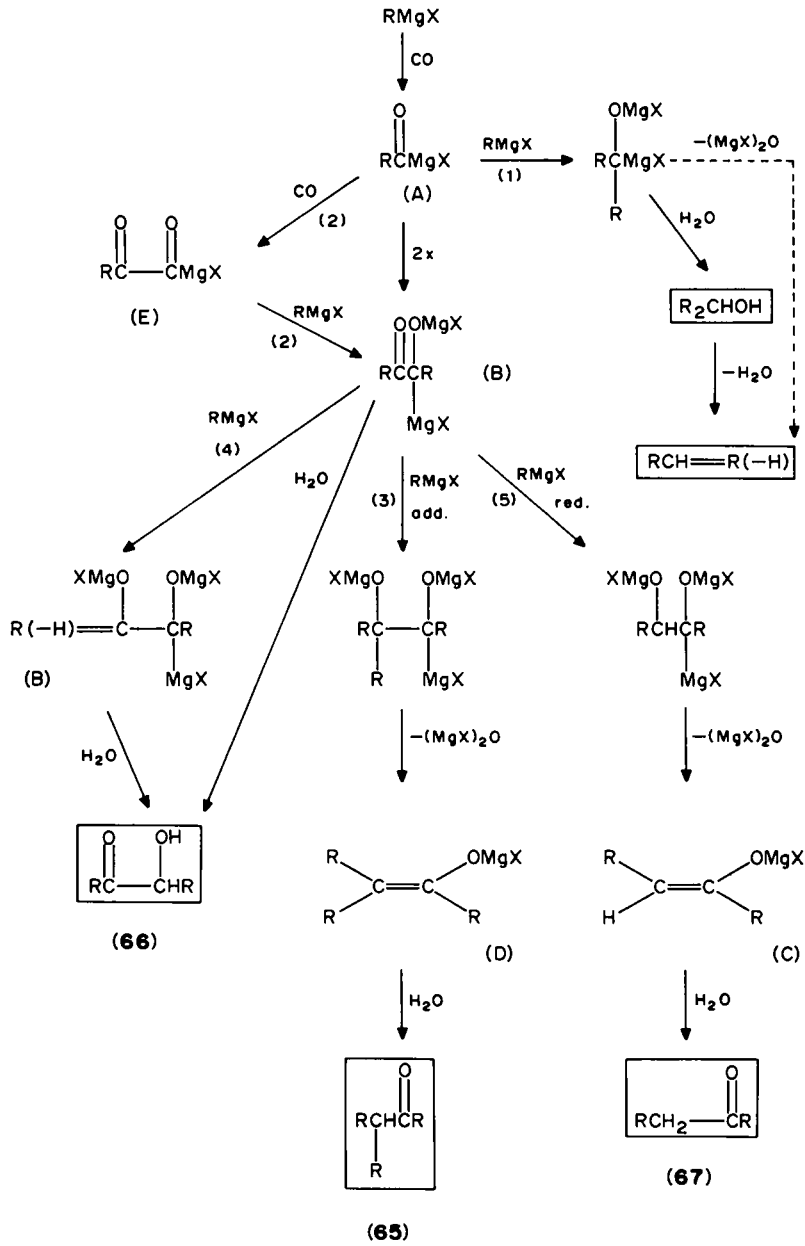


(69)

hydrolysis *ca* 20% yield of benzaldehyde. This proves that the first step is the insertion of CO to give the acylmagnesium compound A and that this is relatively stable under the above conditions (Scheme 7). Very likely, before hydrolysis, hydroxyketones are present in the reaction mixture as their magnesium enolates. These derivatives may well be capable of reacting with, for instance, (starting) Grignard compounds, and thus lead to even more complex molecules. Intermediate A may add another RMgX [step (1)] to give secondary alcohols and/or the corresponding alkene(s). This process appears to be unimportant in the presence of HMPA. Apparently, insertion of a second mole of CO to give (E) [step (2)] and subsequent addition of another RMgX to give (B) is the preferred route. If this pathway obtains, the addition to the CO group next to MgX is understood when accepting that the MgX group, solvated by HMPA, is a stronger electron donor than ethyl[137].

Alternatively, (A) may dimerize to give (B) 'directly' supposedly via a carbenoid analogue RCOMgX. Further addition of RMgX [step(3)] and formation of the 'final' intermediate (D) is straightforward. Although the various reaction steps have not been as thoroughly studied as in the case of the reaction of organolithium compounds, the close


RMgX
CO
RCMgX
(A)
RMgX
(1)
OMgX
RCMgX
R
−(MgX)2O
H2O
R2CHOH
−H2O
RCH=R(−H)
CO
(2)
RC—CMgX
(E)
2x
RMgX
(2)
OOMgX
RCCR
MgX
(B)
RMgX
(4)
H2O
RMgX
(3)
add.
RMgX
(5)
red.
XMgO OMgX
R(−H)=C—CR
MgX
(B)
XMgO OMgX
RC—CR
R MgX
XMgO OMgX
RCHCR
MgX
−(MgX)2O
−(MgX)2O
H2O
O OH
RC—CHR
(66)
R OMgX
C=C
R R
(D)
R OMgX
C=C
H R
(C)
H2O
H2O
O
RCHCR
R
(65)
O
RCH2—CR
(67)

SCHEME 7

similarity between the proposed intermediates and the similar properties of both types of organometallic reagents makes Scheme 7 highly probable.

Although mechanistically interesting, owing to the mixture of products obtained under the present reaction conditions in general, the procedure has no significant preparative value (see Table 14).

The effect of addition of some transition metal salts to the reaction of organomagnesium compounds has also been examined. The reaction of phenylmagnesium bromide with carbon monoxide in diethyl ether at 35 °C in the presence of cobalt(II)chloride gives benzoin (30%) as the main product[130]. However, addition of chromium(III)chloride to the same reaction leads to the production of benzophenone (38%) as the major product besides biphenyl (15%) and α,α-diphenylacetophenone (10%)[134].

Sobota and collaborators[138,139] have recently reinvestigated the carbonylation reaction of dialkyl magnesium derivatives. Although the reaction mixture obtained is complex (see equation 71) they found that the product composition is dependent mainly on the MgR_2

TABLE 14. Carbonylation of etheral RMgX with 1 equiv. of HMPA. Reproduced with permission from *J. Chem. Soc., Perkin Trans. 2*, 1897 (1976)

R	X	Main product(s)	Yield (%)[a]	Furthermore products (%)
Me	I	**65a**	N.d.	$CH_3 \cdot CH \cdot CH_3^b$
Et	Br	**65b**	36 (36)	
Pr^n	Br	**65c**	56 (56)	
Pr^n	Cl	**65c**	31	
$n\text{-}C_7H_{15}$	Br	**65f**	46 (35)	
$Cl[CH_2]_4$	Br[c]	**65g**	N.d.	
Pr^i	Br	**66h**	26 (18)	Pr^i_2CHOH(7)
Pr^i	Cl	**66h**	30	$Pr^i_2CHOH^b$
Bu^s	Br	**66k**	16	butane + butene (4:1);[b]
		67k	10	$Bu^sCH{=}C(Me)Et$ (22)
Bu^s	Cl	**66k**	16	Bu^sOH(4);[d]
		67k	4	$Bu_2CH{=}C(Me)Et$ (24)
Bu^t	Br	**66l**	17	
	Cl	**66l**	40	
$t\text{-}C_5H_{11}$	Br	**66m**	20	$EtC(Me_2)C(Me_2)Et$(20); $(t\text{-}C_5H_5)_2CHOH^c$
Ph	Br	**66n**	22	Ph_2CHOH(15)
$PhCH_2$	Br	**66p**	N.d. (17)	Bibenzyl(69)

[a] Yields are based on starting compound RX; data in parentheses refer to isolated materials.
[b] Not analysed quantitatively.
[c] This Grignard compound was made in THF and the solvent replaced by ether.
[d] Due to blank reaction of RMgX with HMPA.

concentration. At 1.4 mol dm^{-3} they obtained good yields (e.g. 90% of 4-ethylhexanone-3)[138].

$$MgR_2 + CO \xrightarrow{Et_2O} RCOCHR_2 + RCOC(OH)R_2 + RCOCH(OH)R + R_2CO + R_2CHOH \quad (71)$$

The main product, $RCOCHR_2$ (**65**), is probably formed involving nucleophilic attack on the carbon monoxide by MgR_3^-, which is formed in equilibrium with MgR_2 (equation 72).

$$2MgR_2 \rightleftharpoons MgR_3^- + MgR^+ \quad (72)$$

Sobota and Nowak[139] centre their discussion in the state of ionization and solvation of MgR_2. $[MgR_2(THF)_2]$ in THF is monomeric[140] and its ionization state is small. The number of ions in solution could be increased by addition of e.g. a 2, 2, 1-cryptand, which results in the formation of $[MgR(cryptand)][R_2Mg(\mu\text{-}R)_2MgR_2]$ when $R = C_2H_5$. However, when R = neopentyl (Np), the ions $[MgNp(cryptand)]^+$ and $MgNp_3^-$ arise[141,142]. MgR_3^- undergoes dimerization to anion $[R_2Mg(\mu\text{-}R)_2MgR_2]^{2-}$. It seems, however, that without a ligand or an anion to stabilize MgR^+ the latter would undergo solvation in ether solutions, like $MgCl^+$[143], and thus being unstable undergoes subsequent reaction (equation 73)[139]. For this reason, the authors propose that the ionization process of MgR_2 in THF is best described by equation 74[139].

$$[MgR(THF)_5]^+ + [MgR_2(THF)_2] \rightarrow MgR_3^- + [Mg(THF)_6]^{2+} \quad (73)$$

$$3[MgR_2(THF)_2] \rightleftharpoons 2MgR_3^- + [Mg(THF)_6]^{2+} \quad (74)$$

Sobota and Nowak[139] found that the solvent polarity greatly affects the position of the equilibrium of reactions 72–74 and the percentage composition of reaction products (Table 15). Direct reaction between $MgEt_2$ and CO in heptane (or without solvent), in which $MgEt_2$ is not dissociated, produces mainly Et_2CO in 59.0 (78.0)% yield. In polar solvent, however, a compound with a carbon–carbon bond, $EtCOCHEt_2$, is formed. The results indicate that both MgR_2 and the MgR_3^- ion react with CO (equation 75).

$$3MgEt_2 \xrightarrow{k} 2MgEt_3^- + Mg^{2+} \quad (75)$$

$$\begin{array}{ccc} & \overset{k_1}{\downarrow}{\scriptstyle 1.CO \atop 2.H^+} & \overset{k_2}{\downarrow}{\scriptstyle 1.CO \atop 2.H^+} \\ & Et_2CO & EtCOCHEt_2 \end{array}$$

TABLE 15. Effect of solvent on the proportion in which each of the products was obtained from the reaction of $MgEt_2$ with CO. Reproduced with permission from *J. Organomet. Chem.*, **340**, 1 (1988)

Products	Solvent[a]				Without solvent
	Et_2O	Pr_2O	n-C_7H_{16}	THF	
Et_2CO	12.1	15.0	59.0	15.5	78.0
Et_2CHOH	6.4	6.2	–	3.6	–
EtCOCHOHEt	0.6	8.2	5.5	5.2	3.3
$EtCOCHEt_2$	56.6	24.1	12.4	26.2	10.0
$EtCOCHEt_2$	24.3	36.0	22.4	30.0	5.2
$[k]^b$	0.050	0.072	0.044	0.450	0.005

[a]Initial concentration of $MgEt_2$ was 0.5 *M* in all cases.
[b]Rate constant (pseudo-first-order kinetics) with a CO excess versus $MgEt_2$ ($k = k_1 + k_2$).

It was found that the initial rates of $MgEt_2$ reactions with CO in THF were dependent on the concentrations of $MgEt_2$, indicating that the CO molecule reacts with both anion and $MgEt_2$[139]. The observed reaction rates were $0.293\,s^{-1}$ (k_1) and $0.450\,s^{-1}$ (k_2). To control the equilibrium of reaction 74, $MgCl_2$ was added to the THF solution. It was found that addition of $[MgCl_2(THF)_2]$ to $MgEt_2$ solution in THF results in the formation of $[(THF)_4Mg(\mu\text{-}Cl)_2MgEt_2]$, which prevents the shift of the reaction equilibrium so that Et_2CO was formed in 68% yield[139].

The results confirm unambiguously that the percentage of each product of reaction 71 depends primarily on the ionization degree of $MgEt_2$. In polar solvents with high diethylmagnesium concentrations, mainly products containing a carbon–carbon bond between two CO moieties are obtained. $MgEt_2$ without solvent, in hydrocarbon or polar solvents (in the presence of $MgCl_2$), gave mainly Et_2CO with CO[139]. It has been recently shown that dialkylmagnesiums interact also with 15-crown-5 forming RMg(15-crown-5)$^+$ and magnesiate ions[144]. It can be expected that renewed research on this reaction will extend its scope.

5. *Organozinc compounds*

In contrast with the carbonylation of Grignard reagents which has been studied by a large number of workers and using a variety of reaction conditions and catalysts, the action of carbon monoxide on the closely related organozinc compounds has been scarcely studied.

Fischer[145] reported many years ago that phenylzinc bromide is inert to carbon monoxide at atmospheric pressure. More recently, Rathke and Yu[146] found that dibutylzinc does not absorb carbon monoxide at atmospheric pressure either in the absence of solvents or when dissolved in THF, diglyme, ether or benzene. However, the addition of an equivalent amount of potassium *tert*-butoxide to a dyglyme solution of dibutylzinc promotes the absorption of 0.85 equivalent of carbon monoxide which is complete in 3 h at room temperature[146]: butane (1.1 equivalent) and valeroin (0.35 equivalent) are produced. The maximum yield of valeroin (42%, based on dibutylzinc) is obtained using 1 equivalent of potassium *tert*-butoxide and a reaction temperature of $-15\,°C$. Other bases were studied but they did not promote the carbon monoxide absorption.

Diisopropylzinc and diphenylzinc behave similarly to dibutylzinc: in the absence of potassium *tert*-butoxide the compounds are inert to carbon monoxide, but in the presence of the base, absorption of carbon monoxide occurs. Nevertheless, the main product is isovaleroin (35%) in the case of diisopropylzinc, but biphenyl (0.3 equivalent) in the reaction of diphenylzinc. However, butylzinc iodide was inert to carbon monoxide at atmospheric pressure either with or without added potassium *tert*-butoxide[146].

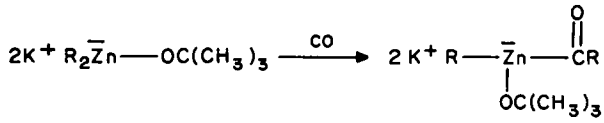
The inertness of organozinc compounds to carbon monoxide is probably due to the low polar nature of the zinc–carbon bond. Potassium *tert*-butoxide is an effective promoter for the reaction when present in stoichiometric amounts; it is possible that the function of the base is to coordinate to the zinc compound to furnish a species with greater carbanion character capable of transferring an alkyl group to carbon monoxide[146] (equation 76). The ability of bases to enhance the reactivity of organometallic compounds has been observed in many other cases[39,147].

$$R_2Zn + K^+\,{}^-OC(CH_3)_3 \rightleftharpoons K^+R_2Zn\text{-}OC(CH_3)_3 \qquad (76)$$

The experimental results agree reasonably well with the partial stoichiometry shown by equation 77.

$$2R_2Zn + 2K^+\,{}^-OC(CH_3)_3 + 2CO \xrightarrow{H_3O^+} 2RH + RC(=O)\text{—}CHR(OH) \qquad (77)$$

By analogy with the reaction of Grignard reagents with carbon monoxide, in which the intermediacy of an acyl magnesium compound has been postulated to explain the formation of acyloins produced among other products[137,145], Rathke[146] proposes an analogous mechanism for the potassium *tert*-butoxide promoted reaction of organozinc compounds (equations 78 and 79). By this mechanism, the dialkylzinc compound could



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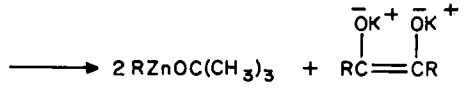
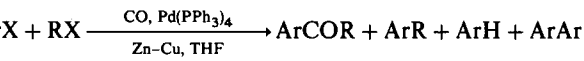


(79)

furnish a maximum of 0.5 mol of acyloin. On this basis, the observed yields of n-valeroin and isovaleroin are 84 and 70% of the theoretical maximum, respectively[146].

Since in the potassium *tert*-butoxide promoted reaction of diphenylzinc with carbon monoxide, benzoin is not formed and the only identified product is biphenyl, it is possible that coupling of the phenyl radicals is faster than the reaction with carbon monoxide. Presumably other organic products are formed which account for the slight uptake of carbon monoxide.

The coupling reaction of organozinc compounds with aryl iodides catalyzed by Pd(0) catalysts under an atmospheric pressure of carbon monoxide has been recently shown to lead to unsymmetrical ketones in good yields[148] (equation 80; Table 16). The reaction is highly catalytic [1% mol of tetrakis(triphenylphosphine-palladium)], easily performed (to a mixture of the catalyst and the zinc–copper couple purged with carbon monoxide a solution of the aryl iodide and the alkyl iodide in THF is added, and the heterogeneous mixture stirred at 50 °C for 20–50 h), and mild reaction conditions are used (1 atm carbon monoxide). Some representative results are summarized in Table 16, which reveals that the present ketone synthesis can be applied both to primary and secondary alkyl iodides. Generally, primary iodides showed the higher conversions than the secondary ones, but the selectivity of **70** to other products (**71**, **72**, and **73**) was almost the same. With respect to aryl iodides, the aryl iodides with electron-donating substituents generally showed better results, judging from conversions and selectivities for **70**[148]. *p*-Nitrophenyl iodide was unreactive under the reaction conditions, and no ketones were formed either for the combination of phenyl bromide and ethyl iodide or for the combination of phenyl iodide and propyl bromide[148]. Biaryl compounds **73** were only obtained in the case of *p*-bromoiodide (27%) and of methyl *o*-iodo benzoate (23%) which does not give ketone **70** under the reaction conditions.



(80)

(70) **(71)** **(72)** **(73)**

In contrast to this, the reaction of benzyl halides and aryl iodides showed rather different reaction features (equation 81). Under the above conditions bibenzyl was obtained in substantial amounts, e.g. 51% of *p*,*p*′-dichlorobibenzyl and 44% of phenyl *p*-chlorobenzyl ketone were obtained by the reaction of phenyl iodide and *p*-chlorobenzyl chloride at 60 °C for 5 h[148]. Formation of bibenzyl, although unavoidable, could be reduced by initiating the reaction at lower temperatures[148]. Again in this case aryl iodides with

TABLE 16. Unsymmetrical ketone synthesis from aryl iodides and alkyl iodides[a]. Reproduced with permission from *Tetrahedron Lett.*, **24**, 3871 (1983)

Entry	ArI	RI	Temp (°C)	Time (h)	Conv[b] (%)	Product (% Yield)[c]
1	PhI	MeI	45	24	63	(88)
2	PhI	n-PrI	50	24	75	90(93)
3	PhI	*i*-PrI	r.t.	42	58	(86)
4	PhI	*i*-BuI	50	28	43	85
5	PhI	$n\text{-}C_8H_{17}I$	50	23	49	90
6	PhI	$c\text{-}C_6H_{11}I$	50	24	42	63
7	$4\text{-}MeOC_6H_4I$	n-PrI	50	22	90	90
8	$4\text{-}MeC_6H_4I$	n-PrI	50	24	80	91
9	$2\text{-}MeC_6H_4I$	n-PrI	50	24	88	56[d]
10	$4\text{-}BrC_6H_4I$	n-PrI	50	8	98	38
11	$2\text{-}MeO_2CC_6H_4I$	n-PrI	50	22	100	0

[a]*Usual scale is as follows:* ArI (2.0 mmol), RI (2.2 mmol), $Pd(PPh_3)_4$ (0.02 mmol) and Zn–Cu (3.0 mmol) in 4 ml of THF under an atmospheric pressure of CO.
[b]Based on ArI, consumed.
[c]Isolated yield based on ArI consumed. *The values in parentheses refer to the vpc yields taking bibenzyl as an internal standard.*
[d]In addition to this, di(*o*-tolyl) ketone was isolated in 29% yield.

electron-donating substituents showed better yields of unsymmetrical ketones **74**. Thus, while the reaction of iodobenzene with *p*-chlorobenzylchloride gives 60% of the unsymmetrical ketone **74**, the reaction of *p*-methoxyiodobenzene yields 81% of **74** under the same reaction conditions[148].

$$Ar^1I + Ar^2CH_2Cl \xrightarrow[Zn\text{–}Cu,\ THF]{CO,\ Pd(PPh_3)_4} Ar^1COCH_2Ar^2 + Ar^1CH_2Ar^2 + Ar^2CH_2CH_2Ar^2 \quad (81)$$

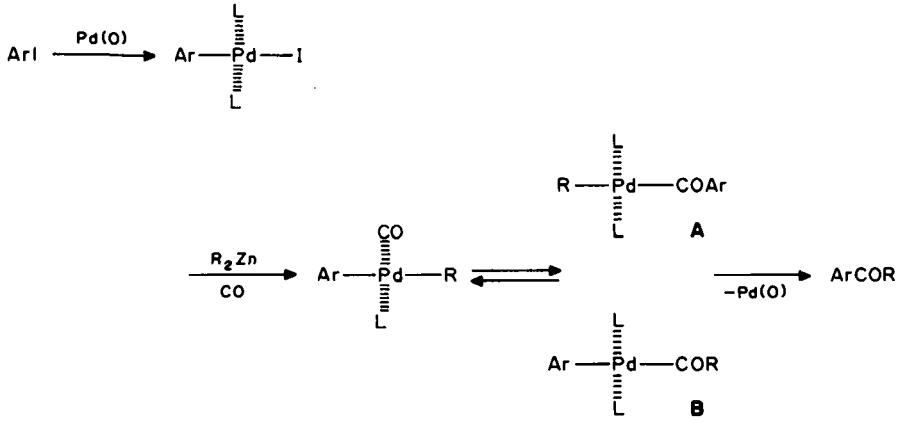
(74)

Under the same conditions as those for benzyl chlorides, allyl or propargyl bromide did not give the expected ketone in any detectable amounts, resulting in formation of a small amount of cross-coupling product detected by vpc.

The mechanism proposed for this reaction is shown in Scheme 8, and consists of an oxidative addition of a palladium(0) species to the aryl iodide, a transmetallation of an alkyl or benzyl group from the organozinc derivative to the arylpalladium complex and a migratory insertion of an aryl (forming complex A) and/or an alkyl or a benzyl group (forming complex B) on carbon monoxide, followed by a reductive elimination of unsymmetrical ketones to reproduce the palladium(0) species. The limited success with benzyl chlorides and the failure with allyl or propargyl bromide may be partly attributed to a relatively unfavourable equilibrium for the complex(es) A and/or B compared with the R = alkyl cases[148]. This is consistent with the usual order of migratory aptitudes: alkyl > benzyl > H and the retardation effects of electronegative substituents[11].

6. *Organomercurials*

Organomercury reagents are among the oldest organometallics known and one of the first synthetically useful ones, but they were almost entirely superseded by the more conveniently prepared and versatile organo-magnesium and lithium reagents. However,



SCHEME 8

many recent developments have demonstrated their new utility in organic synthesis.[149].

Preparation of organomercurials can be achieved by a wide variety of methods[150,151] and several reviews recently published[149,152,153] show their multiple applications in organic synthesis. Furthermore, Barluenga and coworkers[154] have recently reported a new hydrazino mercuration of terminal alkynes and 3-alken-1-ynes. Structural studies on arylmercurials using ^{13}C NMR spectroscopy[155] and bonding energy studies[156] have been performed. The renewed interest in these unique organometallics is largely due to their ability to undergo facile carbon–carbon bond formation and yet tolerate all important organic functional groups.

The direct carbonylation of organomercurials is exceedingly difficult, requiring high temperatures and pressures resulting in only very poor yields of carboxylic acids of their derivatives[157,158]. Depending on the carbon monoxide pressure either simple carboxylic acid derivatives[159,160] or α-keto carboxylic acids[158] are produced in low yields (equation 82). β-Alkoxy carboxylic esters can be obtained in similar fashion via alkoxymercuration–carbonylation of olefins (equation 83)[159,161,163].

$$RCO_2CH_3 \xleftarrow[\Delta,\ CH_3OH]{25\ atm\ CO} RHgNO_3 \xrightarrow[\Delta,\ CH_3OH]{250\ atm\ CO} R\overset{O}{\overset{\|}{C}}CO_2CH_3 \qquad (82)$$

$$RCH{=}CH_2 + R'OH + CO + Hg(OAc)_2 \longrightarrow \underset{OR'}{\overset{|}{R}}CHCH_2CO_2R' \qquad (83)$$

Carbonates, amides, urethanes and ureas can be easily obtained by the direct reaction of mercury salts and carbon monoxide with alcohols or amines as discussed below in Sections III and IV.

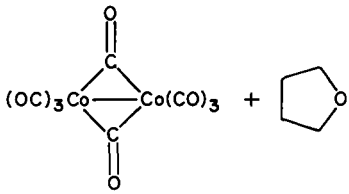
The synthetic utility of these carbonylation reactions has been widely expanded by the use of transition metal reagents. It was early observed that many organomercuric halides react with dicobalt octacarbonyl in tetrahydrofuran solution at room temperature to give the dialkyl ketone derived from the alkyl radical in the organomercurial reagent[164]. The reaction proceeds rapidly and is of good preparative utility.

Thus, ethylmercuric chloride and cyclopropylmercuric bromide react with dicobalt octacarbonyl in THF to give 3-pentanone and dicyclopropyl ketone in yields of 60 and 66%, respectively. A similar reaction of isomerically pure *n*-butylmercuric bromide produces *n*-butyl *sec*-butyl ketone (3-methyl-4-octanone) in 14% yield in addition to the expected di-n-butyl ketone (5-nonanone) in 42% yield. When two different organomercuric halides were allowed to react with dicobalt octacarbonyl, both the symmetrical ketones and the unsymmetrical ketone were produced (equation 84)[165].

$$C_4H_9HgBr \xrightarrow[THF]{Co_2(CO)_8} (C_4H_9)_2C(O) + C_4H_9\text{—}\overset{\overset{O}{\|}}{C}\text{—}\overset{CH_3}{\overset{|}{C}}H\text{—}CH_2CH_3 \qquad (84)$$

42% 14%

These facts, among other evidence, lead the authors to propose the sequence of steps shown in equations 85–89. The sequence includes THF-induced redox disproportionation of dicobalt octacarbonyl (equation 85), nucleophilic displacement of halide from mercury by $Co(CO)_4^+$ (equation 86), electrophilic cleavage of the C—Hg bond (equation 87) (or a less probable sequence 87a–87b), migration of the organic group from cobalt to carbon (equation 88) and ketone formation (equation 89).



$$+ \quad \text{O} \longrightarrow \quad \text{O}\cdot Co(CO)_4^+ \quad + \quad Co(CO)_4^- \qquad (85)$$

$$RHgX + Co(CO)_4^- \longrightarrow RHgCo(CO)_4 + X^- \qquad (86)$$

$$RHgCo(CO)_4 + THF\cdot Co(CO)_4^+ + Co(CO)_4^- \longrightarrow RCO(CO)_4 + Hg[Co(CO)_4]_2 + THF \qquad (87)$$

$$2RHgCo(CO)_4 \longrightarrow R_2Hg + Hg[Co(CO)_4]_2 \qquad (87a)$$

$$R_2Hg + THF\cdot Co(CO)_4^+ + Co(CO)_4^- \longrightarrow RCo(CO)_4 + RHgCo(CO)_4 + THF \qquad (87b)$$

$$RCo(CO)_4 \longrightarrow R\overset{\overset{O}{\|}}{C}Co(CO)_3 \qquad (88)$$

$$R\overset{\overset{O}{\|}}{C}Co(CO)_3 + RCo(CO)_4 \longrightarrow R\overset{\overset{O}{\|}}{C}R + Co_2(CO)_7 \qquad (89)$$

The authors report evidence that $RCo(CO)_4$ compounds are intermediates in the reaction. Alkylcobalt tetracarbonyls are known to undergo isomerization of the alkyl

groups[164,166], and this could be the cause of the results obtained with n-butyl mercuric bromide (equation 84).

Best results are obtained from arylmercurials (equation 90). Thus, 80% yield of benzophenone is isolated from the reaction mixture of diphenylmercury with dicobalt octacarbonyl in THF[167].

$$Ar_2Hg \xrightarrow{Co_2(CO)_8} Ar_2Co \tag{90}$$

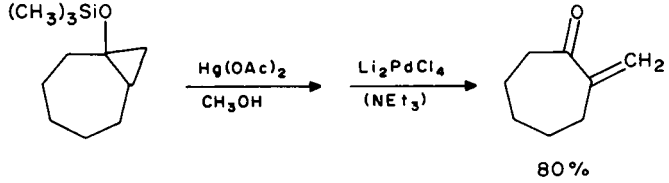
An important improvement is obtained by photochemical activation; thus, the reaction becomes catalytic in cobalt when carried out by photolysis in the presence of either $Co_2(CO)_8$ or $Hg[Co(CO)_4]_2$ (yields 60–90%)[168,169].

The above procedure is unpractical for the preparation of unsymmetrical ketones, since when a mixture of two different organomercuric halides is used overall yields of *ca* 50% are usually obtained and all three possible ketones are formed. Another route to unsymmetrical ketones is the reaction of arylmercuric halide with nickel carbonyl and aryl iodide (equation 91; Table 17)[170,171].

$$ArHgX + Ar'I \xrightarrow[C_6H_6,\ 60\text{–}70\,^\circ C]{Ni(CO)_4} ArC(=O)Ar' + 2Hg + NiX_2 + 3CO \tag{91}$$

60–92%

The palladium-promoted carbonylation of cyclopropyltrimethylsilyl ethers provides a novel route to γ-keto esters[172]. In the absence of carbon monoxide, α-methylene ketones are obtained by palladium hydride elimination (equation 92). Nevertheless, the



80% (92)

TABLE 17. The reaction of arylmercuric halides with $Ni(CO)_4$[a]

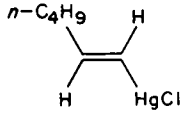
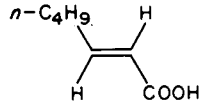
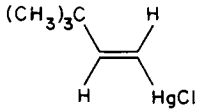
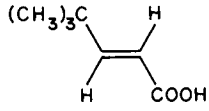
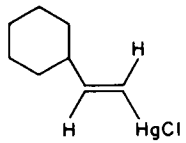
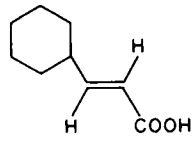
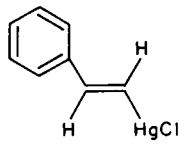
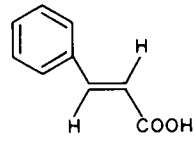
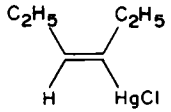
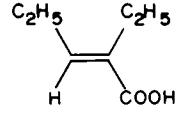
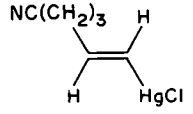
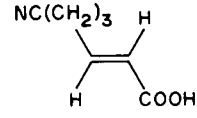
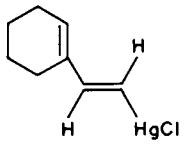
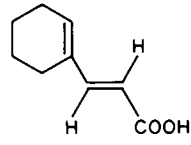
		% Distribution products	
RHgX	Solvent	O ‖ RCR	RHgR
C_6H_5HgBr	DMF	92	0
	THF	94	0
p-$CH_3C_6H_4HgBr$	DMF	100	0
	THF	99	0
n-C_4H_9HgBr	DMF	56	0
i-$C_5H_{11}HgBr$	DMF	59	0
n-$C_6H_{13}HgBr$	DMF	64	0
C_6H_5HgOAc	DMF	0	91
	DMSO	0	86
p-$CH_3C_6H_4HgCl$	THF	trace	90

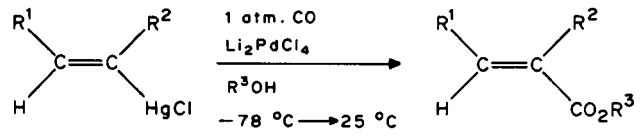
[a]At 60–70 °C for 20–30 h[170].

palladium-promoted carbonylation of alkylmercurials generally gives only low yields of products[173,174]. In contrast, excellent results are obtained by palladium-catalyzed carbonylation of vinyl mercurials[175,176] (equation 93).

Treating a wide variety of vinylmercurials with carbon monoxide, lithium chloride and palladium chloride in an alcohol solvent at low temperature results in near-quantitative

TABLE 18. Preparation of α,β-unsaturated carboxylic acids. Reproduced with permission from *J. Org. Chem.*, **40**, 3240 (1975)

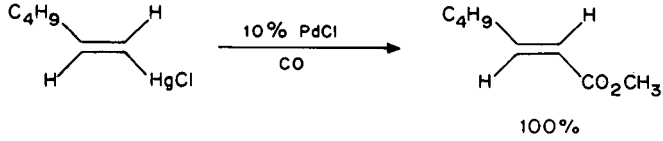
Vinylmercuric chloride	% aqueous THF	Carboxylic acid	% yield
	5 2		98 99
	5		98
	5 2 1 0.5		65 82 90 77
	5 1		80 30
	5 2		85 60
	5 2		72 65
	5 2 1		45 72 57



85—100%

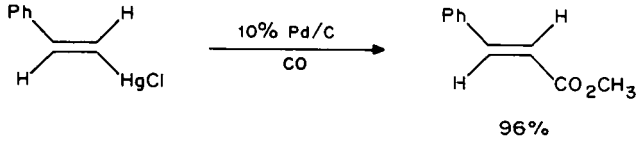
(93)

yields of the corresponding α,β-unsaturated esters (equation 93; Table 18). Catalytic amounts of either palladium chloride or palladium on carbon can be used by adding stoichiometric amounts of anhydrous cupric chloride (2 equivalents)[176], or ferric chloride[177] (equations 94–96).



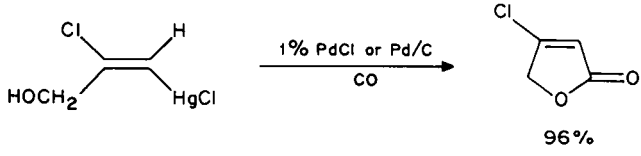
100%

(94)



96%

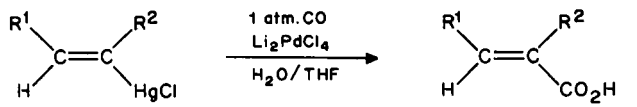
(95)



96%

(96)

Larock[176] could successfully lead the reaction to the production of α,β-unsaturated carboxylic acids by employing 2–5% aqueous THF as the solvent (equation 97; Table 19). Again, only catalytic amounts of either palladium chloride or palladium on carbon are needed if cupric chloride (2 equivalents) is employed (equation 97). In this as well as in the α,β-unsaturated esters, cupric chloride appears essential for high yields. Other catalysts have been examined but results were unsatisfactory. Thus e.g., cupric acetate and 10% $PdCl_2$ under the conditions of equations 98 gave only a 30% yield of *trans*-2-heptenoic acid (equation 98)[176].



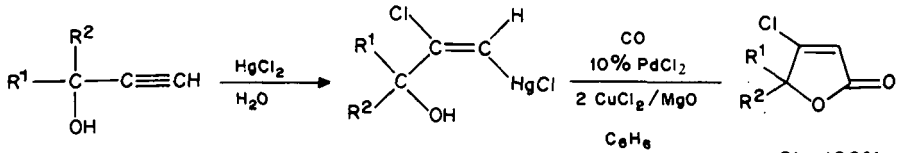
72—99%

(97)

54%

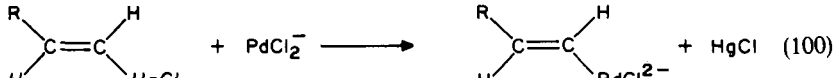
(98)

Particularly interesting is the reaction of substituted propargyl alcohols which, through the formation of the corresponding *trans*-β-chlorovinylmercurial and its further carbonylation in diethyl ether, provides the corresponding β-chlorobutenolide in a convenient procedure in high yields (equation 99).

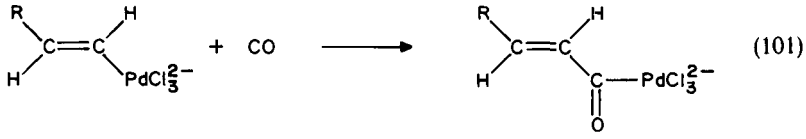


(99)

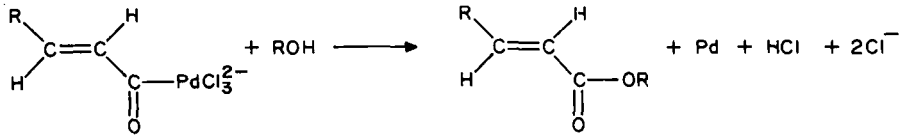
Larock[176] proposed that the palladium-promoted carbonylation of vinylmercurials proceeds by an initial mercury–palladium exchange reaction (equation 100), carbon monoxide insertion into the resultant vinylpalladium compound (equation 101), and subsequent solvolysis to give the α,β-unsaturated acid or ester and palladium metal (equation 102). In the catalytic reactions the palladium metal is reoxidized to palladium(II) by cupric chloride (equation 103). Support for this mechanism is found in the many analogous reactions reported previously[177]. The carbonylation reaction using palladium on carbon in the absence of cupric chloride presumably involves initial mercury–palladium interchange via oxidation–reduction (equation 104)[176].



(100)

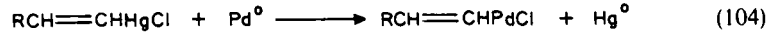


(101)



(102)

(103)



(104)

It can be observed in Tables 18 and 19 that the synthesis of α,β-unsaturated acids and esters by the palladium-promoted carbonylation of vinyl mercurials is highly stereospecific.

Attempts to extend the carbonylation of vinylmercurials to the synthesis of the

TABLE 19. Preparation of α,β-unsaturated carboxylic esters. Reproduced with permission from *J. Org. Chem.*, **40**, 3239 (1975)

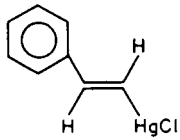
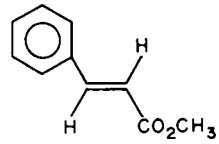
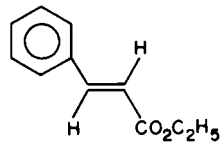
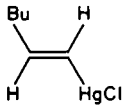
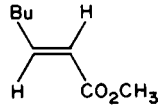
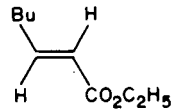
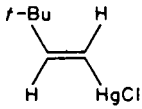
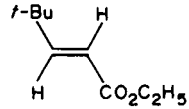
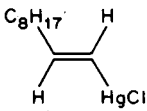
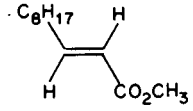
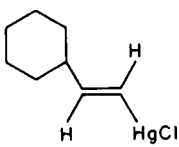
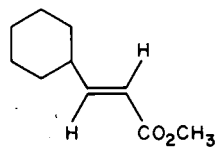
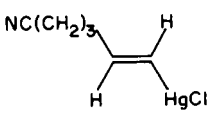
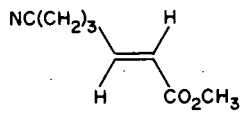
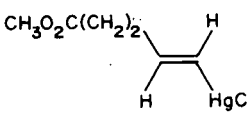
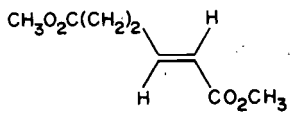
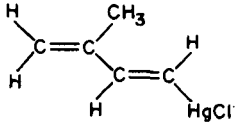
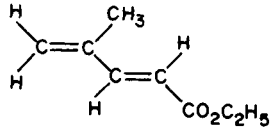
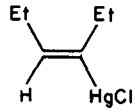
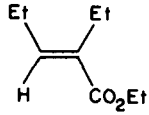
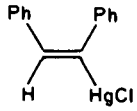
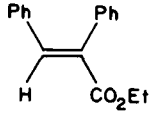
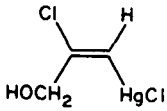
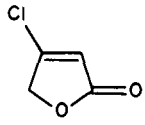
Vinylmercuric chloride	Carboxylic ester	% yield
		100[a]
		99[a]
		98[a]
		93[a]
		90[a]
		98
		96
		98
		98[b]

TABLE 19. (*continued*)

Vinylmercuric chloride	Carboxylic ester	% yield
		93[a]
		85[a]
		99
		96[c]

[a]Yield by GLC analysis using an internal standard.
[b]Vinylmercurial and ester are a mixture of *cis* and *trans* isomers.
[c]Carbonylation in diethyl ether.

corresponding amides were unsuccessful: carbonylation of the corresponding vinyl mercurial in the presence of an amine under conditions identical with those used in the preparation of α,β-unsaturated esters resulted either in a high recovery of the starting material or in vigourous undesired side-reactions.

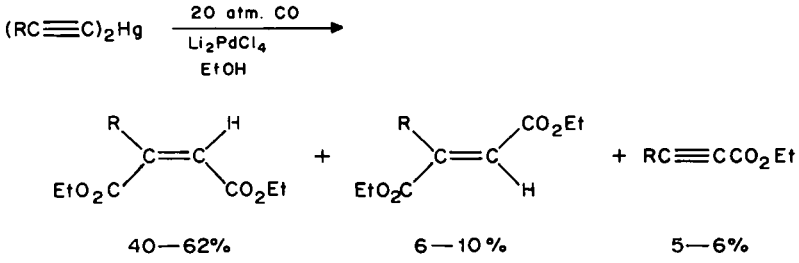
Attempts to catalyze the carbonylation of vinylmercurials by $Cl_2Pd(PPh_3)_2$ at elevated temperatures and pressures have generally given only low yields of the desired products[178], but the reaction can be successfully used for the carbonylation of aryl mercurials (equation 105)[178].

$$\mathrm{ArHgX} \xrightarrow[\text{cat. } Cl_2Pd(PPh_3)_2]{\substack{60-128 \text{ psi CO} \\ 70-110^\circ C \\ \mathrm{ROH}}} \mathrm{ArCO_2R} \quad (105)$$

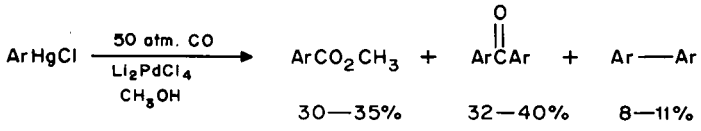
10—99%

On the other hand, the palladium-promoted carbonylation of dialkynyl mercurials affords mainly maleate esters containing small amounts of the corresponding fumarate and acetylenic esters (equation 106)[179].

Similar unappealing results were obtained in the carbonylation of heterocyclic and ferrocenylmercurials, since the desired esters are frequently accompanied by comparable amounts of the corresponding symmetrical ketone and some biaryl (equation 107)[180–182].

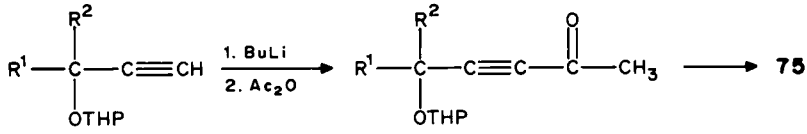


(106)



(107)

A very useful novel route to furan-containing carbonyl compounds has been recently developed by Larock and Liu[183] through the palladium-promoted carbonylation of furylmercurials. These compounds can be easily obtained by the *syn* addition of mercuric chloride to the acetylenic bond of 4-hydroxy-2-alkyn-1-ones (**75**) prepared by the method of Duranti and Balsamini[184]. The commercially available acetylenic alcohols, **76a–c**, were protected as the corresponding tetrahydropyranyl (THP) ethers, deprotonated by butyllithium, and then reacted with excess acetic anhydride at −78 °C (equation 108).

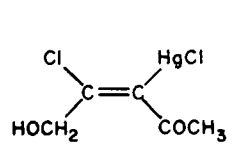
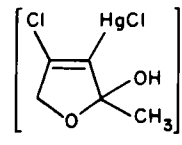
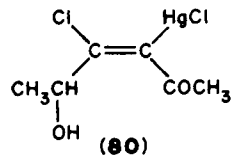
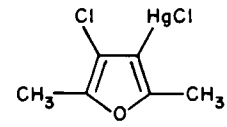
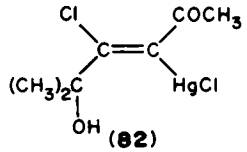
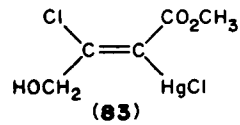
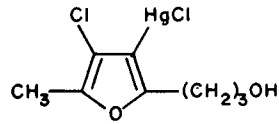


(76 a—c) **(77 a—c)** (108)

	R^1	R^2	isolated yield (%)
(a)	H	H	54
(b)	H	CH_3	61
(c)	CH_3	CH_3	54

Mercuration of the 4-hydroxy-2-alkyn-1-ones proceeds in a *syn* manner with primary and secondary alcohols, but affords *anti* addition compounds with simple propargylic alcohols (Table 20). It is assumed that the mercuration of acetylenes parallels that of simple alkenes and that an initial π complex of mercurinium ion-like structure is initially produced (Scheme 9). With 4-hydroxy-2-alkyn-1-ones, such an intermediate might be additionally stabilized by the presence of an intramolecular hydrogen bond between the alcohol and carbonyl groups (**85**) or by intramolecular hemiketal formation (**86**). Such cyclic structures would prevent backside attack of a chloride anion on the carbon β to the carbonyl and allow only formation of the *syn* addition compounds by frontside attack on

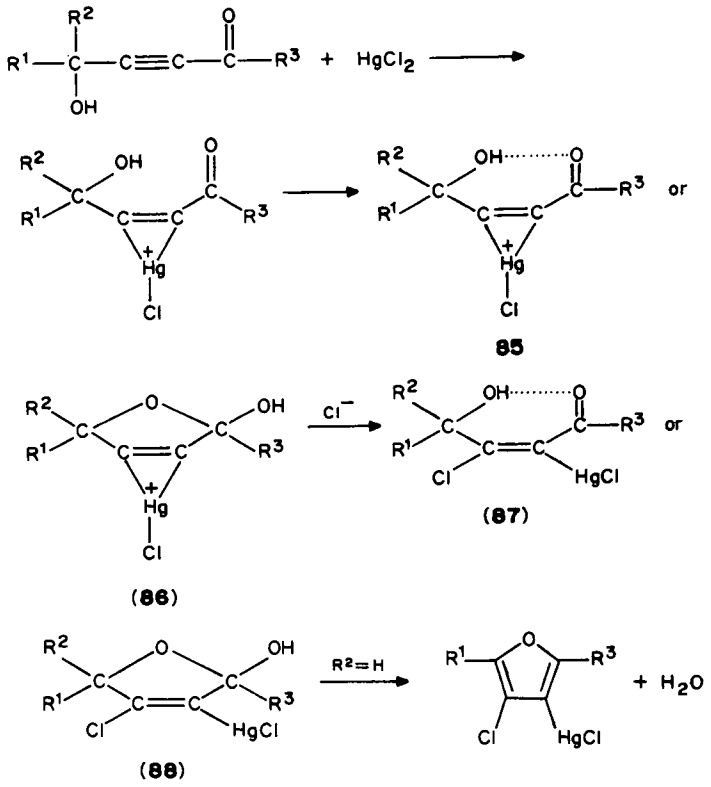
TABLE 20. Mercuration of 4-hydroxy-2-alkyn-1-ones. Reproduced with permission from *J. Org. Chem.*, **48**, 2153 (1983)

4-Hydroxy-2-alkyn-1-one	Product(s)	% yield[a]
75a	 **(78)**  **(79)**	75(30)
75b	 **(80)** +  **(81)**	90(63)
75c	 **(82)**	100(72)
75d[b]	 **(83)**	100(72)
75e[b]	 **(84)**	17(13)

[a]Isolated yield (recrystallized yield).
[b]Compounds **75d** and **75e** were obtained by replacing Ac_2O in equation 108 by $ClCO_2CH_3$ or 1-keto- THF. The THF derivatives were deprotected immediately prior to mercuration.

the mercury-stabilized cation, resulting in products such as **87** and **88** for which the authors have presented evidence[183].

Much of the information used by Larock and Liu[183] to establish the structure of the various organomercurials has been obtained by studying their palladium-promoted carbonylation. When the vinylmercurials **78** and/or **79** are treated with carbon monoxide in the presence of 1 equivalent of Li_2PdCl_4 in either methanol or diethyl ether as the solvent, the furan derivatives **89**, **90** and **91** are observed (equation 109). In ether, compound **89** is the major product, but it proved too volatile to easily isolate. Compound **91** is also formed in 30% isolated yield to this reaction[183]. Pure vinylmercurial **80**, a 95:5 mixture of **80** and **81**, and pure **81** have also been carbonylated (equation 110). Furan-



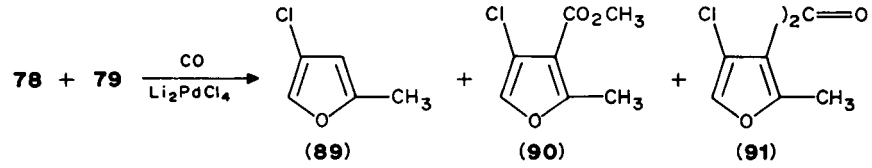
SCHEME 9

TABLE 21. Carbonylation of organomercurials. Reproduced with permission from *J. Org. Chem.*, **48**, 2153 (1983)

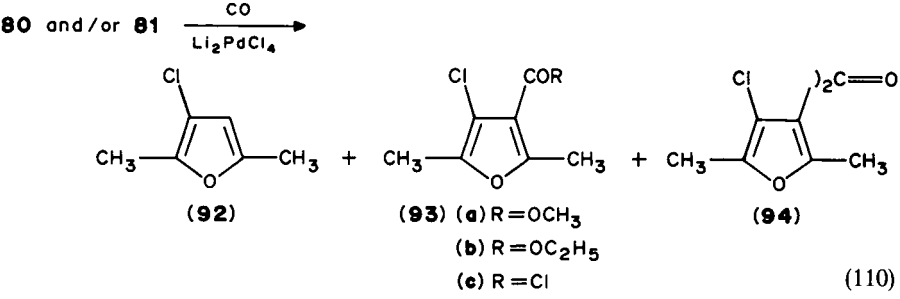
Organomercurial(s)	Solvent	Base added	% yield[a]
80	MeOH	—	11
			4
		MgO	12
	Et_2O	—	
		$2Et_3N$	
	CH_3CN	—	
		$2Et_3N$	(8)
80 + 81	MeOH	—	
		$2Et_3N$	(9)
		MgO	(10)
	CH_3CN	MgO	(10)
		$4Et_3N$	(3)
81	MeOH	$2Et_3N$	(97)
	CH_3CN	$2Et_3N$	(93)

[a]Isolated yield (yield determined by GLC analysis).

containing products analogous to those obtained upon carbonylation of **78** + **79** have been obtained. The results are summarized in Table 21.



(109)



(110)

The furan-containing carbonyl products are most likely formed by cyclic dehydration of the vinylmercurials to furylmercurials followed by carbonylation according to Scheme 10.

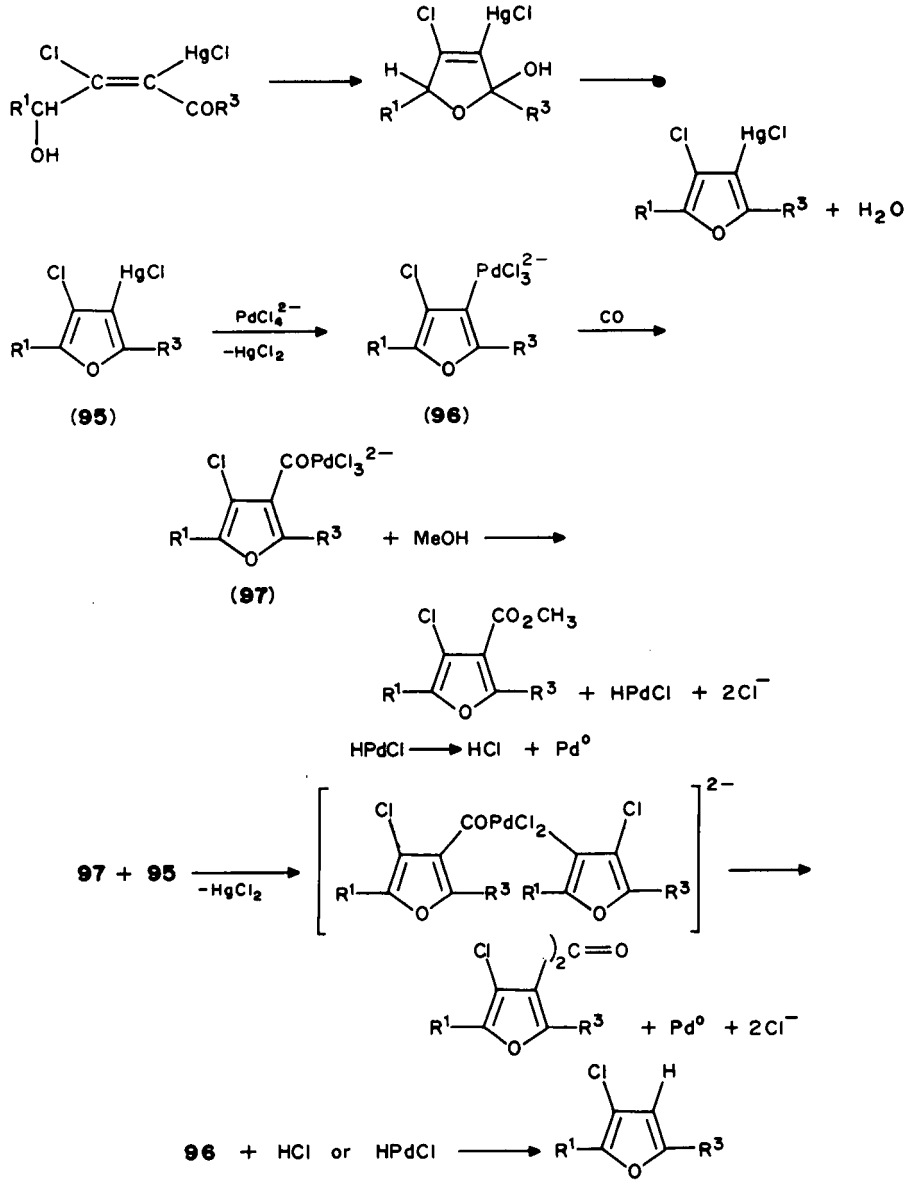
The palladium-mediated reaction of oxidative carbonylation of arylmercury compounds to form the derivatives (particularly anhydrides or esters) of the corresponding carboxylic acids is a reaction of great potential interest[185]. In the original work of Henry[186] the synthesis of aromatic acid derivatives from aryl mercury compounds is reported to occur in solvents such as CH_3CN or CH_3OH (molar ratio of arylmercury acetate to palladium catalyst 1/1) with yields varying from 10 to 30%. The reaction products are the related anhydrides or esters (equation 111), the latter are formed in the presence of an alcohol, which is often added to aprotic polar solvents as a prerequisite in order to obtain reasonable yields. The arylmercury compounds were prepared *in situ* from the aromatic hydrocarbons and the yields are relatively low even under rather drastic conditions (150 °C and 1000 psi CO pressure). Better results were obtained using palladium complex catalyst (equation 105)[178].

The reaction has been fully reinvestigated by Chiesa and Ugo[187] in order to establish its synthetic utility. Yields can be increased by the carefully controlled addition of a co-catalyst such as a base (sodium acetate) and in some cases also strong acids ($HClO_4$ or HBF_4). The best yields are obtained in trifluoroacetic acid, which is an ideal solvent for carrying out the reaction; conditions are very mild (rt and 1 atm of CO).

In addition to the known effect of perchloric acid in favouring the oxidative coupling of aromatic hydrocarbons, catalyzed by the palladium-soluble catalyst, the authors have found that under the reaction conditions the reaction takes place at high $HClO_4$ concentration, with parallel formation of $PdCl_2$ and partial deactivation of the palladium catalyst corresponding to a decrease in the total catalytic activity (equation 112).

$$ArHgX \xrightarrow[ROH]{CO(Pd)} ArCO_2R + (ArCO)_2 \tag{111}$$

$$HClO_4 + CO \rightarrow HCl + 4CO_2 \tag{112}$$



SCHEME 10

Some results obtained with different palladium salts are summarized in Table 22. The temperature of the reaction and the carbon monoxide pressure have little effect on the overall yields.

Rhodium catalysts have also shown promise in organomercurial carbonylation reactions[152]. Symmetrical diaryl ketones are easily obtained from arylmercuric chlorides

TABLE 22. Oxidative carbonylation of phenylmercury acetate (0.1 *M*) with different palladium salts (0.1 *M*) carried out at room temperature and 1 atm of CO pressure. Yields are referred to the palladium salt. Reproduced with permission from *J. Organomet. Chem.*, **279**, 215 (1985)

Catalyst	Solvent	Yield (%)
$PdCl_2$	CH_3CN	18
$[Pd(CH_3COO)_2]_3$	CH_3CN	57[d]
$PdCl_2$	DMF/CH_3OH[a]	27
$[Pd(CH_3COO)_2]_3$	DMF/CH_3OH[a]	70[d]
$Pd(PPh_3)_2Cl_2$	DMF/CH_3OH[a,b]	8
$Pd(PPh_3)_2Cl_2$	$i\text{-}C_4H_9OH$[b]	33
$Pd(DPE)Cl_2$	$i\text{-}C_4H_9OH$[b,c]	37.5

[a]Volume ratio of aprotic polar solvent to CH_3OH 5/1.
[b]Under reflux conditions.
[c]DPE = 1,2-diphenylphosphinoethane.
[d]Yields in other solvents are CH_3OH (72%), $PhCH_2CN/CH_3OH$[a] (50%), propylencarbonate/CH_3OH[a] (70%), acetic acid (18%), trifluoroacetic acid (60.5%).

using $RhCl_3 \cdot 3H_2O$[100], $ClRh(CO)(PR_3)_2$[188] or $[ClRh(CO)_2]_2$[189]; the highest yields are obtained with this last catalyst (equation 113). To avoid coupling of the aryl moieties producing substituted biphenyl derivatives, relatively vigorous reaction conditions have to be used. If the reaction is carried out in THF at 70 °C and carbon monoxide pressures 1000–1500 psi (70–100 atm) with a 0.5 mol% concentration of the catalyst, good to excellent yields of diarylketones are obtained (Table 23a; equation 113).

$$2\,ArHgCl \xrightarrow[\substack{0.5\%\ [ClRh(CO)_2]_2 \\ 2\ LiCl \\ 70\,°C\ THF}]{>\ 800\ psi\ CO} Ar{-}\overset{\overset{O}{\|}}{C}{-}Ar \qquad 60\text{–}100\% \tag{113}$$

Baird and Surridge[190] prepared carboxylic acids and esters by the carbonylation of alkyl- and phenylmercuric acetates catalyzed by Wilkinson's catalyst (equation 114). Thus, carbonylation of phenylmercury acetate proceeds smoothly to give methyl benzoate (38%) and benzoic acid (50%). A comparable yield of mercury was recovered[190].

$$RHgOAc \xrightarrow[CH_3OH]{CO,\ cat.ClRh(PPh_3)_3} RCO_2CH_3 + RCO_2H \tag{114}$$

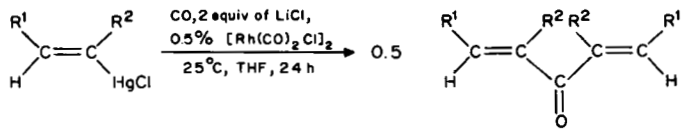
TABLE 23a. Synthesis of symmetrical diaryl ketones. Reproduced with permission from *J. Org. Chem.*, **45**, 3840 (1980)

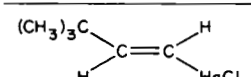
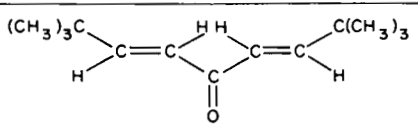
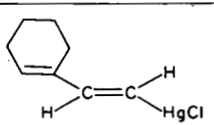
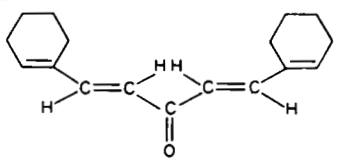
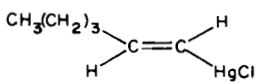
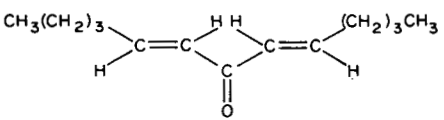
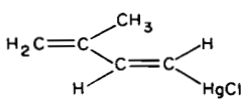
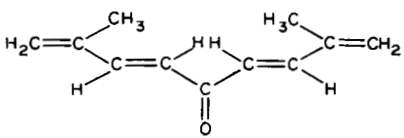
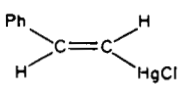
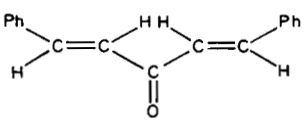
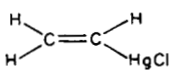
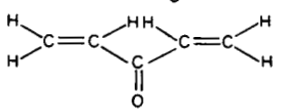
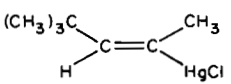
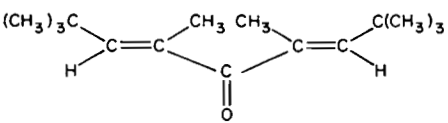
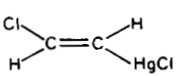
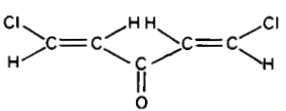
$$ArHgCl \xrightarrow[70\,°C,\ THF,\ 24\,h]{2\ equiv\ of\ 2\ LiCl,\ >\ 800\ psi\ of\ CO,\ 0.5\%\ [Rh(CO)_2Cl]_2} 0.5\ ArC(O)Ar$$

Arylmercurial	Diaryl ketone	% Yield[a]	mp, °C(lit. mp, °C)
PhHgCl	PhC(O)Ph	80(66)	23–25 (26 or 48)
β-NaphHgCl	$\beta\text{-Naph}_2CO$	100(95)	159–161 (164.5)
ThiHgCl	Thi_2CO	89(78)	89–90 (90.5)
$m\text{-}O_2NC_6H_7HgCl$	$(m\text{-}O_2NC_6H_7)_2CO$	60(38)	152–153 (155–155.5)

[a]Crude isolated yield (recrystallized yield).

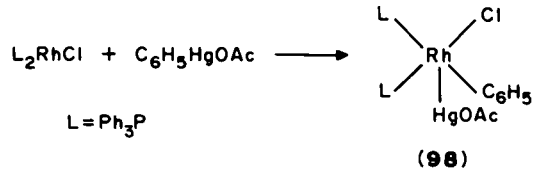
TABLE 23b. Synthesis of symmetrical divinyl ketones. Reproduced with permission from *J. Org. Chem.*, **45**, 3840 (1980)



Vinylmercurial	Divinyl ketone	% Yield[a]	Vinylmercurial	Divinyl ketone	% Yield[a]
		96 (78)			100[c]
		94 (78)			41[c,d]
		99 (88)			89[e]
		64 (47)[b]			*d*

[a] Crude isolated (purified yield).
[b] Reaction time of 4 days.
[c] Attempted purification resulted in decomposition.
[d] Purity of organomercurial is questionable or unknown.
[e] GC yield.

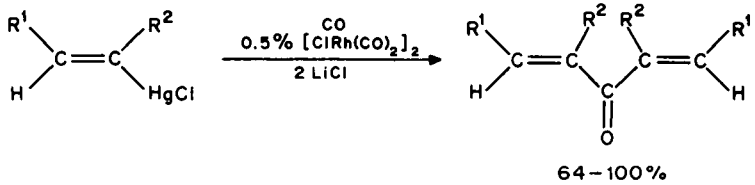
The rhodium–mercury bimetallic complex **98** (equation 115) was also tested for carbonylation activity. The hydroformylation of 1-heptene gave 98% of C_7 aldehydes in which the normal:branched ratio was 70:30. Complex [**98**] was inactive for the carbonylation of methanol to acetic acid[190].



(115)

(**98**)

Wilkinson's catalyst can be also used in the carbonylation of vinylmercuric halides, but best results are obtained by using $[ClRh(CO)_2]_2$[189], which provides a highly convenient procedure for the synthesis of symmetrical divinyl ketones (equation 116; Table 23b)[189].



(116)

Almost quantitative conversion of the vinylmercurial to divinylketone can be effected by using 1 equivalent of the substrate, 2 equivalents of lithium chloride, and as little as 0.5% mol of $[Rh(CO)_2Cl]_2$ under 1 atm of carbon monoxide in THF. This set of reaction conditions also provides a very smooth isolation procedure. In all cases, the stereochemistry of the vinylmercurial is preserved in the resulting divinyl ketone.

Vinylmercurials derived from terminal alkynes[190,191] produce nearly quantitative yields of divinyl ketones after 24 h, while diminished yields are observed with vinylmercurials derived from internal alkynes even with longer reaction times. Organomercurials derived from enynes are also transformed into the corresponding symmetrical polyenones. However, these compounds proved very difficult to purify due to their instability[189].

Although the mechanism of divinyl ketone formation has not been rigorously investigated, Larock and Hershberger[189] propose the scheme shown by equations 117–120. The reaction involves oxidative addition of the vinylmercurial to a rhodium(I) species (equation 117), insertion of carbon monoxide to form an acylrhodium derivative (equation 118), transmetallation of this species by another vinylmercurial (equation 119) and, finally, reductive elimination of the divinyl ketone to regenerate the rhodium(I) catalyst (equation 120).

$$RhCl + RCH{=}CHHgCl \rightarrow RCH{=}CHRhCl(HgCl) \quad (117)$$

$$RCH{=}CHRhCl(HgCl) + CO \rightarrow RCH{=}CHC(O)RhCl(HgCl) \quad (118)$$

$$RCH{=}CHC(O)RhCl(HgCl) + RCH{=}CHHgCl \rightarrow RCH{=}CHC(O)Rh(CH{=}CHR)(HgCl) + HgCl_2 \quad (119)$$

$$RCH{=}CHC(O)Rh(CH{=}CHR)(HgCl) \rightarrow RCH{=}CHC(O)CH{=}CHR + RhCl + Hg \quad (120)$$

The $[Rh(CO)_2Cl]_2$ promoted carbonylation of vinylmercurials constitutes an excellent procedure for the stereospecific production of divinyl ketones. The neutral, mild

conditions under which this reaction occurs permit this acid- and base-sensitive class of compounds to be isolated in high yield.

Attempts to extend this symmetrical ketone synthesis to dialkynyl or dialkyl ketones were unsuccessful. Bis(3,3-dimethyl-1-butynyl)mercury forms 2,2,7,7-tetramethyl-3,5-octadiyne when reacted with carbon monoxide, 2 equivalents of lithium chloride, and 0.5 mol% of $[Rh(CO)_2Cl]_2$ in THF at rt (equation 121)[189].

$$RC{\equiv}CC(O)C{\equiv}CR + RhCl[P(C_6H_5)_3]_3 \rightarrow RC{\equiv}CC{\equiv}CR + Rh(CO)Cl[P(C_6H_5)_3]_2 \quad (121)$$

R = Ph or *t*-Bu

Bird's group[192] has recently reinvestigated the details of the chemistry and the synthetic utility of the carbonylation of organomercury compounds as a general method for the synthesis of carboxylic acids and esters (equation 122).

$$RHgX + CO + R'OH \xrightarrow{\text{catalyst}} RCOOR' + Hg + HX \quad (122)$$

The reaction is catalyzed by group 9 and 10 metal complexes; it proceeds rapidly at mild conditions and gives moderate to excellent yields of carboxylated product. Metallic mercury is easily separated from the product. The reaction is capable of broad application: R = aryl, alkyl, allyl, vinyl, β-oxyalkyl; R'OH = water, alcohols, phenols, polyols, acids. Several organomercurial anions were tested, but it was found that using mercury(II)acetate or trifluoroacetate the reactivity of these anions afforded high yields of mono- and dimercurated products simply and selectively. Many group 9 and 10 metal complexes are effective as catalysts; thus, tripling of yield was obtained when triphenylphosphine was added to palladium(II)chloride.

Baird and coworkers[192] have examined the various mechanisms which give rise to the carbonylation of alkyl, vinyl and allyl mercurials in methanol. The yield reported for a specific organomercurial does not represent the maximum achievable at conditions optimal for that substrate[192]. The mercuriation/carbonylation sequence offers only one advantage over the carbonylation of Grignard and lithium compounds: it allows the presence of functional groups normally reactive toward the latter metals.

The synthetic potential of this reaction is most evident in the carbonylation of aryl mercurials (Table 24). Direct synthesis of the arylmercury salts by mercuration followed by carbonylation is an effective route to aroyl esters. Selectivities in the mercuration reaction are reflected in the isomer distributions listed in Table 24. For example, monomercuration and carbonylation of biphenyl gives 4-phenylbenzoate selectively. Dimercuration/carbonylation is equally selective to 4,4'-dicarbomethoxybiphenyl. There exists an interesting reversal in the product selectivities for anisole depending upon the choice of the mercurating agent[192]. The high *ortho* subtitution in the trifluoroacetate (TFA) case is ascribed to the contribution of methoxy oxygen coordination with the more electrophilic $[HgOOCCF_3]^+$ cation. Carbonylation of the mercurials derived from *N*,*N*-dimethylaniline and acetanilide proceeded normally, indicating that blocking the reactive amino group inhibits those side-reactions occurring in the case of aniline.

Baird and coworkers[192] have examined the various mechanisms which give rise to the three principal products observed in the carbonylation of organomercurials. In nearly all carbonylations the formation of a hydrocarbon by-product occurs and formally results from the replacement of the C—Hg bond by a C—H bond. This hydrogenolysis reaction can take place in the absence of a catalyst but fails to occur in the absence of carbon monoxide. This side-reaction is rationalized by equations 123–126[192].

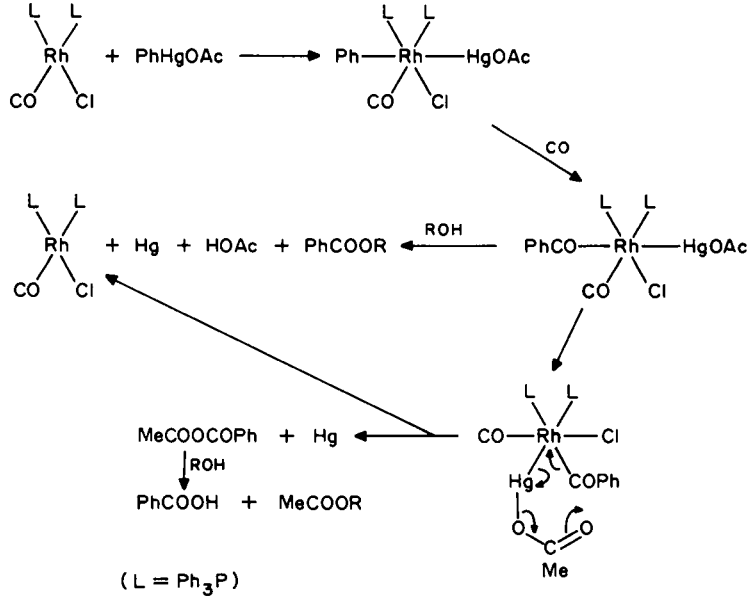
$$2RHgX \rightarrow RHgR + HgX_2 \quad (123)$$

$$HgX_2 + CO + 2CH_3OH \rightarrow (CH_3O)_2CO + Hg + 2HX \quad (124)$$

TABLE 24. Conversion of aromatics to methyl esters by the mercuration/carbonylation sequence[a]. Reproduced with permission from *J. Org. Chem.*, **50**, 4601 (1985)

Aromatic	X	yield, %	Isomer distribution, % (locant)		
			ortho	*meta*	*para*
		Monomercuration			
benzene	OAc	83			
toluene	TFA	88	47	25	28
ethylbenzene	TFA	89	35	8	57
tert-butylbenzene	TFA	75	0	28	72
o-xylene	OAc	85	15(3)	0	85(4)
m-xylene	OAc	64	80(4)	0	20(5)
p-xylene	OAc	84			
mesitylene	TFA	30			
pseudocumene	OAc	69	92% 2,4,5-, 6% 2,3,5-, 2% 2,3,6-trimethyl		
biphenyl	TFA	60			100(4)
naphthalene	TFA	60	30(α)	70(β)	
chlorobenzene	TFA	75	14	0	86
anisole	OAc	70	16	0	84
anisole	TFA	79	86	0	14
methyl benzoate	TFA	68	70	30	0
dimethyl terephthalate	TFA	30	100(3)	0	0
aniline	OAc	10	2	0	98
N,*N*-dimethylaniline	OAc	47	0	0	>98
acetanilide	OAc	78	0	0	>98
		Dimercuration			
biphenyl	TFA	67	0	0	100(4,4′)
o-xylene	TFA	67	dimethyl 4,5-dimethylphthalate, 94		
m-xylene	TFA	30	dimethyl 4,6-dimethylisophthalate, 72		
p-xylene	TFA	33	dimethyl 2,5-dimethylterephthalate, 30		

[a]Conditions: 75–100 °C; 50–100 psi; 1–3 h; L_2PdCl_2; ArHgX/Pd = 100–200.
(TFA = trifluoroacetate)



SCHEME 11

$$RHgR + HX \rightarrow RH + RHgX \quad (125)$$

$$RHgX + HX \rightarrow RH + HgX_2 \quad (126)$$

All four reactions are well known in mercury chemistry but have not been reported in combination previously[192]. The ratio of hydrocarbon to carbonylated products tends to increase with (1) increasing steric hindrance around the C—Hg bond, (2) increasing electron-donor ability of the aromatic substituents and (3) decreasing basicity of the mercury anion. These relationships help to account for the low yields of carbonylated products in those cases where the C—Hg bond is subject to steric hindrance and the mercury anion is TFA.

The reaction paths leading to the formation of ester and acid products are depicted in Scheme 11. The initial step is the oxidative addition of the organomercurial to the low-valent group 9 or 10 metal complex; such an addition to generate a Rh—Hg bimetallic complex containing a C—Rh bond has been described[193]. Insertion of carbon monoxide and alcoholysis of the phenacyl–rhodium complex leads directly to ester, metallic mercury and the regenerated catalyst[194]. Internal acetate transfer, or the attack of external acetate on the phenacyl–Rh bond, releases the mixed methyl phenyl anhydride, which is known to react with alcohols to yield principally benzoic acid and the corresponding methyl acetate. Relative stability of the acyl–metal complexes is also a factor in product selectivity since the rhodium complex favours carboxylic acid formation over that of ester. This distinction suggests greater stability for the rhodium adduct, while the more labile palladium complex undergoes facile alcoholysis to produce ester. Sterically hindered alcohols also favour formation of esters. In carboxylic acid and aqueous solvents, carboxylic acids are the exclusive carbonylation products[192]. Impro-

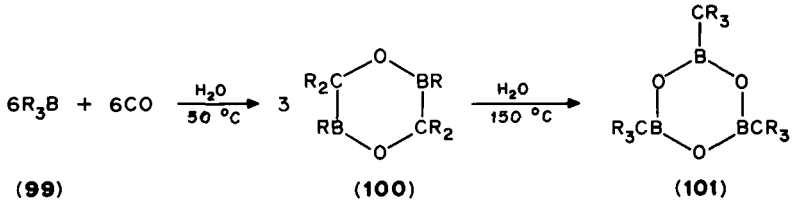
ved syntheses of symmetrical diaryl ketones using palladium and rhodium complex catalysis have been recently reported[195].

In summary, the direct carbonylation of organomercurials is difficult, must be performed under vigorous reaction conditions and usually low yields are obtained. However, by employing transition metal reagents of palladium, nickel, cobalt or rhodium the scope of these carbonylation reactions is greatly expanded and a variety of useful carbonyl-containing products can be obtained in high yields, including carboxylic acids and esters, as well as ketones[152].

7. Organoboron compounds

The reaction with carbon monoxide is one of the most general and versatile reactions which organoboranes undergo[24]. The organoboron chemistry pertinent to organic synthesis has been extensively reviewed[196–201] and the review by Brown[197] contains a number of detailed experimental procedures. The reaction has a wide scope and a variety of primary, secondary and tertiary alcohols, aldehydes and ketones have been synthesized by this method. Only a brief summary is presented here.

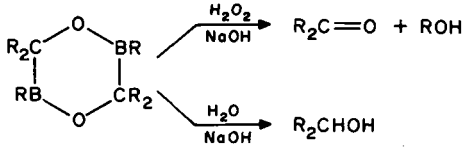
The reaction of diborane and of its methyl derivative with carbon monoxide was first reported in 1937 by Schlesinger and coworkers[202,203] and the structure of the compounds derived from the reaction of carbon monoxide with trialkylboranes (**99**) was established in 1962 by Hillman[204]. He reported that the products of the reaction of the organoborane with carbon monoxide at very high pressures, about 10,000 psi at 25 to 75 °C, were 2,5-dibora-1,4-dioxanes (**100**). At 140 °C, compounds **100** were smoothly converted into the corresponding boroxines **101**. In the absence of protic solvents, mixtures of **100** and **101** are formed. No interconversion between **100** and **101** takes place even at 200 °C (equation 127).



(**99**) (**100**) (**101**)

(127)

Oxidation of **100** produces a 1:1 mixture of a ketone ($R_2C{=}O$) and an alcohol (ROH) whereas its hydrolysis gives a dialkylcarbinol (R_2CHOH) (equation 128). On the other hand, oxidation of **101** gives the corresponding trialkylcarbinol (R_3COH).

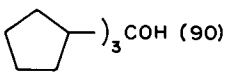
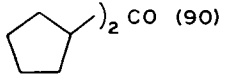
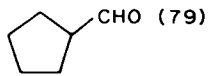
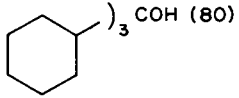
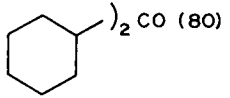
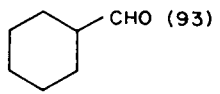
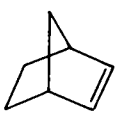
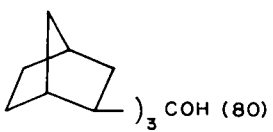
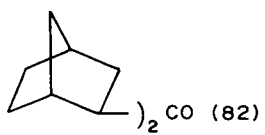
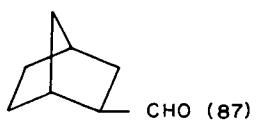


(**100**)

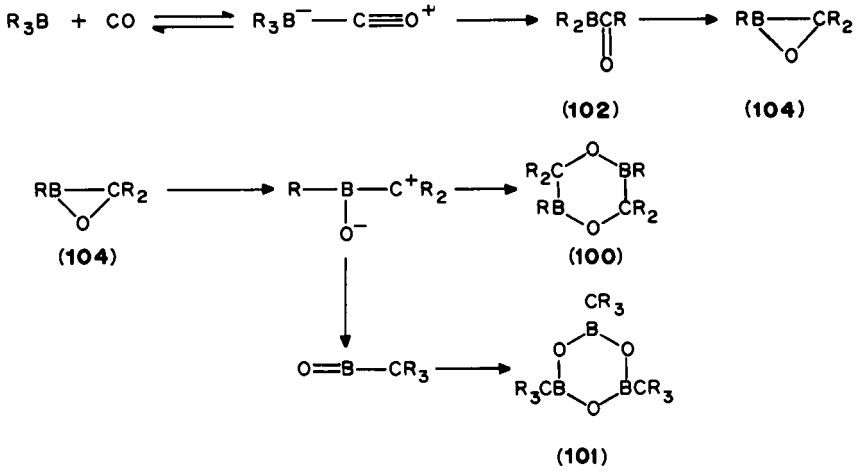
(128)

Brown and his collaborators[196,205,206] found conditions to run this reaction at atmospheric pressure and examined its wide scope and versatility. For example, trialkylboranes can be converted to trialkylcarbinols, dialkylketones, secondary alcohols, primary alcohols or aldehydes under appropriate conditions[197,200,201] and in good to excellent yields in each case (Table 25).

TABLE 25. Carbonylation of organoboranes

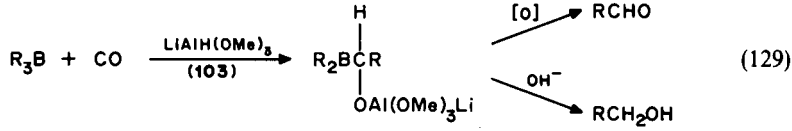
Alkenes	Alcohols (% yield)	Ketones (% yield)	Aldehydes (% yield)
$CH_3CH_2CH{=}CH_2$	Bu_3COH (90)	Bu_2CO (85)	BuCHO (98)
$CH_3CH{=}CHCH_3$	*sec*-Bu_3COH (87)	*sec*-Bu_2CO (80)	*sec*-BuCHO (94)
$(CH_3)_2C{=}CH_2$	*i*-Bu_3COH (90)	*i*-Bu_2CO (81)	*i*-BuCHO (91)
			
			
			

Since the reactions of two different organoboranes do not give any crossover product, the transfer of the alkyl groups from boron to carbon must be an intramolecular process. The mechanism, first proposed by Hillman[204] and slightly modified by Brown[200], consistent with the available data, in shown in Scheme 12.



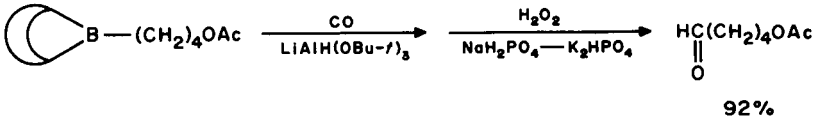
SCHEME 12

Under the usual carbonylation conditions, it has not been possible to obtain the product of single alkyl migration **102**. It has, however, been possible to stop the reaction in the presence of $LiAlH(OMe)_3$, (LTMA, **103**)(equation 129)[129].



(129)

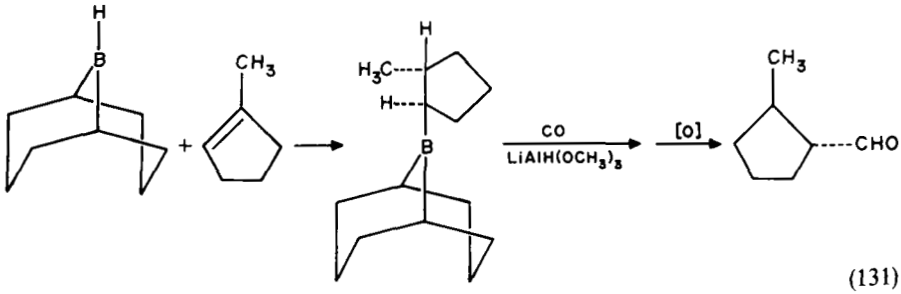
The boraepoxide **104** is presumably the precursor (by dimerization) of the 2,5-diboradioxane **100**. Once the latter is formed, the transfer of the third alkyl group becomes very slow and requires heating at elevated temperatures in the presence of water or other materials to open up the stable diboradioxane system. The boronic anhydride trimerizes into the corresponding boroxine **101**. On oxidation of the intermediates thus obtained, aldehydes were formed in high yields[207]. It has also been possible to obtain the corresponding methylols[208]. An obvious disadvantage of this procedure is the fact that only one of the original three alkyl groups on boron is utilized. To circumvent this difficulty Brown's group use the remarkably stable 9-borabicyclo[3.3.1]nonane (9-bbn) which permits a high-yield conversion of olefins into aldehydes, while $LiAlH(OBu\text{-}t)_3$ (LTBA) makes this aldehyde synthesis highly chemoselective, since it conducts the preferential reaction of the B-alkyl group in the B-R-9-bbn derivatives (equation 130).



92%

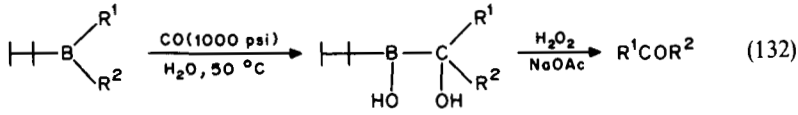
(130)

The introduction of the aldehyde group takes place with retention of configuration (equation 131) and the reaction can be carried out in the presence of many functional groups.

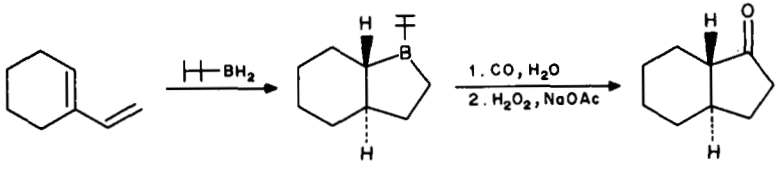


(131)

The thexyl group exhibits a very low migratory aptitude for migration in the carbonylation of thexyldialkylboranes. This makes it possible to synthesize mixed and cyclic ketones in high yields (equations 132 and 133).



(132)

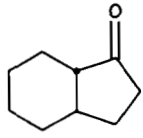


66%

(100% *trans*)

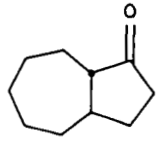
(133)

The reaction appears to be of considerable generality, as indicated by the following syntheses (the yields shown are based on diene; equations 134–138).



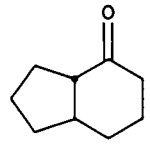
66%

(134)



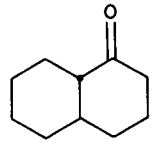
71%

(135)



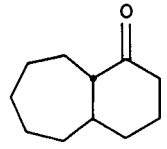
54%

(136)



73%

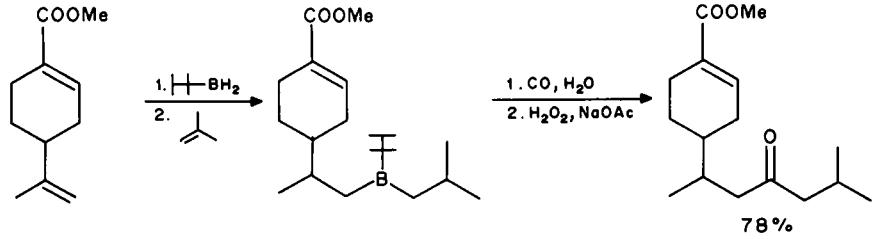
(137)



68%

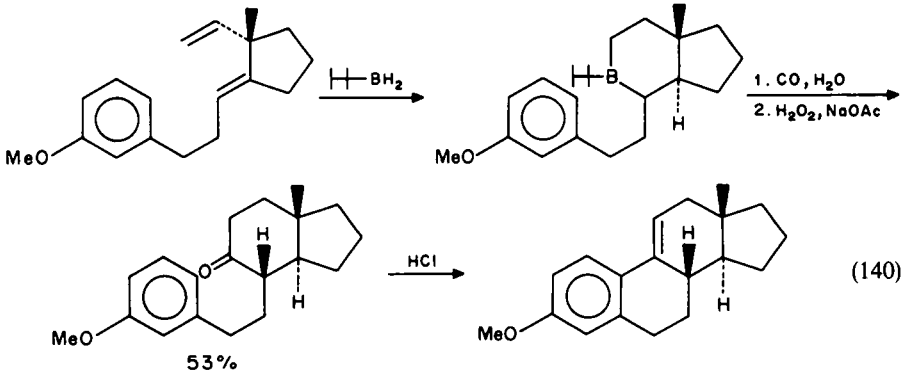
(138)

This ketone synthesis has been applied to the synthesis of juvabione, shown in equation 139[209], and a steroidal compound, shown in equation 140[210].



78%

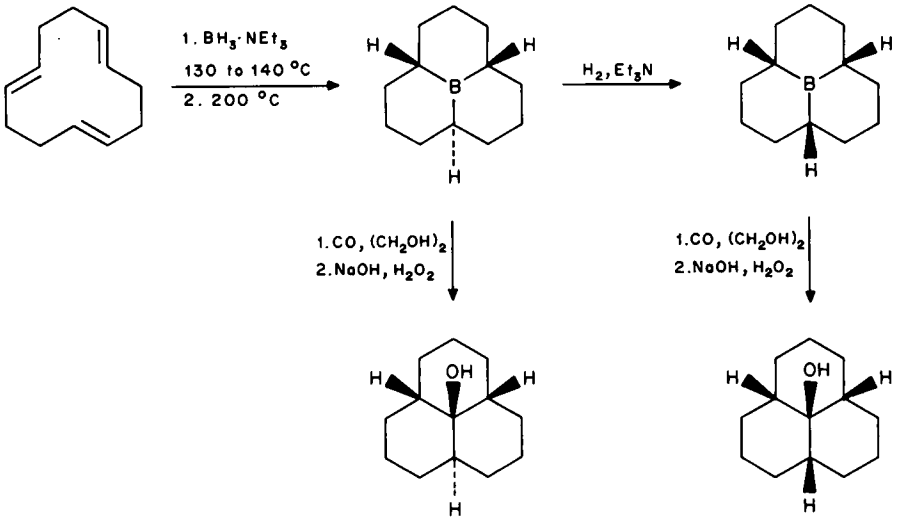
(139)



53%

(140)

The remarkably easy addition of the boron–hydrogen bond to carbon–carbon double and triple bonds, the less easy but still facile substitution of carbon–hydrogen bonds by boron–hydrogen bonds and the ready isomerization of organoboranes make it possible to combine the unique characteristics of boron to bring together widely separated portions of a carbon structure into a more compact cyclic or polyciclic entity[200]. Then, the boron atom in these 'stitched together' structures can be easily replaced by carbon on treating the boron complex with carbon monoxide. These transformations occur with complete retention of the overall and stereochemical integrity of the organoboranes as shown in equation 141.



(141)

Hydride-induced carbonylation is a very useful synthetic reaction: it provides a number of valuable transformations, including an approach for clean anti-Markownikov hydroformylation of alkenes (equation 142).

$$RCH{=}CH_2 \xrightarrow{\text{9-bbn}} BCH_2CH_2R \xrightarrow[2.H_2O_2]{\text{1.CO,'MH'}} RCH_2CH_2C(O)H \qquad (142)$$

The reaction can be accomplished using a variety of complex metal hydrides, including lithium trimethoxyaluminohydride (LTMA)[211].

The method has also been used for the homologation of organoboranes[212]. Thus, carbonylation of B-alkyl-9-bbn (in the presence of LTMA)[211], followed by reduction of the intermediate with lithium aluminium hydride, provides a high yield, stereospecific synthesis of the homologous borane. The effect of the ring size is negligible (5 to 8 member rings were tested) and the sequence is particularly attractive for those cases where stereoisomers are possible.

Hydroboration of alkynes, followed by carbonylation of the resulting alkenylborane by Pd_2, has been used for the stereoselective synthesis of α,β-unsaturated esters[213,214].

The carbonylation of organoboranes with ^{13}CO provides carboxylic acids, ^{13}C[217]. The palladium-catalyzed carbonylation of alkenyl- and aryl-borates and boronic acids[215] as well as other carbonylations of organoboron compounds have recently been reported[216].

8. Organoaluminium compounds

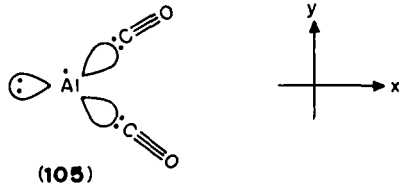
The chemistry of organoaluminium derivatives was developed through the mid-1960s and some extensive reviews have since been published[218,219]. The synthetic aspects have been reviewed by Bruno[220], Reinheckel[221] and Negishi[24,222].

Organoaluminium compounds resemble in many aspects organoboranes; many of the characteristics of organoboranes associated with the availability of the empty *p* orbital are also found in organoalanes. There are, however, a number of significant differences: the Al—C bond is considerably more ionic than the corresponding B—C bond, and the former is considerably longer and more polarizable than the latter. These properties combine to make organoaluminium derivatives better carbanion sources than the corresponding organoboranes[24]. For this reason organoalanes undergo Grignard-like reactions, in particular intermolecular transfer reactions, with a variety of organic and inorganic electrophiles.

However, with respect to carbonylation the reactivity of organoalanes differs significantly from organoboranes, organolithiums and Grignard reagents. In fact, the reaction with carbon monoxide is only effective in the presence of a catalyst.

Nevertheless, it has been recently shown that aluminium carbonyls can be generated in argon matrices by co-condensation of aluminium atoms and carbon monoxide; the aluminium carbonyl consists of one aluminium atom and two CO molecules[223]. The structure has been determined by ESR and IR studies, and perhaps the most intriguing revelation of these studies is that, while aluminium dicarbonyl is readily formed, aluminium monocarbonyl is not.

Stability of transition-metal carbonyls $M(CO)_n$ has been attributed to a σ bond resulting from dative interaction between the lone-pair electrons of the carbon atom of CO and a vacant σ orbital of M and a π bond resulting from back-donation from a filled d_x orbital of M into a vacant π^* orbital of CO[10]. An $sp^2_{x,y}$-hybridized aluminium atom with its lone-pair electrons in one of the hybridized orbitals and the unpaired electron in the remaining p_z orbital should be receptive to a σ-type dative approach of two carbon–carbon monoxides as depicted in **105**.



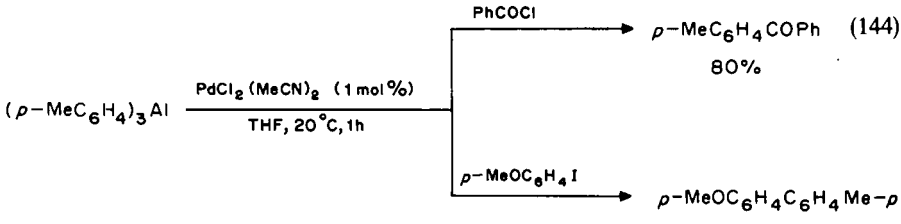
(105)

The possibility of π-type back-bonding from the semifilled p_z orbital of Al into the vacant π^*_z orbitals of CO follows naturally[223]. Synergism between the two types of dative interactions must be crucial: aluminium monocarbonyl does not appear to have a bound state. INDO molecular orbital calculations performed with the aluminium dicarbonyl are consistent with the above conclusions[223].

The high stability of aluminium carbonyls may be the reason why, in spite of the high resemblance of organoaluminium to organolithium, Grignard reagents and organoboron in their reactions with carbonyl compounds, the reaction of organoaluminium compounds with carbon monoxide is only effective in the presence of a catalyst. It has been recently shown that organoaluminium compounds undergo carbonylation under mild conditions in the presence of palladium complexes[225]. Unsymmetrical diaryl ketones have been prepared by carbonylation of the mixture of organoaluminium compounds and aryl iodides (equation 143).

$$RAlR'_2 + R''X + CO \xrightarrow{\text{'Pd'}} RCOR'' + RR'' + R_2 + R_2CO \qquad (143)$$

In preliminary experiments it had been observed that triarylaluminium reacted with benzoyl chloride in the presence of $PdCl_2(MeCN)_2$ in THF much faster than with *p*-iodoanisole (equations 144 and 145). Since carbon monoxide insertion into the Ar—Pd bond in the $ArPdH_2$ complexes proceeds easily[226], it was expected that the unsymmetrical ketone should be the main product in the reaction of *p*-methoxyiodobenzene with *p*-tritoluyl-aluminium in the presence of carbon monoxide. However, the reaction of triphenylaluminiums with *p*-iodoanisole and carbon monoxide in the presence of $PdCl_2(MeCN)_2$ in THF at rt yielded only traces of *p*-methoxybenzophenone along with palladium black precipitation[225]. The reaction was significantly improved when carried out in DMSO instead of THF. DMSO likely stabilizes the complex and the ketone is obtained in quantitative yield. Under these conditions the temperature increase accelerates the reaction; the yield of *p*-methoxybenzophenone at 50 °C is 98% in 4 h (equation 146).



(144)

(145)

$$Ph_3Al + p\text{-}MeOC_6H_4I + CO \xrightarrow[DMSO,\ 50\,^\circ C,\ 4\,h]{PdCl_2(MeCN)_2} p\text{-}MeOC_6H_4COPh \qquad (146)$$

Good results were also obtained with iodobenzene and 2-iodothiophene. However, when aryl iodides containing electron-withdrawing substituents are used, cross-coupling reactions compete with carbonylation (for example, equation 147).

$$Ph_3Al + p\text{-}NO_2C_6H_4I + CO \xrightarrow[1\,h]{\text{'Pd'}} \underset{41\%}{p\text{-}NO_2C_6H_4COPh} + \underset{55\%}{p\text{-}NO_2C_6H_4Ph} \qquad (147)$$

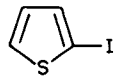
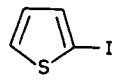
However, using THF–HMPA mixtures of broad composition range as solvents, nearly quantitative yields of ketones could be achieved for all substituted aryl iodides (Table 26).

Since only one organic group of Ar_3Al takes part in the carbonylation, $(i\text{-}Bu)_2AlPh$ obtained *'in situ'* from $(i\text{-}Bu)_3Al$ can be used as a reactant instead of Ph_3Al. Under the reported conditions the yields of diaryl ketones are 80–97%. 2-Iodothiophene and *p*-nitrobenzyl bromide were also converted into the corresponding ketones (Table 26).

It can be noted that only traces of the homocoupling product R_2 (equation 143) are observed in all cases. However, with aryl iodides containing electron-donating groups formation of R_2CO in fairly large quantities is observed and is likely to result from palladium-catalyzed exchange processes[225].

Attempts to use the reaction for the synthesis of aryl vinyl ketones have not been successful; the formed ketone is consumed under the reaction conditions (possibly through reaction with the organoaluminium compound). For example, $p\text{-}NO_2C_6H_4COCH{=}CH_2$ is consumed by $(i\text{-}Bu)_2AlCH{=}CH_2$ in 30 min in THF at rt. Even the fastest reaction of $(i\text{-}Bu)_2AlCH{=}CH_2$ with $p\text{-}NO_2C_6H_4I$ and CO gives $p\text{-}NO_2C_6H_4COCH{=}CH_2$ in only 45% yield. Nevertheless, this reaction is of special interest due to the availability of alkenylalanes, obtained via hydro- or carboalumination of alkynes. At

TABLE 26. Reactions of $RAlR'_2$ (0.75 mmol) with R″X (0.5 mmol) and carbon monoxide (1 atm) in the presence of $PdCl_2(MeCN)_2$ (0.05 mmol). Reproduced with permission from *Tetrahedron Lett.*, **26**, 4819 (1985)

R	R′	R″X	Solvent[a]	T(°C)	Time (h)	Yield[b] (%) RCOR″	RR″	R_2CO
Ph	Ph	*p*-$NO_2C_6H_4I$	A	50	1	41	55	—
		p-CNC_6H_4I	B	50	2	96	3	trace
		p-ClC_6H_4I	A	50	1.5	57	40	—
		PhI	A	40	4	95	—	—
		p-$MeOC_6H_4I$	A	40	4	98	—	14
			A	55	3	99	—	5
Ph	*i*-Bu	*p*-$NO_2C_6H_4I$	C	50	40 min	90	trace	—
		p-CNC_6H_4I	C	50	1	94	5	—
		p-ClC_6H_4I	D	40	2	97	—	16
		PhI	D	50	3	80	trace	—
		p-$MeOC_6H_4I$	B	50	3	84	—	34
		p-$NO_2C_6H_4CH_2Br$	C	40	40 min	68[c]	—	10
			D	50	1.5	82	—	13
CH_2=CH—	*i*-Bu	*p*-$NO_2C_6H_4I$	E	30	40 min	45°	—	—

[a]A—DMSO; B—THF:HMPA = 2:1; C—THF; D—THF:HMPA = 5:1; E—THF:HMPA = 1:2.
[b]Yield of R_2CO is based on organoaluminium compound.
[c]Tar formation is observed.

present, aryl vinyl ketones can be easily prepared using organomercurial compounds (see Section II.C.6).

The competitive side-reactions usually exhibited by the organoaluminium compounds usually arise from their two fundamental characteristics: alkylation and reduction that compete in the general reaction[227]. Kojima and coworkers[227] have recently performed a detailed study of the reaction conditions that could affect the palladium-promoted carbonylative cross-coupling reaction of aryl iodides with alkylaluminiums to obtain secondary and/or tertiary alcohols and unsymmetrical ketones. The reaction is carried out under very mild conditions (20–50 °C, 1 atm of carbon monoxide) and the type of reaction product depends on the aluminium reagent employed, and on the conditions under which the reaction is carried out.

Thus, using *i*-Bu_3Al and the iodide in 1.5 molar ratio and running the reaction in DME at 50 °C, the desired secondary alcohols, **107**, are obtained selectively (equation 148).

$$\underset{\textbf{(106)}}{ArI} + CO + i\text{-}Bu_3Al \xrightarrow[DME,\ 50\,^\circ C]{PdCl_2(PPh_3)_2,\ PPh_3} \underset{\textbf{(107)}}{ArCH(OH)CH_2CH(CH_3)_2} \qquad (148)$$

(**a**) Ar = Ph; (**b**) Ar = *p*-Tol; (**c**) Ar = *p*-An; (**d**) Ar = *p*-$CH_3O_2CC_6H_4$; (**e**) Ar = *p*-BrC_6H_4; (**f**) Ar = *p*-$HO_2CC_6H_4$

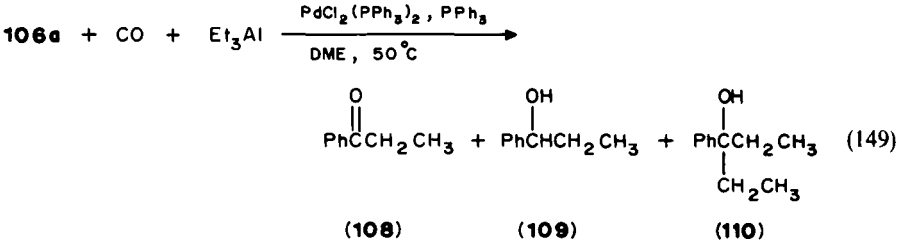
TABLE 27. Palladium-catalyzed carbonylation of aryl iodides in the presence of triisobutylaluminium[a]. Reproduced with permission from *J. Organomet. Chem.*, **288**, 261 (1985)

Run	**106** Halide	Molar ratio (Al/halide)	Temperature (°C)	Time (h)	Product **107**	Yield[b] (%)
1	a	1.5	50	19	a	95
2	a	1.5	40	23[c]	a	40
3	b	1.5	50	20	b	82
4	c	1.5	50	42	c	(73)
5	c	2.0	50	10	c	73
6	d	1.5	50	30	d	(22)[d]
7	e	1.5	50	56	e	83
8	f	2.5	50	7	no reaction	

[a]The reactions were carried out in dry DME using 1 mol of the halide, 5 mol% of $PdCl_2(PPh_3)_2$ and 10 mol% of PPh_3 under a balloon of carbon monoxide.
[b]Yields are based on the starting iodides and were determined by GLC; isolated yields in parentheses.
[c]During this reaction time 50% of iodobenzene was consumed.
[d]About 60% of the starting halide was recovered.

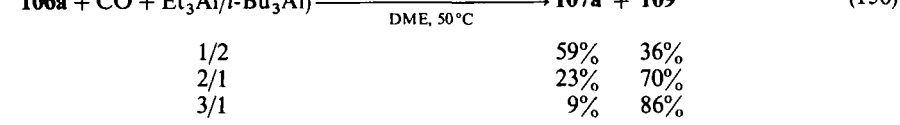
In contrast to the smooth reaction of aryl iodides, aryl bromides remained unaffected; thus, *p*-bromoiodobenzene was readily converted to the corresponding alcohol with the *p*-bromo moiety remaining. The ester functionality is also tolerated. Some other results are summarized in Table 27.

The use of Et_3Al instead of *i*-Bu_3Al gave different reaction products; three products were obtained (equation 149) and their yields varied with the molar ratio.



(149)

The differences in the reaction pathways, between the reactions with *i*-Bu_3Al and with Et_3Al, can be ascribed to the substantial differences in both the alkylating and reducing character of the two aluminium reagents[228]. The second alkylation of the initial product is due to the ability of Et_3Al to function as a strong alkylating agent, unlike *i*-Bu_3Al which has higher reducing power. Using a 3/1 mixture of Et_3Al with *i*-Bu_3Al the desired secondary alcohol **109** was obtained as the main product (equation 150).

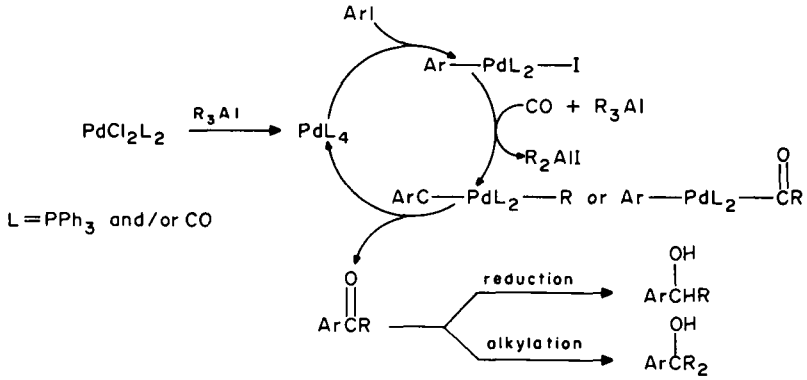


(150)

Interestingly, the direct cross-coupling reaction did not occur even under drastic conditions in the absence of carbon monoxide[227]. This result contradicts the results reported for a Pd–Sn system[229] and suggests that carbon monoxide plays an important

role in facilitating the transmetallation with aluminium reagents. Furthermore, a much used β-hydride elimination[230,231], which easily occurs when organic halides or organometallics containing β-hydrogens are employed in palladium-mediated reaction systems, did not interfere in the above reaction[227].

Kojima and coworkers[227] propose the pathway shown in Scheme 13. The reaction involves oxidative addition of aryl iodides to the palladium(0) catalyst, insertion of carbon monoxide and transmetallation with the aluminium reagents, reductive elimination of ketones and reduction or second alkylation of the ketones by the aluminium reagents.



SCHEME 13

Although the inability to tolerate many functionalities limits the scope of this reaction, the above study is important for the development of alkylaluminium compounds as reagents for organic synthesis[227]. Alper and collaborators[232] have reported the carbonylation of benzyl and aryl bromides in the presence of aluminium alkoxydes using 1,5-hexadienerhodium(I) chloride dimer which affords ethyl esters (equation 150a).

$$3RBr + 3CO + Al(OR')_3 \rightarrow 3RC(O)OR' + AlBr_3 \qquad (150a)$$

The reaction occurs under mild conditions (75 °C, 1 atm), is easy to execute and the yields are good.

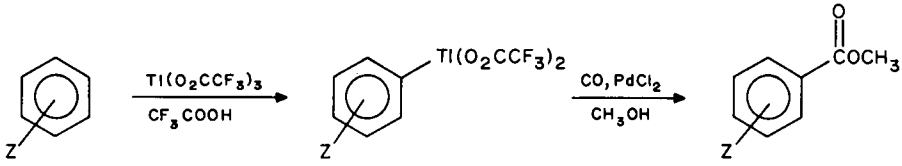
9. *Organothallium compounds*

Organothallium compounds are very useful synthons, and many novel methods have been recently proposed by which the thallium moiety can be substituted by a variety of functional groups of great importance to the organic chemist. Thus, e.g., they provide a number of important routes to substituted arenes[233,234]. Some important applications in organic synthesis have been reviewed[233–237].

Direct carbonylation of organothallium compounds has been studied by Davidson and Dyer[238], but it requires high temperatures and pressures and the yields are generally poor.

The reaction conditions and the yields of the direct carbonylation or organothallium compounds can be highly improved by the addition of palladium salts[239]. It has been shown that arylthallium compounds suffer transmetallation by addition of palladium chloride[240,241]. This has been successfully used by Larock and coworkers[239,242] who use catalytic amounts of palladium chloride to get clean and smooth carbonylation reactions.

Thus, arylthallium bis(trifluoroacetate), prepared by treatment of the corresponding arene with thallium tris(trifluoroacetate) (TTFA)[233] (equation 151), can be converted to aryl esters.



(151)

Apparently, the thallium(III) salt generated upon transmetallation with the palladium(II) salt continually reoxidizes the palladium metal formed upon carbonylation and esterification (equations 152–155).

$$ArTlX_2 + PdX_4^{2-} \longrightarrow ArPdX_3^{2-} + TlX_3 \quad (152)$$

$$ArPdX_3^{2-} + CO \longrightarrow ArC(=O)PdX_3^{2-} \quad (153)$$

$$ArC(=O)PdX_3^{2-} + ROH \longrightarrow ArC(=O)OR + HX + Pd + 2X^- \quad (154)$$

$$Pd + TlX_3 \longrightarrow PdX_2 + TlX \quad (155)$$

In a previous report on the transmetallation of arylthallium compounds[241] cupric chloride was added to reoxidize the palladium, but according to the findings by Larock's group the thallium(III) salt is a sufficiently strong oxidant and the catalyst is regenerated as shown by the equations.

Isolated phenylthallium bis(trifluoroacetate) was used as the model system to study the effect of different variables that influence the reaction. An undesired usual side-reaction is the palladium-promoted coupling of phenylthallium bis(TFA)[240] producing biphenyl, which could be inhibited by the addition of lithium chloride and magnesium oxide. Therefore, the yields of aryl esters shown in Table 28 were obtained running the carbonylation reactions with 0.1 equivalent of palladium chloride and 2 equivalents of lithium chloride and magnesium oxide at room temperature.

To perform the direct carbonylation, isolation of the toxic arylthallium intermediates is not necessary. The arene can be thallated with TTFA in trifluoroacetic acid (TFA)[233], excess TFA evaporated from the reaction and the crude material subsequently dissolved in methanol can be directly carbonylated under 1 atm of carbon monoxide. Fair to good yields of essentially isomerically pure methyl esters are obtained, using the carbonylation procedure described above.

An industrial application of a direct carbonylation of arenes closely related to these reactions has been patented by Van Venrooy[242] for the production of aromatic carboxylic acids. The procedure uses TTFA, 0.1–10% palladium acetate and 4–7 atm of carbon monoxide and elevated temperatures. Since the arene is used in excess, the aromatic starting material must be either cheap or recyclable to make the procedure useful (equation 156).

$$p\text{-TolH} \xrightarrow[\text{cat. } Pd(O_2CCH_3)_2,\ Tl(O_2CCF_3)_3]{CO} \xrightarrow{NaOH} \xrightarrow{HCl} p\text{-TolCOOH} \quad (156)$$

TABLE 28. Synthesis of aryl esters via thallation–carbonylation. Reprinted with permission from *J. Am. Chem. Soc.*, **104**, 1901 (1982) Copyright (1982) American Chemical Society

Entry	Arene	Product	% Yield[a]
1	C_6H_6	$C_6H_5—\overset{\overset{O}{\|}}{C}—OCH_3$	55
2	C_6H_5	$F—C_6H_4—\overset{\overset{O}{\|}}{C}—OCH_3$	42[b]
3	$CH_3O—C_6H_5$	$CH_3O—C_6H_4—\overset{\overset{O}{\|}}{C}—OCH_3$	62
4	$(CH_3)_3C—C_6H_5$	$(CH_3)_3C—C_6H_4—\overset{\overset{O}{\|}}{C}—OCH_3$	80[c]

[a]GLC yield based on 1 mmol of arene. Carbonylation conditions: 0.1 mmol of $PdCl_2$, 2 mmol of LiCl, 1 mmol of MgO, 10 ml of CH_3OH at room temperature for 24 h.
[b]Thallated for 48 h.
[c]Carbonylated for 96 h.

A variety of interesting cyclic carbonyl compounds can be obtained from direct carbonylation of *ortho*-substituted arylthallium compounds. The regioselectivity in metallations of substituted arenes was a subject of special interest, since appropriately substituted aryl metallated compounds are useful intermediates to afford clean functionalization in the desired position. Thallation of heteroatom-containing arenes leads almost exclusively to *ortho*-substituted arylthallium compounds which can then be carbonylated to afford cyclic carbonyl compounds.

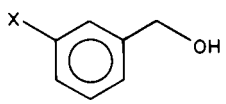
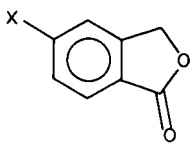
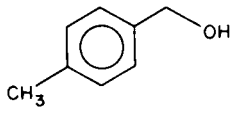
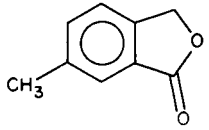
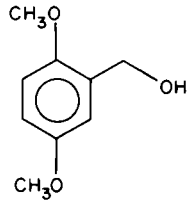
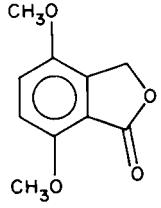
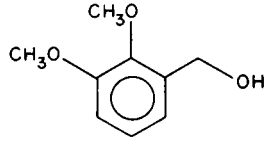
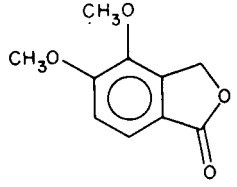
Thus, intramolecular attack on the thallium electrophile by the alcohol oxygen in benzyl alcohol leads to thallation occurring almost exclusively (> 99%) in the *ortho* position as reported by Taylor and McKillop[233]. Incomplete thallation cannot be overcome by longer reaction times or excess TTFA. Larock and Fellows[239] determined the best thallation conditions of substituted benzylic alcohols to optimize the yield of the arylthallium compounds: since benzyl trifluoroacetate was formed as a side-product under strongly acidic conditions, the best results with activated aromatics were usually obtained by diluting the TFA with THF. Thus, good yields of thallation were usually obtained at room temperature with a 5:1 THF/TFA mixture and reaction times varying between 15–48 h, while for the *m*-methoxy substituted benzyl alcohol 15 min thallation time is enough.

Excellent regioselectivity is exhibited by the thallation–carbonylation sequence procedure developed by Larock and Fellows[239]. As shown in Table 29, the *meta*-substituted benzyl alcohols (entries 1b, 1c, and 1d in Table 29) all gave exclusively the 5-substituted phthalides indicated. No. 7-substituted products were observed; the 2 position (between substituents) seems to be simply too crowded for attack by the large thallium electrophile.

The results with *m*-methoxybenzyl alcohol can be compared with the work by Uemura and coworkers[243], in which the same starting material is lithiated in the 2 position, eventually affording 7-methoxyphtalide. This reaction is a good example of how appropriate arenemetallic compounds can be carbonylated to obtain the carbonyl functionality in the desired position. While with the lithium atom complexation leads the *m*-methoxybenzyl alcohol to become lithiated almost exclusively in the 2 position (between substituents), the steric requirements of the thallium atom lead thallation

TABLE 29. Synthesis of cyclic compounds via thallation–carbonylation[a]

A. Synthesis of Phthalides from Benzyl Alcohols

Alcohol	Thallation time	Product	% Yield[b]
			
a, X = H	1 day		33(18)
b, X = CH_3O	15 min		89(47)
c, X = HO	19 h		(95)
d, X = Cl	3 h		45
	2 days		23(22)
	16 h		(32)
	18 h		64(54)

B. Synthesis of 3,4-Dihydroisocoumarins from β-Phenethyl Alcohols

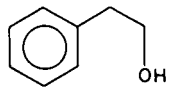
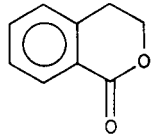
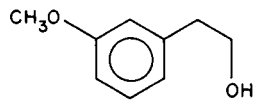
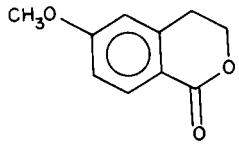
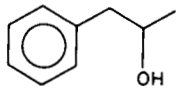
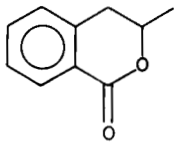
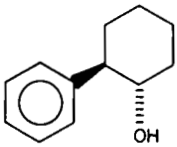
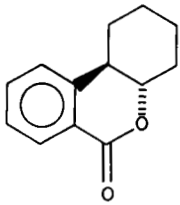
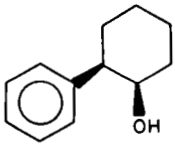
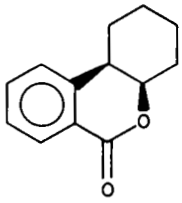
	1 day		51
	1 day		58(45)

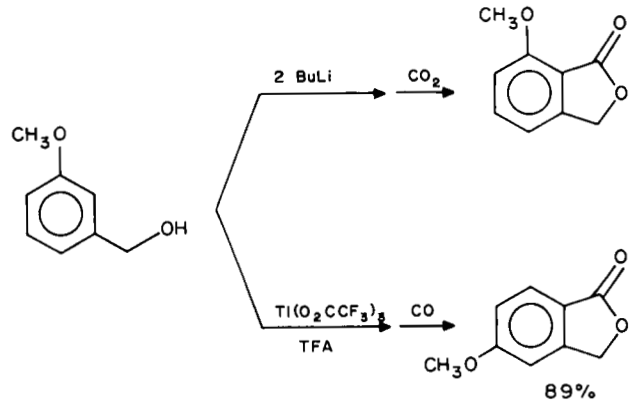
TABLE 29. (*continued*)

B. Synthesis of 3,4-dihydroisocoumarins from β-phenethyl alcohols

Alcohol	Thallation time	Product	% Yield[b]
	1 day		75(58)
	16 h		77(48)
	16 h		88

[a]Thallations were carried out in TFA at 25 °C, or in some cases in 5:1 THF/TFA.
[b]GLC analysis with an internal standard (isolated, purified yield).

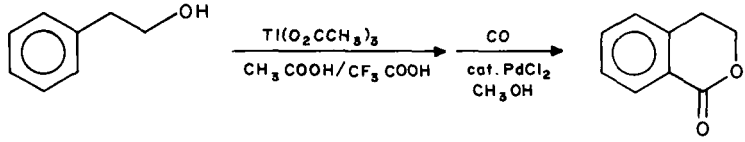
exclusively towards the less croweded *ortho* position affording the 3-methoxy-6-thallium-benzyl alcohol. Thus the lithiation–carbonylation approach from benzyl alcohols to phthalides is nicely complemented by the thallation–carbonylation approach providing together a useful procedure for the synthesis of both types of substituted phthalides (equations 157 and 158).



Application of the thallation–carbonylation sequence to 2,3-dimethoxybenzyl alcohol (Table 29A) gave a 64% yield of 4,5-dimethoxyphthalide, also called pseudomeconin[239]. This method affords a much higher overall yield of pseudomeconin in fewer steps than the previously reported syntheses[244–247]. A very similar approach has been almost simultaneously developed by Stille[248] using organopalladium compounds.

An undesirable side-reaction that can prevent obtaining good yields in the direct thallation–carbonylation reaction is the thallium-promoted biaryl formation[249]. Other parallel reactions as well as incomplete thallation can be responsible for the failure of the reaction with some substrates. Thus, poor results were obtained with 4-nitro and 4-methoxybenzyl alcohols, producing starting alcohol and undesired products.

Thallation–carbonylation of β-phenethyl alcohols is a potentially valuable new route to 3,4-dihydroisocoumarins (equation 159). Thallation of β-phenylethyl alcohol by Taylor and McKillop's method produces an *ortho*:*meta*:*para* isomer distribution of 83:6:11[234]. In the thallation–carbonylation sequence of β-phenylethyl alcohol no *meta* substitution product was observed[239]. Preparation of the parent compound in this series (entry 1, Table 29B) could be successfully accomplished by thallation of β-phenylethyl alcohol for 1 day, followed by carbonylation in methanol with 1 or 2 equivalents of magnesium oxide added. Yields are very sensitive to reaction conditions: changing the carbonylation solvent from methanol to THF drastically reduced the yield (to 14%). A careful examination of the reaction mixture indicated that starting alcohol and its trifluoroacetate ester were also present in addition to methyl *p*-(2-hydroxyethyl)benzoate; this latter product indicates that some thallation occurs in the *para* position followed by carbonylation.



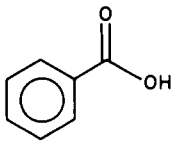
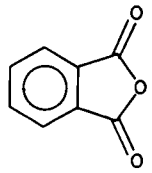
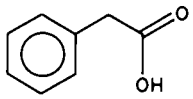
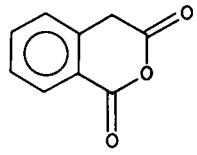
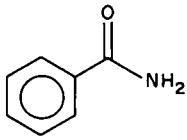
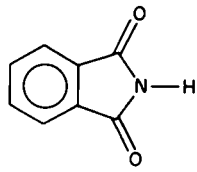
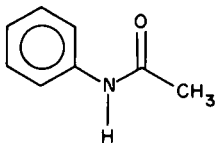
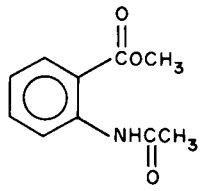
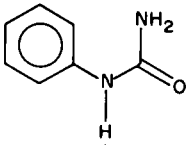
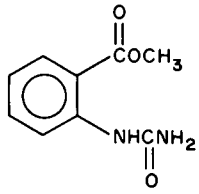
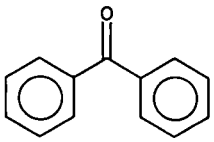
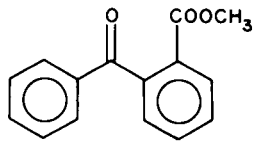
(159)

Yields of substituted 3,4-dihydroisocoumarins are very sensitive to reaction conditions which have to be optimized for each case. Thus, 3-methoxy-β-phenethyl alcohol (entry 2, Table 29B) gave best results when thallated in the diluted solvent system developed for activated benzyl alcohols. Significant amounts of the starting alcohol (30%) and the corresponding trifluoroacetate ester (18%) were obtained, but thallating the starting alcohol for longer periods of time did not improve the yield. Contrarily to the parent alcohol, yields of products were higher when THF (58%) rather than methanol (41%) was used as the carbonylation solvent.

With α-phenylethyl alcohol the secondary benzylic alcohol apparently undergoes elimination, but β-phenylethyl alcohols with alkyl substituents on the side-chain gave good results (entries 3, 4, and 5, Table 29B). The improved yield may be due to the non-benzylic nature of the alcohol group or to the fact that steric interference at the thallation site is reduced[239]. Reaction conditions have to be optimized in each case: changing the temperature, the thallation time or the solvent (methanol and THF were tested) appeared to have little effect. Addition of bases to the carbonylation mixture had a more noticeable impact, with magnesium oxide or lithium carbonate giving significantly improved yields. In all cases less than 10% of the starting alcohol was recovered.

High yields of the corresponding lactones were also obtained with *trans*- and *cis*-2-phenyl-1-cyclohexanol (entries 4 and 5, Table 29B) although the thallation sites in these compounds are more sterically hindered than in 1-phenyl-2-propanol. The good results may be due in part to the somewhat rigid conformation of the alcohol as was observed in the *ortho* lithiation of benzylic alcohols[243]. In the present reactions the *trans* alcohol gave exclusively the *trans* fused lactone, whereas the *cis* alcohol gave only the *cis* lactone.

TABLE 30. Thallation–carbonylation of aromatic carboxylic acids, amides and ketones[a]

Starting material	Thallation time	Product	% Yield[b]
	16 h[c]		44
	2 days		(46)
	16 h[c]		83
	16 h		(39)
	15 h		(17)
	4 days		(63)

[a]Reactions were carried out in TFA at 25 °C except otherwise stated.
[b]GLC yield with an internal standard (isolated, purified yield).
[c]Reflux.

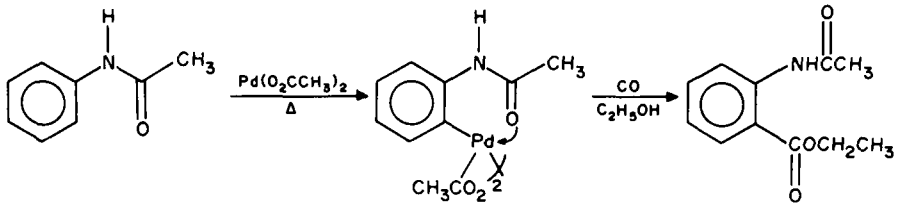
Thallation–carbonylation of 2-(β-naphthyl)ethanol and of β-(2,5-dimethoxyphenyl)ethyl alcohol failed to give the desired 3,4-dihydroisocoumarins under the conditions of Larock and Fellows[239]. A few variations were tested but none of them appeared to improve the results.

Thallation–carbonylation of aromatic carboxylic acids, amides and ketones affords anhydrides, imides and *ortho*-substituted methyl esters (Table 30)[239].

The thallation of arenes bearing a variety of heteroatom-containing groups proceeds with a high degree of *ortho* selectivity[234]. Thus, although the carboxyl group is *meta*-directing in electrophilic substitution, benzoic acid is reported to give an isomer distribution of 95:5:0 for *ortho*:*meta*:*para* thallated material in 76% overall yield[233,234]. Similarly, for phenylacetic acid the reported isomer distribution ratios are 92:3:5 in overall yields up to 72%. Carbonylations of these compounds in THF render the unoptimized yields shown in Table 30.

Studies on several substituted benzene derivatives show that high *ortho* selectivity is observed when the heteroatom is close to the benzene ring, indicating the probable intermediacy of a substrate–electrophile complex. Because of the size of the thallium electrophile, intramolecular chelate-controlled *ortho* delivery of thallium is extremely sensitive to steric hindrance. Thus, replacement of one α hydrogen atom by a methyl group in phenylacetic acid results in a decrease in *ortho* substitution, whereas replacement of both hydrogens by methyl groups totally inhibits it. Appropriate manipulation of conditions can lead to control over orientation in the same substrate. *Meta* substitution is achieved under conditions of thermodynamic control (elevated temperatures). Under conditions of kinetic control, *ortho* substitution results when chelation of TTFA with the directing substituent permits intramolecular delivery of the electrophile, and *para* substitution results when such capabilities are absent[234].

The thallation–carbonylation sequence applied to benzamide gave an 83% GLC yield of phthalimide. Since the acetylanthranil which is produced by the thallation–carbonylation procedure applied to acetanilide is very sensitive to moisture, the carbonylation was run in methanol in order to isolate the corresponding methyl ester: pure methyl *N*-acetylanthranilate was isolated in a 37% yield[239]. This result can be compared with the 42–55% overall yield of the same product which was obtained by the direct palladation–carbonylation of acetanilide (equation 160)[250]. This last procedure requires a stoichiometric amount of palladium acetate, while the preceding one is catalytic.



(160)

Thallation–carbonylation of *N*-phenylurea affords 17% yield of pure recrystallized methyl 2-ureidobenzoate (entry 5, Table 30). [The authors attempted carbonylation in methanol (to obtain the ester) due to the very low solubility of 2,4-(1*H*, 3*H*)-quinazolinedione in most organic solvents.]

Thallation of benzophenone followed by carbonylation in methanol gave a 63% yield of methyl 2-benzoylbenzoate. Such compounds are of interest owing to the ease with which they can be cyclized to the very valuable anthraquinone ring system.

As shown above, the thallation–carbonylation sequence provides a route to a variety of phthalides, 2,4-dihydroisocoumarins, anhydrides, imides and other carbonyl compounds, and it should prove useful in natural products synthesis.

10. Organotin compounds

Organotin compounds have the advantage, over the classical alkali–metal complexes, to be tolerant of most functional groups. Thus, they allow the allylation of functionalized aromatic halides[251] as well as the alkylation of acid halides[252] catalyzed by palladium complexes.

The carbonylation of organotin compounds has been successfully used by Tanaka[253] for the synthesis of unsymmetrical ketones from organic halides in the presence of a palladium complex catalyst (equation 161). The reaction is carried out in a stainless steel autoclave which is charged with catalytic amounts (*ca* 1% mol) of $C_6H_5PdI[P(C_6H_5)_3]_2$, HMPA, the organic halide and the alkyltin compound in a 2:1 molar ratio. Carbon monoxide (30 atm at rt) is introduced and the mixture stirred at 120 °C overnight (judging from the pressure decrease, the reaction seemed to have finished within a few hours)[253a]. Conventional work-up renders the desired ketone; GLC analysis of the reaction mixture showed that it is not contaminated by by-products coming from the coupling of the organic halides and organotin compound radicals, which readily occurs when the reaction is conducted in the absence of carbon monoxide.

$$RX + CO + R'_4Sn \xrightarrow{\text{'Pd'}} R{-}\underset{\underset{O}{\|}}{C}{-}R' + R'_3SnX \qquad (161)$$

Some typical results are collected in Table 31 (the yields have not been optimized). Since a second alkyl group of organotin compounds [i.e. $(CH_3)_3SnI$] also has some reactivity for this reaction, the yield for iodobenzene reactions with tetramethyltin exceeded 100%.

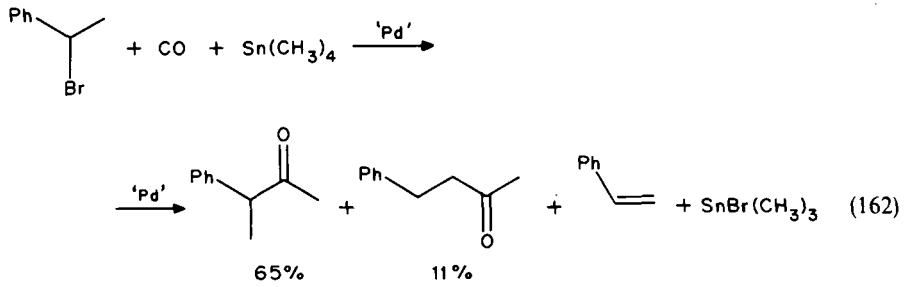
The carbonylation of alkyl halides that have β-hydrogens was accomplished by heating with tetramethyltin using $PdCl_2(AsPh_3)_2$ as a catalyst, under CO atmosphere (equation 162)[253b].

The reaction in Scheme 14, which involves oxidative addition of a halide, insertion of carbon monoxide and reductive elimination of a ketone, has been postulated for this

TABLE 31. Ketone synthesis from RX, CO and R'_4 Sn with $PhPdI(PPh_3)_2$ as catalyst (~ 1%). Reproduced with permission from *Tetrahedron Lett.*, **28**, 2602 (1987)

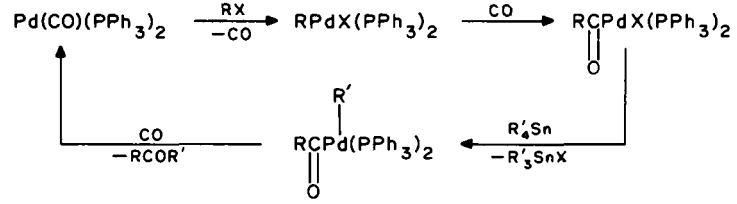
RX	R′ in R'_4 Sn	Product	Yield (%)[a]
C_6H_5I	CH_3	$C_6H_5COCH_3$	123 (85)
C_6H_5I	CH_3	$C_6H_5COCH_3$	105[b]
C_6H_5I	C_4H_9	$C_6H_5COC_4H_9$	79 (73)
C_6H_5I	C_6H_5	$C_6H_5COC_6H_5$	68
$C_6H_5CH_2Cl$	CH_3	$C_6H_5CH_2COCH_3$	— (86)
trans-$C_6H_5CH{=}CHBr$	CH_3	*trans*-$C_6H_5CH{=}CHCOCH_3$	— (62)[c]
$C_2H_5OOCCH_2Br$	C_6H_5	$C_2H_5OOCCH_2COC_6H_5$	— (67)

[a]The figures in parentheses indicate isolated yields.
[b]The catalyst amount used was one tenth of the standard run.
[c]A polymeric material was also formed in 14% yield: its amount increased when the reaction was not discontinued as soon as the carbon monoxide absorption ceased.



(162)

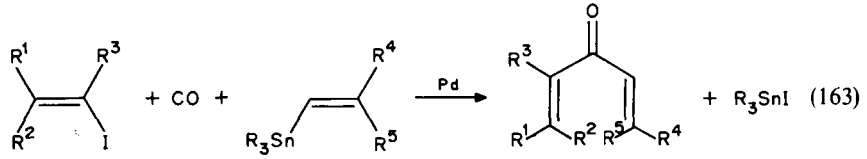
reaction. In view of the tolerance of most functional groups, this reaction might have considerable utility for ketonization of organic halides[253a].



SCHEME 14

The introduction of the carbonyl function from the carbon monoxide instead of from the acid chloride should allow the introduction of functional groups into divinyl ketones that ordinarily could not be brought unprotected into the coupling reaction. The outstanding work by Stille's group[254–258] on this subject is remarkable.

Thus, they[254] have shown that the palladium-catalyzed cross-coupling of allyl halides with aryl- and vinyltin reagents in the presence of carbon monoxide (1–3 atm) gives high yields of the unsymmetrical allyl vinyl or allyl aryl ketones (equation 163).



(163)

Stille and coworkers[255] have also shown that the palladium-catalyzed reaction of vinyl iodides with vinyltin reagents in the presence of carbon monoxide leads to an efficient synthesis of unsymmetrical divinyl ketones (equation 162). Unsymmetrical divinyl ketones are important intermediates in the synthesis of a wide variety of organic compounds, because not only are they Michael acceptors for different nucleophiles, but they also undergo the Nazarov reaction to provide, in some cases, an efficient route to cyclopentenones[259] (see below).

Symmetrical divinyl ketones can be synthesized by the reaction of vinylmercuric chlorides with carbon monoxide under mild conditions with rhodium catalysis. Acylations with divinylcuprates gives uniformly high yields of the unsymmetrical divinyl ketones[260], but many functional groups have to be protected. Stille's[255] method takes place under neutral, mild reaction conditions (45–50 °C) and low carbon monoxide pressures (15–50 psi). The reaction is highly catalytic, requiring only 1–2 mol% of

TABLE 32. Carbonylative cross-coupling of vinyl iodides with organostannanes. Reprinted with permission from *J. Am. Chem. Soc.*, **106**, 6418 (1984). Copyright (1984) American Chemical Society

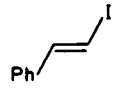
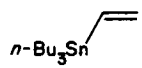
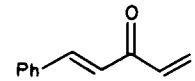
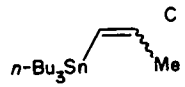
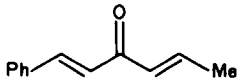
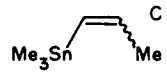
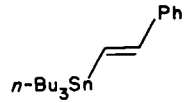
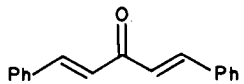
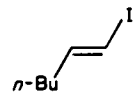
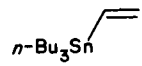
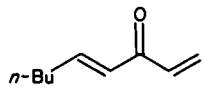
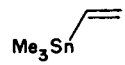
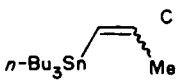
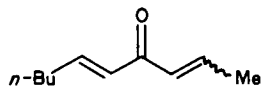
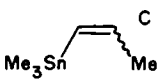
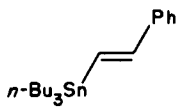
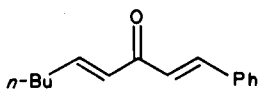
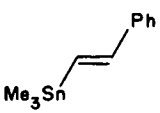
Example	Vinyl iodide	Tin reagent	Time (h)	Product	% Yield[b]
1			13		65(63)
2			22		46[d]
3			12		75
4			65		70
5			12[a]		70(75)
6			5[a]		65
7			45		62
8			44		70
9			23		40
10			15		65

TABLE 32. (*continued*)

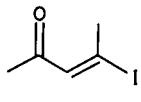
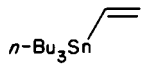
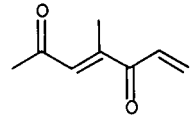
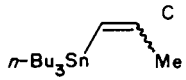
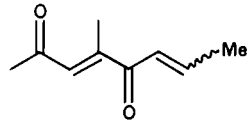
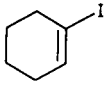
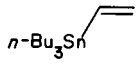
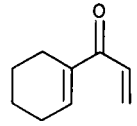
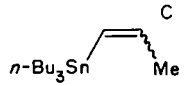
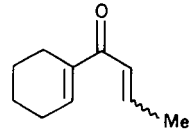
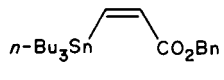
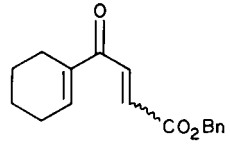
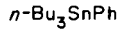
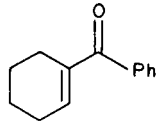
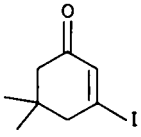
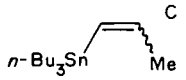
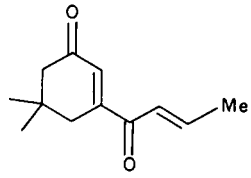
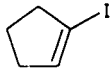
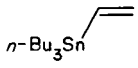
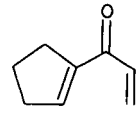
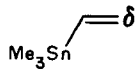
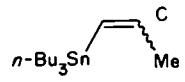
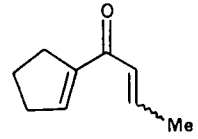
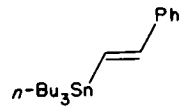
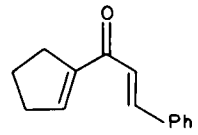
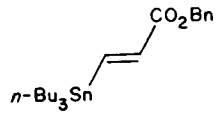
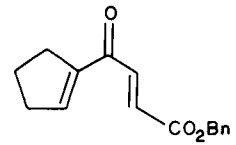
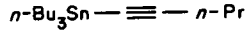
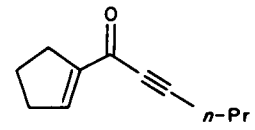
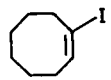
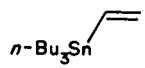
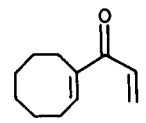
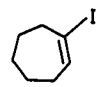
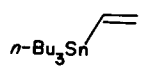
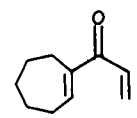
Example	Vinyl iodide	Tin reagent	Time (h)	Product	% Yield[b]
11			2		50
12			55		56
13			24		93
14			24		83
15			80		45
16			45		40
17			12		71
18			13		70(90)

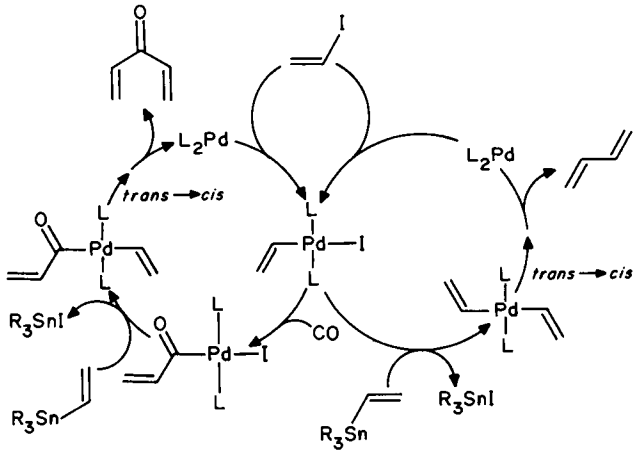
TABLE 32. (*continued*)

Example	Vinyl iodide	Tin reagent	Time (h)	Product	% Yield[b]
19			6		86 (90)
20			24		63
21			8		60
22			10		40 (65)
23			7		54
24			8[f]		74
25			8[f]		65

[a] All reactions were run under 50 psi of carbon monoxide at 45–50 °C, unless otherwise noted.
[b] Isolated yields. Yields in parentheses were determined by ^{1}H NMR. *Z*:*E* isomer ratios with reaction times for the various entries are as follows: entry 7, 48 h, *E* only; 24 h, 2.5. Entry 12, 0.9. Entry 14, 24 h, 0.7. Entry 15, 25 h, 1.6. Entry 17.24 h, 0.12; 12 h, 1.2. Entry 20, 24 h, 0.3; 18 h, 0.4. Entry 20, 12 h, 1.2.
[c] The vinyltin reagents had the following *Z*/*E* ratios: $Bu_3SnCH{=}CH{-}CH_3$, 6; $Me_3SnCH{=}CH{-}Me$, 2.
[d] When this reaction was run in the dark, the *Z*/*E* ratio of the propenyl double bond was 0:2.
[e] Run at 35–40 °C.
[f] Run at 65 °C.

palladium(II) catalyst. As can be seen in Table 32, ester and ketone functionalities as well as the vinyl ketone product can be present.

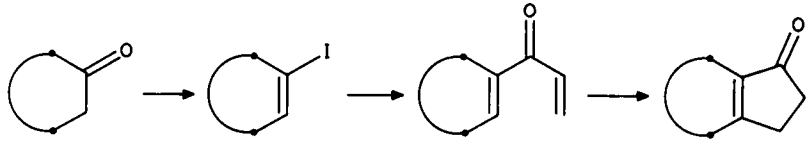
Transmetallation of the vinyltin reagent to the vinylpalladium(II) complex and subsequent reductive elimination can compete with carbon monoxide insertion at low carbon monoxide pressures (Scheme 15). For example, in the reaction of (*E*)-β-iodostyrene with (*E*)-β-stiryltributylstannane (Table 32) under 1 atm of carbon monoxide, a 1:1 mixture of carbonylated and directly coupled products was obtained. In contrast, the coupling of (*E*)-1-iodohexene with tributylvinylstannane under 1 atm carbon monoxide gave exclusively the carbonylated product, in moderate yield[255].



SCHEME 15

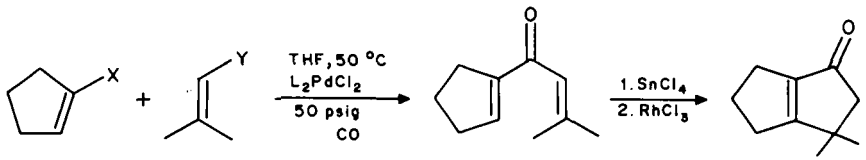
The *E* geometry of the double bonds in both the vinyl iodide and vinyltin partners is maintained in the coupled product. Although the *Z* geometry of the double bond in the vinyltin partner was retained through the coupling sequence, partial isomerization of the coupled product was observed under the reaction conditions[255]. Examination of different substrates indicates that the *E* isomer reacted much faster than the *Z* isomer. Yields in the coupling reactions are sensitive to steric hindrance, particularly on the vinyl partner. Vinyltin reacts faster than any of the other linear vinyl reagents.

Cycloalkenyl iodides were prepared from the cyclic ketones by the reaction of the corresponding hydrazone with iodine[261]. The above-described coupling procedure allows the overall annelation of a cycloalkanone by a sequence which concludes with a Nazarov cyclization[260], thereby affording entry into functionalized bicyclo[*n*.3.0] ring systems[256]. (A report on silicon-directed Nazarov cyclizations has been published recently[262].)



This strategy was applied to the synthesis of 3,3-dimethyl-4,5,6-trihydro-2*H*-pentalen-1-one, by cyclization of the divinyl ketone prepared by the reaction of 1-(tributylstannyl)cyclopentene with 3,3-dimethylacryloyl chloride[255] (equation 164). This

pentalenone is a key intermediate in a synthesis of modhephene.

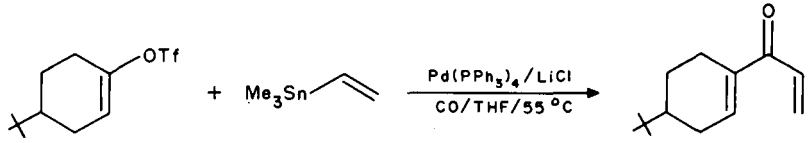


X	Y	% Yield 1
I	$SnBu_3$	0
$SnBu_3$	I	40
$SnBu_3$	COCl	85

(164)

However, since an expeditous route to the cyclic vinyl iodide was not currently available, Stille's group[263] developed an alternative strategy: since regioselective generation of vinyl triflates has been achieved[264] as well as the direct coupling of the latter with organostannanes[265], carrying out the coupling in the presence of carbon monoxide serves as a means of introducing the carbonyl functionality between organic fragments, and the coupling is regiospecific.

Thus, the reaction between vinyl triflate **111** and trimethylvinyltin **112** at 55 °C in THF in the presence of 3 mol% tetrakis(triphenylphosphine)palladium(O), $Pd(PPh_3)_4$, 2–3 equivalents of lithium chloride and 50 psi carbon monoxide afforded **113** and Me_3SnCl as the only products observable by GC analysis (equation 165). This reaction does not take place in the absence of lithium chloride, and is extremely slow at temperatures below 45 °C, while at temperatures above 65 °C a considerable quantity of the non-carbonylated coupled product was observed. Although $Pd(PPh_3)_4$ proved to be the most convenient catalyst for the reaction, bis(dibenzylideneacetone)palladium(O) and 2 equivalents of triphenylphosphine were equally efficacious[263].



(111) (112) (113)

(165)

The reaction is quite general with both cyclic and acyclic vinyl triflates affording good yields of the corresponding divinylketones (Table 33). Although little of the non-carbonylated coupled product was observed for reactions involving vinylstannanes under standard conditions, this was not true for the acetylenic stannane. Thus, reaction between **111** and **114** in the temperature range 40–60 °C under 50 psi of carbon monoxide gave predominantly the directly coupled product, whereas reactions carried out at 20 °C under 50 psi of carbon monoxide produced the desired carbonyl-containing product (Scheme 16).

The reaction between the vinyl triflate **111** and tetramethyltin or aryl stannanes under the above standard conditions does not take place, but good yields could be obtained by the addition of 1 equivalent of zinc chloride to the reaction mixture[263] (see entries 9–12 of

TABLE 33. Palladium-catalyzed carbonylative coupling of vinyl triflates with organostannanes[a]. Reprinted with permission from *J. Am. Chem. Soc.*, **106**, 7501 (1984). Copyright (1984) American Chemical Society

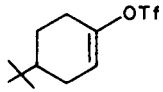
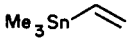
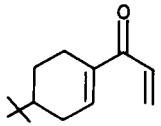
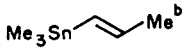
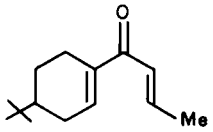
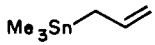
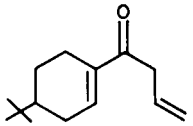
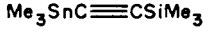
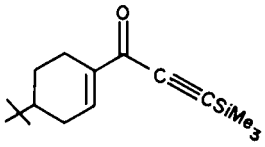
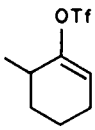
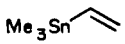
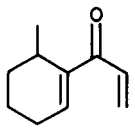
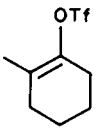
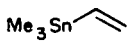
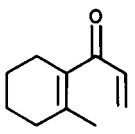
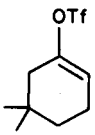
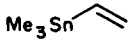
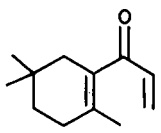
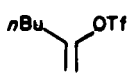
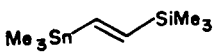
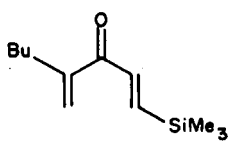
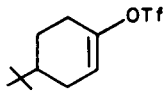
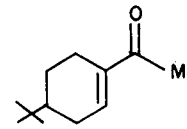
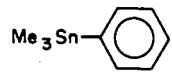
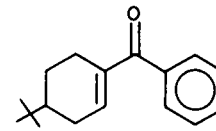
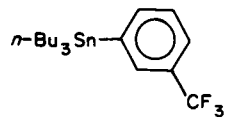
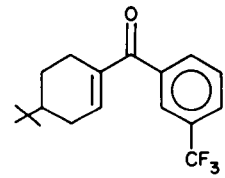
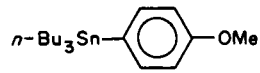
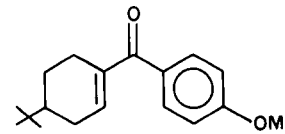
Example	Triflate	Organostannane	Product	Isolated yield (%)
1				76
2				70[c]
3				95[d]
4				95[e]
5				78
6				77
7				73
8				77

TABLE 33. (*continued*)

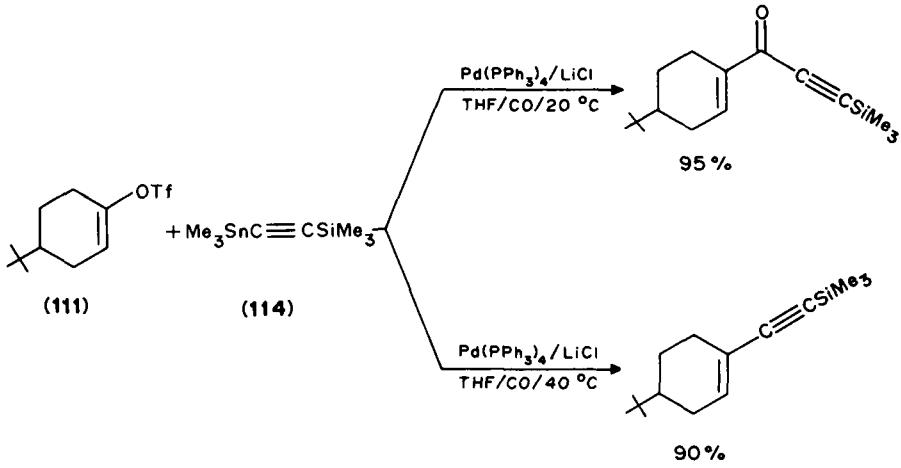
Example	Triflate	Organostannane	Product	Isolated yield (%)
9		Me_4Sn		73[d]
10				93[d]
11				76[d]
12				88[d]

[a]Reactions carried out at 55 °C in THF under 15 psi carbon monoxide and in the presence of 3 mol% Pd $(PPh_3)_4$, unless otherwise stated.
[b]The vinylstannane was a.2:1 mixture of *Z*:*E* isomers.
[c]The product was a 2:1 mixture of *Z*:*E* isomers.
[d]Reactions carried out at 75 °C in THF under 50 psi of carbon monoxide in the presence of 3 mol% $Pd(PPh_3)_4$ and 1 equiv of $ZnCl_2$.
[e]Reaction carried out at 20 °C in THF under 50 psi of carbon monoxide in the presence of 3 mol% $Pd(PPh_3)_4$.

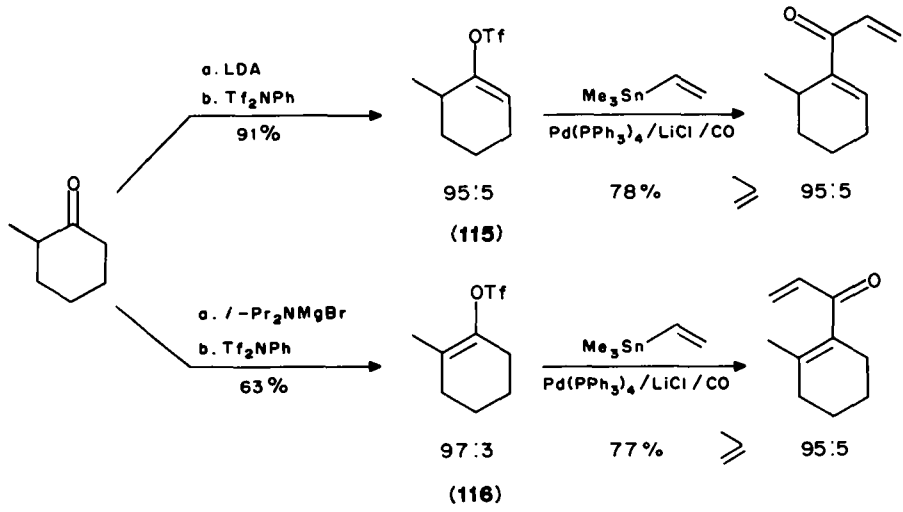
Table 33). Although the exact role of zinc chloride has not been clarified, the possible intermediacy of an organozinc species is assumed[236,266].

An important aspect of this reaction is the ability to generate a vinyl triflate regioselectively utilizing well-known enolate chemistry[267], and couple this with an organostannane under a carbon monoxide atmosphere to give only one regioisomeric product (Scheme 17). Thus, 2-methylcyclohexanone was converted into the kinetic triflate, **115**, and into the thermodynamic triflate, **116**. Carbonylative coupling of these triflates with trimethylvinyltin gave the desired divinyl ketones as greater than or equal to 95% isomerically pure products[263].

The regiochemical integrity of the vinylstannane is maintained during the course of the coupling. Thus, when a 2:1 mixture of the *Z*:*E* isomers of trimethylpropenyltin **117** was allowed to react with vinyl triflate **111**, the *Z* compound **118** and the *E* compound **119** were obtained in a 2:1 ratio (equation 166).



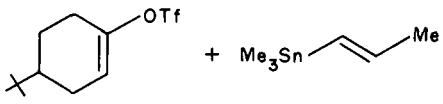
SCHEME 16



SCHEME 17

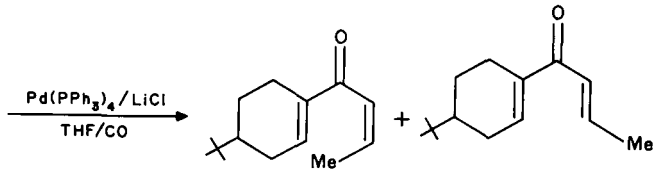
These results indicate that no loss of regiochemistry occurred during the course of the coupling, nor at the product stage. On the contrary, in the carbonylative coupling of vinyl iodides with vinylstannanes, a loss of regiochemical integrity was observed at the product stage for an analogous *Z* isomer[255].

The combination of the carbonylative coupling of vinyl triflates with vinylstannanes just described and a Nazarov reaction could be expeditiously applied to an iterative three-carbon annulation procedure for the synthesis of fused polycyclopentanoids. Thus,



Z:E = 2:1

(111) (117)

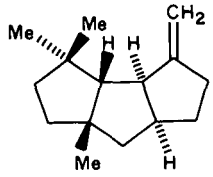


(166)

Z:E = 2:1

(118) (119)

Stille and collaborators[263] applied the above-described procedure to the total synthesis of the marine natural product[9(12)-] capnellene **120**[263].

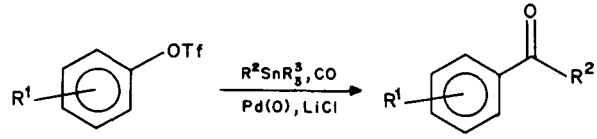


(120)

Palladium-catalyzed stereospecific homoconjugation of vinylstannanes is a convenient method for the synthesis of symmetric 1,3-dienones[268].

In summary, the palladium-catalyzed carbonylative coupling of vinyl triflates with various organostannanes gives good yields of the desired products, is regiospecific, and shows synthetic potential as a means of introducing a carbonyl group between unsaturated organic fragments[264].

The palladium-catalyzed carbonylative coupling of aryl halides with organostannanes has been recently reinvestigated. Echavarren and Stille[259,269] have fully examined its scope and shown how this reaction is a valuable synthetic procedure for the preparation of a variety of aryl ketones (equation 167)[270].



(167)

Several catalysts were tested. The best results were obtained by using dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)], $PdCl_2$(dppf); other seemingly similar chelating phosphines failed to furnish the desired coupling products. The carbonylative coupling of aryl triflates with organotin reagents is a quite general reaction (Table 34). Vinyl, alkyl, aryl and acetylenic groups on the tin partner all transfer in good yields[270]. However, the presence of strong electron-withdrawing substituents on the stannane led to no coupling (entries 8, 9, 19 and 22 in Table 34).

In none of the carbonylative cross-coupling reactions were products from further addition of the stannane to the aryl ketone product detected[270]. Echavarren and Stille[270] found that the high Michael acceptor ability of the vinyl ketone is responsible for the formation of the dimeric product (entries 20a and 20b).

A variety of functional groups in both the aryl triflate and the organotin are tolerated in the coupling reaction. A free hydroxyl group in the organostannane does not interfere with the cross-coupling reaction (entry 2). However, a nitro group is not tolerated (entry 9). A particularly interesting transformation occurred with the *o*-allyltriflate (entries 15a and 15b), which under the standard carbonylative coupling conditions did not furnish any of the expected vinyl ketone and, instead, the diketone shown in Table 34 was obtained in 50–60% yield[270]. Treatment of the same triflate with the allyltin nucleophile gave *o*-diallylbenzene as the major product (entry 16).

Stille[270] also studied briefly the palladium-catalyzed reaction of the triflates of 2-tropolone with organostannanes in the presence of carbon monoxide. The cross coupling affords troponyl ketones under neutral conditions.

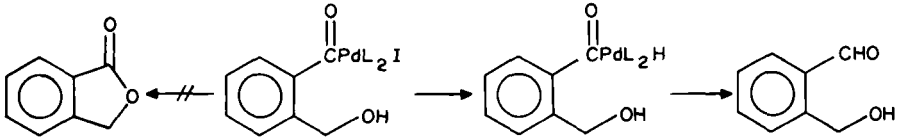
Another very useful reaction using organotin hydride and carbon monoxide has been studied by Baillargeon and Stille[254]. Although it cannot be considered a carbonylation of the organotin compound, the reaction is worth mentioning in the context of this chapter since it constitutes a useful method for the direct conversion of organic halides to aldehydes. An organic halide can be catalytically converted directly to an aldehyde in the presence of carbon monoxide and tributyltin hydride, using palladium catalysts. The transformation of a variety of organic halides to aldehydes takes place with these reagents under mild reaction conditions (1–3 atm of CO, 50 °C) giving good yields of aldehydes (Table 35; equation 168).

$$RX + CO + Bu_3SnH \xrightarrow[50\,^\circ C]{Pd(0)} RCHO + BuSnX \qquad (168)$$

Aryl, benzyl, vinyl and allyl halides can be converted to aldehydes, and other functional groups in the molecule (nitro, ketone, ester and alcohol) remain unaffected under the reaction conditions. Closely related to this reaction is the palladium-catalyzed conversion of vinyl or aryl halides to aldehydes by carbon monoxide and hydrogen (1:1); this reaction, however, requires higher temperatures (~ 100 °C) and pressures (1200–1500 psi)[254].

Again, the reaction with tin hydride and carbon monoxide has the advantage over lithium or Grignard reagents in the conversion of organic halides to aldehydes, in that other reactive functionalities may be present.

In the conversion of 2-iodobenzyl alcohol to the corresponding aldehyde, the acylpalladium complex under the reaction conditions, apparently undergoes transmetallation and reductive elimination of the acylpalladium hydride much faster than direct reductive elimination to the lactone[271] (equation 169).

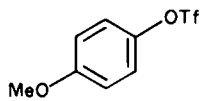
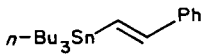
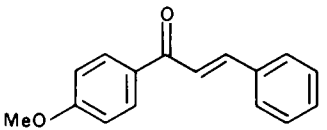
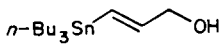
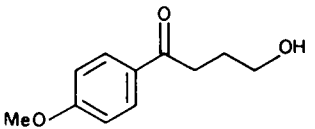
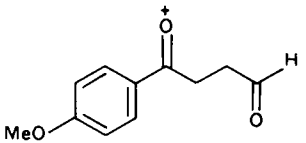
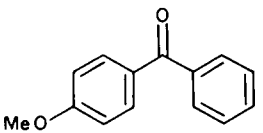
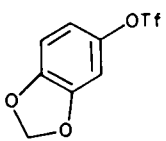
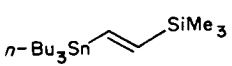
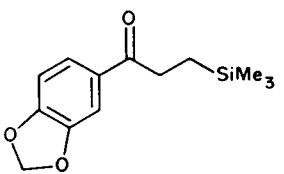


1

(169)

A limiting side-reaction in the conversion of halides to aldehydes appears to be the direct reduction of the halide without carbon monoxide insertion. This reduction proceeds only very slowly under the standard reaction conditions in the absence of a palladium

TABLE 34. Palladium-catalyzed carbonylative coupling of aryltriflates with organostannanes[a]. Reprinted with permission from *J. Am. Chem. Soc.*, **110**, 1560 (1988). Copyright (1988) American Chemical Society

Entry	Triflate	Organostannane	Catalyst	T(°C)	CO Pressure (atm)	Reaction time (h)	Product(s)	Yield (%)
1			$PdCl_2(dppl)$	70	1	23		68
2				100		2		37
								20
3		$PhSnMe_3$				21		69
4a				75		5		96

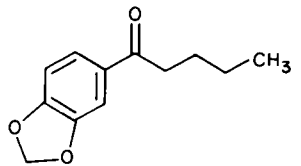
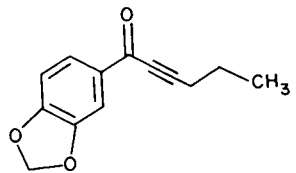
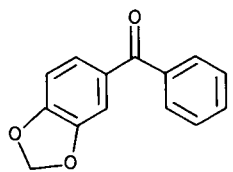
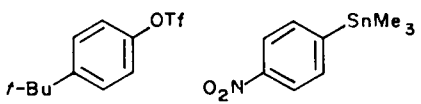
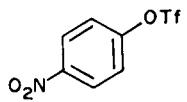
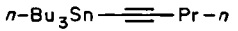
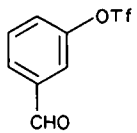
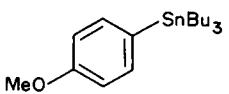
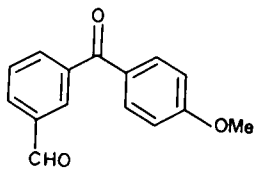
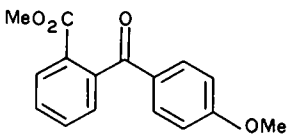
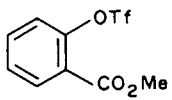
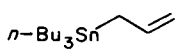
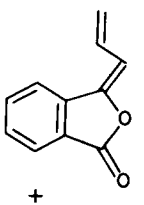
4b		$Pd(PPh_3)_4$[b]	80	3.5	34		22
5	n-Bu_4Sn	$PdCl_2$(dppl)	110	1	44		65
6a	n-Bu_3Sn—≡—Pr-n		70		6		68
6b		$PdCl_2$(dppp)			6.5		< 5[c]
7a	$PhSnMe_3$	$PdCl_2$(dppl)	90				88
7b		$Pd(Ph)_4$[b]	80	3.5	40		39
7c		$PdCl_2(PPh_3)_2$			9		27
8		$PdCl_2$(dppl)	95	1	11	no reaction[d]	

TABLE 34. (*continued*)

Entry	Triflate	Organostannane	Catalyst	T(°C)	CO Pressure (atm)	Reaction time (h)	Product(s)	Yield (%)
9				100		6	no reaction[c]	
10a				90		8		98
10b[f]								33
10c			$PdCl_2$(dppp)					< 5[c]
11a			$PdCl_2$(dppl)	95		14		35
11b				90	3.5	21		64
12				80		21		*ca* 15[g]

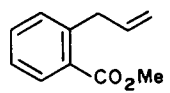
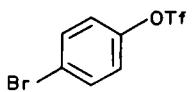
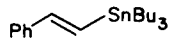
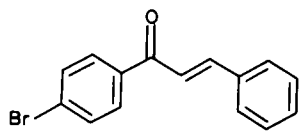
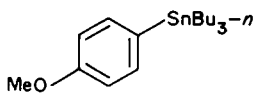
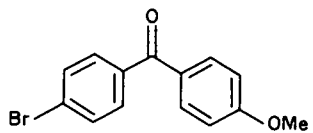
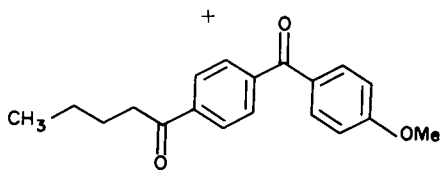
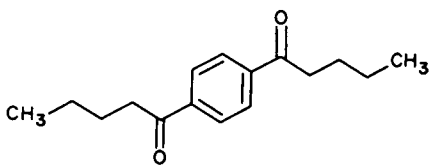
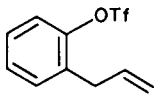
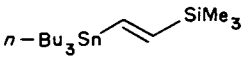
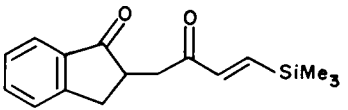
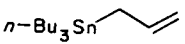
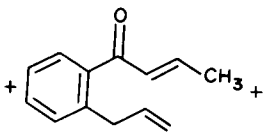
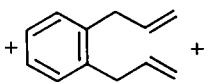
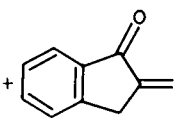
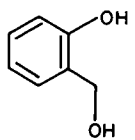
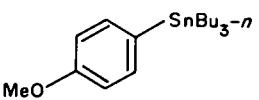
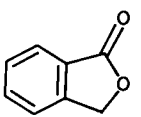
							45[h]
13a			70	1	7		80
13b[f]							84
14a			95		27		45
							17
							6
14b[f]			100	1	30		39[j]

TABLE 34. (*continued*)

Entry	Triflate	Organostannane	Catalyst	T(°C)	CO Pressure (atm)	Reaction time (h)	Product(s)	Yield (%)
15a			1	50		72		52[k]
15b				70	3.5	15		60
16								16
								44
								19
17				90	1	13		62

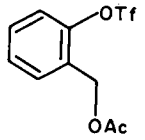
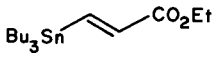
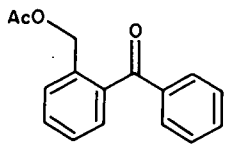
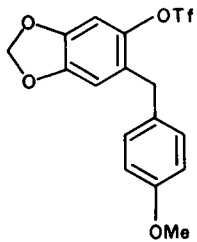
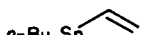
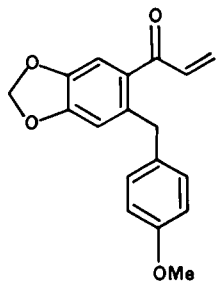
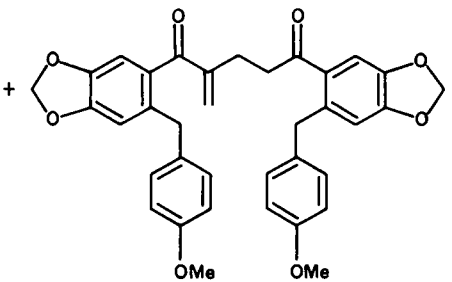
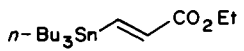
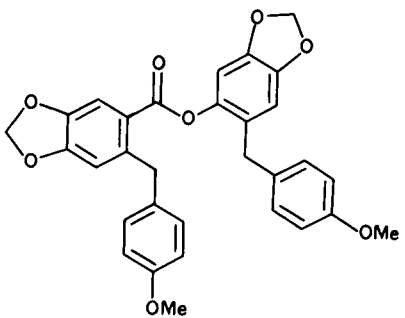
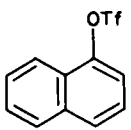
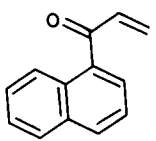
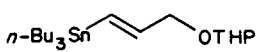
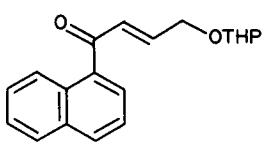
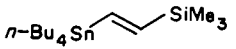
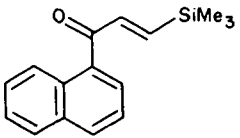
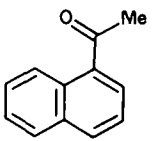
18			90	18	no reaction[d]	
19		$PhSnMe_3$	100	15		78
20a			75	21	 + 	67[l] 5

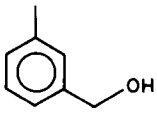
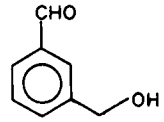
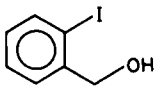
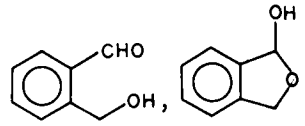
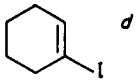
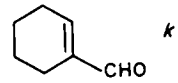
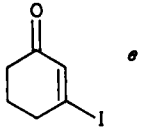
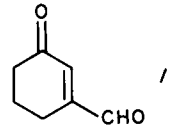
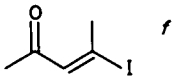
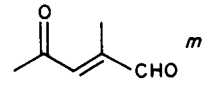
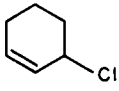
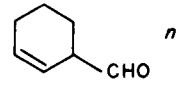
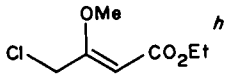
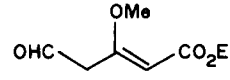
TABLE 34. (*continued*)

Entry	Triflate	Organostannane	Catalyst	T(°C)	CO Pressure (atm)	Reaction time (h)	Product(s)	Yield (%)
20b				100	1	23	5	21
							+	
							6	44
21				95	1	100		35[m]
22			$PdCl_2$(dppl)	90	1	2		84
23a				70	3.5	3		54

23b		$PdCl_2(PPh_2)_2$	60	1	5		36
23c		$PdCl_2PdCl(PPh_2)_2$		2	11		< 5[c]
24a		$PdCl_2$(dppl)	70		4		72
24b		$PdCl_2$(dppe)	75		10		< 5[c]
25	Me_4Sn	$PdCl_2$(dppl)	90	3.5	1.5		83

[a] Unless otherwise stated the carbonylations were carried out in DMF (*ca* 0.2 M substrate) in the presence of 3.0 equiv of LiCl with 4% of the corresponding palladium catalyst.
[b] PPh_3 (12%) was also added.
[c] Product not observed in the ^1H NMR of the crude reaction mixture.
[d] The triflate was recovered.
[e] The triflate decomposed to unidentified products.
[f] Reaction run in the absence of LiCl.
[g] The phthalide was contaminated with starting material.
[h] *Product contained 10% of a 1:1 E/Z mixture of the conjugated isomers.*
[i] Several other minor products formed were not isolated.
[j] 6% of catalyst was used.
[k] Conversion: 58%.
[l] Conversion: 71%.
[m] Conversion: 64%.

TABLE 35. Formylation of organic halides[a]. Reprinted with permission from *J. Am. Chem. Soc.*, **105**, 7175 (1983). Copyright (1983) American Chemical Society

Halide	Solvent	*p* CO (atm)	Product(s)	% Yield[b]
C_6H_5I	toluene	1	C_6H_5CHO	95[c]
p-MeC_6H_4I	toluene	1	*p*-MeC_6H_4CHO	100
o-MeC_6H_4I	toluene	1	*o*-MeC_6H_4CHO	70
p-BrC_6H_4I	THF	3	*p*-BrC_6H_4CHO	88 (70)
			C_6H_5Br	9
			C_6H_8	4
p-$MeOC_6H_4I$	toluene	1	*p*-$MeOC_6H_4CHO$	100 (77)
p-$NO_2C_6H_4I$	toluene	3	*p*-$NO_2C_6H_4CHO$	38
			$C_6H_5NO_2$	62
	toluene	1	 *i*	(76)
			$C_6H_5CH_2OH$	12
	toluene	1	 *i*	(55)
			$C_6H_5CH_2OH$	20
$C_6H_5CH_2Br$	THF	1	$C_6H_5CH_2CHO$	75
			$C_6H_5CH_3$	12
 *d*	toluene	1	 *k*	89 (53)
 *e*	toluene	3	 *l*	83
 *f*	toluene	3	 *m*	95
 *g*	toluene	3	 *n*	65
 *h*	THF	3	 *n*	86

catalyst. The slow addition of tributyltin hydride to the reaction mixture under carbon monoxide is necessary in order to optimize the ratio of aldehyde to reduced product, and the reduction also can be suppressed somewhat by increasing the carbon monoxide pressure[271]. For example, the conversion of 4-bromoidobenzene to 4-bromobenzaldehyde by the slow addition of 1 equivalent of tributyl tin hydride gives 73% yield under 1 atm CO and 88% yield under 3 atm. The reduction pathway becomes more important with an aryl halide that is a good electron acceptor (one-electron transfer) and/or carries $+\sigma$ substituents. The yields of 4-nitrobenzaldehyde and nitrobenzene from 4-nitroiodobenzene are 9% and 84%, respectively, under 1 atm of carbon monoxide but 38% and 62% under 3 atm[271].

Typically, reactions were run under a balloon of carbon monoxide or in a pressure bottle(3 atm) with 1–5 mmol of the organic halide in THF or toluene with 3.5–4% mol% of tetrakis(triphenylphosphine)palladium(0)[271].

Closely related to these reactions is the synthesis of aromatic acid derivatives by carbonylation of aryl iodides and R_3SnNu (Nu = MeO, Et_2N, PhS, EtS)[272].

III. INSERTION OF CARBON MONOXIDE INTO N—M BONDS

Carbonylation of metal amides to produce mainly alkylformamides has been of interest in the past[273–277] and a renewed interest in the subject is observed at present[278–284]. The nitrogen-carbonylated compounds usually formed in these reactions are useful and versatile intermediates in organic syntheses[285] and in the formation of different heterocycles present in natural products[286,287].

A. Structural Studies of Reagents and Intermediates

The insertion of carbon monoxide into the two-centre two-electron nitrogen–metal bond of organometallic amides is assumed to lead to the formation of a usually active 'carbamoyl' reagent, **122** (equation 170).

As in the case of the insertion reactions into metal–carbon bonds, the carbamoyl anion formed has been sometimes postulated as having a 'carbene-like' structure, **123**. In some cases (see Sections III.C.1 and III.C.5) indirect evidence for this structure has been achieved by their reactivity toward special reagents. In most cases the carbamoyl

TABLE 35. (*continued*)

[a]Reactions were run at 50 °C with tetrakis(triphenylphosphine) palladium(0), 3,5–4 mol%. All compounds gave satisfactory spectra (IR, ^{1}H NMR, ^{13}C NMR) and GC retention times by comparison to authentic samples or known compounds.

[b]Yields determined by GC; isolated yields in parentheses.

[c]The same yield was obtained with either tetrakis(triphenylphosphine)palladium(0) or bis(dibenzylidene acetone)palladium (3.7 mol%) plus 8.7 mol% triphenylphosphine.

[d]A. Pross and S. Sternhall, *Aust. J. Chem.*, **23**, 989 (1970).

[e]E. Piers, J. R. Grierson, C. K. Lau and I. Nagakura, *Can. J. Chem.*, **60**, 210 (1982).

[f]Piers, E.; Nagakura, I. *Synth. Commun.* (1975), 193.

[g]Grob, C. A.; Knu, H.; Gagneun A. *Helv. Chim. Acta* (1957), **40**, 130.

[h]DuBois, G. E.; Crosby, G. A.; Stephenson, R. A. *J. Med. Chem.* (1981), **24**, 408.

[i]Leznoff, C. C.; Wong, J. Y. *Can. J. Chem.* (1973), **51**, 3756.

[j]Rieche, A.; Schultz, M. *Justus Liebigs Ann. Chem.* (1962), **653**, 32.

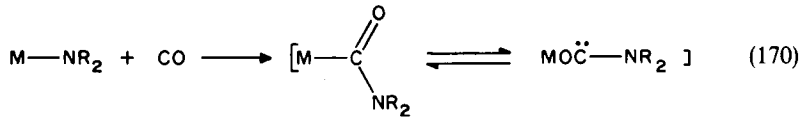
[k]Kraus, J. L.; Sturtz, G. *Bull. Soc. Chim. Fr.* (1971), *11*, 4012.

[l]Quesada, M. L.; Schlessing, R. 11. *Synth. Commun.* (1976), *6*, 555.

[m]This compound has the correct spectra (NMR, IR) and analysis.

[n]The product of reaction by NMR. However, the double bond isomerizes in conjugation with aldehyde function on workup.

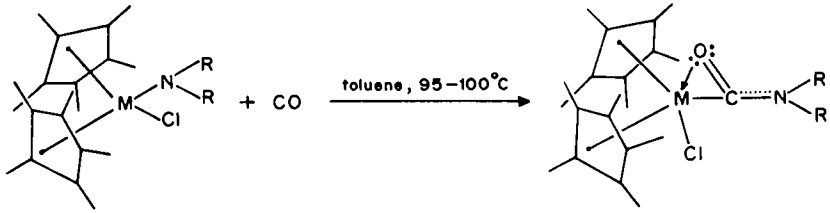
compound is not stable enough to allow structural determinations. Important and useful structural information, however, can be afforded by analogy with studies carried out on the more stable organotransition and organoactinide carbamoyls, some of which have been isolated as crystalline complexes.



(121) (122) (123) (170)

The initial structural studies have been carried out by infrared spectroscopy[288]. A broad (medium intensity) signal averaging in the zone of 1520–1560 cm^{-1} has been assigned to the C···O and C···N bond vibrations and interpreted as an indication that the carbamoyl group is partially bonded to the metal as a carbene-type ligand[288a,b]. Thus, in the clear red solution of dimethylcarbamoylnickel carbonylate, $(CH_3)_2NCONi(CO)_3$, obtained by addition of nickel carbonyl to an ether solution of lithium dimethylamide, the infrared spectrum shows peaks at 1973(vs), 1954(s) ($\nu_{C=O}$ of the terminal carbonyl group of the anionic complex), and 1560 cm^{-1} (m, broad) ($\nu_{C=O}$ and $\nu_{C=N}$ of the carbamoyl group bonded to nickel). These data suggest that the carbamoyl group is bonded to nickel as a carbene-type ligand[289].

More recently, Marks and coworkers[290] reported a thorough study on the first examples of CO insertion into a d- or f-element metal-to-dialkylamide bond and the properties of the resulting carbamoyl insertion products. Crystalline uranium and thorium bis(pentamethylcyclopentadienyl) carbamoyls, **125**, have been prepared from the reaction of chlorobis(pentamethylcyclopentadienyl) uranium and thorium dialkylamido complexes (equation 171), and the solid-state structures have been determined by X-ray diffraction. The ORTEP drawing of the non-hydrogen atoms in the solid-state structure of thorium chlorobis(pentamethylcyclopentadienyl) carbamoyl, **125a**, shown in Figure 11, indicates that the Th–C and Th–O distances are shorter than expected for an acyl-like structure while the C–O length is longer than those observed in regular carbonyl compounds. These results suggest the contribution of a 'carbene-like' structure (**126**) like that depicted in equation 172[290].



(124) (125)

(125a) M = Th, R = CH_3

(126b) M = U, R = CH_3

M = Th, R = C_2H_5

M = U, R = C_2H_5

(171)

The solid-state structural results for **125a** show some structural parameter disorders and raise questions of whether some structures (**A** and **B**) are both significantly populated

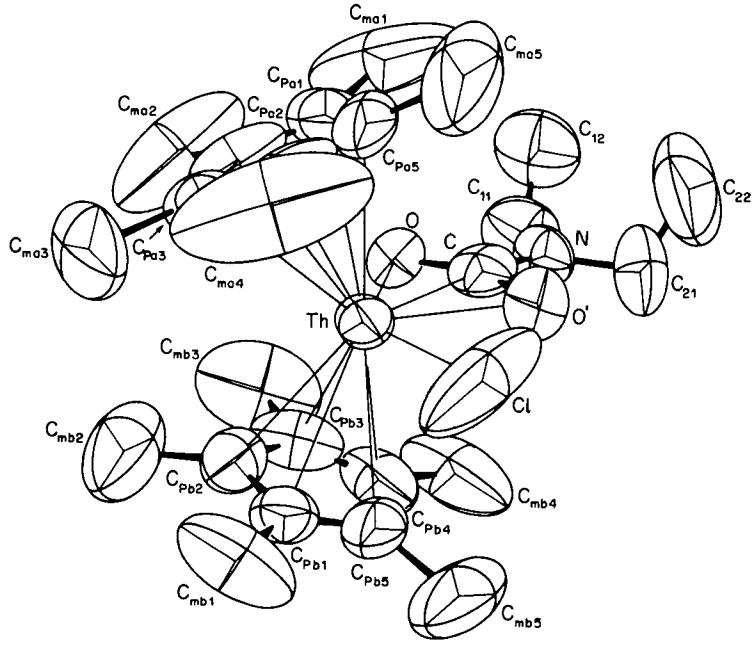
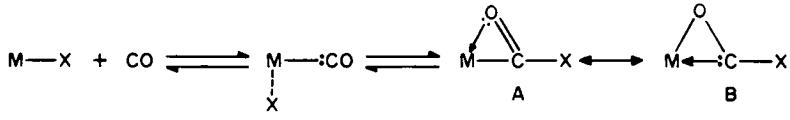
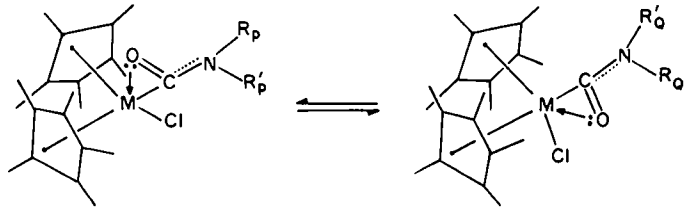


FIGURE 11. ORTEP drawing of the non-hydrogen atoms in the solid-state structure of $Th[\eta\text{-}(CH_3)_5C_5]_2\{\eta^2\text{-}CO[N(C_2H_5)_2]\}Cl$. All atoms are represented by thermal vibrational ellipsoids drawn to encompass 50% of the electron density. The inserted CO has two possible orientations in the 'equatorial girdle' with the oxygen atom disordered between two sites (O and O'). Reprinted with permission from *J. Am. Chem. Soc.*, **103**, 2215 (1981). Copyright (1981) American Chemical Society.

in solution at room temperature and whether rapid passage between them can take place (equation 173)[290,291].



(126) (172)



(173)

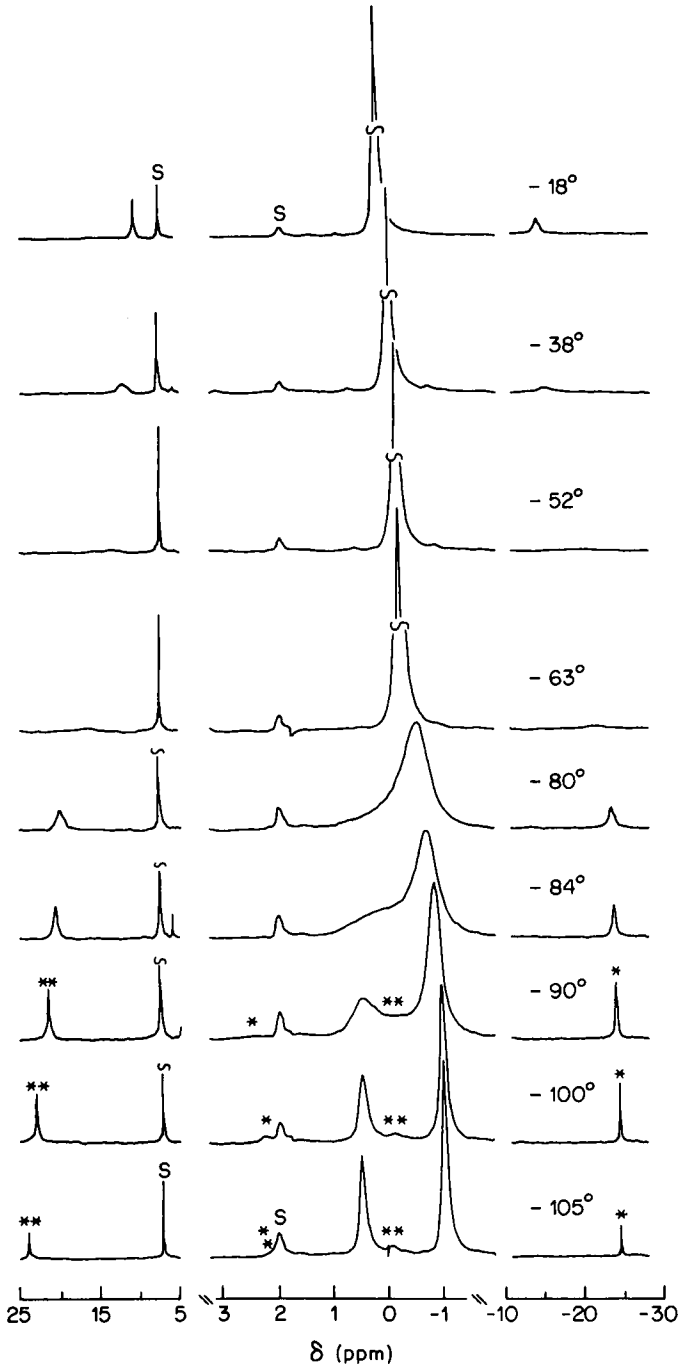


FIGURE 12. Variable-temperature FT 90-MHz ^{1}H NMR spectra of U-[η-$(CH_3)_5C_5$]$_2${η^2-$CO[N(CH_3)_2]$}Cl **125b** as a solution in 1:1 C_6D_5C-D_3—CF_2Cl_2. The resonances labeled asterisk and double asterisk indicate related pairs of exchanging N—CH_3 groups. The resonances labeled S (top and bottom spectrum) are due to toluene-d_7. The vertical scale may vary somewhat from spectrum to spectrum. Reprinted with permission from *J. Am. Chem. Soc.*, **103**, 2216 (1981). Copyright (1981) American Chemical Society.

Variable-temperature ^{1}H NMR spectra of uranium and thorium carbamoyls have been determined[291] and in Figure 12 the NMR spectra of $U[\eta\text{-}(CH_3)_5C_5]_2\{\eta^2\text{-}CO[N(CH_3)_2]\}Cl$, **125b**, as a solution in 1:1 $C_6D_5CD_3$–CF_2Cl_2 is presented. At −18 °C, singlets at δ −0.38 (30 H), 10.1 (3 H), and −14.1 (3 H) are observed which were assigned to the pentamethylcyclopentadienyl and the magnetically non-equivalent N–CH_3 resonances, respectively. Upon lowering the temperature, the η-Me_5C_5 resonance begins to broaden by *ca* −70 °C, and in the limiting spectrum at −105 °C, this resonance has split into a doublet of unequal intensities at δ0.62 (minor isomer) and −0.86 (major isomer). The two N–CH_3 resonances already began to broaden at *ca* −18 °C, eventually collapse at *ca* −63 °C and, in the limiting spectrum at −105 °C, two new pairs of N–CH_3 resonances which are assigned to methyl groups in the isomers **A** and **B** are observed at δ 23.7 and −24.4 (major isomer) and at δ 2.13 and 0.10 (minor isomer)[290]. All spectra changes are reversed upon raising the temperature and are independent of concentration, confirming the temperature dependence of equilibrium **A**⇌**B**. The above assignments were verified by magnetization transfer experiments and it was shown that the η^2-carbamoyl ligand reorients as a rigid unit, without permutation of non-equivalent R and R′ substituents[290].

In summary, the data indicate that the equilibrium shown by equation 172 exists with the indicated delocalization of nitrogen—lone pair electron density onto the 'carbenoid' carbon. This dative-bonding contribution in organoactinide carbamoyls appears to be significantly greater than in organic amides and probably in transition-metal η-carbamoyls as well. A careful comparison of spectroscopic data suggests a reduction in the carbenoid character of the C—O functionalities in the actinide carbamoyls relative to the acyls. Similar conclusions can be achieved for organolithium compounds by reactivity comparison of the lithium acyl and carbamoyl intermediates (see Sections II.C.1 and III.C.1).

As shown in the earlier sections on insertion of carbon monoxide into carbon–metal bonds (and as will be shown in subsequent sections), aggregation plays an important role in determining the reactivities and regioselectivities of the reagents. X-ray structures are available for a number of lithium salts of secondary amines. These structures include a monocyclic tetramer[292], cyclic trimers[293,294] as well as a number of dimeric[292,294–296] and monomeric[297] species. No cubic tetrameric structures have been observed for secondary lithium amides and, furthermore, even in the case of the lithium derivative of the relatively unhindered secondary amine, dibenzylamine, each lithium atom in the dimer is only monosolvated by diethyl ether or hexamethylphosphoric triamide[295]. The monolithium salt of the primary amine, 2, 4, 6-tri-*tert*-butylaniline, which crystallizes as a monomer from TMEDA, also has a lithium atom which is formally only tricoordinate[298]. $Ph_2C{=}NLi{\cdot}$pyridine, in which steric effects in the vicinity of the N—Li bond are greatly reduced, does however exist as a cubic tetramer[299]. The recently determined X-ray structure of the ether solvate of lithium *N*-(3, 3-dimethylbut-1-en-2-yl) anilide, $[PhNLiC(Bu^t){:}CH_2{\cdot}Et_2O]$, **127**[300], shows that it is a dimer, with one solvent molecule per lithium atom. Evidently, steric factors are important in controlling the degree of association and solvation[301]. Nevertheless, in solution, where most of the carbonylation reactions are carried out, aggregation is important to know because of its involvement in controlling the reactions.

Jackman and Scartmouzos[301] have recently studied the structures of the lithium salts of aromatic amides in weakly polar aprotic solvents, using ^{6}Li/^{15}N multiplicities, ^{13}C chemical shifts and ^{7}Li nuclear quadrupole coupling. Thus, the ^{15}N resonance of the ^{6}Li, ^{15}N isoptomer in lithium *N*-methylanilide is resolvable at −100 °C into a 1:2:3:2:1 pentuplet (J = 3.8 Hz) (Figure 13a) indicating that each nitrogen atom is attached to two lithium atoms, consistent with the conclusion that this species is a dimer reached by ^{13}C NMR studies. Similarly, the ^{15}N resonances in the NMR spectrum of lithium *N*-

TABLE 36. ^{13}C chemical shifts for lithium amides[a]. Reprinted with permission from *J. Am. Chem. Soc.*, **109**, 5351 (1987). Copyright (1987) American Chemical Society

Compound	Solvent	Concn (M)	Temp (°C)	C(1)	C(2/6)[a]	C(3/5)	C(4)
127 (R = CH_3)	Et_2O	0.54	26	162.6	112.1	130.4	111.2
			−100	162.6	115.4	131.2	110.3
					109.0	129.2	
	Et_2O/HMPT[b]	1.5	26	163.7	112.3	128.1	103.1
	C_6D_6/TMEDA[c]	0.4	26	163.7	115.8	131.1	109.3
					108.8	*d*	
	THF	0.16	26	163.9	112.9	129.2	108.4
			−60	163.7	119.4	129.8	108.0
					107.2	127.3	
127 (R = *n-Bu*)	THF	0.31	26	162.5	112.7	129.7	108.1
	e		−100	162.2	117.1	129.6	103.8
					106.5	127.9	
				163.2	119.9	*f*	107.7
					109.1	*f*	
127 (R = Pr^i)	Et_3N	0.33	26	160.4	114.1	130.5	111.3
	Et_2O	0.28	26	160.7	113.0	130.6	110.7
			−100	160.0	113.7	131.8	110.4
					111.3	130.4	
	THF	0.11	26	161.6	112.7	129.5	106.1
			−100	161.1	116.7	129.7	103.6
					107.0	128.1	
127 (R = Bu^i)	THF	0.31	26	161.1	115.6	128.8	104.6
			−110	160.8	119.1	128.5	103.1
					112.2	128.1	
	Et_2O	0.56	26	159.6	118.3	129.9	111.0
	g		−110	159.6	117.9	130.3	110.8
				159.1	117.7	130.0	110.7
127 (R = $CH_3OCH_2CH_2$)	THF	0.31	26		113.4	129.3	110.3
			−100	161.9	119.2	129.7	107.9
					108.7	128.6	

Compound	Solvent	Concn (M)	Temp (°C)	C(3)	C(4)	C(5)	C(6)	C(1)	C(2)
128 (R = H; $n = 1$)	THF	0.73	26	123.3	108.1	127.5	106.7	167.8	131.4
			−100	123.1	107.5	127.3	107.1	168.1	
	Et_2O	0.33	26	124.3	110.8	128.2	104.4	166.2	
	h		−120	124.1	109.7	128.1	105.1	166.7	131.9
				123.9	109.6	*i*	106.8	167.1	131.8
128 (R = CH_3; $n = 1$)	THF	0.45	26	123.9	108.6	128.0	104.3	166.1	130.7
	j		−95	123.6	108.1	127.5	107.9	165.8	129.8
				122.7	103.2	128.0	103.0	166.6	*k*
Compound	Solvent	Concn (M)	Temp (°C)	C(3)	C(4)	C(5)	C(6)	C(1)	C(2)
128 (R = H; $n = 2$)	THF	1.0	26	120.4	109.0	127.1	114.7	158.9	130.1
			−60	119.0	107.5	125.7	118.1	160.0	129.6
128 (R = CH_3; $n = 2$)	THF	0.27	26	119.4	107.6	127.3	114.0	158.6	129.7
	l		−60	116.7	103.0	126.7	114.6	158.9	128.9

[a] In cases where both signals are separately observed, the down field resonance is assigned to the carbon *syn* to the Li, on the basis that it is more strongly coupled to ^{15}N in the *N*-methyl- and *N*-isopropylanilides.
[b] 4 equiv of HMPT.
[c] 1 equiv TMEDA.
[d] Obscured by C_6D_6.
[e] Monomer:dimer = 2.8:1.
[f] Obscured by monomer resonance.
[g] Relative intensities of 110.8:110.7 ppm = 1.3:1 at 0.31 M 110.8:110.7 ppm = 1.3:1.
[h] Relative intensities of 124.1:123.9 ppm = 1:2.2, at 0.17 M 124.1:123.9 ppm = 1:2.1.
[i] Unresolved.
[j] Monomer:dimer = 1:1.4, at 0.22 M monomer:dimer = 1.3:1.
[k] Obscured by dimer resonance.
[l] Evidence of dimer formation.

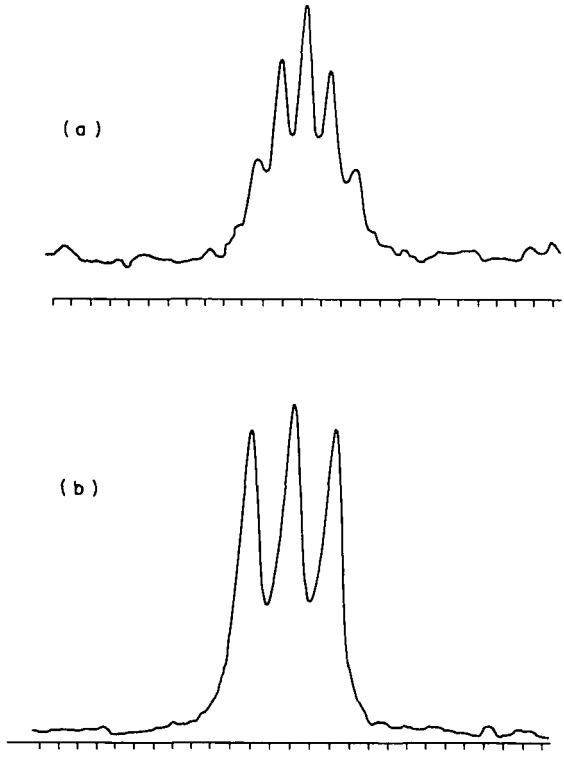
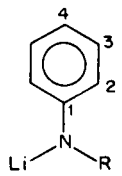


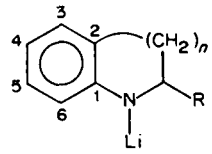
FIGURE 13. The ^{15}N resonance at 20.3 MHz of (a) lithium [$^{15}N_1$]-*N*-methylanilide in diethyl ether at $-100\,^{\circ}C$ and (b) lithium [$^{15}N_1$]-*N*-iso-propylanilide in tetrahydrofuran at $-80\,^{\circ}C$. Reprinted with permission from *J. Am. Chem. Soc.*, **109**, 5353 (1987). Copyright (1987) American Chemical Society.

isopropylanilide in THF at $-80\,^{\circ}C$ was observed as a 1:1:1 triplet consistent with a monomeric species (Figure 13b).

Table 36 shows the ^{13}C chemical shifts of various lithium anilides (compounds **127**) and indolides (compounds **128**) as a function of solvent, concentration and temperature. It can be observed that, in particular, the shielding of C(4) and C(6) exhibit marked decreases and increases, respectively, with temperatures above $-40\,^{\circ}C$ and their difference is therefore a



(127)



(128)

sensitive parameter with which to examine the changes which occur with increasing temperature. Jackman and Scartmouzos[301] have shown that the monomeric and dimeric forms are not unique but there is a variety of solvent aggregates. The changes in chemical shifts observed by changes in the temperature are independent of concentration and they suggest that a variety of solvent (S) molecules are interacting. The authors reported evidence for the following equilibria:

$$LiAS_3 \rightleftharpoons LiAS_2 \rightleftharpoons Li_2A_2S_4 \rightleftharpoons [Li_2A_2S_3] \rightleftharpoons Li_2A_2S_2$$

(130) **(131)** **(132)** **(133)** **(134)**

where A stands for anion and S for solvent. The authors[301] have no direct evidence for the mixed solvate **133**, since at the temperature at which it is likely to occur all species will exchange rapidly on the NMR scale, but the known crystallographic structure of Schollkopf's reagent[302] (a lithium dienamide which is a 5:1 mixture of a monomer and dimer, and which crystallizes as a trisolvated dimer)[303] is evidence for the possibility of its existence. Table 37 gathers useful information concerning the degree of aggregation and solvation of several lithium amides in different solvents. It is clear that steric factors play a dominant role in determining their degree of aggregation: in the *N*-alkylanilide series the state of aggregation in THF at $< -50\,^{\circ}C$ decreases from mainly dimer for methyl, through a mixture of monomer and dimer for *n*-butyl, to exclusively monomers for isopropyl and *tert*-butyl[60]. The role of solvent is also striking: the entire series of salts studied (Table 37) exists exclusively as the dimers **134** in diethyl ether. The structure of

TABLE 37. Solution structures of the lithium amides **127** and **128**. Reprinted with permission from *J. Am. Chem. Soc.*, **109**, 5355 (1987). Copyright (1987) American Chemical Society

Anion (A)	Structure	Solvent (S)
127 ($R = CH_3$)	$ALiS_3$	$HMPT/Et_2O$; THF[a]
	$A_2Li_2S_2$	Et_2O
	$A_2Li_2S_4$	THF; $TMEDA/C_6H_6$
127 ($R = n$-Bu)	$ALiS_3$	THF
	$A_2Li_2S_4$	THF
127 ($R = Pr^i$)	$ALiS_3$	THF
	$A_2Li_2S_2$	Et_2O; Et_3N; THF[b]
	$A_2Li_2S_4$	THF[b]
127 ($R = Bu^t$)	$ALiS_2$	THF
	$ALiS_3$	THF
	$A_2Li_2S_2$	Et_2O
127 ($R = CH_3OCH_2Ch_2$)	$A_2Li_2S_4$	THF
128 ($R = H$; $n = 1$)	A_2Li_2	Et_2O; THF[a]
	$A_2Li_2S_4$	THF
128 ($R = CH_3$; $n = 1$)	$ALiS_3$	THF
	$A_2Li_2S_2$	THF[a]
	$A_2Li_2S_4$	THF
128 ($R = H$; $n = 2$)	$A_2Li_2S_2$	THF[a]
	$A_2Li_2S_4$	THF
128 ($R = CH_3$; $n = 2$)	$ALiS_3$	THF
	$A_2Li_2S_2$	THF[a]
	$A_2Li_2S_4$	THF

[a]Complete conversion to this species was not attained at the temperatures studied.
[b]At certain temperatures, coexistence of $A_2Li_2S_2$, $A_2Li_2S_4$, $ALiS_3$ and, possibly, $ALiS_2$ is observed.

lithium isopropylcyclohexylamide in THF solution has been recently studied using ^{6}Li, ^{13}C and ^{15}N NMR spectroscopy[304].

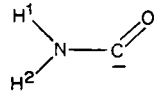
The systems studied by Jackman and Scartmouzos[301] exhibit a rich variety of dynamic processes which are accessible on the NMR time scale, and which include amine–amide exchange, phenyl ring rotation, interaggregate exchange and stereomutation in dimers. It is expected that kinetic studies of these processes will throw additional light on the electronic structure and reactivities of the various types of ion pairs and their aggregates[301].

Comparison of data in the crystal and in solutions is also useful. Thus, an interesting structural feature of compound **127** in the solid state is the participation of the aromatic system in an apparent π bonding of lithium across the 1 and 2 positions of the phenyl ring, although the essentially a character of the Li_2amine_2 framework is mantained[300]. On the other hand, the results of Table 36 and studies with ^{6}Li NMR suggest that, e.g. in *N-tert*-butylanilide, the π interaction is energetically unimportant[301]. Other mechanistically significant features can be deduced from the structural studies.

B. Theoretical Studies

As in the case of the acyl anions the thermodynamic stability of carbamoyl species was examined by molecular orbital calculations, especially by group Schleyer's group[305–307].

'*Ab-initio*'[308] molecular orbital calculations with complete geometry optimization using diffuse orbitals afford the following geometry description for the unsubstituted carbamoyl anion:



$CO = 1.219$ Å, $CN = 1.346$ Å, $NH^1 = 1.003$ Å, $NH^2 = 0.989$ Å
$< NCO = 113.0°$, $< CNH^1 = 120.8°$, $< CNH^2 = 119.8°$

The calculated energies for the above species and its isomer $NHCHO^-$ show that proton loss is 23.6 kcal mol^{-1} more favourable than from the (amide) aldehyde group. Comparison of the '*ab-initio*' calculated proton affinities (PA) of the anions indicates that the formamide (PA = 399.6) is a stronger acid than the acetaldehyde (PA = 398.3)[305].

Substituent effects have been examined with the methyl group. The MNDO calculated heat of formation (ΔH_f) of this anion is -23.3 kcal mol^{-1} and the proton affinity 383.6, while the same data for $(CH_3)_2NCO^-$ are -27.3 and 379.6, respectively.

The size of highly substituted carbamoyl anions, or of other intermediates usually proposed to explain the products found in the carbonylation of nitrogen–metal bonds, prevents '*ab-initio*' MO calculations. Recent MO calculations by all-valence electron SCF semi-empirical methods have been performed[309]. The optimized GEOMO–INDO calculation on lithium dimethylamide shows a strong deformation from standard values: both methyl groups are moved closer to the lithium atom ($< LiNC = 79°$; this value is close to $< LiNC = 76.5°$ found in the lowest acyclic isomeric form calculated from '*ab-initio*' procedures and it is also in good agreement with the X-ray structure of $[Li(NR_2)\cdot Et_2O]_2$ for both $R = (CH_3)_3Si$[292] and $PhCH_2$[293]). Lithium amides are known to form a variety of aggregates[310,311] (see Section III.A) and the dimer was also calculated. The optimized structure indicates that each lithium atom is mainly coordinated to both nitrogen atoms and to the other lithium (the four atoms are located at the vertices of a rhombus) and to a lesser extent to two carbon atoms. X-ray diffraction studies show that the lithium bis(trimethylsilyl)amide etherate exists as a dimer[312]; the nitrogen and lithium atoms are located at the opposite vertices of a rhombus and the lithium atom is tricoordinated (to both nitrogen and one oxygen atoms). '*Ab-initio*' calculations of $LiNH_2$

TABLE 38. Heats of formation of amide and carbamoyl anions by the MNDO method

Anion	ΔH_f° (kcal mol^{-1})	Anion	ΔH_f° (kcal mol^{-1})
Me_2N^- (135)	17.08	Me_2NCOCO^- (138)	−58.50
Me_2NCO^- (136)	−21.62	$Me_2NC\bar{O}{=}\bar{C}ONMe_2$ (139)	45.19
$Me_2NC(O^-)-NMe_2$ (137)	*a*	$Me_2NCOC^-(O^-)-CONMe_2$ (140)	−11.10

[a] No convergence attained.

oligomers performed by Schleyer and coworkers[307] show that the dimer is a planar Li_2N_2 array with the four hydrogens in a plane perpendicular to it.

GEOMO–INDO and MNDO semiempirical calculations for the carbamoyl anion show a planar structure similar to that found by '*ab-initio*' procedures. The INDO calculation localizes almost the whole extra charge on the carbonylic carbon atom while the MNDO distributes it between carbon, oxygen and nitrogen, giving a more carbene-like structure[309] (Table 38).

The geometries of other anions usually proposed in carbonylations of nitrogen–metal bonds were also calculated[309], GEOMO–INDO and MNDO gave the same structure for the glyoxalyl anion, which is shown in Figure 14a. For the other intermediates, MNDO and GEOMO–INDO (Figures 14b and 14c) structures are slightly different: extended

TABLE 39. Calculated total energies of neutral and anion species in a medium of $D = 5$ by CNDOSOL method

Species	Energy	Anion	Energy
CO	−23.96	H_2N^-	−13.03
NH_3	−13.38	H_2NCO^-	−37.99
		$H_2NC(O^-)=NH_2$	
H_2NCHO	−37.76	$H_2NC^-O=C^-ONH_2$	−52.37
Me_2NH	−30.28	H_2NCOCO^-	−62.75
Me_2NCHO	−54.61	$H_2NC(O^-)COC(O^-)-CONH_2$	−77.74
135	−30.85	$H_2NCOCH(O^-)-NH_2$	−102.88
136	−55.53	$H_2NCH(O^-)-CONH_2$	−52.11
137	−88.76	$H_2NCO-CH(O^-)-CONH_2$	−101.80
138	−80.23		

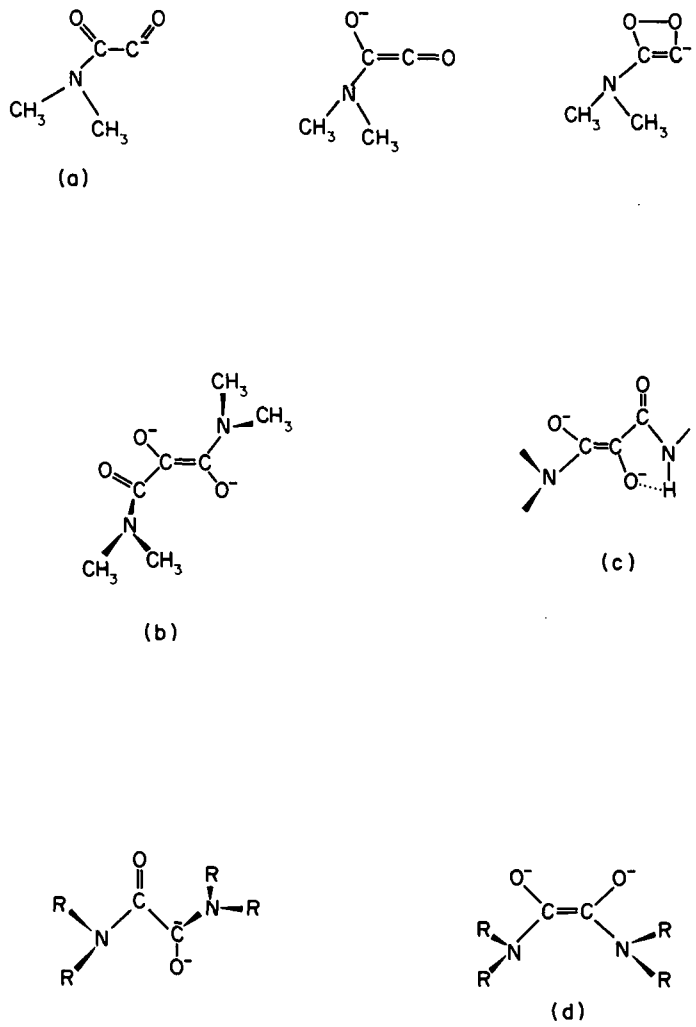
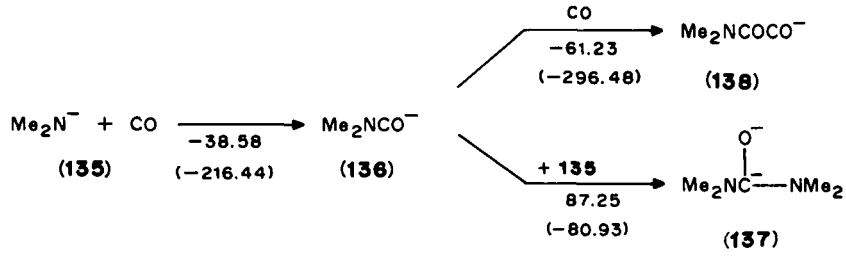


FIGURE 14. Structures of mono and dianions formed in carbonylation of lithium dialkyl amides.

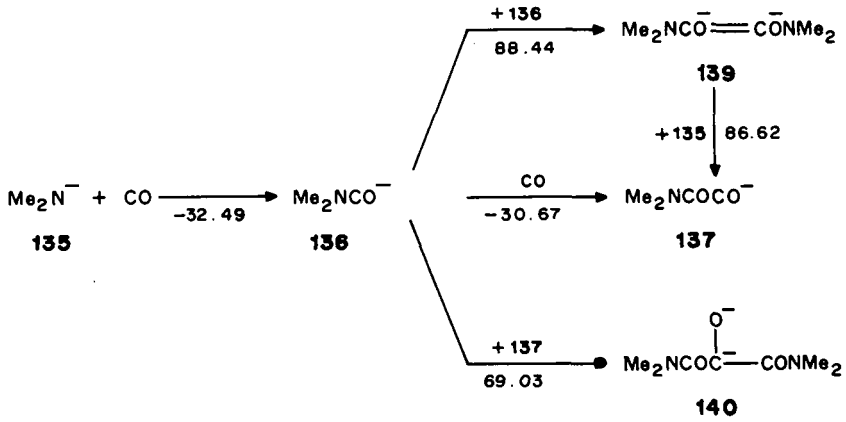
conjugation and a strong intramolecular hydrogen bond is observed in the structure in Figure 14c. Finally, the intermediate of Figure 14d gave the shown structure: the double bond and the four substituents are almost coplanar and the nodal planes containing each nitrogen lone pair are almost perpendicular to the double-bond plane. This geometry is preferred regardless of whether the amino group is substituted (by CH_3) or not. The rest of the intermediates calculated in Tables 38 and 39 and in Scheme 18 showed geometries very close to the standard starting geometries[309].

Nudelman and Perez[283,284] suggest a double carbonylation of the reagent to account for the formation of intermediates. This process has been found to be thermodynamically

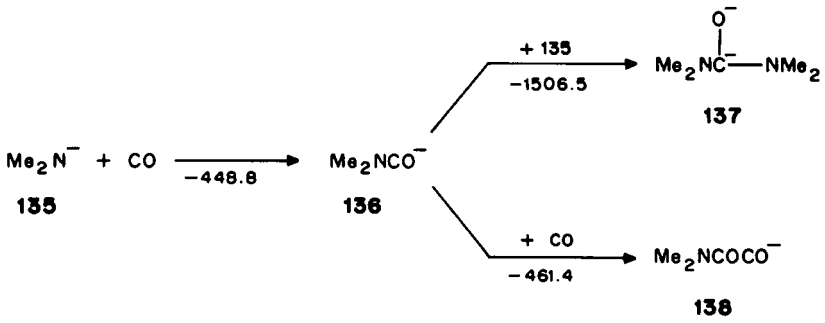


SCHEME 18

unfavourable for the case of M—R substrates[313,314], but in the case of amide compounds the values in Schemes 18 (MINDO method) and 19 (MNDO) show that the double carbonylation is a thermodynamically favourable process. INDO calculations (values in parentheses in Scheme 18) show a similar trend. The energies of the dianionic intermediates calculated by these procedures are overestimated. This high instability is expected in vacuum for compounds carrying two close negative charges. It could be partially solved by considering the interaction with some solvent molecules. This was done by introducing the solvent interaction terms into the Hamiltonian of a SCF–CNINDO program producing the CNDOSOL[315] method. Calculations were performed for several values of the dielectric constants in the range 1–50 with input geometries given by the GEOMO–INDO procedure. The results in Table 39 show the energies given by CNDOSOL for a value $D = 5$ (close to $D_{ether} = 4.3$). Although the values have no absolute meaning, they are useful to show the extra stabilization of the dianionic species provided by the solvent interaction. Scheme 20 shows the solvent effect of a medium of $D = 5$. Compared with the data of Scheme 18 (values in parentheses) the effect of the solvent is noticeable. Formation of the double carbonylation intermediates (which will produce dialkylglyoxylamide upon work-up) would have a higher energy of activation than formation of the dianionic intermediates (that will produce the dialkyl formamide), as is actually found experimentally (see Section III.C.1 and Table 41).



SCHEME 19



SCHEME 20

Nudelman and Perez[283] pointed out the influence of some acid–base equilibria between these intermediates and any proton donor present in the medium. Since data of the pK_a of the intermediates are not experimentally available, some equilibria were also calculated. The calculated equilibrium positions are consistent with what is expected on the basis of the acid–base properties of some of the compounds involved. The relative numbers obtained by calculations can be used to estimate the effect that the presence of proton donors may have on the course of the reaction (equations 174a–c).

$$H_2NCHO + \mathbf{135} \underset{}{\overset{-362.8}{\rightleftharpoons}} \mathbf{136} + NH_3 \qquad (174a)$$

$$H_2NCH(O^-)—NH_2 + \mathbf{135} \overset{-383.5}{\rightleftharpoons} \mathbf{138} + NH_3 \qquad (174b)$$

$$H_2NCOCH(O^-)—CONH_2 + \mathbf{135} \overset{-898.9}{\rightleftharpoons} \mathbf{140} + NH_3 \qquad (174c)$$

In fact, taking into account the data of Tables 38 and 39 and of the proton transfers indicated in equations 174a–c, it can be observed that protonation of the intermediate leading to tartronamide is a much more difficult process than protonation of the other intermediates. This could explain the spectacular effect observed in the carbonylation of lithium amides by the addition of free amines[283,284,317] which leads to the production of glyoxylamides in high yields (see Section III.C.1).

C. Carbonylation Reactions

1. *Organolithium amides*

In the reaction of lithium dialkylamides (**141**) with carbon monoxide[273–276,283,284,317–319] dialkylformamides have been isolated in variable yields, and this has been considered good evidence of the stability of the 'carbamoyl anions' (**142**, equation 175) formed and said to 'represent an unexplained "island of stability" in the area

$$R_2NLi + CO \longrightarrow R_2NC(=O)Li \qquad (175)$$

(**141**) (**142**)

of acyl anions'[275]. But some recently reported experimental facts cast doubt on the existence of free carbamoyllithium once the carbon monoxide absorption has ceased[283,284].

Structural determinations of the lithium carbamoyls are not possible at present, but even so it is useful to consider the structure of the reagents since there is now abundant evidence that aggregation plays an important role in determining the regioselectivities of these reactions. In addition, strong interactions between the anions and the lithium cation are evidently involved in the formation of the different products obtained under different reaction conditions.

Abundant effort has been recently devoted to the structural determinations of lithium amides. Bauer and Seebach[316] have determined, cryoscopically, the degrees of aggregation of several lithium amides in THF at $-108\,^{\circ}C$; they showed that most are dimers while others (e.g. lithium diisopropylamide) are a mixture of a dimer and monomer. Other structural studies in crystals and in solution have been summarized in Section III.A.

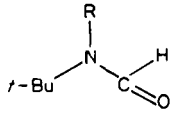
One of the earlier reports of carbon monoxide insertion into N—Li is the reaction of lithium dimethylamide in heptane at $0\,^{\circ}C$ in excess of carbon monoxide[319]. The reaction is said to produce dimethylformamide (among other products) but no yield is reported.

The first intermediate formed in the reaction is the carbamoyllithium which, in the case of bulky amines, could be trapped by the addition of electrophiles[276] (equation 176). The reaction was carried out in benzene–ether at $50\,^{\circ}C$ and overall yields reached 55% in some cases.

$$t\text{-BuNHLi} + CO \rightarrow t\text{-BuNHCOLi} \xrightarrow[-ClLi]{t\text{-Bu}_3MCl} t\text{-BuNHCOM}t\text{-Bu}_3 \qquad (176)$$

$$M = Si,\quad Ge,\quad Sn$$

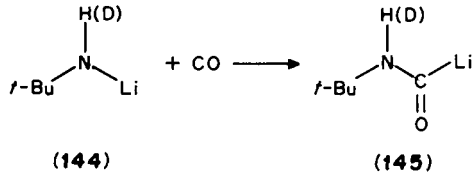
Further work on this reaction by Rautenstrauch and Joyeux[320] has proved that the products did not have the structure shown in equation 176 but most likely are of type **143**.



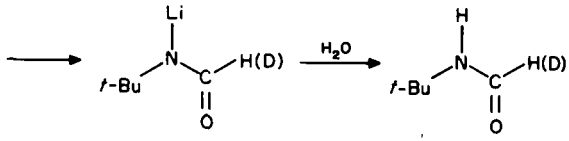
(143)

$R = SiMe_3,\ GeMe_3,\ PbMe_3$

In fact, reaction of the lithium *tert*-butylamide with CO in 1,2-dimethoxyethane (DME)/THF/hexane at *ca* $-75\,^{\circ}C$ and subsequent hydrolysis affords *N-tert*-butylformamide in variable yields (30–50%) (equation 177).



(144) **(145)**



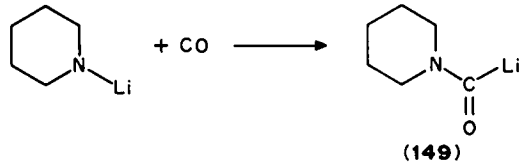
(146) **(147)**

(177)

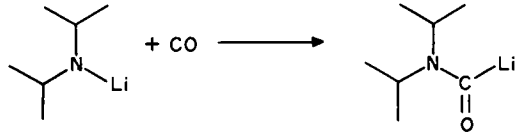
Hydrolysis with D_2O (instead of H_2O) and work-up with H_2O leads to unlabelled **147**. Analogous carbonylation of the labelled amide [D_1]-**144**-prepared from labelled *tert*-butylamide ([D_2]-**148**) and hydrolysis yields the labelled formamide [D_1]-**147** (91%) and a small amount of **147** (9%; yield of [D_1]-**147** + **147** *ca* 15%). This shows that the carbamoyllithium **145** first formed rearranges rapidly to give the *N*-lithioformamide **146**.

On the basis of the pK_a values of **145** [pK_a of RN*H*CHO *ca* 18[321], and of R_2NCHO *ca* 38[322]], this result can be generalized; it can be expected that the carbonylation of lithium monoalkylamides should afford *N*-lithio(alkyl)formamides[320].

The carbonylation of lithium dialkylamides has been more thoroughly studied than that of lithium monoalkylamides because of the utility and versatility as intermediates of the former. Thus, passing carbon monoxide into a *ca* 0.6 M solution of lithium piperidide in DME/THF/hexane at *ca* − 75 °C affords 20–30% of the piperidyl carboxaldehyde (**149**), among other products (equation 178). The carbamoyl lithium intermediate could, apparently, be trapped by addition of cyclohexanone or methyl iodide and stirring for 1–3 h prior to hydrolysis. Similar results have been reported for the reaction of lithium diisopropyl amide (equation 179)[275].

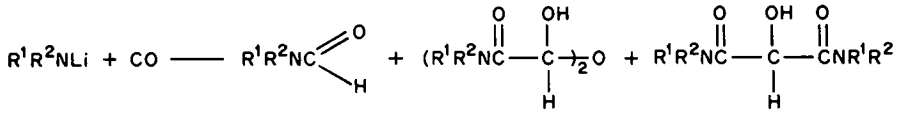


(149) (178)



(179)

Significant improvement for the application of this reaction in synthesis[323] has been found by Nudelman and coworkers[283,284,317]. A considerable increase in the yield of the dialkylformamide can be obtained by the addition of lithium salts (Table 40), or by running the reaction in THF at low temperatures (Table 41)[284], and the reaction can also be useful for the synthesis of more complex compounds (**151** and **152**) (equation 180).



(150) (151) (152)

(a) $R^1=R^2=c\text{-}C_6H_{11}$; (b) $R^1=R^2=n\text{-}C_4H_9$; (c) $R^1=R^2=n\text{-}C_5H_{11}$; (180)

(d) $R^1, R^2=$  ; (e) $R^1=i\text{-}C_3H_7$, $R^2=c\text{-}C_6H_{11}$

A detailed examination of the mechanism of the reaction allows one to find conditions which lead to the production of any of the three products shown in equation 180 in good to excellent yields. Assuming that an equilibrium could exist between the first intermediate, the carbamoyl anion **141** and any free amine present in the system (equation 181), the

TABLE 40. Reaction of lithium dibutylamide in THF at 0 °C. Effects of amine, lithium salts and alkyl halides[a]. Reproduced with permission from *J. Org. Chem.*, **53**, 409 (1988)

Reaction media	Yield		
	150	**151**	**152**
THF	13.2	79.1	
THF–Bu_2NH (3:1)	27.7	69.1	
THF–LiCl[b]	32.3	12.2	28.3
THF–LiBr[b]	5.7	43.4	33.0
THF–BuOLi[c]	36.4	35.6	3.5
THF–BuCl[d]	5.9	57.8	26.9
THF–BuCl[e]	56.9	41.8	
THF–BuBr[f]	4.4	15.8	
THF–BuBr[g]	15.0	39.4	6.4

[a] Yields represent percent conversion.
[b] 500 mg of Li salt. LiBr is completely dissolved, LiCl remains partially solid.
[c] 200 mg of LiBuO.
[d] Dibutylvaleramide (DBVA), 5.3%, also obtained.
[e] Tributylamine (TBA), 1.4%, also obtained; reaction at −60 °C.
[f] TBA, 69.4%, also obtained.
[g] TBA, 23.6% and DBVA, 15.0% also obtained; reaction at −60 °C.

TABLE 41. Reaction of lithium dibutylamide with carbon monoxide in THF. Effect of the reaction temperature and stirring[a]. Reproduced with permission from *J. Org. Chem.*, **53**, 409 (1988)

Variable	Yield			Reaction half-time (min)
	150	**151**	**152**	
Temp (°C)				
50[b]	3.1	83.3		1.90
25[b]	7.4	72.4		1.92
−40	8.0	63.8	23.0	3.38
−78	32.5	47.8	17.3	6.84
−95	82.7	17.3		11.00
stirring[c]				
vigorous	17.2	71.6		
feeble	32.5	64.2	0.3	
nil	38.7	45.0	0.6	

[a] Yields represent percent conversion.
[b] In the reactions at 25 and 50 °C dibutylglycolamide and tetrabutylurea (5–10%) were also obtained.
[c] At 0 °C.

influence of free amine was surveyed. (Similar equilibrium has also been suggested between lithium diisopropylamide and diisopropylformamide[274].)

$$R_2NC(=O)Li + R^1R^2NH \rightleftarrows HCONR^1R^2 + R^1R^2NLi \quad (181)$$

It can be observed in Table 42 that while the yield of dibutylformamide is almost

TABLE 42. Reaction of lithium dibutylamide with carbon monoxide in THF at 0 °C. Effect of the [amine]/[amide] ratio[a]. Reproduced with permission from *J. Org. Chem.*, **53**, 409 (1988)

		Yield		
Amine	[Amine]/[$LiNBu_2$]	**150**	**151**	**152**
Bu_2NH	0.17		14.7	85.3
	0.21	3.8	14.6	81.6
	0.25	5.3	25.6	69.1
	4.29	3.9	22.7	73.4
	0.42	5.6	41.4	53.0
	0.47	5.1	52.4	42.5
	0.76	14.8	85.2	
	0.78	6.0	94.0	
	0.97	6.8	78.4	14.8
	1.10	9.4	83.2	7.4
Bu_3N[b]	0.30	10.9	14.4	74.8
	1.15	13.7	14.0	72.2
	1.24	9.9	16.3	73.8

[a] Yields represent percent conversion to the three major products.
[b] [$LiNBu_2$] = 1 M; [$HNBu_2$]/[$LiNBu_2$] = 0.2.

insensitive to the amount of amine present in the reaction mixture, the production of compounds **151** and **152** is strongly influenced. A higher yield of tetrabutyltartronamide **152b** is obtained working at very low amine concentration, while yields higher than 80% of dibutylglyoxylamide (**151b**) are obtained at relatively high [amine]/[amide] ratios. A plot of the yields of **151b** and **152b** against [amine]/[amide] (not shown) indicates that formation of **151b** increases at the expense of **152b**, suggesting a common intermediate[283].

Optimization of the reaction conditions for the production of compounds **151** shown that quantitative production of dibutylglyoxylamide is achieved in a 1:1 THF–HMPT mixture (Table 43a). Non-optimized yields of other dialkylglyoxylamides are shown in

TABLE 43a. Reaction of lithium dibutylamide and carbon monoxide at 0 °C. Solvent effects[a]. Reproduced with permission from *J. Org. Chem.*, **53**, 409 (1988)

	Yield		
Solvent	**150**	**151**	**152**
hexane	5.6	46.8	45.0
hexane–THF (3.5:0.5)	7.8	42.5	45.0
Et_2O	16.9	67.0	12.7
hexane–THF (1:1)	14.8	78.9	
THF	12.4	79.4	
THF–DABCO (12:1)	1.9	45.3	48.3
THF–HMPT (5:1)		89.6	7.5
THF–HMPT 4:0.8)		89.6	7.0
THF–HMPT (4:1.2)		90.0	5.3
THF–HMPT (4:2.0)		97.0	< 2.0
THF–HMPT (4:4.0)		100.0	

[a] Yields represent percent conversion.

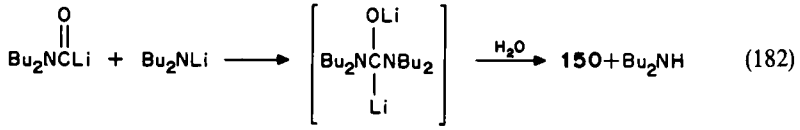
TABLE 43b. Reaction of lithium alkylamides with carbon monoxide at 0 °C[a]. Reproduced with permission from *J. Org. Chem.*, **53**, 409 (1988)

Amide	Solvent	Yield			$t_{1/2}$ (min)
		R^1R^2NCOH	$(R^1R^2NC(=O)C(OH)H)_2O$	$(R^1R^2NC(=O))_2CHOH$	
$LiN(n\text{-}C_5H_{11})_2$	ligroine–THF 1:2)	19.0	68.5		5.0
	THF	7.7	79.2		2.3
	THF–HMPT (1:2)	3.7	89.9		1.0
$LiN(CH_2)_2OCH_2CH_2$	THF	80.0	18.9		1.0
	THF–HMPT (1:1)	16.3	81.1		0.4
LiN-*i*-Pr(c-C_6H_{11})	ligroine	38.5	27.5	29.0	15.5
$LiN(n\text{-}C_4H_9)_2$	hexane	5.6	46.8	45.0	6.0
	THF–HMPT (1:1)		100.0		1.5
$LiN(c\text{-}C_6H_{11})_2$	hexane	24.5	10.0	45.0	19.5
	THF–HMPT (1:1)	7.0	85.5	1.0	4.7

[a]Yields represent percent conversion.

Table 43b. Reaction times are short (1–20 min), the reaction conditions are mild (0 °C, 1 atm carbon monoxide pressure) and the isolation procedures are simple.

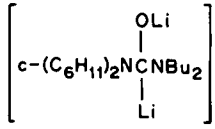
The formation of the carbamoyl anion at the onset of the reaction has been proved by the isolation of dibutylvaleramide (15%) when the reaction is carried out in the presence of butyl bromide at low temperature[283]. Attempts to trap the carbamoyl anion intermediate once the carbon monoxide absorption is complete have been unsuccessful, and evidence indicates that the carbamoyl anion is not stable under the reaction conditions[283,318], as was formerly suggested[275]. On the basis of the accumulated evidence, Nudelman and Perez[283] proposed an alternative route for the formation of compounds **150** (equation 182).



(182)

(153)

Formation of intermediate **153** was proved by two different pathways that also constitute useful synthetic routes. When dicyclohexylformamide is treated with lithium dibutylamide, the formation of a mixed intermediate of structure **154** was detected[318]. Similar results were obtained when dibutylformamide was treated with lithium dicyclohexylamide[318].



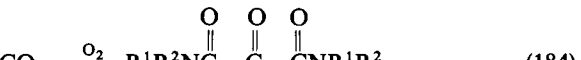
(154)

Further evidence for the existence of intermediate **153** in the carbonylation of lithium dialkylamides is provided by oxidation studies. If the reaction is carried out under conditions to produce mainly compounds **151** and the reaction mixtures is treated with oxygen prior to the regular work-up, tetraalkyl ureas **155** are obtained in the same yield as expected for compound **151** (equation 183). The formation of compound **155** is good evidence for the existence of intermediate **153** and the route discussed is a suitable method for the preparation of these compounds.

(183)

(155)

Carbonylation of lithium dialkylamides can be also used for the synthesis of tetrabutylketomalonamide in excellent yields[283,318]. Exposing a 10% lithium amide solution in THF to carbon monoxide (*ca* 900 mm Hg) at 0 °C for a short time (the reaction is over in 1–15 min), quenching with oxygen and working-up in the usual way provides good to excellent yields of tetraalkylketomalonamides **156** (equation 184)[284,318].

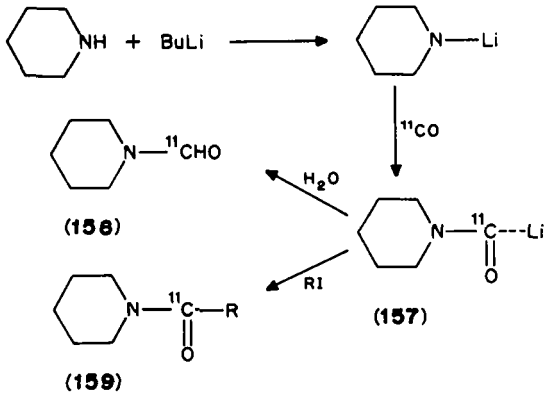


(184)

(156)

In summary, carbonylation of lithium dialkylamides can be used to prepare dialkylformamides, dialkylglyoxylamides, tetralkyltartronamides, tetraalkylureas and tetraalkylketomalonamides. Although the carbamoyl anion is the first intermediate formed in these reactions, evidence has been accumulated to prove that the carbamoyl anion is not stable under the reaction conditions and alkyl formamides are formed by hydrolysis of a second precursor, the dilithium tetralkylurea dianion.

Kilbourn and collaborators[279] applied the reaction to the synthesis of carbon-11 labelled amides, in a single step and a single reaction vessel. The synthesis has the novel aspect of *in situ* forming a highly reactive radiolabelled intermediate, which could in turn be converted into other products. The advantage of this method over other previously reported ones is the need for only trace amounts of ^{11}CO and very short reaction times (5–7 min). Bubbling a stream of ^{11}CO in helium into a cold (−78 °C) solution of lithium piperidide in THF/DME resulted in the trapping of 10–20% of the ^{11}C activity, presumably in the form of the unstable acyl anion salt **157** (Scheme 21).



SCHEME 21

Quenching of this intermediate with water or a solution of alkyl iodide resulted in the formation of the formamide **158** and the amide **159**, respectively. In this manner, Kilbourn and coworkers[279] prepared [^{11}C]*N*-formylpiperidine (14%), [^{11}C]*N*-acetylpiperidine (12%) and [^{11}C]*N*-propionylpiperidine (15%). These amides can be readily reduced to the corresponding ^{11}C-amines; thus, [^{11}C]*N*-methylpiperidine in 5% overall yield was prepared by diborane reduction of the formamide **158**. As has been mentioned above, acyl anions such as **157** will also add to carbonyl compounds, providing a method for the synthesis of ^{11}C labelled α-hydroxycarboxamides. These results suggest that carbonylation reactions using trace amounts of carbon monoxide may provide the means to label numerous types of compounds with isotopes of carbon (^{11}C, ^{13}C, ^{14}C)[279].

Finally, these '*in-situ*' formed lithium amides could be successfully used as a variant of a recently developed method for the preparation of enaminones, based on the use of lithium(triphenylsilyl)acetylide[324].

2. *Organocopper amides*

Although copper is not a main group metal, the reaction of copper amide derivatives with CO is included in this chapter because of its connection with the carbonylation of N—Li bonds. (Section III.C.1). In fact, direct carbonylation of the N—Cu bond of copper

amides has no synthetic interest. Insertion reactions of carbon monoxide into several copper complexes involving, among others, Cu—N bonds have been reported to cause the coupling of the ligands[325-328] and there is no precedent for the intermediate formation of a stable CO-incorporated copper complex which can be utilized for the further organic reactions[329]. Furthermore, direct carbonylation of copper diethylamide could not be achieved[329] and this compound was found to be inert toward carbon monoxide at room temperature.

Nevertheless, Saegusa and collaborators[329] have recently developed a useful carbamoylating reagent by the combination of copper and lithium amides. The reaction of CuCl and lithium diethylamide in a mixed solvent of THF and HMPA (4:1) at $-20\,^{\circ}C$ produces $CuNEt_2$ which, with an additional mole of lithium diethyl amide, forms a homogeneous solution of lithium bis(*N*,*N*-diethyl)cuprate **161**. This reagent readily absorbed carbon monoxide under ordinary pressure at room temperature, and treatment with allyl bromide gave *N*,*N*-diethyl-3-butenamide (**163**) in 45% yield. These results may be reasonably interpreted by the intermediacy of bis(*N*,*N*-diethylcarbamoyl)cuprate **162** generated by carbon monoxide insertion into lithium bis(*N*,*N*-diethylamino)cuprate (equation 185).

$$CuCl + LiNEt_2 \longrightarrow$$

$$CuNEt_2 \xrightarrow{LiNEt_2} (Et_2N)_2CuLi \xrightarrow{CO} (Et_2NCO)_2CuLi \xrightarrow{Br} CONEt_2$$

(160) **(161)** **(162)** **(163)** (185)

The same reaction under a CO pressure of $50\,kg\,cm^{-2}$ produced **163** in 76% yield. Similarly, lithium bis(carbamoyl)cuprate derived from morpholine gave the corresponding 3-butenamide. Formation of the corresponding carbamoylcopper complexes derived from butylamine and aniline was examined, but the results were not as satisfactory as with **162** (Table 44).

The low yields obtained with monosubstituted amides may be due to a rearrangement of the lithium bis(*N*-monosubstituted carbamoyl)cuprate intermediate, similar to that reported for the lithium monoalkylcarbamoyl reagents mentioned in Section III.C.1[320].

The results of the reactions of **162** with various organic halides are summarized in Table 45. The reactions are carried out under relatively mild conditions and the yields of amides are reasonably good. The reaction of **162** with acid halide provides a convenient method for the synthesis of α-keto acid, for which existing methods are often laborious[329].

The lithium bis(*N*,*N*-diethylcarbamoyl)cuprate underwent conjugate addition to methyl vinyl ketone (mvk). An equimolar reaction of **162** with mvk in THF–HMPA (4:1) at $-78\,^{\circ}C$ gave *N*,*N*-diethyllevulinamide in 38% yield based on mvk. Use of an excess of **162** with mvk (4:1) gave the adduct in 78% yield[329]. This is an example of direct introduction of a carbonyl group by the conjugate addition of lithium organocuprate. The reaction of **162** with cyclohexenone, however, was not successful[329]. The reactivity of **162** could be increased by addition of a transition metal catalyst. Thus, the carbamoylation of β-bromostyrene which did not take place with **162** could be achieved in the presence of 10 mol% $Ni(OAc)_2$ to yield 51% of *N*,*N*-diethylcinnamide based on $LiNEt_2$. The transmetallation reaction using **162** may be expected to enlarge the scope of these carbamoylation reactions[329].

Finally, a convenient use of the *N*,*N*-disubstituted lithium bis(carbamoyl)cuprate, **164**, for the one-pot conversion of amines to formamides, oxamides, carbamates and oxamic acids has been recently published[330]. Most of the efforts of this study have been

TABLE 44. Formations of lithium bis(carbamoyl)cuprates and their reactions with allyl bromide:

$$(R^1R^2N)_2CuLi \xrightarrow[THF\text{-}HMPA]{CO} (R^1R^2NCO)_2CuLi \xrightarrow[rt,\,2h]{Br^b} \text{allyl-}CONR^1R^2$$

Reproduced with permission from *J. Org. Chem.*, **44**, 3735 (1979)

R^1	R^2	formations of $(R^1R^2NCO)_2CuLi$ CO, kg/cm²	temp, °C	time, h	% Yield of allyl-$CONR^1R^2$[a]
Et	Et	1	rt	12	45
Et	Et	50	rt	12	76
Et	Et	1[c]	60	2	0
Et	Et	50	60	2	64
Et	Et	50	80	1.5	67
Et	Et	50	100	1.5	39
$-(CH_2)_2O(CH_2)_2-$		1	rt	12	47
$-(CH_2)_2O(CH_2)_2-$		50	rt	12	93
n-Bu	H	50	rt	12	22
Ph	H	50	rt	12	28

[a]The yield was based on $LiNR^1R^2$.
[b]The reaction of allyl bromide with lithium bis(carbamoyl)cuprate generated under pressure of 50 kg/cm^{-2} was carried out after the purge of the compressed CO gas.
[c]**162** prepared under CO pressure of 50 cm^3 at room temperature was heated at 60 °C after the purge of the compressed CO gas.

TABLE 45. Reactions of **162** with organic halides[d]:

$$(Et_2NCO)_2CuLi \xrightarrow{RX} RCONEt_2$$

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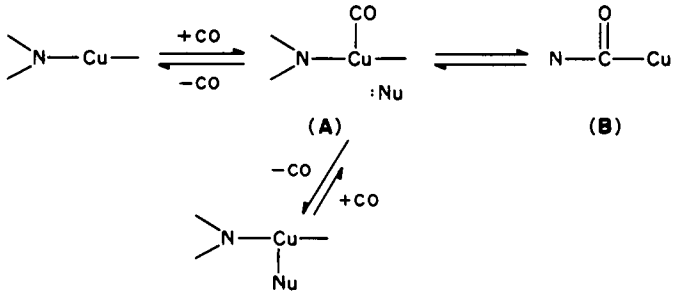
RX	Temp (°C)[b]	Time (h)	% $RCONEt_2$[a]
MeI	80	1	10
PhI	80	2	49
PhCH=CHBr	60	0.5	trace
MeCOBr	−78 → rt[c]	1 → 0.5[c]	70
MeCOBr	80	1	65
PhCOBr	−78 → rt[c]	1 → 0.5[c]	64
PhCOBr	60	1	74
PhCOCl	−78 → rt[c]	1 → 0.5[c]	23
PhCOCl	80	0.5	61
EtOCOCl	60	1	36

[a]The yield was based on $LiNEt_2$.
[b]The reaction above room temperature was carried out under CO pressure of 60 kg/cm².
[c]After the reaction of **162** with acid halide at −78 °C for 1 h, the resulting mixture was allowed to stand at room temperature for 0.5 h.
[d]In runs 5–9, amides, $RNEt_2$ were formed as by-products in 10–20% yields.

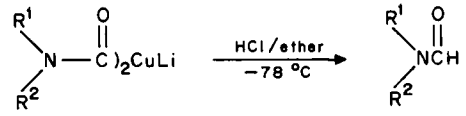
concentrated on the search for conditions to stabilize the complex **164**, which was found to be prone to carbon monoxide liberation in further reactions.

From solvent effect studies (the observed CO evolution follows the order HMPA > THF > DME > diethyleter) it was suggested that the equilibrium lies between the carbamoyl complex **B** and the CO-coordinated copper complex **A** as shown in Scheme 22, and nucleophilic attack of electron donor molecules (represented by 'Nu' in Scheme 22)



SCHEME 22

suppresses the coordination of CO to the copper atom and facilitates the CO liberation from the CO-containing copper complex. Successful high-yield conversions of **164** to formamides **165**, which were achieved by protolysis with HCl in dry ether (equation 186), support the above suggestion.



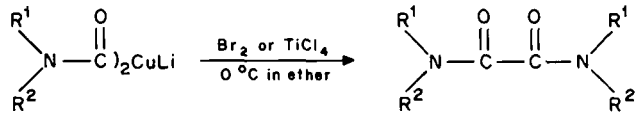
(186)

(164) (165)

R^1	R^2	
Me	Ph	91%
Et	*p*-ClC_6H_4	98%
Me	CH_2Ph	89%
Et	C_2H_5	85%

Oxidations of intermediate **164** with bromine or titanium tetrachloride are suitable procedures for the high-yield conversions of **164** to the corresponding oxamides **166** (equation 187); in addition to the high oxamide yields, the reaction conditions (0 °C, 1 atm CO) are milder than those previously reported for carbonylation of amines or metal amides to form oxamides[329,331].

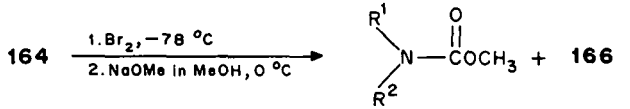
The formation of oxamides may be partly attributable to the reaction of carbamoyl bromides, which were formed by bromination of **164**[331]. Actually, the carbamoylcopper complexes **164** underwent bromination by bromine to give the corresponding carbamoyl bromides. Thus, facile conversions of **164** to methyl carbamates could be achieved by subsequent treatment of the reaction mixtures with NaOMe (equation 188).



(187)

(164) (166)

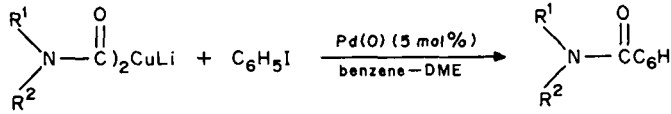
R^1	R^2	
Me	Ph	88–95%
Et	*p*-ClC_6H_4	79–91%
Me	CH_2Ph	75–87%
Et	Et	75–89%



(188)

(167)

Catalysis by a Pd(0)–PPh_3 complex was observed in the reactions carried out in benzene. The palladium-catalyzed coupling reaction with iodobenzene in benzene containing a small amount (7%) of DME as a cosolvent was found to produce the coupled product in good yields (equation 189)[331].



(189)

R^1	R^2	
Me	Ph	71%
Et	*p*-C_6H_4	67%
i-Pr	*i*-Pr	49%
Et	Et	58%

Closely related to these reactions is the palladium-catalyzed double carbonylation of aryl halides in the presence of amines (equation 190) to give mainly α-ketoamides, **168**, and amides in a lesser extent.

$$ArX + 2HNR'_2 + 2CO \xrightarrow{[Pd]} ArCOCONR'_2 + R'_2NH_2X \qquad (190)$$

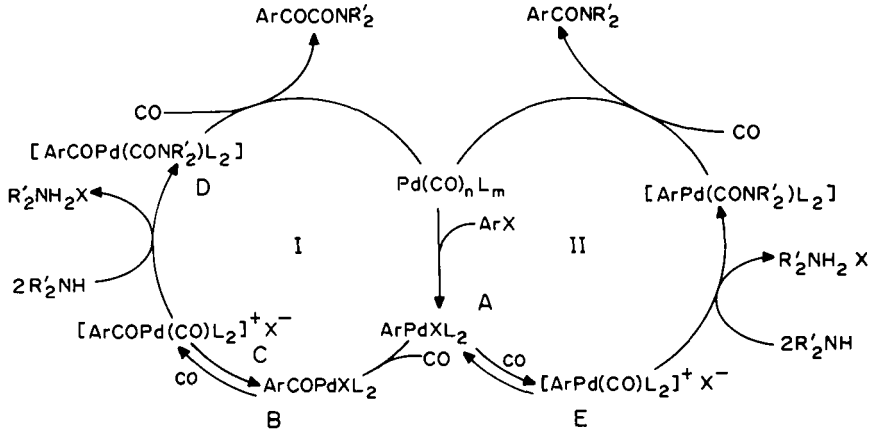
(168)

Although a complete description of the extensive research recently carried out on these reactions, especially by the group of Yamamoto[332–335], lies outside the scope of this chapter, a brief discussion of the mechanistic conclusions will help in understanding the role of the catalyst in the above-discussed reactions, as well as in the transition-metal

catalyzed insertion reactions of carbon monoxide into carbon–metal bonds, discussed in Section II.C.

Yamamoto and coworkers[335] have found that the total yield as well as the product ratio are dependent on the nature of the catalyst. Several other factors including the substrate, amine, CO pressure, solvent and temperature were examined[335]. By taking into account their extensive experimental evidence, the authors were able to propose a mechanism represented in Scheme 23 to account for the double carbonylation and monocarbonylation of aryl halides catalyzed by the palladium-based catalysts[335].

Scheme 23 consists of two catalytic cycles: cycle I produces an α-ketoamide whereas cycle II yields amine. The first step in the catalytic reactions is the oxidative addition of aryl halide to zero-valent palladium species to give the arylpalladium complex A, which is the common intermediate for both cycles. When a very reactive amine such as the sterically less demanding and nucleophilic pyrrolidine and piperidine is used under CO pressure, the amine attacks the coordinated CO in arylcarbonylpalladium species E. The reaction gives an arylcarbamoyl species F, which reductively eliminates amide to generate the zero-valent palladium species as the carrier of the catalytic cycles. When a less reactive amine is employed, the arylpalladium complex A undergoes the CO insertion before the CO ligand in E is attacked by the amine, to give the aroylpalladium species B. Coordination of CO to give an ionic species C followed by attack of amine on the coordinated CO ligand gives an aroylcarbamoyl species D, which liberates α-keto amide on reductive elimination. The regenerated zero-valent palladium species further carries the catalytic cycles. Since the rate of CO insertion would not vary very much depending on the nature of the amine, the selectivity for α-ketoamide formation is predominantly determined by the reactivity of amine toward the CO-coordinated arylpalladium complex in agreement with the experimental results.

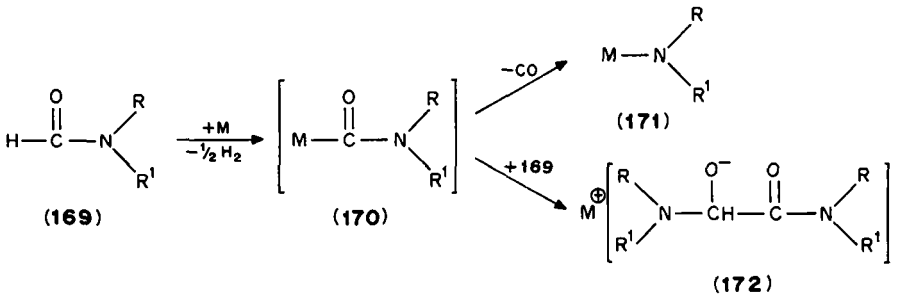


SCHEME 23. Proposed mechanism for the catalytic double carbonylation and monocarbonylation of aryl halides catalyzed by *tert*-phosphine-coordinated palladium complexes

3. *Organosodium and potassium amides*

Direct carbonylations of sodium or potassium alkylamides have no synthetic value. The reaction of *N*, *N*-disubstituted formamides (**169**) with alkali metals in inert solvents to form glyoxylamides derivatives **172** (equation 190a) can be considered to be an indirect analogue of equation 180.

The alkali salt **170** of the formamide first formed partially decomposes into alkali



(190a)

dialkylamide **171** and partly forms the alkali salt **172** of the substituted glyoxylamide. The reported yields are shown in Table 46[319b].

Since the yields of glyoxylamides obtained through the more simple carbonylation of lithium amides (see Section III.C.1) are higher and the reaction conditions smoother this procedure is synthetically less appealing.

4. *Organomagnesium amides*

The insertion of carbon monoxide into the nitrogen–metal bond of bromomagnesium alkyl- and aryl-amides using pentacarbonyliron has been reported[336]. Although this is not a direct carbonylation using carbon monoxide, it is included here since it represents an interesting and facile synthesis of unsymmetrical ureas derived from nitro compounds (equation 191) for which few examples have been reported before[337]. Bromomagnesium alkyl- or aryl-amides are prepared *in situ* by the reaction of amines with butylmagnesium bromide in THF, and allowed to react with pentacarbonyl iron for 30 min at 0 °C under argon, when the nitro compound is injected. Good to excellent yields of the *N,N'*-substituted ureas are obtained (see Table 47).

Although the mechanism is obscure, the reaction is assumed to occur through the intermediacy of carbamoyltetracarbonylferrates (**173**) formed from the bromomagnesium amides and pentacarbonyliron (equation 192). The intermediate would react with the nitro compounds in a similar manner to acylcarbonylferrates[338].

$$R^1NHMgBr + Fe(CO)_5 \xrightarrow{R^2NO_2} \xrightarrow{H^+} R^1NHCONHR^2 \qquad (191)$$

TABLE 46. Synthesis of *N,N*-disubstituted glyoxylamides[a]

R	R^1	Temp. (°C)	Solvent	M	Glyoxylamides yield (%)
CH_3	CH_3	35	Ether	Na	21
CH_3	CH_3	80	Benzene	Na	37
C_2H_5	C_2H_5	80	Benzene	Na	3,4
C_6H_5	CH_3	80	Benzene	Na	34
CH_3	CH_3	35	Ether	Li	34
CH_3	CH_3	80	Benzene	K	42

[a]Isolated as 2,4-dinitrophenylhydrazones.

TABLE 47. Synthesis of substituted ureas

Amide $R^1NHMgBr$ R^1	Nitro-compound R^2NO_2 R^2	% Yield of urea[a] $R^1NHCONHR^2$
Ph	Ph	99
Ph	*p*-Tol	71
Ph	*p*-Ar	80
Ph	*p*-ClC_6H_4	92
$Me[CH_2]_{11}$	Ph	42
p-Tol	$Me[CH_2]_2$	50
Ph	c-Hex	60
c-Hex	Ph	72
c-Hex	c-Hex	55

[a]Isolated yields based on the amount of nitro compound.

$$RNHMgBr + Fe(CO)_5 \rightarrow [RNHCOFe(CO)_4]^-[MgBr] \quad (192)$$

(173)

Treatment of a mixture of bromomagnesium anilide and pentacarbonyliron with excess of methyl iodide gave acetanilide [60% yield based on an amount of $Fe(CO)_5$], strongly suggesting the formation of phenylcarbamoyl ferrate as an intermediate[338]. This conclusion is reached by analogy with the treatment of acyl tetracarbonylferrates with alkyl iodide which renders the corresponding ketones[339].

A similar reagent has been used to transform nitro compounds into carboxylic amides in excellent yields[338]; the ferrates act as both reducing and acylating reagents in this reaction (equation 193).

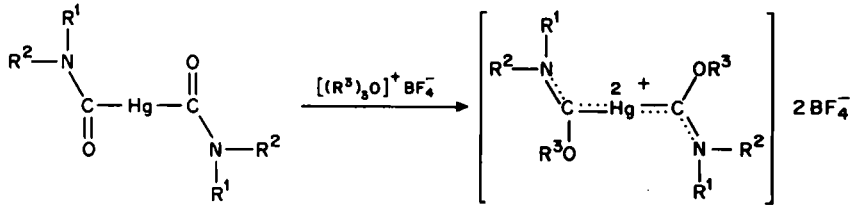
$$R^1MgX \xrightarrow{Fe(CO)_5} R^1COFe(CO)_4^- + R^2NO_2 \xrightarrow{H_2O} R^1CONHR^2 \quad (193)$$

Addition of a Grignard reagent to pentacarbonyliron produces the acyl ferrate which is treated *'in situ'* with an equimolar amount of the nitro compound. The facility of the procedure, mildness of conditions and the excellent yields make this a useful amide synthesis from nitro compounds.

A general methodology, closely related to the synthons shown in this and the previous section, has been recently developed for the synthesis of optically pure α-amino acids[340]. The method involves the Cu(I)-catalyzed Grignard (RMgCl) addition to both mono- and di-N-protected serine β-lactones to afford N-protected amino acids in fair to excellent yields with 99–100% retention of optical purity[340]. The procedure produces derivatives which are suitable for direct incorporation into peptides or can be deprotected in a single step to the free amino acids.

5. *Organomercury amides*

Several years ago Schollkopf and Gerhardt[341] reported the preparation of biscarbamoylmercury compounds, **174**, as stable, crystalline compounds. Treatment of the methylene chloride solutions of compounds **174** with 2 mol equivalents of trimethyl- or triethyl-oxonium fluoroborate gave, after work-up, crystalline compounds formulated as adducts of alkoxy (dialkylamino)carbenes with Hg^{2+} ions **175** (equation 194).



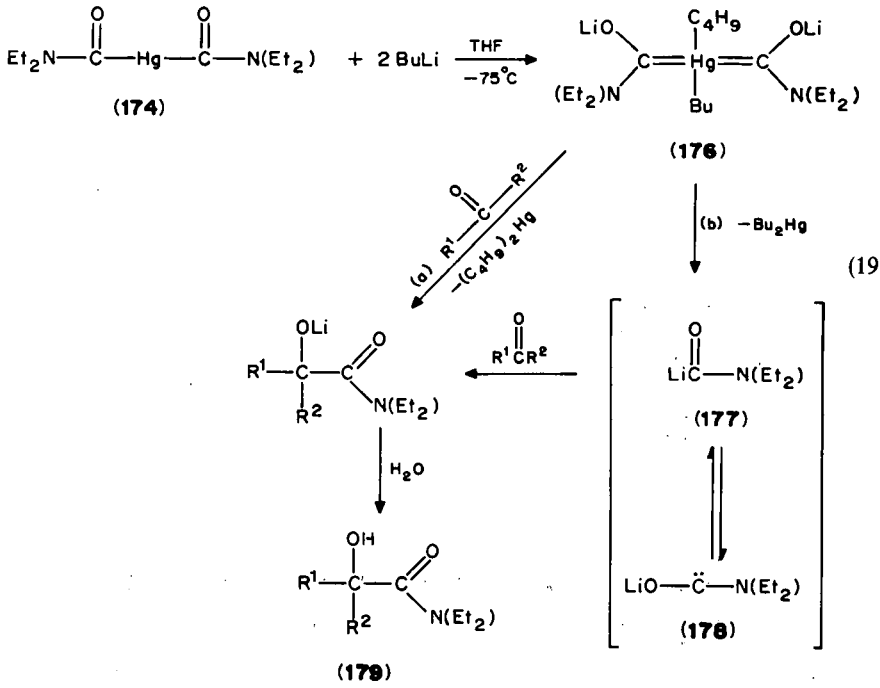
(174) (175)

(194)

The structure of **175** is based on satisfactory elemental analysis, NMR spectra in good agreement with the proposed structure and on the reaction of the complexes with hydroxide ions. Treatment of **175** ($R^1 = R^2 = R^3 = Et$) with aqueous sodium hydroxide led to mercury, *N*, *N*-diethylurethane, diethylformamide and ethanol[342]. The reaction can be formulated as attack by the base on one of the two carbon atoms.

Although it is not yet clear how much weight attaches to the limiting structure with a mercury–carbon double bond, on the basis of other organometallic carbamoyl compounds whose structures have been well determined, description of compounds **175** as metal–carbene adducts seems reasonably justified.

Schollkopf and Gerhardt[343] used compounds **174** for the preparation of α-hydroxy-*N*, *N*-dialkylcarboxamides **179** by reaction of alkyllithiums followed by treatment with carbonyl compounds[343] (equation 195). Thus, the reaction of bis(diethylcarbamoyl)-mercury with butyllithium in THF at −75 °C, followed by addition to a THF solution of acetophenone, afforded 66% of *N*, *N*-diethylatrolactamide.



(174) (176) (177) (178) (179)

(195)

TABLE 48. Preparation of α-hydroxy-dialkylcarboxamides

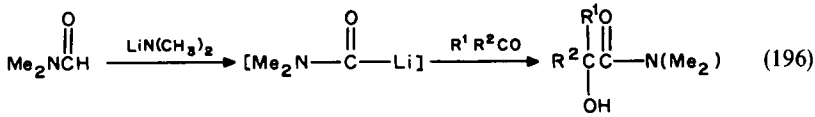
Electrophile	Product (after hydrolysis)	Yield (%)
Benzaldehyde	*N,N*-Diethylmandelamide	71
Acetophenone	*N,N*-Diethylatrolactamide	66
Benzophenone	*N,N*-Diethyldiphenylglycolamide	75
Benzoyl chloride	*N,N*-Diethylphenylglyoxylamide	65
Ethyl benzoate	*N,N*-Diethylphenylglyoxylamide[a]	31
Methanol	*N,N*-Diethylformamide	54
[O–D]-Methanol	*N,N*-Diethyldeuterioformamide	51
Methyl iodide	*N,N*-Diethylacetamide	23

[a]As well as α-hydroxy-α-phenylmalonic acid bis(diethylamide).

The reaction is thought to proceed through the formation of a dibutylmercury–(diethylamino)lithiooxycarbene complex **176**. The authors could not decide between two alternative routes for the formation of the α-hydroxy-dialkylcarboxamides **179**: in one complex **176** reacts directly with the electrophile (route a), in the other reaction takes place via a (diethylcarbamoyl) lithium **177** which they formulate in equilibrium with a (diethylamino)lithiooxycarbene, **178** (route b).

In the light of recent studies with dialkylcarbamoyl lithiums the proposed equilibrium **177–178** seems reasonable and route b seems preferable. The procedure is useful for the preparation of α-hydroxydialkylcarboxamides by the introduction of the carbamoyl group into carbonyl compounds. The yields of α-hydroxydialkylcarboxamides obtained using other electrophiles are shown in Table 48[343].

Since the preparation of bis(diethylcarbamoyl)mercury is rather troublesome[343] and not without danger, Schollkopf designed a simpler access to carbamoyllithium derivatives (equation 196).



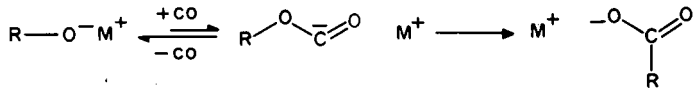
(196)

Treatment of dimethylformamide with lithium diisopropylamide in THF/ether at −78 °C in the presence of carbonyl compounds led to the production of α-hydroxy *N,N*-dimethylcarboxyamides with good yields in some cases. The intermediate was assumed to be (dimethylcarbamoyl)lithium but the authors did not succeed in unambiguously preparing it by metallation of diisopropylformamide with e.g. butyllithium[343]. As we have shown before (see Section III.C.1) lithium carbamoyls are not stable and many undesired side-reactions occur under these conditions. This method of preparation of the carbamoyl lithium reagent has the disadvantage that only *N,N*-dimethyl substituted carboxyamides are obtained. Direct carbonylation of lithium amides would widely expand the scope of the synthesis to α-hydroxy-*N,N*-dialkylcarboxyamide.

IV. INSERTION OF CARBON MONOXIDE INTO O—M BONDS

Carbonylation of metal alkoxides, **180**, would in principle lead to the production of metal carboxylates, **182**, by rearrangement of the carbanion **181** first formed (equation 197). Although many other methods of preparing carboxylates are known, this reaction

has a potential synthetic utility in the conversion of complex alcohols and in the preparation of the homologous acid or ester of naturally occurring alcohols.



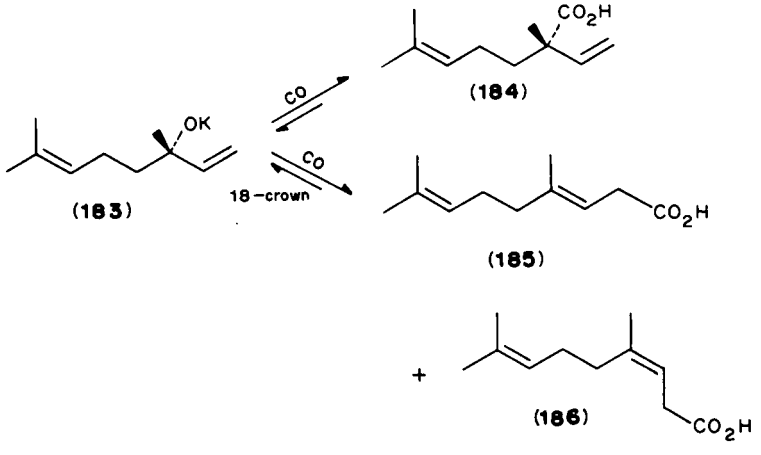
(180) (181) (182) (197)

As shown in equation 197, oxygen–metal bonds are largely ionic. Nevertheless, the carbonylation reaction is considered here formally as insertion reaction to maintain homogeneity of the headings.

A. Carbonylation of Organopotassium Compounds

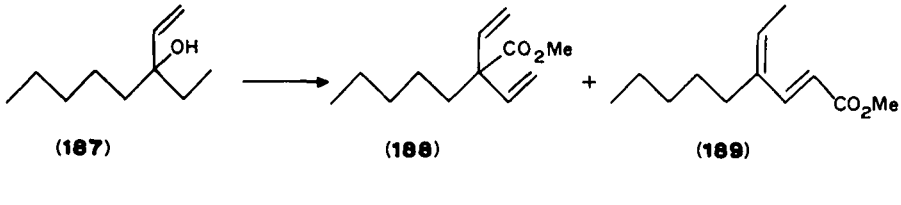
Recently, the direct carbonylation of potassium alkoxides has been successfully achieved by Rautenstrauch[344]. Although this carbonylation is almost without precedent, it can be formally related to Berthelot's early (1855) synthesis of formate salts by addition of hydroxide to CO[345] and the synthesis of alkyl formates (1914) via addition of alkoxides to CO in excess alcohol which traps **181** by protonation[346]. Both reactions are well understood and used industrially. A patent[345] also describes the carbonylations of sodium ethoxide to give sodium propionate and of sodium butoxide to produce sodium pentanoate in diethyl ether at 70–140 bar and 20–60 °C.

The process **180** → **181** → **182** should be favoured under the following conditions: strongly nucleophilic alkoxides, high CO pressure, a non-acidic medium (to block protonation of **181**) and radicals R with high migratory aptitude to facilitate the rearrangement **181**–**182**. Rautenstrauch[344] has found that the potassium alkoxide of linalool **183** reacts in benzene, at elevated temperature (120–130 °C) and pressure (425–440 bar), with CO to give the potassium salt of the tertiary acid (**184**) (average yield *ca* 25%; equation 198). Using the [K^+ < 18-crown-6] alkoxide of **183**[346] the reaction can be carried out at room temperature and low CO pressures (50–55 bar) to afford mainly the [K^+ < 18-crown-6] salt of **184** accompanied by the salts of its allylic isomers **185** and **186** (combined yields 35–40%; equation 198). Reaction times of uncomplexed **183** are 12–30 h in an autoclave, whereas the reaction of the complexed salt under mild conditions required longer times (90–140 h at 40 °C) but were nevertheless preferred because the [K^+ < 18-



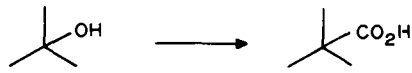
(183) (184) (185) (186) (198)

crown-6] alkoxides are thermally unstable. Attempts to carbonylate the potassium alkoxide of geraniol or the [K^+ < 18-crown-6] complex failed[344]. In contrast, with the bis-allylic alcohol **187** the carbonylation proceeded remarkably well[344]. Thus, treatment of the [K^+ < 18-crown-6] alkoxide of **187** with CO at 50 bar and rt for 70 hours led to a mixture of 67% of the tertiary ester **188** and 11 and 22% of the isomeric esters **189** and **190** in a *ca* 90% combined yield based on *ca* 65% converted **187**. Similar results were also obtained with the uncomplexed potassium alkoxide of **187** (45 bar, 120 °C, 12 h; equation 199).

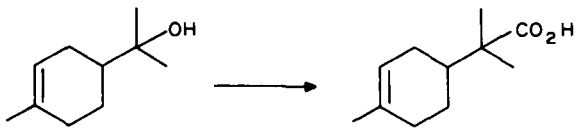


(187) (188) (189) (190) (199)

Non-allylic, tertiary alkoxides barely reacted with CO, and only as the uncomplexed potassium alkoxides at elevated temperature. Thus, the potassium alkoxide of *tert*-butyl alcohol **192** reacted with CO at 70 bar and 160 °C for 2 h to give the potassium salt of pivalic acid (**193**) in a 4% yield based on the total of **192** started with, and the potassium alkoxide of α- terpineol **194** reacted (210 bar, 200 °C, 15 h) to give the potassium salt of **195** in a *ca* 1% yield based on the total of **194** used (equations 200 and 201).

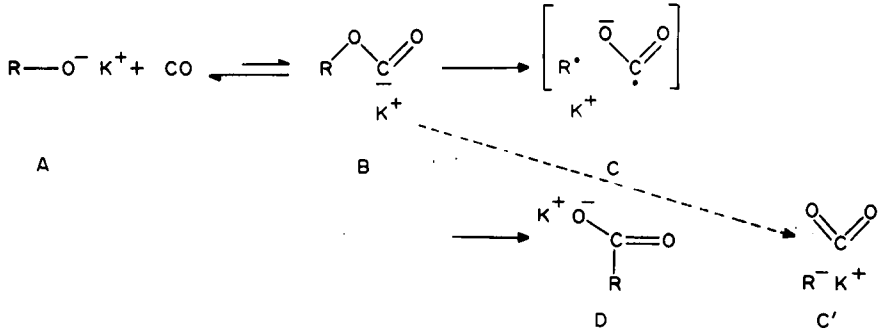


(192) (193) (200)



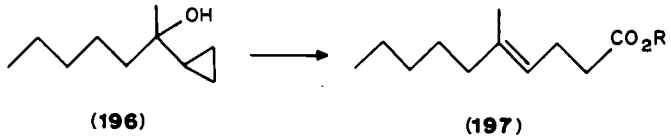
(194) (195) (201)

Rautenstrauch[344] proposes Scheme 24 to account for the results: a dissociation/recombination mechanism following the addition of the potassium alkoxides A to CO to give the alkoxycarbonyl anion-K^+ salts B. Dissociation of B to give the alkyl or allyl radical/$CO_2^{-\bullet}/K^+$ triplets C seems more likely (despite one inconsistency, see below) than dissociation leading to carbanion/$CO_2^{\bullet}/K^+$ triplets C'. Recombination starting from C or C' would give the carboxylates D. Analogous mechanisms can be written with [K^+ < 18-crown-6] replacing K^+.

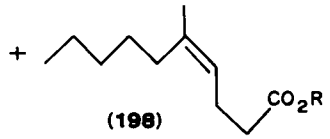


SCHEME 24

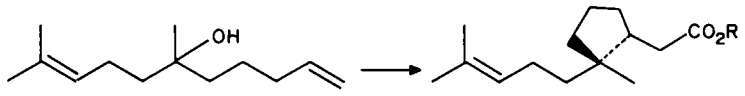
Mechanistic tests were conducted with the carbonylation (350 bar, 120 °C, 12 h) of the potassium salt of the tertiary cyclopropylmethanol **196** [a 67:33 mixture of the potassium salts of the ring opened acids (**197**, **198**) was obtained] and with the potassium alkoxide of the tertiary alcohol **199** containing a 5-hexen-1-ol unit (380 bar, 160 °C, 12 h) which gave a 82:18 mixture of the potassium salts of the ring-closed acids **200**, **201** in low yield (equations 202 and 203). This last result is puzzling[344]. Since geminate recombination within C would be faster than ring closure in solution[347], this would mean that these are formed from R·radicals that escape their partners (C) and encounter other $CO_2^{-\cdot}$ which seems unlikely. The R·radicals that escape would probably not react with the CO that is present in high concentration. It has recently become clear that the cyclizations could in principle also involve carbanions(C')[348–350], but the cyclization and recombination rates for these are unknown. The R^- that escape would react with the CO[344].



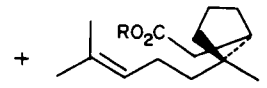
(196) (197)



(198) (202)



(199) (200)



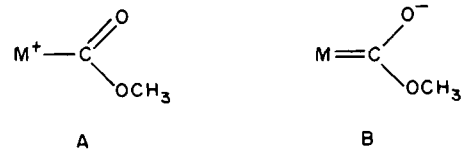
(201) (203)

Comparison of the present carbonylation mechanism with the rearrangement of alkoxycarbenes RO—C—R to give ketones[351], or with the Wittig rearrangement[352], have been made but since they are really very different only the faintest of resemblances is expected.

B. Formal 'Carbonylation' of Sodium Salts

It was mentioned in Section IV.A that Rautenstrauch's carbonylation[344] requires extremely nucleophilic alkoxides. Thus potassium and complexed potassium alkoxides gave good results, but attempts to carbonylate Li^+, Na^+, Cu^+ and Mg^{2+} alkoxides (uncomplexed or complexed) were unsuccessful[344].

A reaction that can be formally considered as a carbonylation is the reaction of sodium methoxide catalyzed by metal carbonyls $M(CO)_5$ [M = Fe, Ru, Os], yielding the methoxycarbonyl adduct $M(CO)_4(CO_2CH_3)^-$[353]. The infrared spectrum of the adduct (M = Ru) is shown in Figure 15. The differences in the position of the $\nu_{C=O}$ band of the methoxycarbonyl group for the Na^+ and the $(Ph_3P)_2N^+$ (= PPN) salts suggest specific interactions between the Na^+ and the CO_2CH_3 group. A and B represent resonance extremes for this group.



A B

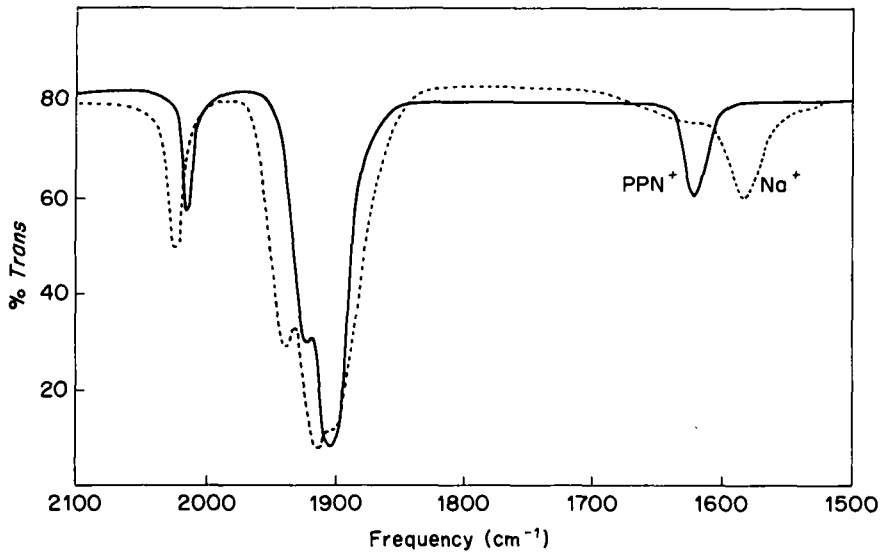


FIGURE 15. Infrared spectra (CO) of [PPN][$Ru(CO)_4(CO_2CH_3)$] (solid line) and of [Na][$Ru(CO)_4(CO_2CH_3)$] (dashed line) in THF solution; PPN = $[(Ph_3P)_2N]^+$. Reprinted with permission from *J. Am. Chem. Soc.*, **107**, 2357 (1985). Copyright (1985) American Chemical Society.

Stabilization of the latter by interaction with Na^+ at the methoxycarbonyl oxygen would raise the $\nu_{C=O}$ values of terminal carbonyl groups owing to the decreased negative charge on the metal and similarly decrease $\nu_{C=O}$ for the CO_2CH_3[353]. The potential importance of such counterion interaction with anionic organometallic complexes has been illustrated by Collman and coworkers[354], who demonstrated that the cation has a major influence on alkyl migratory insertion reactions of $M^+[RFe(CO)_4^-]$ species. The terminal $\nu_{C=O}$ bands for these adducts occur at substantially higher frequencies than for the analogous $HM(CO)_4^-$ salts, suggesting substantial delocalization of the negative charge onto the methoxycarbonyl group, i.e. the contribution of the canonical structure **B** in each case.

Careful kinetic determinations allowed formulation of the mechanism of carbonylation of the sodium methoxide, which is shown in equations 204–209.

$$Fe(CO)_5 + OCH_3^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Fe(CO)_4(CO_2CH_3) \tag{204}$$

$$Fe(CO)_5 + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Fe(CO)_4(CO_2H) \tag{205}$$

$$Fe(CO)_4(CO_2H)^- + OR^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} Fe(CO)_4(CO_2)^{2-} + HOR \tag{206}$$

$$Fe(CO)_4(CO_2H)^- \xrightarrow{k_c} HFe(CO)_4^- + CO_2 \tag{207}$$

$$Fe(CO)_4(CO_2)^{2-} \xrightarrow{k_d} Fe(CO)_4^{2-} + CO_2 \tag{208}$$

$$Fe(CO)_4^{2-} + H_2O \overset{\text{fast}}{\rightleftharpoons} HFe(CO)_4^- + OH^- \tag{209}$$

In alkaline THF/methanol/water solution the base is present as OH^- and CH_3O^-. Addition of $Fe(CO)_5$ led to the rapid formation of the equilibrium mixture shown by equations 204 and 205. Each one of the rates of the several steps could be evaluated and the influence of a variety of parameters on the kinetics of the reactions has been examined. Details of the discussion are beyond the scope of this chapter. Quantities k_c and k_d are the rates of the decarboxylative processes and k_c is larger in the more protic solvent, an observation suggesting that water or methanol may somehow mediate the transfer of hydrogen from the hydroxycarbonyl oxygen to the metal[354]. A similar observation has been made by Catellani and Halpern[355], who noted that the platinum hydroxycarbonyl complex *trans*-$[PtCl(CO_2H)(PEt_3)_2]$ underwent decarboxylation more rapidly in the presence of water than in dry, aprotic solvents.

Closely related to these reactions is the hydroxycarbonylation of aryl halides with formate salts, recently studied by Pri-Bar and Buchman[356] (equation 210).

$$ArBr + MO_2CH + CO \xrightarrow{\text{catalyst}} ArCO_2H + MBr + CO \tag{210}$$

The catalyzed hydroxycarbonylation reaction is in competition with the reductive formylation by formates[357,358] (equation 211). Indeed, it was found that the formylation reaction (path A) is accompanied by the much slower hydroxycarbonylation reaction (path B). The reaction of sodium formate with 4-chlorobromobenzene, in DMF, and in the

$$ArBr + MO_2CH + CO \begin{cases} \xrightarrow{\text{path A}} ArCHO + MBr + CO_2 \\ \xrightarrow{\text{path B}} ArCO_2H + MBr + CO \end{cases} \tag{211}$$

TABLE 49. Distribution of products (formylation vs hydroxycarbonylation) in the reaction of aromatic halides with various formate salts[a]. Reproduced with permission from *J. Org. Chem.*, **53**, 625 (1988)

Entry	Formate	Reaction condition[b]	Conv (mol%)	Products	
				aldehyde[d] (mol%)	benzoic acid[e] (mol%)
1	LiO_2CH	A	96	76(71)[f]	18
2	LiO_2CH	B	93	29	56
3	NaO_2CH	A	95	70(66)[f]	15
4	NaO_2CH	B	97	28	58
5	KO_2CH	A	90	64	24
6	KO_2CH	B	88	10	78
7	$Ca(O_2CH)_2$	A	48	8	36
8	$Ca(O_2CH)_2$	B	96	3	85(80)[f]
9	$Ba(O_2CH)_2$	A	65	40	35
10	$Ba(O_2CH)_2$	B	93	10	71

[a]Reactions conditions: 4-chlorobromobenzene (1 mmol), formate salt (1.1 equiv), $PdCl_2$ (0.05 mmol), PPh_3 (0.3 mmol), under 50 psi carbon monoxide (measured at ambient temperature).
[b](A) temperature 100 °C, reaction time 18 h, solvent DMF; (B) temperature 120 °C, reaction time 20 h, solvent DMF/benzene (1:1).
[c]Determined from residual aryl halide. Small amounts of hydrogenolysis products (2–10%) make up to a total of 100%.
[d]Yields determined by HPLC and GC.
[e]GC yields determined as methyl ester (obtained from the acid by treatment with methyl iodide).
[f]Isolated yield.

presence of 5 mol% homogeneous palladium catalyst, results in 4-chlorobenzaldehyde (70%), chlorobenzene (4%) and 4-chlorobenzoic acid (18%).

Table 49 shows the several formate salts that were tested. It can be observed that calcium formate reacted with a higher chemoselectivity in the hydroxycarbonylation pathway, giving only 8% of 4-chlorobenzaldehyde and 36% of 4-chlorobenzoic acid after 18 h of reaction at 100 °C. Barium and potassium formate were found less chemoselective as shown in Table 49. Increasing the temperature and performing the reaction in a solvent of lower polarity tends to avoid aldehyde formation. Thus, in order to achieve higher selectivity of hydroxycarbonylation, the reaction was conducted at 120 °C in a DMF–benzene mixture (Table 49, reaction conditions, B). Under these conditions a selectivity of 97% for the hydroxycarbonylation was achieved by the use of calcium formate[356].

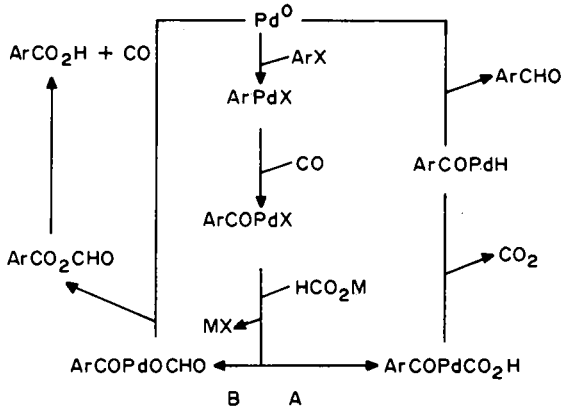
Various substituted bromo- and iodoaromatic compounds were subjected to the hydroxycarbonylation reaction (Table 50). *Para* substituents like methyl, methoxy, hydroxy, acetyl, nitro and chloro derivatives were found compatible with the reaction; however, *ortho* substitution tends to retard the reaction.

The mechanism of the hydroxycarbonylation could be related to that of the methoxycarbonylation. The latter was shown[359] to proceed through fast oxidative addition and carbonylation steps, a slow nucleophilic attack on the acylpalladium species being produced. Pri-Bar and Buchman[356] propose that the nucleophilic attack of a formate ion could proceed in two different reaction patterns (Scheme 25, A and B). One pathway (A) involves a C—H bond cleavage, giving an aldehyde, another route (B) is the generation of a palladium formate species, which subsequently produces mixed formic anhydride by reductive elimination. As a result of the thermal instability of formic anhydrides[360], this is followed by thermal decarbonylation of the anhydride and gives the

TABLE 50. Hydroxyformylation of substituted aryl halides[a]. Reproduced with permission from *J. Org. Chem.*, **53**, 625 (1988)

Entry	Aromatic halide	Aromatic acid (yield) (mol%)[b]
1	C_6H_5Br	$C_6H_5CO_2H$ (73) (70)[c]
2	C_6H_5I	$C_6H_5CO_2H$ (85)
3	$4\text{-}CH_3C_6H_4Br$	$4\text{-}CH_3C_6H_4CO_2H$ (77) (72)[c]
4	$3\text{-}CH_3C_6H_4Br$	$3\text{-}CH_3C_6H_4CO_2H$ (76)
5	$2\text{-}CH_3C_6H_4Br$	$2\text{-}CH_3C_6H_4CO_2H$ (55)
6	$4\text{-}CH_3OC_6H_4Br$	$4\text{-}CH_3OC_6H_4CO_2H$ (75)
7	$3\text{-}CH_3OC_6H_4Br$	$3\text{-}CH_3OC_6H_4CO_2H$ (78)
8	$4\text{-}CH_3COC_6H_4Br$	$4\text{-}CH_3COC_6H_4CO_2H$ (88) (85)[c]
9	$4\text{-}ClC_6H_4Br$	$4\text{-}ClC_6H_4CO_2H$ (85)
10	$3\text{-}ClC_6H_4Br$	$3\text{-}ClC_6H_4CO_2H$ (66)
11	$2\text{-}BrC_6H_4Br$	$2\text{-}C_6H_4(CO_2H)_2$ (5)
12	$4\text{-}NCC_6H_4Br$	$4\text{-}NCC_6H_4CO_2H$ (87)
13	$4\text{-}HOC_6H_4Br$	$4\text{-}HOC_6H_4CO_2H$ (45)
14	$2\text{-}HOC_6H_4Br$	$2\text{-}HOC_6H_4CO_2H$ (22)
15	$4\text{-}(H_3C)_2NC_6H_4Br$	$4\text{-}(H_3C)_2NC_6H_4CO_2H$ (80)
16	$4\text{-}O_2NC_6H_4Br$	$4\text{-}O_2NC_6H_4CO_2H$ (74)
17	1-bromonaphthalene	1-naphthoic acid (82)
18	2-bromonaphthalene	2-naphthoic acid (85) (81)[c]

[a]Reaction conditions: aromatic halide (1 mmol), calcium formate (0.6 mmol), $PdCl_2$ (0.05 mmol) and PPh_3 (0.3 mmol) were heated (120 °C/20 h) in DMF/benzene (1:1) under 3 atm of carbon monoxide.
[b]Determined as the methyl esters by GC or HPLC.
[c]Isolated yields.



SCHEME 25

benzoic acid derivative. Indeed, the uncatalyzed reaction of benzoyl halide and sodium formate, at 120 °C in benzene/DMF solution, gave a quantitative yield of equivalent amounts of benzoic acid and carbon monoxide (determined by GLC), as a result of rapid decomposition of the formed anhydride (equation 212).

$$ArCOCl + NaO_2CH \rightarrow [ArCO_2CHO] \rightarrow ArCO_2H + CO \qquad (212)$$

The differences in the reaction pattern of formate salts with various metallic counterions support a mechanism that involves formation of two different benzoylpalladium intermediates: formyl (route B) and hydroxycarbonyl benzoylpalladium (route A). A rapid equilibrium between such intermediates is incompatible with the observed differences in reactivity of various metal ions. Factors such as reaction temperature and solvent polarity seem to control the selection of one or two reaction modes A or B[356]. No carbonylation occurs when calcium formate is reacted with an aryl bromide in the absence of carbon monoxide. A reaction with ^{13}C-labelled calcium formate (99.9% enriched) showed that the carbonyl group in the product is introduced via a carbonylation process and not by a direct carboxylation with a formate ion[356].

V. CONCLUDING REMARKS

Some of the most extensively studied carbonylations of main group organometallic compounds have been described. A wide variety of carbonyl-containing derivatives can be prepared by the use of organolithium compounds. Organomercurials have the advantage of tolerating most important organic functional groups; organoboron, -thallium and -tin compounds are very useful in retaining stereochemistry; different arene–metal compounds can be chosen to obtain the carbonyl functionality in the desired position; carbonylation of the nitrogen–metal bond is becoming important for the synthesis of highly functionalized known and new compounds.

There is little doubt that the new applications of carbonylation of main group organometallic compounds studied in this decade, as well as the effect of catalysts, have opened spectacular vistas for synthetic organic chemists. The creation of carbon–carbon bonds selectively and under mild conditions, regiospecific carbonylations and asymmetric syntheses are among some of the recent achievements. After the extensive studies on organotransition metal compounds in the last decade and in the light of recent results, one can expect important development in structural, theoretical, mechanistic and synthetic applications of the carbonylation of main group organometallic compounds in the future.

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The Chemistry of Double-bonded Functional Groups
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CHAPTER **14**

Rearrangements involving allenes

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I. INTRODUCTION

The remarkable expansion of allene chemistry during the last decade is probably best illustrated by a variety of comprehensive monographs[1–4], reviews[5–7] and a symposium in-print[8], which have been published during this period. Rearrangements involving allenes have played an important role in this development and these major literature surveys also include a discussion of this subject. Of particular interest is the excellent and detailed review by Huntsman[9] on rearrangements involving allenes in general, and the more confined one on sigmatropic arrangements of allenes by Hopf[10]. Since the comprehensive and systematic review by Huntsman has surveyed the literature up to 1978, an attempt has been made to scan the literature since that date and through 1988, as far as possible, so as to cover the most significant and most important advances during the last decade. For the sake of continuity and the convenience of the reader, the original format of the Huntsman chapter[9] has generally been retained.

Rearrangements have been included in which allenes participate not only as reactants and products, but occasionally also as intermediates. Reactions has been classified according to mechanism, but although the main emphasis has been on mechanism and stereochemistry, special attention to synthetic applications has also been given, wherever appropriate. Obviously, due to space and electronic retrieval limitations on the one hand, and the extensive documentation on the other hand, only selected and representative results of general importance, as judged by the concern of the reviewer, are presented. Thus, the exclusion of a particular piece of work in no way passes judgement on its scientific value.

It is hoped that this chapter, which is intended to serve experts and students alike, will help them include its knowledge in their research programs, and will stimulate further creative work in the area.

II. PROPARGYLIC AND RETROPROPARGYLIC REARRANGEMENTS

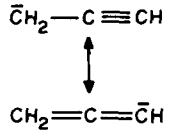
A. Prototropic

1. Hydrocarbons

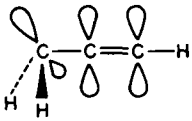
The base-catalyzed isomerization of acetylenes to allenes is known to involve propargyl/allenyl anions as intermediates, and the organometallic derivatives of these species are of considerable importance in the synthesis of both acetylenes and allenes. A number of theoretical and spectroscopic studies have attempted to classify the geometries and charge distribution of these anions. For example, the unsubstituted anion **1** may be generated by removal of a proton from either propyne or allene. If no rehybridization

occurs durig these operations, the first hydrocarbon produces the anion in an acetylene-like geometry (**2**) in which the CH_2 center is sp^3 hybridized and the CH center is sp hybridized, whereas the second leads to an 'allene-like' anion (**3**) in which both CH_2 and CH centers are sp^2 hybridized. However, because of the tendency of carbanionic centers next to conjugating substituents to rehybridize and thus maximize conjugation, an alternative 'planar' geometry for the anion (**4**) can also be suggested. In this the CH_2 center is sp^2 and the CH center sp hybridized.

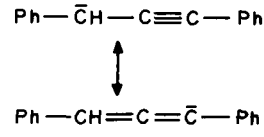
Ab initio MO calculations on the nature of the anion **1** suggest that it adopts an allene-like geometry (**3**), which implies concentration of charge at the CH end of the anion. On the other hand, both CNDO II calculations and spectroscopic studies on the 1,3-diphenyl substituted anion (**5**) suggest that it adopts a 'planar' geometry with the charge concentration at the CHPh end of the anion[11]. This indicates the dependence of geometry and charge distribution on degree of conjugation.



(1)



(2) 'Acetylene-like'



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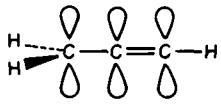
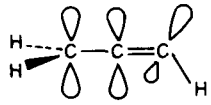
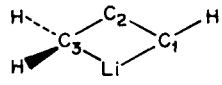


(4) 'Planar'



(3) 'Allene-like'

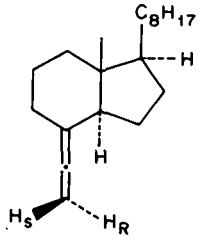


(6)

The suggestion that the allenic anion **1** has a bent structure has also been supported by another study[12], which has also indicated that the barrier to inversion is about 7 kcal mol^{-1}. Interestingly, an inversion barrier of minimum 22 kcal mol^{-1} was observed experimentally for α-chlorinated allenic anions[13,14] and a bridged molecule with a bent carbon skeleton and simultaneous Li bonding to C-1 and C-3 was suggested for allenyllithium (**6**)[15].

The configurational stability of chiral allenic anions, using a vitamin D derived CD fragment as a stereochemical probe, has been investigated by Okamura and coworkers[16-18]. These authors have made the unusual observation that metallation of steroidal hydrocarbon fragment **7** with *tert*-butyllithium in ether at − 78 °C, followed by quenching of the resultant allenyllithium species with a suitable electrophile, affords **8** and **9** in ratios as high as 13.5 to 1[16,17]. In order to better understand the origin of the observed diastereoselectivity the same authors have studied the configurational behavior of allenic anions derived from epimeric substituted allenes such as **10**. The results indicate that metallation of (*S*)-allenes **10a–c** with the complex *n*-BuLi/*t*-BuOK, in THF, followed by quenching with DCl/D_2O, occurs primarily with retention of configuration, whereas that of (*R*)-allenes **10d–e** occurs mainly with inversion[18]. The explanation offered for these observations was that alkyl substituted allenic anions, unlike α-chloroallenic anions, are configurationally unstable.

Since Favorskii's first proposal that allenes are intermediates in the base-catalyzed isomerization of alkynes, more than 100 years ago[19], this type of rearrangement has been studied and reviewed extensively[9,20]. Straight chain monoacetylenes are rearranged by a wide variety of bases generating mixtures of isomeric allenes and acetylenes. In the



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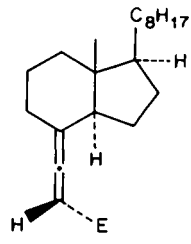
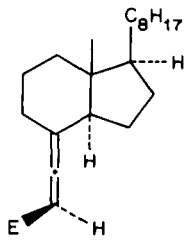
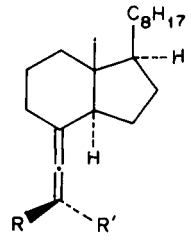


(8)



(9)

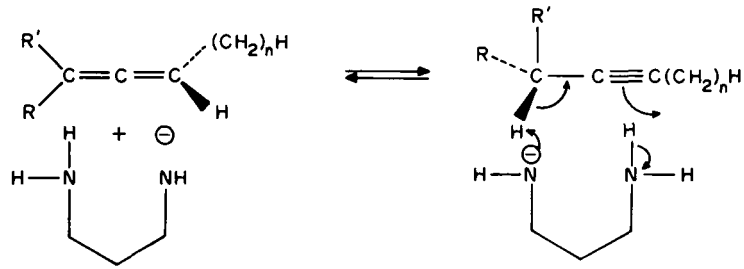


(10)

(10a) $R = CH_3$; $R' = H$
(b) $R = CH_3$; $R' = D$
(c) $R = C(CH_3)_3$; $R' = H$
(d) $R = H$, $R' = CH_3$
(e) $R = H$, $R' = C(CH_3)_3$

generally accepted mechanism the base is thought to abstract a proton from a carbon next to the triple bond to give an anion which may be reprotonated to yield an isomeric allene. Further reversible 1,3-proton shifts lead to new acetylenes and allenes. The ratios of products formed reflect the relative thermodynamic stabilities of the components.

For cases where the base is the metal derivative of a diamine such as 1,3-diaminopropane, the base may be able to abstract and donate a proton in a cyclic fashion (equation 1). In this concerted mechanism the proton transfers take place without discrete

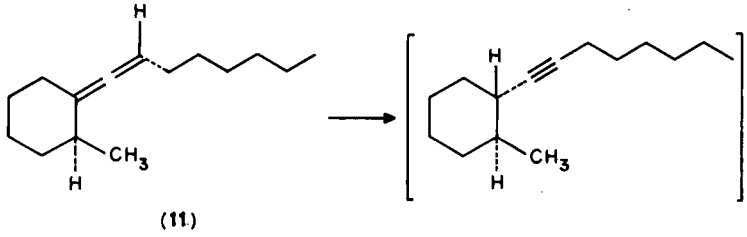


(1)

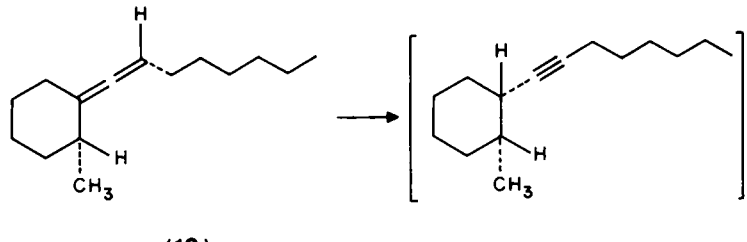
carbanionic intermediates. However, it has been recently reported that the lithium amide of 1,3-diaminopropane-mediated isomerization of the two diastereomeric allenes **11** and **12**, differing only in the relationship of a methyl group on a cyclohexane ring to the allene, afford identical mixtures containing both terminal acetylenes **13** and **14**. These results exclude the concerted mechanism and seem to favor a mechanism involving discrete anionic intermediates[21].

Rearrangement of dienyne **15** to the butadienylallene **16** occurs under relatively mild conditions, due to increased acidity of the propargylic hydrogens in **15** (equation 2)[22].

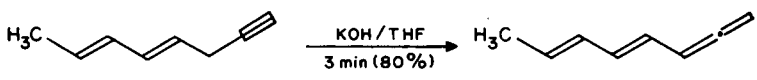
A rather unusual allene–acetylene rearrangement was observed when the bicyclobutane-bridged diallene **17** was treated with a large excess of butyllithium, which afforded the benzene derivative **18**[23].



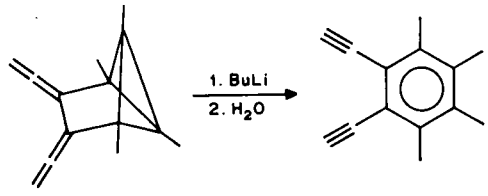
(11) (13)



(12) (14)



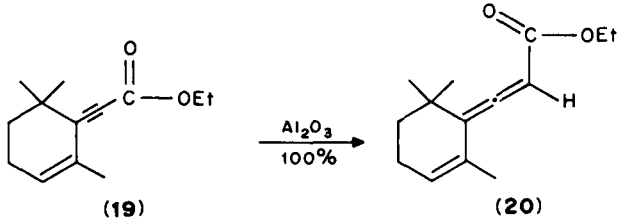
(15) (16) (2)



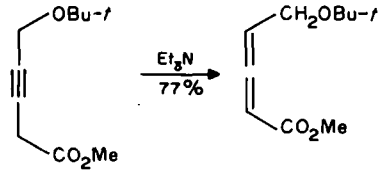
(17) (18)

2. Functionally substituted derivatives

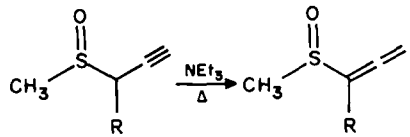
The allenic ester **20** was obtained quantitatively by fast elution with hexane of α,β-acetylenic ester **19** through a chromatography column packed with basic activated alumina[24]. Similar facile rearrangements of β,γ-acetylenic esters to allenic carboxylates using aqueous potassium carbonate[25] or small amounts of triethylamine (equation 3)[26] have also been reported. An analogous base-catalyzed rearrangement of a propargyl sulfoxide to an allenyl sulfoxide is shown in equation 4[27].



(19) (20)



(3)



(4)

R = n-C_6H_{13}

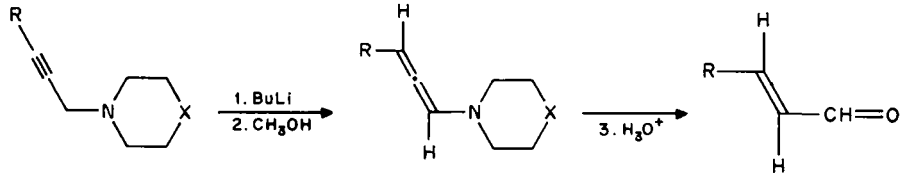
The base-catalyzed rearrangement of 2-propynyl ethers, sulfides and selenides into their allenic isomers or 1-propynyl compounds has been carefully studied by Brandsma and coworkers. These investigations have led to practical syntheses of a number of allenic ethers and their sulfur and selenium analogues[4]. In continuation, the same authors[28] have shown that dialkylamino allenes **22** can be obtained in excellent yields by isomerization of dialkyl-2-propynylamines **21** with potassium *tert*-butoxide in THF, while the use of DMSO instead of THF as solvent leads to equilibrium mixtures of allenic amines **22** with dialkyl-1-alkynylamines **23**.

$$HC{\equiv}CCH_2NR_2 \rightleftharpoons CH_2{=}C{=}CHNR_2 \rightleftharpoons CH_3C{\equiv}CNR_2$$

(21) **(22)** **(23)**

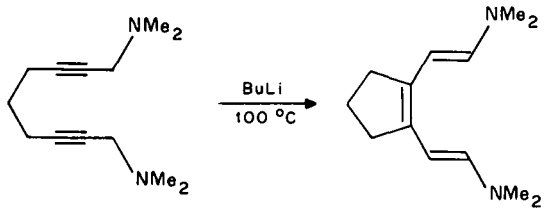
A detailed kinetic study of the prototropic rearrangement of the system $RMCH_2C{\equiv}CH$, $RMCH{=}C{=}CH_2$, $RMC{\equiv}CCH_3$, where M = NR, O, S, Se was subsequently reported by Purcelot and coworkers[29]. Using deuterated substrates, the nature of the reactive intermediate and, in the case of M = S, the activation energy–reaction coordinate profile were established. This study has demonstrated the facility of the propargyl–allenic isomerization of heteroatom substituted substrates which is particularly remarkable in the case of sulfur and selenium. The prototropic rearrangement of propargyl amines to allenic

amines followed by acid hydrolysis affords a novel synthesis of α,β-unsaturated aldehydes in overall yields from 62 to 88% (equation 5)[30].



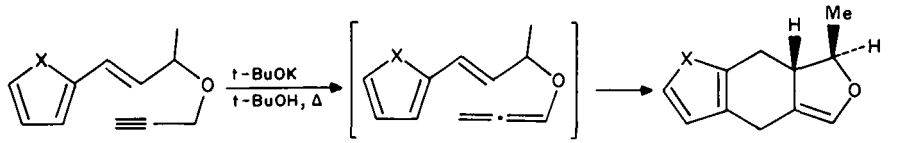
(5)

In a related study, it has been found that the diacetylene diamine **24**, when heated with butyllithium at 100 °C, instantaneously and quantitatively rearranges via an allenic carbanion intermediate to the triene double enamine **25**[31].



(24) (25)

Treatment of propargyl ethers **26a,b** with *t*-BuOK in refluxing *t*-BuOH resulted in the smooth formation of the intramolecular Diels–Alder adducts **27a,b** via allenyl ether intermediates (equation 6)[32].

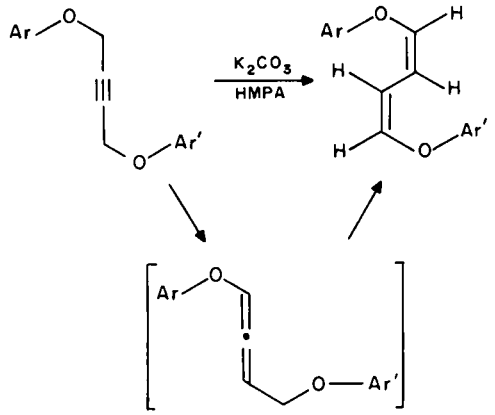


(26,a,b) (27)(a) X=O (98%)
(b) X=NMe (87%)

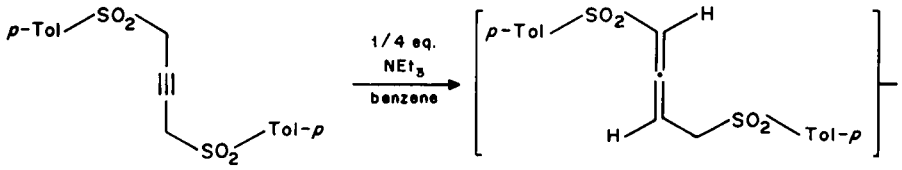
(6)

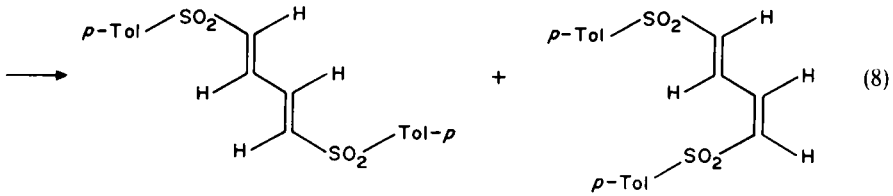
The 'unexpected' isomerization of 1,4-diaryloxy-2-butynes to *Z,Z*-1,4-diaryloxybutadienes which takes place in refluxing HMPA in the presence of potassium carbonate can also be explained by a mechanism involving acetylene–allene rearrangement, followed by an allene → diene rearrangement (equation 7)[33].

Support for the mechanism shown in equation 7 can be found in the contemporaneous study by Thyagarajan and coworkers[34–36] on the analogous rearrangement of 1,4-diarylsulfonyl-2-butynes to a mixture of isomers of 1,4-diarylsulfonyl-1,3-butadienes which occurs readily and in high yields under ambient temperatures in benzene solution with triethylamine as catalyst (equation 8). The intermediacy of allenyl sulfones has been demonstrated by trapping with thiophenol. The products under these conditions are not the 1,3-dienes shown in equation 8, but the vinyl sulfide generated by Michael addition of the thiophenol to the allenyl sulfone intermediate.



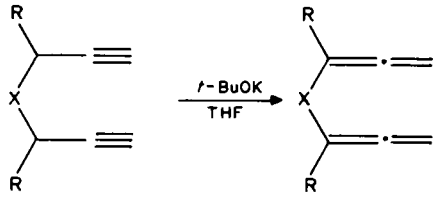
(7)





(8)

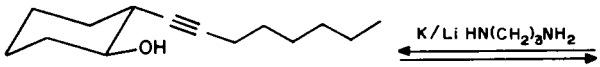
The bis-allenes **29a–d** were prepared by base-catalyzed rearrangement of the corresponding bis-acetylenes **28a–d**. The conditions required to effect rearrangement varied from compound to compound and in a number of cases strict control of the conditions was required to prevent further rearrangement of the bis-allenes[37]. For example, treatment of dipropargyl sulfide **28a** with *t*-BuOK in THF at −70 °C for only 40 s is converted to



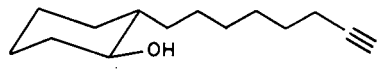
(28)(a) R = H, X = S **(29 a-d)**
(b) R = H, X = O
(c) R = Me, X = S
(d) R = H, X = SO_2

diallenyl sulfide (**29a**) in 93% yield[38a], a considerable improvement over the first preparation of this unstable bridged diallene (*vide infra*) using t-BuOH as solvent at 0 °C[38b].

An exceptionally easy isomerization of acetylenic alcohols initially reported by Brown and Yamashita[39] has subsequently received considerable attention[40]. By this method, potassium 3-aminopropylamide (KAPA), readily prepared *in situ* from KH and 3-aminopropylamine, effects rapid multipositional isomerizations of the triple bond in α- and other acetylenic alcohols to the chain terminus remote from the hydroxy function within minutes at 0–20 °C. The mechanism of this contrathermodynamic process, coined the 'acetylenic zipper' reaction[39], is thought to involve a random-walk process in which a series of allene–alkyne interconversions take place along the carbon chain until the terminal acetylene is formed. Subsequently, the use of potassium amide[40] or sodium amide[41] instead of KH has been introduced for safety reasons, and the method has been developed into a convenient procedure for preparing 1-alkynes by isomerization of internal triple bonds, which is inexpensive, safe and amenable to large-scale syntheses[42–46]. In addition, a novel method has been developed by Abrams[47] that allows efficient perdeuteration of all or part of a methylene chain employing deuteriated isomerization reagents. More recently, the same author has performed a detailed mechanistic study of the 1,3-prototropic shifts in acetylene–allene rearrangements mediated by alkali metal amides of 1,3-diaminopropane, with the object of determining the value of multipositional acetylene isomerization in the synthesis of long-chain compounds containing chiral centers. Rearrangement of an acetylenic alcohol **30** with defined relative stereochemistry gave two terminal acetylene products **31** and **32** in a ratio of 7 to 1. These results demonstrate that 1,3-prototropic shifts effected by alkali metal amides of diamines proceed with some loss of stereochemical integrity, which is most likely due to discrete anionic intermediates. A cyclic concerted bimolecular mechanism (equation 1) may be operating in part, but cannot be the exclusive mechanism of proton transfers.

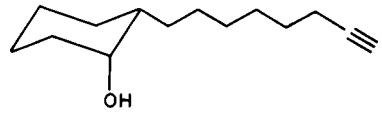


(**30**)



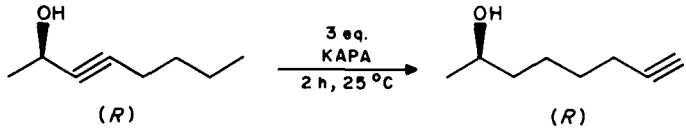
(**31**)

+



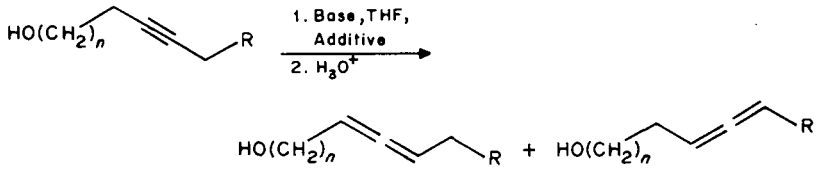
(**32**)

The isomerization of secondary optically active propargyl alcohols to terminal acetylenes using KAPA as base has been reported to proceed without loss of configuration at the carbinol center. Thus (*R*)-3-octyn-2-ol was converted to (*R*)-1-octyn-7-ol without racemization (equation 9)[48].



(9)

Internal acetylenes bearing a hydroxyl group at the appropriate position of an alkyl chain isomerized regioselectively to allenes by treatment with alkyllithium in the presence of TMEDA[49]. High to moderate selectivities were realized with $n \leqslant 3$ (equation 10).

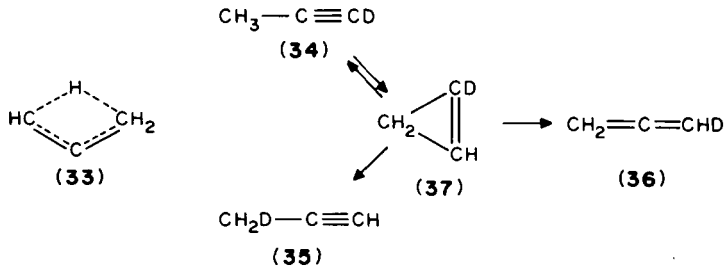


(10)

3. *Thermal interconversion of allene and propyne*

A study of the equilibrium between allene and methylacetylene over silica supported iron catalyst in the temperature range of 150–200 °C with either allene or methylacetylene as the intial reactant indicates similar equilibrium product distribution (allene 16% and methylacetylene 84%), fairly close to the calculated value[50].

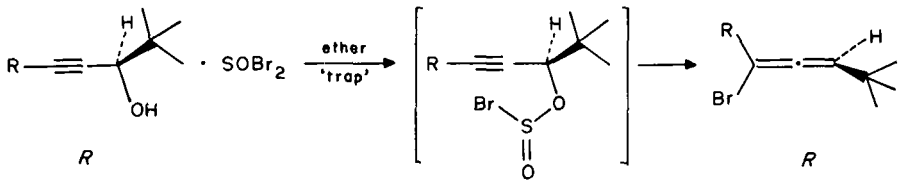
Uncatalyzed interconversion of propyne and allene which occurs at high temperatures has also been observed in the past[9], and was believed to occur by a direct [1, 3] sigmatropic hydrogen shift involving the four-center transition state **33**, although the possibility of a two-step rearrangement involving cyclopropene as an intermediate has also been proposed[9]. Subsequently, a study of the thermal rearrangements of C_3H_4 isomers in the range of 500–750 °C using deuterium labelling was performed, in order to test the role of cyclopropene in the allene to propyne isomerization[51]. Thus, starting from propyne-1-d_1 (**34**), for instance, a concerted process would predict allene-d_1 (**36**) as the sole initial product. The mechanism via cyclopropene **37** on the other hand is likely to produce propyne-3-d_1 (**35**) in addition to allene-d_1. This is because the intermediate cyclopropene-1-d_1 (**37**) can revert to propyne-d_1 in two ways which are equivalent by symmetry to produce **34** as well as **35**. This latter process is likely to be in effective competition with formation of **36**, since it has been previously shown that cyclopropene iosomerization favors the formation of propyne rather than allene[52]. From the results obtained with regard to distribution of products in flow pyrolysis of propyne-1-d_1 at different temperatures, as well as a kinetic study of the system, the authors conclude that between 50 and 100% of the allene is formed via the cyclopropene pathway[51].



B. Anionotropic

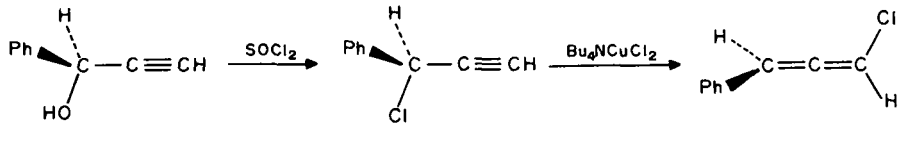
1. Replacement of OH by halogen

Haloallenes are versatile intermediates in organic chemistry[1-4] and their synthetic utility in the preparation of leukotrienes has been recently demonstrated[53-55]. One of the best methods for the preparation of haloallenes involves S_Ni' rearrangement of halosulfite esters generated by reaction of propargylic alcohols with thionyl halides[9,56-59]. For example, a stereospecific synthesis of chiral α,γ-disubstituted bromoallene has been recently reported by Corey and Boaz[56]. These authors have found that optically active α,γ-disubstituted propargyl alcohols undergo S_Ni' rearrangements with thionyl bromide in the presence of propylene oxide to yield bromoallenes with >99% optical purity (equation 11). This remarkable resut may be a consequence of the efficient removal of HBr

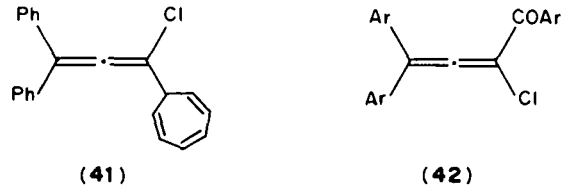


(11)

by propylene oxide, since in the absence of this scavenger the optical purity of the allenic product and its yield were lower. The S_Ni' mechanism is apparently not always observed. For example, the reaction of optically active (*R*)-(−)-α-phenylpropargyl alcohol (**38**) has been reported to yield the corresponding propargyl chloride (**39**) in 67% yield and 22% net retention of configuration on reaction with thionyl chloride in ether at 0 °C. The latter compound undergoes stereoselective *anti* S_N2' rearrangement to the optically active chlorallene **40** on treatment at room temperature with cuprous chloride, solubilized in dry acetone by tetrabutylammonium chloride[57]. However, in addition to numerous previous examples[9], the chlorallenes **41** and **42** were easily prepared by reaction of the appropriate propargyl alcohol with $SOCl_2$ in the presence of an excess of triethylamine[58,59].



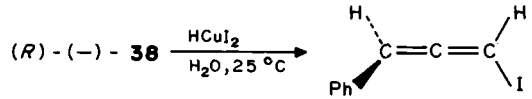
R-(**38**) *R*-(**39**) *R*-(**40**)



(**41**) (**42**)

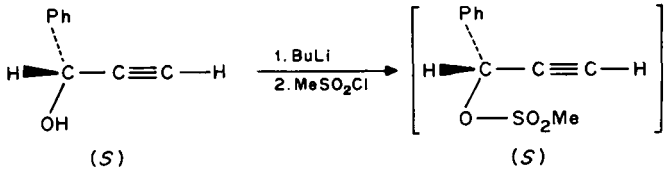
Allenic halides can also be obtained in excellent yields and almost instantaneously on treatment of secondary or tertiary propargylic alcohols with aqueous HX in the presence of $HCuX_2$, prepared by mixing equimolar amounts of CuX_2 and HX with water as solvent

at room temperature. A stereochemical study of this reaction using optically pure (*R*)-(−)-α-phenylpropargyl alcohol (**38**) with $HCuI_2$ produced (*S*)-(+)-γ-phenylallenyl iodide (**43**) indicating *syn* stereoselectivity but with only a small enantiomeric excess (ee 6%)[60]. Quite remarkably, *anti* stereoselectivity was observed when the same alcohol was allowed to react with $HCuCl_2$ and $HCuBr_2$, although the ee was still 4% and 22%, respectively. These results contrast with the previously reported high *syn* stereospecificity in the reaction of (*S*)-α-methyl-α-*t*-butylpropargyl alcohol with $HCuBr_2$[9,61].



(*S*)-(+)-(**43**)

A better and more stereoselective strategy for the preparation of optically active haloallenes has been described by Vermeer and coworkers[62,63]. This procedure, first reported for the preparation of racemic bromoallenes[64], involves first conversion of the propargyl alcohol into the corresponding methanesulfonate or sulfinate esters, with subsequent treatment with lithium halocuprate in THF at room temperature or below. A number of optically active haloallenes, some in the steroidal series, have been efficiently prepared by application of this mild and stereoselective method (equations 12 and 13)[62,63]. The observed *anti* stereospecificity in the steroidal series is quite smilar to that observed for organocopper-induced 1,3-substitution with the same substrates (*vide infra*)[65,66].



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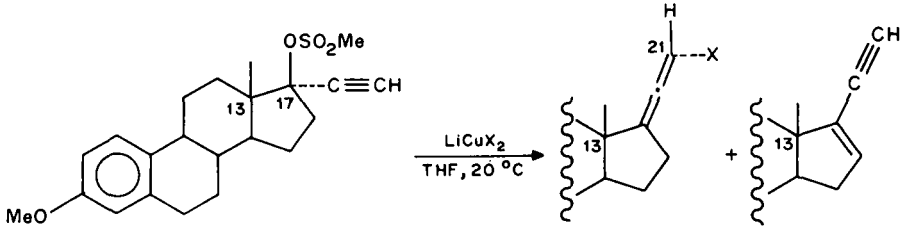
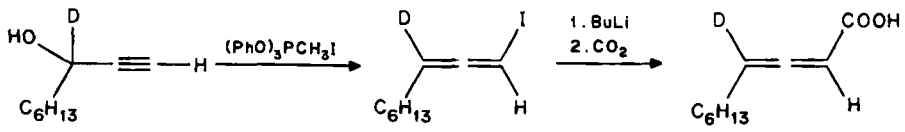


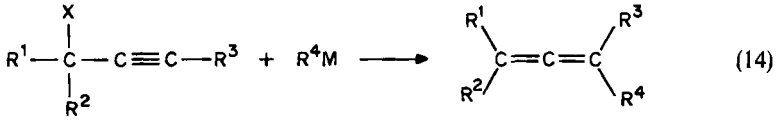
(13)

Recently, the conversion of α-deuterated-α-hexyl propargyl alcohol to 1-iodo-3-deutereo-1,2-nonadiene using triphenyl phosphite methiodide has also been reported[67].



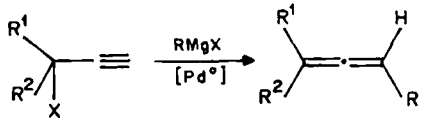
2. Reaction of organometallics with propargylic derivatives

The general reaction shown in equation 14 illustrates a well-known and synthetically very useful S_N2' rearrangement that occurs when organometallic reagents RM react with propargylic substrates. A wide variety of organometallic reagents have been used in the past[9], but during the last decade organocopper reagents have been generally preferred. Common leaving groups include sulfonates, acetates, sulfinates and occasionally halides and alkoxides. Normal S_N2 reactions may also occur in certain reactions. A major feature of this reaction is the *anti* stereoselectivity, which has been widely exploited for the synthesis of various optically active allenes, including natural products. A general review of copper-catalyzed reactions of Grignard reagents and organolithium[68] and a brief review on the use of lithium dialkylcuprate reagents in allene synthesis[69] have appeared.



(14)

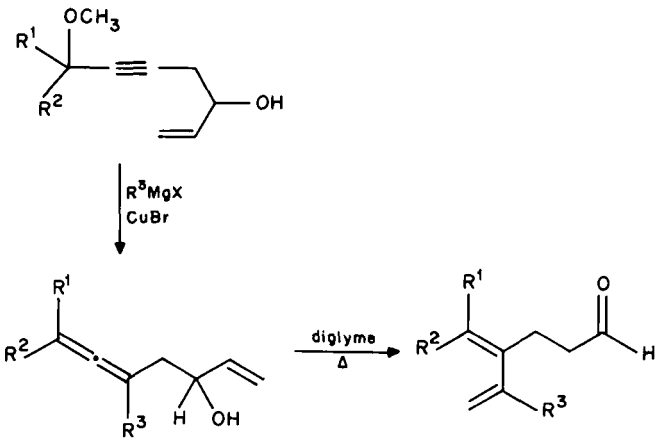
Subsituted allenes are selectively obtained in good yields from the reactions of Grignard reagents with propargylic or allenic halides in the presence of catalytic amounts of palladium chloride, triphenylphosphine and diisobutyl aluminum hydride in tetrahydrofuran at room temperature (equation 15)[70]. The reaction is believed to proceed by formation of allenic Pd complexes by oxidative addition of the substrate to Pd $(PH_3)_x$, formed *in situ* by reduction of $PdCl_2$, followed by cross coupling with Grignard reagents. A completely regioselective synthesis of allenes is directly achieved via organocuprate-mediated γ-coupling of propargyl alcohols by γ-(methylphenylamino)tributyl phosphine iodide. The reaction is applicable to primary, secondary and tertiary propargyl alcohols, regardless of steric influence[71].



(15)

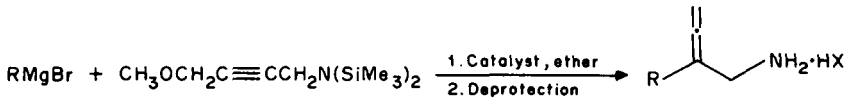
A number of α-vinyl-β-allenic alcohols are readily available by reaction of organocopper reagents with propargylic alcohols or ethers (equation 16)[72,73]. The products undergo an oxy-Cope rearrangement to dienic aldehydes in moderate yields.

In a related study, a direct and efficient route to various 2,3-diaryl-1,3-butadienes were obtained through a double S_N2' attack of aryl Grignard reagents on 1,4-dimethoxy-2-butyne in the presence of copper(I) salt (equation 17)[74]. Similarly, copper or nickel catalyzed substitution of Grignard reagents on the *bis*-trimethylsilyl protected 4-methoxybutynylamine provides β-substituted-α-allenyl primary amines in high yield (equation 18)[75]. This method appears superior to previously reported methods for the preparation of β-substituted-α-allenyl primary amines[76–78] which are of considerable recent interest as suicide substrates and mechanism-based enzyme inactivators[79–82].



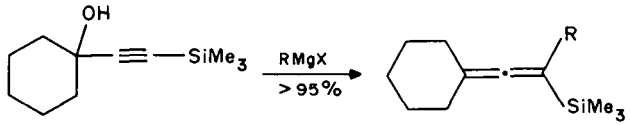
(16)

$$H_3COCH_2C{\equiv}CCH_2OCH_3 + 2ArMgBr \xrightarrow[\text{ether}]{\text{CuBr}} CH_2{=}C(Ar){-}C(Ar){=}CH_2 \qquad (17)$$



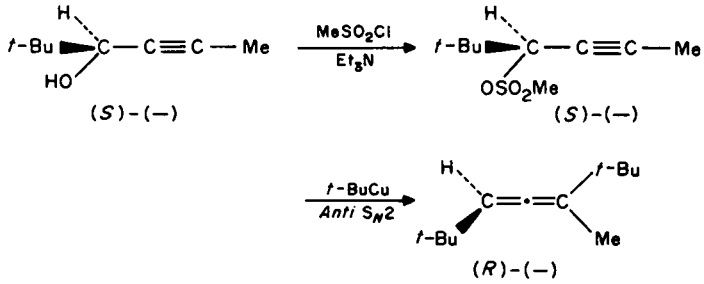
(18)

A catalytic S_N2' displacement of OH by organometallics has also been reported[83]. Thus, nickel-catalyzed reactions of γ-silylated secondary or tertiary propargyl alcohols with Grignard reagents produce silylated allenes in practically quantitative yields (equation 19), but the reaction with aromatic reagents is much faster than that of the aliphatic ones, and desilylation can be easily effected with CsF in acetonitrile[83].



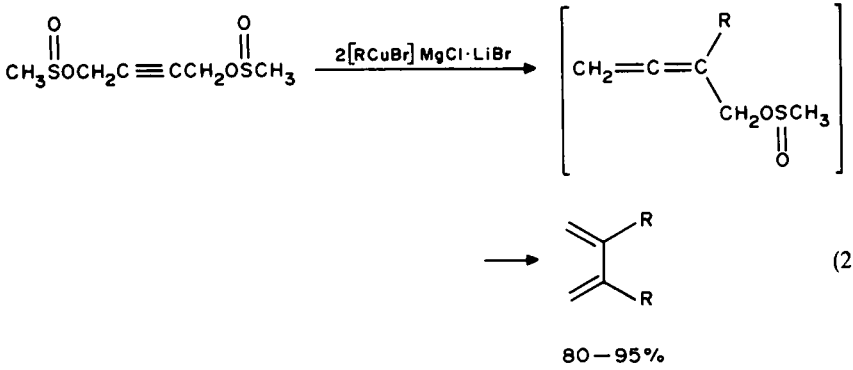
(19)

The most popular propargylic precursors for the organocuprate mediated formation of allenes appear to be the sulfonate esters[84–90]. This reaction, which is illustrated by equation 20[85], also proceeds with *anti* stereoselectivity and is useful for the preparation of practically pure optically active allenes, including allenic steroids. This reaction has also been used for the preparation of a variety of trimethylsilylallenes. The latter have been employed in a new regiospecific [3 + 2] annulation approach to highly substituted five-membered carbocycles, involving reaction with electron-deficient alkenes in the presence of titanium tetrachloride. Annulation employing α,β-unsaturated ketones proceeds stereoselectively via suprafacial addition to the enone and affords TMS-cyclopentenes in a single step[89,90].



(20)

In addition to the propargylic halides, alcohols, ethers and sulfonates mentioned so far, a variety of propargylic sulfinates and carboxylates has also been used in the organocopper-induced S_N2' allene formation[91–106]. The utility of sulfinate esters is especially important with tertiary propargylic alcohols, in view of the well-known difficulty to prepare the corresponding sulfonates and their reduced stability. These reactions have been studied with both acyclic and cyclic systems and have found extensive application in the synthesis of various natural products, particularly of vitamin A and D analogues by Okamura and coworkers[17,94–98,104]. Several selected examples are shown below and include a convenient synthesis of specifically substituted conjugated dienes (equation 21)[91], vinylallenes (equation 22)[94] and allenic retinoids (equation 23)[98].



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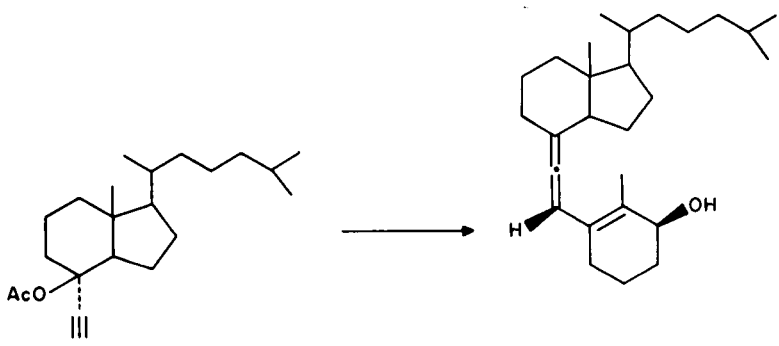

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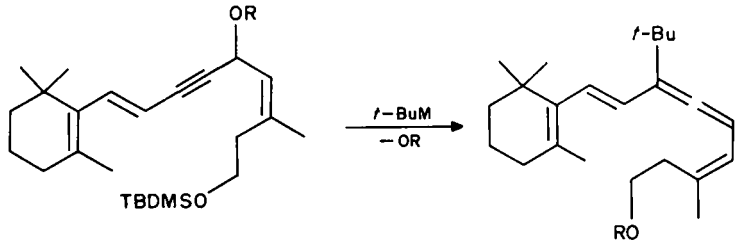
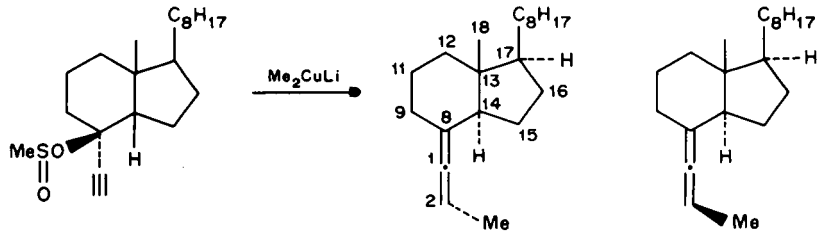


(23)

Recently, a detailed study of the stereochemistry of organocopper-mediated conversion of propargylic esters to allenes has been described by Okamura and coworkers[104]. Using a vitamin D-related steroidal fragment as a stereochemical probe, the effect of various factors on the stereochemical course of the reaction has been investigated. In all cases, an *anti* mode of S_N2' attack by the organocopper species was found to be preferred. For example, reaction of propargyl methanesulfinate **44** with $(CH_3)_2CuLi$ in ether afford (*R*)-allene **45** and (*S*)-allene **46** in a ratio of 64:1. This result is in agreement with previous findings by the same authors[17,94–97] as well as by others[65,105]. A study of the effectiveness of Gilman-type reagents (R_2CuLi) versus that of the Lipshutz-type higher-order mixed cuprate systems ($R_2CuCNLi_2$)[109] in promoting the reaction indicated that optimal yields are obtained with the Gilman reagents for R = Me or Bu, and with the Lipshutz reagents when R = *s*-Bu or *t*-Bu. An *anti* mode of attack has also been reported for the Pd(O)-catalyzed conversion of propargylic acetates, trifluoroacetates and methanesulfinates into allenes using phenylzinc chloride[107,108].



(44) *R*-**(45)** *S*-**(46)**

3. *Reaction of organometallics with allenic derivatives*

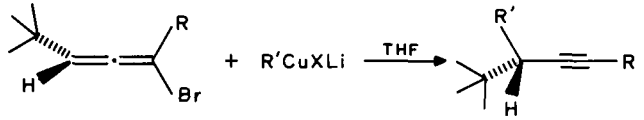
Similar to the organometallic-induced S_N2' displacement observed with propargylic derivatives, discussed in the preceding section, an organocuprate induced S_N2' displacement with allenic derivates has also been studied, though to a more limited extent. Practically all the reports involve allene → acetylene rearrangements of allenic halide substrates[53–55,110–114]. One of the first reactions of this type has been described by Vermeer and coworkers[110] and used to prepare 1-alkynyl ethers from 1-iodo-1-methoxypropadiene (equation 24).

More recently, Corey and Boaz[111,112] have investigated the stereochemistry of this reaction, and have found that optically active 1,3-disubstituted bromoallenes react with a variety of cuprate reagents, preferentially in an S_N2' fashion with very high *anti* selectivity.

For example, reaction of optically active bromoallenes (*R*)-**47a, b** with the heterocuprate $CH_3(CN)CuLi$ in THF afforded the corresponding optically active acetylenes **48a, b** in practically quantitative yield and with *anti*:*syn* ratios of 99:1 and 98:2, respectively (equation 25).

$$H_2C{=}C{=}CI(OCH_3) + n[RCuY]M \xrightarrow[\text{THF TMED or } Me_2SO \text{ TMED}]{\text{THF,THF HMPT}} RCH_2{-}C{\equiv}C{-}OCH_3 \qquad (24)$$

R = alkyl, vinyl, Ph or C≡CR′
Y = Br ($n = 1.0$) or R ($n = 0.5$)
M = Li or MgX·LiBr



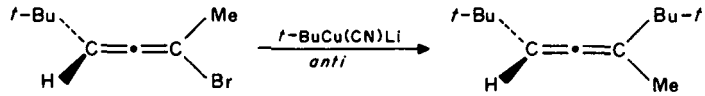
(25)

R-(**47**) (**48a,b**)

(**a**) R = *t*-Bu, ≤ 76.2% ee
(**b**) R = *t*-CH_3, ≤ 94.2% ee

This strong *anti* selectivity has been rationalized by the same authors[112] as a stereoelectronic effect arising from 'bidentate' binding involving a d orbital of nucleophilic copper with both the C-2/C-3 π^* and the C—Br/σ^* orbitals of the substrate. The synthetic utility of this reaction in the total synthesis of several natural products has also been demonstrated by Corey and coworkers[53-55,113].

Interestingly, while $CH_3(CN)CuLi$ proved very efficient[114] in the conversion of bromoallenes **47** to alkylacetylenes **48**, the use of *t*-Bu(CN)CuLi gave only 2% of the expected S_N2' product and 98% of the corresponding alkylallene (equation 26). Although the reaction shown in equation 26 was first believed to occur with inversion of configuration due to incorrect assignment of the absolute configuration of the product[111], it was subsequently shown by an independent route of known stereochemistry to proceed with rentetion of configuration, as shown[85].



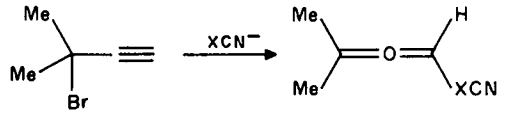
(26)

(*R*)-(−)-(**47b**) (*S*)-(−)-(**49**)

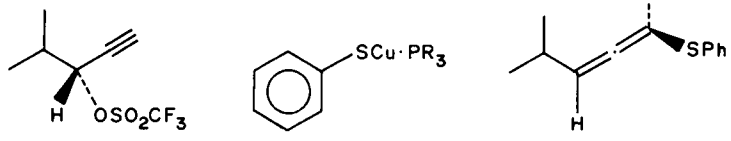
4. S_N2' displacement reactions

In addition to the extensively documented S_N2' reactions of organometallic reagents with propargylic and allenic derivatives described in the preceding two sections, a number of reports on the S_N2' reaction of propargyl derivatives with some sulfur and selenium nucleophiles have also been published[115-121].

For example, the S_N2' displacement reaction by thiocyanate or selenocyanate anion on α,α-dimethylpropargyl bromide (**50**) results in the formation of γ,γ-dimethylallenyl thiocyanate (**51**) and seleocyanate (**52**), respectively[115]. Similarly, the reaction of α,α-

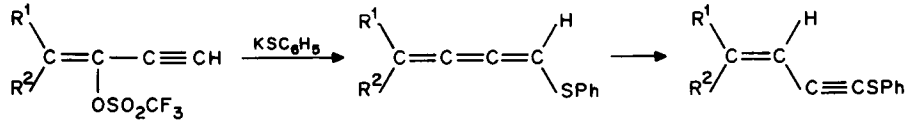


(50) (51) X = S
(52) X = Se



(53) (54) (55)

dimethylpropargyl chloride with either thiophenol under phase transfer conditions[116,117] or phenylthiocopper trimethylphosphite complex in TMDA[118] affords γ,γ-dimethylallenyl phenyl sulfide by the same type of mechanisms. Subsequently, a stereochemical study of the latter reaction has also been reported[119]. Using the chiral secondary propargylic triflate **53** and phenylthiocopper trimethylphosphite complex **54**, the reaction afforded optically active allenyl sulfide **55** with complete inversion of configuration and clean *anti* stereochemistry. However, the corresponding mesylate ester reacts with the same complex to give racemic products. This result contrasts with the high *anti* selectivity observed in the S_N2' displacement reactions of organometallics with propargylic and allenic derivatives described above, but seems to be in agreement with the wide variability of S_N2' stereochemical preference observed with conventional nucleophiles[122]. The reaction of nucleophiles with enyne triflates also proceeds via an S_N2' process, and results in functionalized enynes by way of a 1,3-hydride shift from the initially formed butatriene intermediate, as illustrated in equation 27[120].

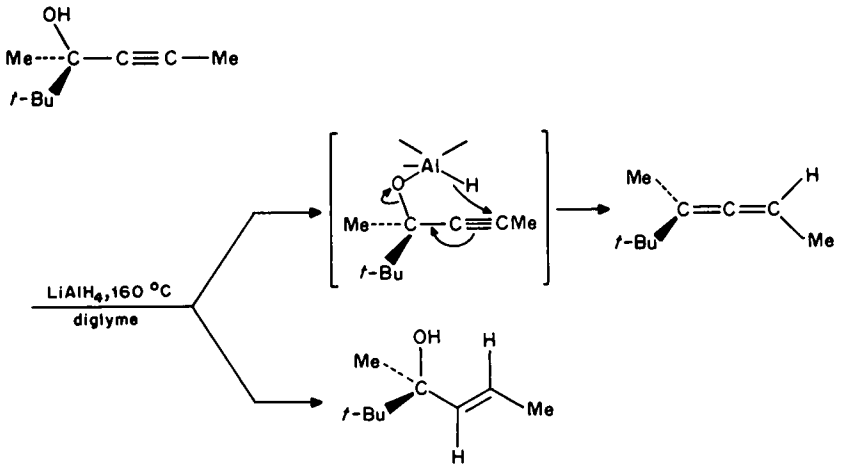


(27)

5. Reduction of alcohols, esters and halides

The reduction of propargylic alcohols with $LiAlH_4$ in boiling solvents has been previously shown to afford mixtures of allenes and allylic alcohols, and was suggested to proceed by the mechanism shown in equation 28[9]. A study of the solvent and temperature effects on the $LiAlH_4$ reduction of α-*t*-butyl-α-phenyl-γ-methylpropargyl alcohol has subsequently indicated that the formation of the corresponding allene product is favored by both an increase in reaction temperature and the use of ether instead of THF[123]. More recently, however, exclusive formation of allenes and allyl alcohols during the reduction of aryloxymethylethynylcarbinols and ethynylcarbinols, respectively, with $LiAlH_4$, has been reported[124]. For example, reduction of the propargyl alcohol **56** proceeds at room temperature and affords the corresponding allene **57** in 92% yield. The reaction is not

limited to the norbornyl system but is a general one. However, in the absence of the aryloxymethyl substituent, complete reduction to the corresponding alkyl alcohol occurs. Thus, reaction of α,α-diphenylpropargyl alcohol under the same conditions affords the corresponding allyl alcohol, exclusively. The formation of allene **57** has been rationalized as outlined in equation 29. This mechanism could also account for the regioselective and stereoselective formation of only one allenic product (**57**). With simple ethynylcarbinols, the reduction takes the normal course giving allylic alcohols, since the internal solvation of the alkoxyaluminium intermediates is not possible[124].



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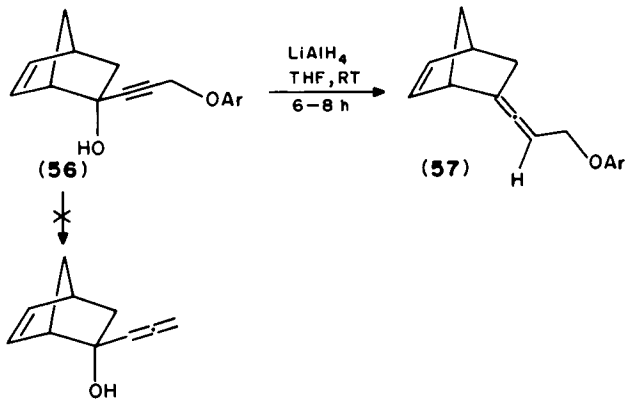
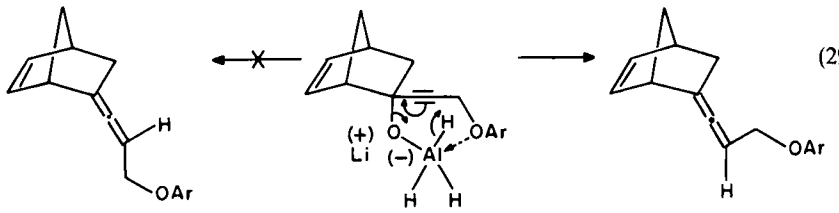
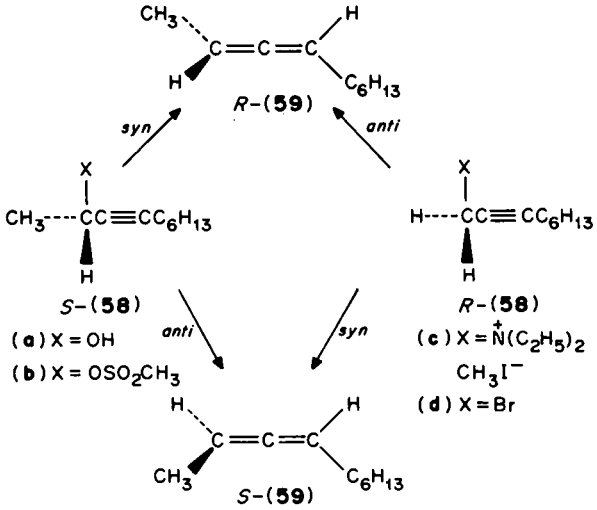




(29)

A detailed mechanistic study of the allene-forming reductions of chiral propargylic alcohols and other derivatives with hydride reagents has been reported by Claesson and Olsson[125]. These authors have treated the four chiral α-methyl-γ-hexyl-propargyl derivatives **58a–d** shown in equation 30 with various aluminum hydride reagents selected to give high yields of 2, 3-decadiene in THF solvent. The preferred mode of substitution was deduced from the known absolute configurations of starting material and product. It was thus found that the use of hydroxy, tertiary amine or bromide as the leaving group (in compounds **58a**, **58c** and **58d**, respectively) yielded the allene in a preferred *overall syn* mode of substitution, the degree of which increased with temperature. However, the mesylate (**58b**) with lithium trimethoxyaluminum hydride yielded the allene in an *anti* displacement which was more predominant at lower temperature.



(30)

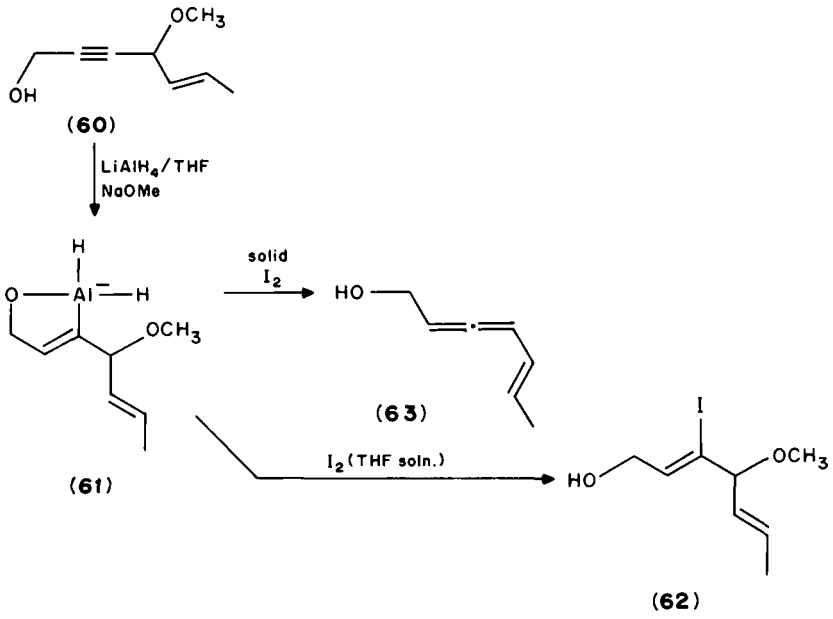
Although the δ-methoxy propargyl alcohol **60** is readily reduced by $LiAlH_4$ in THF at room temperature to afford the alanate **61**, no allene could be obtained from this species on heating in refluxing THF or even dioxane[126]. However, a remarkable observation was made, in that addition of iodine to **61**, as a THF solution at − 78 °C, afforded the expected vinyl iodide **62**, whereas addition as the solid at − 78 °C led directly to allene **63**. While no reasonable explanation could be offered for these surprising findings, the method has been applied for the preparation of a variety of allenic alcohols in good to excellent yields.

C. Rearrangements Involving 'Propargylic' Organometallic Reagents

One of the most active areas of research in allene chemistry in recent years involved propargylic and allenic organometallic reagents. This is well illustrated by the number of major reviews dedicated to this subject during the last decade[127–129].

1. Structure of 'propargylic' organometallics

The importance of the propargylic anions in synthesis emerged from the recognition of their utility for the extension of the carbon chain and facility in the interconversion of the functionality. Their applicability in organic synthesis, however, may sometimes be limited because of the difficulties in controlling the regio- and stereoselectivities of the reaction.

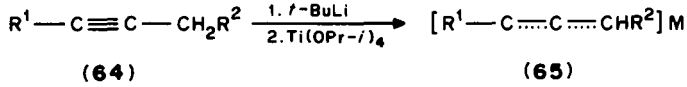


This is a consequence of the postulated equilibrium between propargylic and allenic anions, or, alternately, of the metallotropic shift[127] between allenylmetal and propargylmetal compounds (equation 31). Functionalization of mesomeric acetylenic–allenic

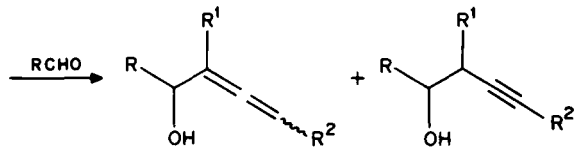
(31)

carbanions may, in principle, give a mixture of the acetylenic and allenic derivative. The ratio of the two isomeric products depends upon the counterion (MgX, Li, Na, K, Cu, ZnX, etc), the solvent and the substitution pattern, as well as upon the nature of the functionalization reagent and its substituents. Furthermore, in the reaction with certain electrophiles such as in the condensation with carbonyl compounds each of the two products, acetylenic and allenic alcohols, may consist of two stereoisomers, i.e. *erythro* and *threo* isomers. The following example reported by Yamamoto and coworkers[130,131] will illustrate the striking dependence of regioselectivity on the counterion and substitution pattern. The lithio reagent **65a** (R^1 = Me, R^2 = H) derived from 2-butyne reacted with cyclo-hexanecarbaldehyde in THF solvent to give a mixture of α-allenic and β-acetylenic alcohols **66** and **67**, respectively, in the ratio of 42:58. On the other hand, the titanium derivative **65b** (R^1 = alkyl or R_3Si, R^2 = H) gave the α-allenic alcohol **66** without contamination of any β-acetylenic alcohol **67** (equation 32). However, a dramatic change in the product distribution occurred when the reactions of the homologous titanium reagents derived from 1,3-disubstituted propyne **65b** (R^1 = alkyl or R_3Si, R^2 = Me) were conducted with the same aldehyde. Thus, none of the corresponding α-allenic alcohols was detected, and instead the β-acetylenic alcohols **67** were obtained stereoselectively. The additions of the allenic and acetylenic organometallics to the carbonyl are assumed to take place by an allylic rearrangement of the organometallic and the chelate transition states

shown in equations 33 and 34. According to this mechanism an allenic organometallic produced the β-acetylenic alcohol while the α-allenic alcohol was derived from an acetylenic reagent. This mechanism has been supported by the IR spectra of the appropriate titanium reagents, which indicated that the titanation of the initial propargylic anions took place with extreme regioselectivity to produce either allenic or acetylenic titanium derivatives depending on the substitution patterns of the original alkynes[130].



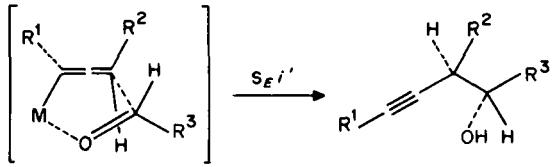
(64) (65)



(66) (67)

(a) M = Li

(b) M = $Ti(OPr\text{-}i)_4$ (32)



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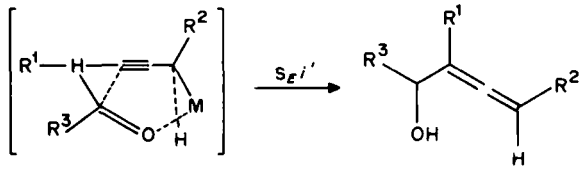
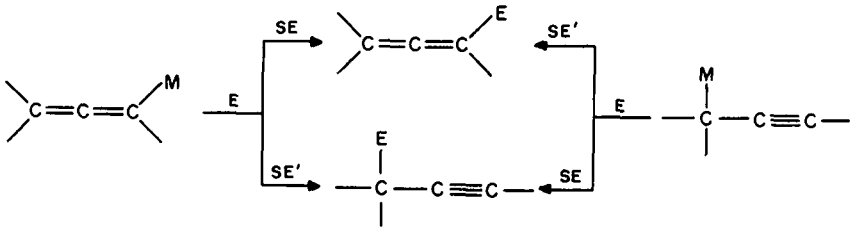


(34)

2. Electrophilic substitution reactions

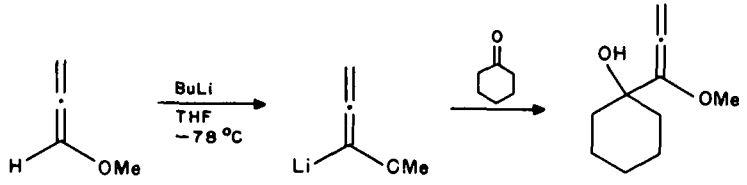
The general behavior of propargylic and allenic organometallic reagents during electrophilic substitution is shown in Scheme 1 below. As indicated in the preceding section, the reaction of either form of the ambident anion may proceed with either retention of structure (S_E) or rearrangement ($S_{E'}$). Although formation of isomeric mixtures may be expected, formation of single products is not uncommon. Product composition is highly dependent on the nature of the metal and electrophile, pattern of substitution in both substrate and electrophile and the solvent.

A brief discussion of some representative reactions of the various organometallics with some common electrophiles is presented below.

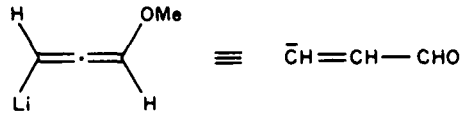


SCHEME 1

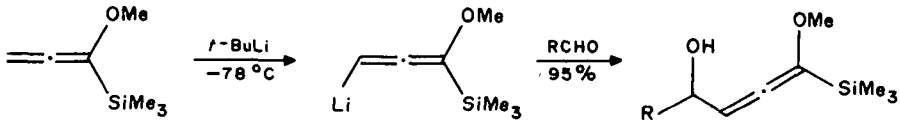
a. With aldehydes and ketones. Methoxyallene (**68**), first prepared and metalated by Brandsma and coworkers[132], has gained considerable popularity due to its easy preparation and highly regioselective metalation and electrophilic substitution. Thus deprotonation with BuLi in THF at −78 °C gives the corresponding α-lithio compound (**69**), which on treatment with aldehydes and ketones, including conjugated enones, affords α-allenic alcohols in good yields. The reaction has found wide application in synthesis including natural products[133–137]. The latent carbonyl functionality which is transferred to the product makes this lithiated species (**69**) an excellent acyl anion equivalent of acrolein. An equally, or even more, synthetically useful reagent should be the γ-lithio derivative of α-methoxyallene **71**, which can be employed as a homoenolate equivalent. A change of regioselective α-lithiation to γ-lithiation is not easy to achieve, but it has been observed during lithiation of *t*-butoxyallene with the bulky lithium dicyclohexylamide in THF at −55 °C[138]. However, functionalization at the α-position provides an alternative method to achieve this goal, especially by treatment with chlorotrimethylsilane. Thus, treatment of α-silylated α-methoxyallene **72** with *t*-butyllithium in THF at −78 °C gave the lithio species **73**, which on treatment with butyraldehyde was transformed into the adduct **74** in 95% yield; attempts to prepare α,γ-dilithio-methoxyallene were not successful[139].



(**68**) (**69**) (**70**)

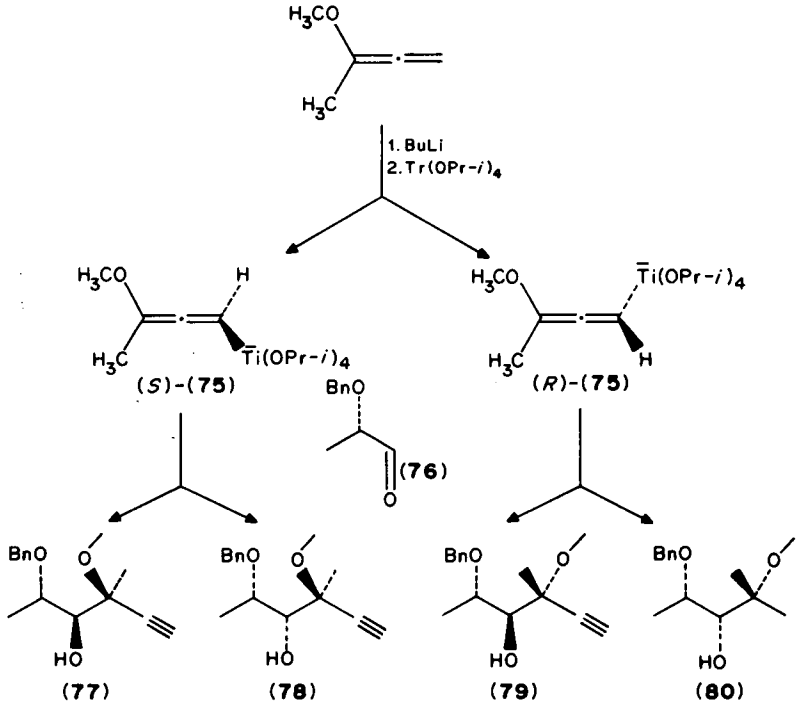


(**71**)



(**72**) (**73**) (**74**)

Interestingly, unlike allenyllithium reagent **73**, γ-methoxy-γ-methyl-allenyllithium reacts with aldehydes in a nonregioselective manner. However, the reaction of the corresponding titanium reagent (**75**) produced only propargylic-type adducts. Furthermore, the use of racemic 2-(benzyloxy)propionaldhyde (**76**) resulted in significantly altered diastereomeric product ratios, relative to the use of optically active aldehyde **76** (equation 35)[140]. This is a consequence of the fact that **75** is a racement of an apparently configurationally stable allenyl metal compound[141]. Therefore, upon reaction with optically active **76** there are two different pairs of reactants, (*S*)-**75** and (*S*)-**76** versus (*R*)-**75** and (*S*)-**76**, one combination leading to the products **77** and **78**, the other combination to **79** and **80** in an approximately 50:50 ratio.



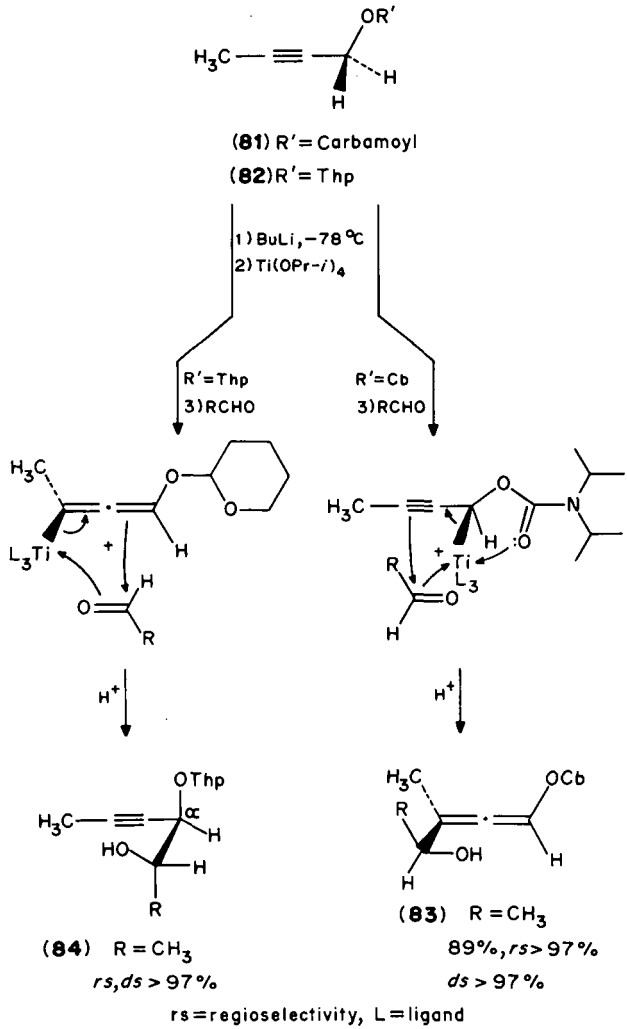
(35)

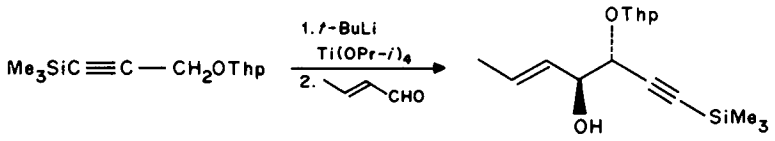
A (*S*)-(−)-(**76**)	50	:	1	:	35	:	14
B *rac*-(**76**)	*rac*-**77**		*rac*-**78**		*rac*-**79**		*rac*-**80**
	92	:	<1	:	6	:	2

Another example of the dramatic effect on the regio- and stereoselectivity of propargylic anions by titanium reagents is the diastereoselective allene synthesis using titanated alkynyl carbamates, reported by Hoppe and coworkers[142–144]. These authors have found that the 2-butynyl carbamate **81** is rapidly deprotonated to the lithium compound under standard conditions. After exchanging the cation with titanium isopropoxide, addition to aliphatic aldehydes gives diastereomerically pure α-allene alcohol **83** with over 95% *ds* (diastereomeric selectivity). This reaction sequence is remarkable in two respects: The corresponding tetrahydropyranol (Thp) ether **82**, reported by Yamamoto and coworkers[130], affords only the propargylic adduct **84** upon lithiation and titanation under

conditions nearly identical to the former experiment, and evidence for an allenic titanium intermediate was obtained by IR spectroscopy. The complete inversion of regioselectivity on changing the oxygen substituent clearly demonstrates the active role of the carbamoyloxy group in locating the cation. The second surprising aspect is the high degree of diastereoselectivity observed on fusion of axial prochiral and centro-pro-chiral groups, which appears to have been unknown before. A stereocontrolled synthesis of (±)-Asperlin and related stereoisomers using the reaction shown in equation 36 as the key step, was reported by Yamamoto and coworkers[145]. The remarkable utility of organotitanium compounds as selective nucleophilic reagents in organic synthesis in general has been reviewed[146].

Similar to the conversion of propargyl ether **82** to the β-acetylenic alcohol **84**, lithiation of 1-methoxy-2-butyne at −70 °C followed by the addition of one equivalent of $ZnCl_2$ generates the very reactive and unsoluble organozinc intermediate **85**. Reaction of the





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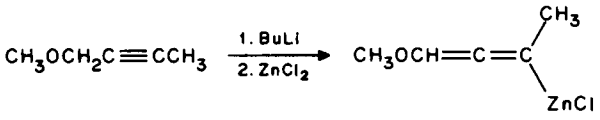

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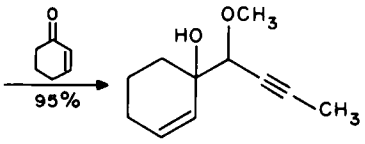
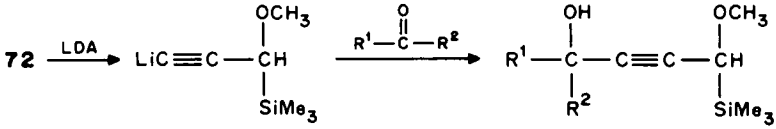


(86)

latter with cyclohexenone affords the homopropargylic alcohol **86** in 95% yield as a 65:35 mixture of diastereomers[147].

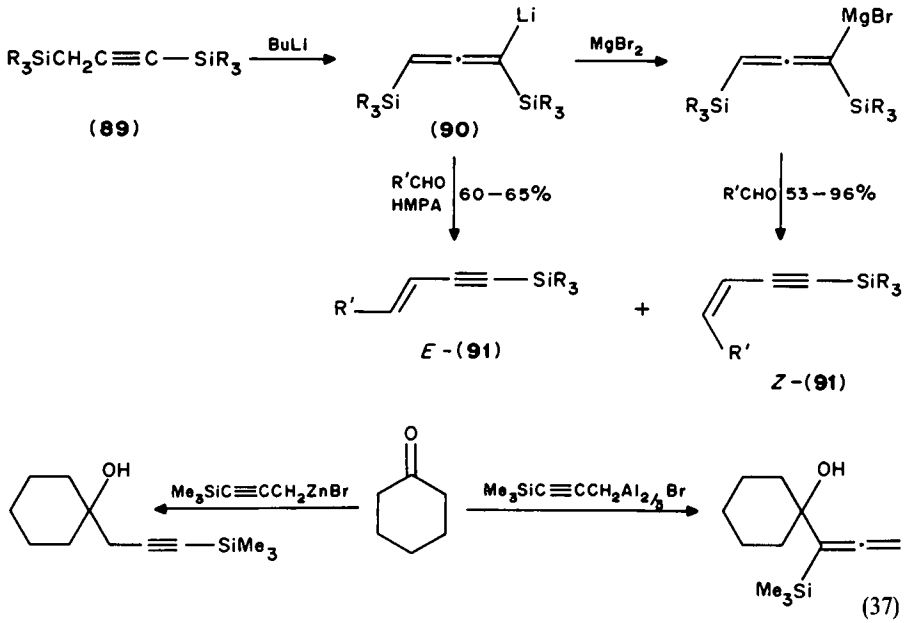
Returning to the γ-lithiation of α-protected methoxyallene **72**, it was subsequently found that if the reaction is performed with LDA instead of *t*-BuLi, isomerization to the lithio acetylene **87** takes place[148]. Reaction of the latter with aldehydes or ketones provides the propargyl alcohols **88** in high yields. This is another example of the strong dependence of selectivity on reaction conditions.



(87) (88)

In addition to the trimethysilyl substituted allenes and acetylenes mentioned so far, a variety of other silylated propargylic or allenic derivatives have been prepared and utilized for the functionalization of these systems in recent years[149–157]. For example, bis-1,3-disilylpropynes (**89**) are easily metallated with *t*-BuLi (−78 °C)[150] or *n*-BuLi (−20 °C)[152] to generate allenyllithium derivatives **90**. The latter react with aldehydes and afford *E* or *Z* enynes in ratios ranging from 1:10 to 1:20, depending on the size of the silyl substituent, the counterion and reaction conditions. The predominance of the *Z*-enynes is further increased on transmetallation to magnesium or titanium[153]. On the other hand, addition of excess HMPA causes an inversion of the stereoselectivity of carbonyl olefination indicated above, using R = *i*-Pr in the starting material[152].

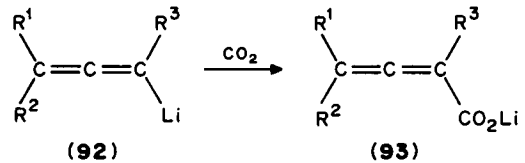
An interesting contrast between the reactions of propargyl aluminum and zinc bromides has been observed. While the organometallic produced by reaction of trimethylsilylpropargyl bromide with aluminum amalgam in THF condenses readily with aldehydes and ketones to yield α-allenic alcohols[151], the reaction of the corresponding zinc reagent gives β-acetylenic alcohols regioselectively[159] (equation 37).

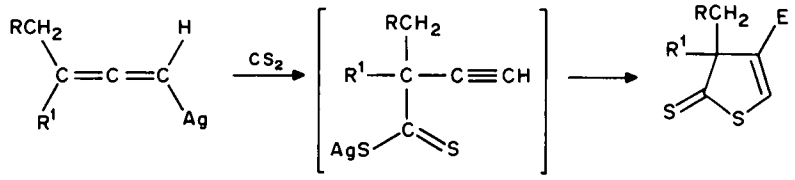


b. With carbon dioxide and disulfide. When treated with carbon dioxide, a series of alkyl substituted and unsubstituted allenyllithium reagents (**92**) reacted regioselectively to yield the corresponding allenic acids (**93**). The preparation of the allenyllithium reagents **92** from the corresponding hydrocarbons by metallation with BuLi also proceeded regioselectively[159].

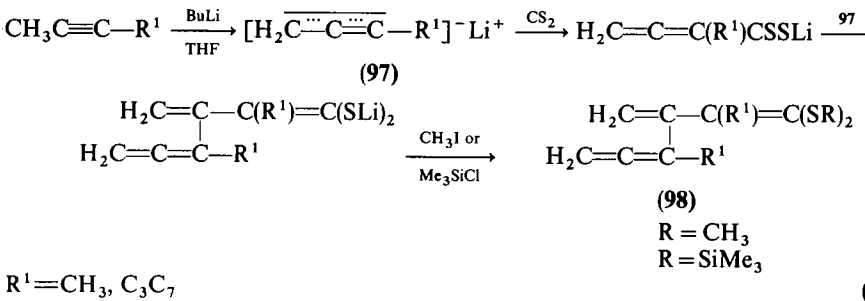
Allenyl silver reagents (**94**), easily prepared by treatment of the corresponding allenyllithium compounds with silver bromide, have been reported with both carbon dioxide and carbon disulfide, but with opposite regioselectivity. Thus, the reaction with carbon dioxide provides the corresponding allenic acids in excellent yields[160]. On the other hand, the reaction with carbon disulfide affords a convenient route to γ-dithiolactones **96**, apparently by way of the silver propargyl dithiocarboxylate intermediate **95**[161,162]. Interestingly, the lithio salt of **95** can be isolated[161], but is converted to **96** on treatment with $AgBr/H^+$.

Recently, de Jong and Brandsma[163] reported that addition at low temperature of carbon disulfide to a solution of the lithium compound $[CH_2{=}C{=}CR^1]Li^+$ ($R^1 = CH_3$, C_3H_7, Ph, OCH_3, SCH_3) results in the initial formation of an allenic carbodithioate $H_2C{=}C{=}C(R^1)CSSLi$, while for $R^1 = t$-Bu or $SiMe_3$ acetylenic carbodithioates $R^1C{\equiv}CCH_2CSSLi$ are formed. The initial products undergo very rapid subsequent reactions. For example, for $R^1 = CH_3$ or C_3H_7 the lithium compound undergoes self-addition and yields after quenching conjugated enallenes **98** (equation 38).





(94) (95) (96)

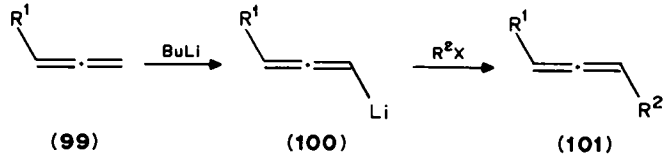


(97)

(98)
R = CH_3
R = $SiMe_3$

R^1=CH_3, C_3C_7 (38)

c. With alkylating agents and other electrophiles. Linstrumelle and coworkers[164] have shown that a variety of mono-, di- and trisubstituted allenic hydrocarbons undergo facile lithiation with BuLi in THF in the presence or absence of 1 equivalent of HMPA. Thus, metallation of monosubstituted allene **99** ($R^1 = n\text{-}C_8H_{17}$) and alkylation gave the disubstituted allene **101** in 90% yield.

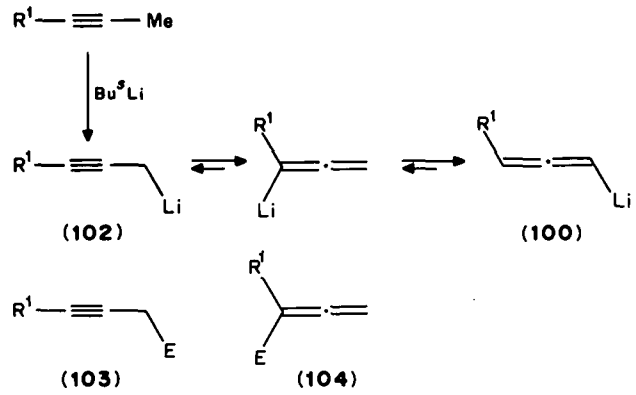


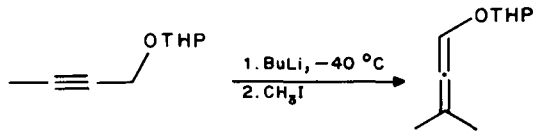
(99) (100) (101)

Rearrangement of the propargyllithium compound **102** into allenyllithium **100** was subsequently reported by the same author[165]. The lithio derivative **102** can be prepared by treatment of 2-alkynes with *s*-butyllithium in THF–cyclohexane at 0 °C. Addition of electrophiles gave a mixture of propargylic and allenic products **103** and **104** in about 1:1 ratio. However, in the presence of 0.5 equivalent of HMPA the reaction becomes more regioselective and affords mainly product **104**, while in the presence of 5 equivalents of HMPA the isomeric 1,3-disubstituted allenic product (**101**) is observed, invoking rearrangement of **102** to **100**. It has been assumed that with a larger amount of HMPA, a more dissociated ion pair is formed which is easily converted into the more thermodynamically stable allenic species **100**.

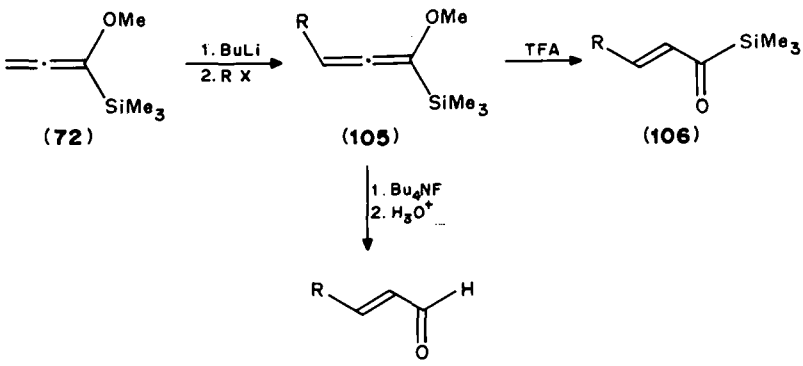
Unlike the electrophilic substitution of 1-alkoxy-1-allenyllithium reagents which proceeds regioselectively to give allenic products, as discussed above, the sequential reaction of propargylic ethers with BuLi and CH_3I affords allenic products instead (equation 39)[166,167].

γ-Methoxy-γ-trimethylsilylallenyllithium (**73**) undergoes alkylation stereoselectively to allenic products **105**, which on treatment with trifluoroacetic acid in THF–water at room temperature afforded the *trans*-α,β-unsaturated acylsilane **106**. Desilylation of **105** with Bu_4NF in THF–methanol, followed by mild acid hydrolysis, gave the *trans*-α,β-unsaturated aldehydes in high yield (R = n-C_4H_9, 92%). A series of various silyl ketones,



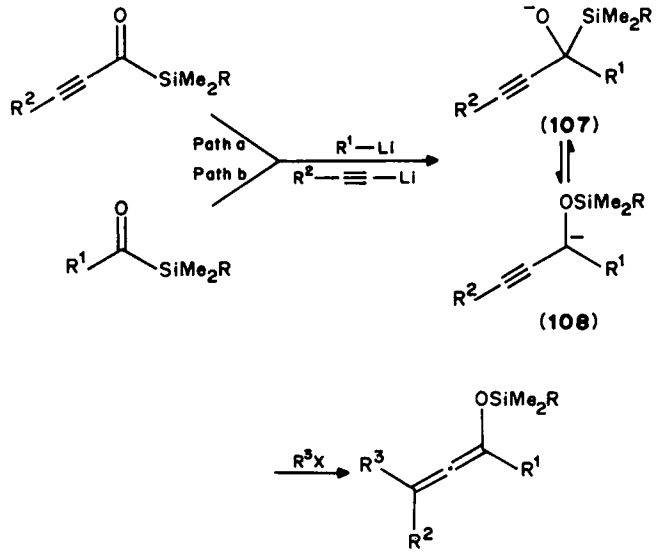


(39)



including alkenyl and alkynyl silyl ketones, has been similarly prepared by Reich and coworkers[166,169]. A special case of allenol ethers, which has received considerable attention in recent years, is that of silyl allenyl ethers[170–177] which can be conveniently obtained by addition of organolithium reagents to silyl ketones, followed by a [1,2] sigmatropic rearrangement of the α-silyl alkoxide intermediate **107** to the siloxypropargyllithium species **108** (the Brooke[177] rearrangement), and alkylation of the latter (equation 40)[170]. A typical reaction of the siloxyallenes is their acid hydrolysis to α-β-unsaturated carbonyl compounds[176].

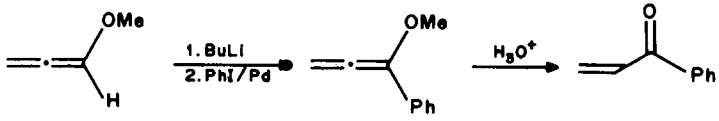
The behavior of β-lithioallenyl selenides, easily obtained by deprotonation of the corresponding allene, generally parallels the oxygen analog. Thus, protonation and alkylation occur predominantly to give allenic products ($CH_3I > 20:1$), but reaction with aldehydes gives predominantly acetylenic products[178]. A convenient route to aryl allenes,



(40)

1,2,4-alkatrienes and conjugated enones is provided by the palladium-catalyzed arylation and vinylation of allenyllithium reagents (equation 41)[179].

Besides alkylating agents and the carbonyl compounds mentioned so far, a number of other electrophiles have been used for various allenyllithium compounds in recent years. These include expoxides[159,160], disulfides[159] substituted ureas[159] and conjugated α,β- unsaturated keto enol ethers (equation 42)[181–183] and alkylboranes[184].



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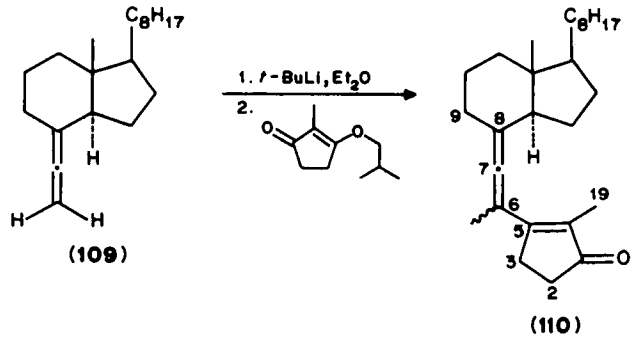
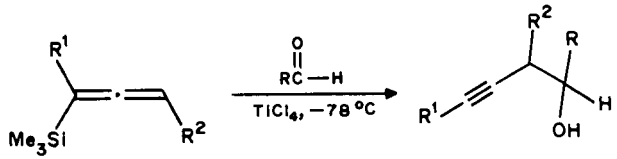


(42)

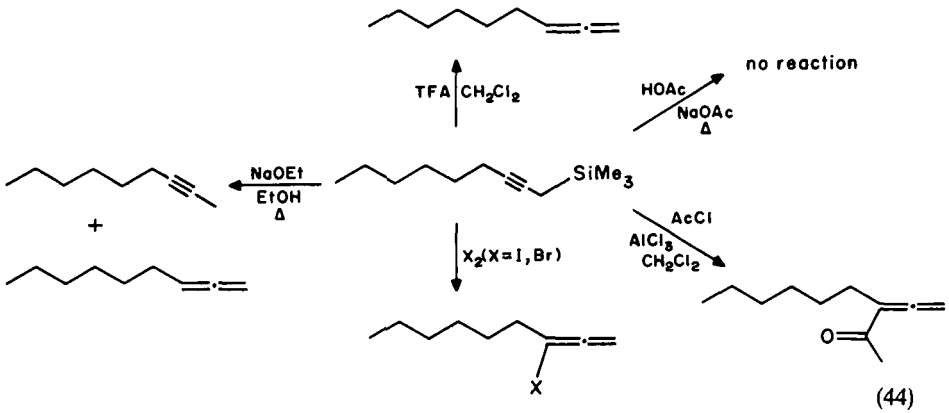
3. Electrophilic substitution of silicon

Danheiser and Carini[149] have shown that trimethylsilylallenes can act as propargylic anion equivalents and afford homopropargylic alcohols directly on reaction with aldehydes and ketones in the presence of titanium tetrachloride (equation 43).



(43)

The considerable interest in allyltrialkylsilanes due to their ability to undergo electrophilic carbon–carbon bond formation with concomitant double-bond shift and cleavage of silicon[185] has prompted interest in the analogous propargyltrialkylsilanes[186–189]. Such compounds are readily accessible from the reaction of lithium salts of alkynes with (trimethylsilyl)methylhalides[186] or trifluoromethanesulfonates[187], and their rearrangement to terminal allenes has been observed[187]. For example, the preparations of 1,2-alkadienes, 3-halo-1,2-alkadienes and 3-acyl-1,2-alkadienes from reaction of propargyltrimethylsilanes with trifluoroacetic acid, bromine or iodine, or acetyl chloride–aluminum chloride, have been reported by Flood and Peterson[188] (equation 44). Although the yields are only moderate, these reactions have the advantage over alternative methods in that they afford pure products. Another example that shows the synthetic utility of this rearrangement is the electrophilic cyclization to 8-(trimethylsilyl)-6-octyn-2-yl tosylate (**111**) to the exocyclic five-membered ring allene (**112**) under solvolytic



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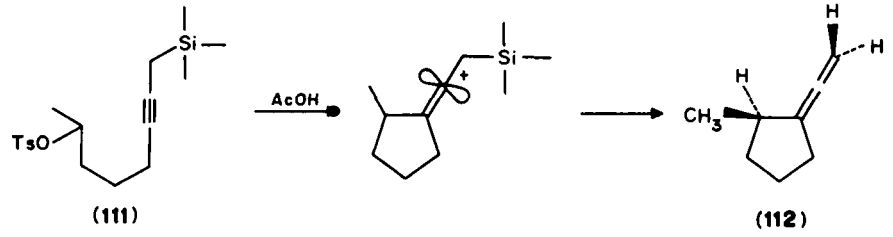
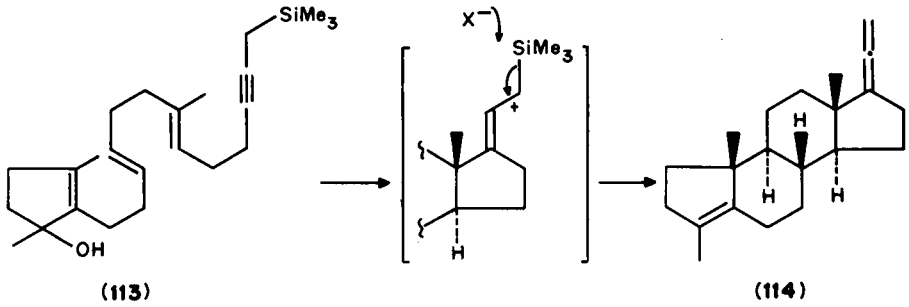


(111) (112)

conditions. In a truly remarkable application of this methodology, Johnson and coworkers[189] have achieved a one-step polyene cyclization of propargylsilane **113** to the exocyclic steroidal allene **114**, on treatment with a catalytic amount of trifluoroacetic acid at −35 °C (equation 45).

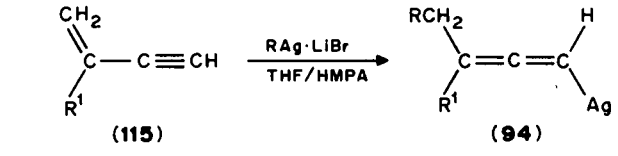


(113) (114)

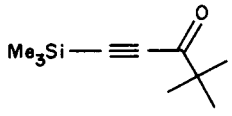
(45)

4. Conjugate addition of organometallic reagents

The following two acetylene–allene rearrangements involve conjugate additions of organosilver or organocuprate reagents to conjugate enynes and ynones. In the first rearrangement of this type, allenyl silver-compounds **94** are prepared *in situ* by the reaction of alkyl silver(I) lithium bromide complexes with butenynes **115**[190,191]. In the second example of conjugate addition, treatment of β-silylynone **116** with methylcopper followed by chlorotrimethylsilane gave the doubly silylated allenol ether **117**, in high yield. Titanium-catalyzed phenylthioalkylation of the latter affords α,β-unsaturated ketones, also in high yields[192].



(115) (94)



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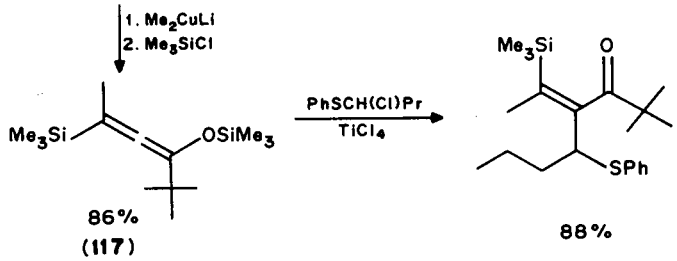
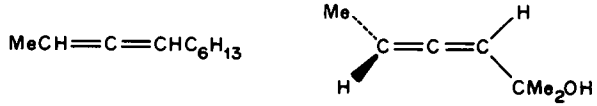


86% 88%

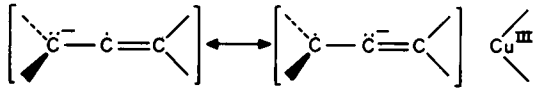
(117)

5. Configurational stability of allenic organometallic reagents

In addition to the problem of the propargyl–allenyl equilibrium discussed in Section II.C.1 above, the question of configurational stability of chiral allenes upon treatment with organometallic reagents has also been investigated during the last decade. For example, Claesson and Olsson[193,194] have observed that chiral disubstituted allenes such as (*R*)- and (*S*)-**118** and (*R*)-**119** undergo racemization in the presence of twofold excess of organocuprates such as Bu_2CuLi, or in the case of the chiral alcohol in the presence of MeMgI alone. The racemization, which occurs within hours even at 0 °C or below, has been suggested to involve electron transfer from the organocuprate reagent to the allene and rotation around the single bond of the radical anion intermediate **120**[193]. Similar results have been subsequently reported by Vermeer and coworkers[106]. These authors have found that the two epimeric steroidal allenes **121** and **122** are readily interconverted at 0 °C by treatment with threefold excess of Me_2CuLi or MeCuMgCl in THF, and have also suggested a radical anion mechanism for this process. More recently, however, Okamura and coworkers[104] have tested the stability of steroidal allenes (*R*)-**45** and (*S*)-**46** using various organocuprates, including Me_2CuLi and Bu_2CuLi, under similar con-



(118) *R* -(119)



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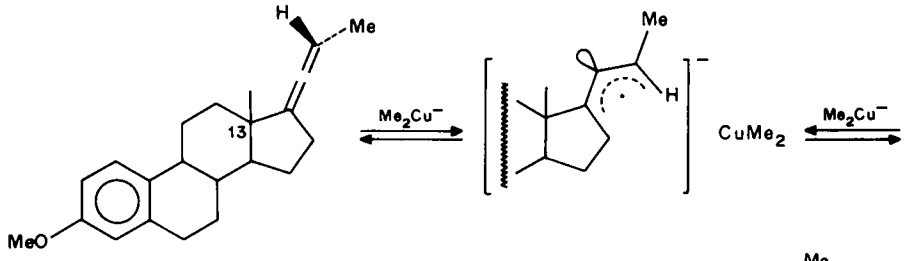

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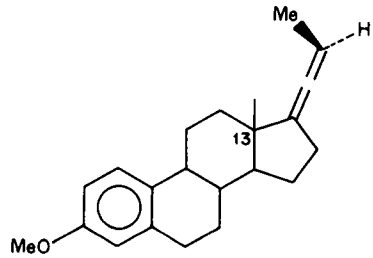
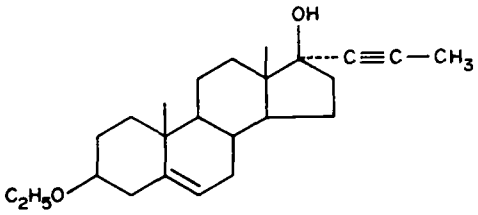
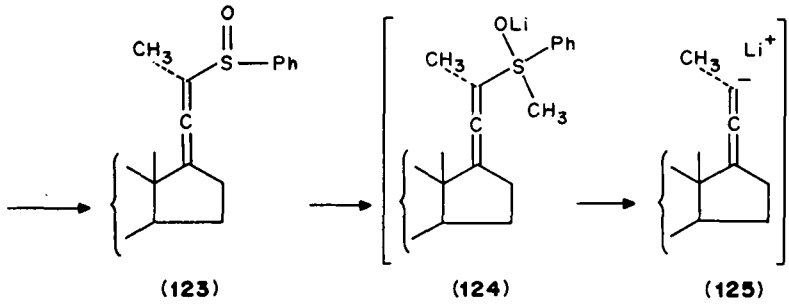


(122)

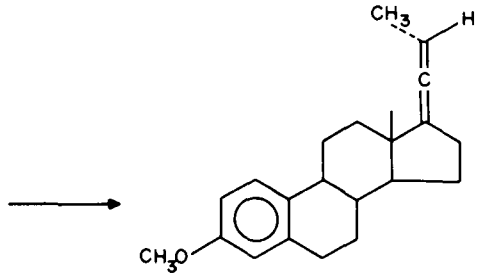
ditions, and have obtained different results. For example, no significant isomerization was observed with the former reagent at 0 °C in ethers after 6 hours and only partial isomerization occurred with the latter reagent under conditions similar to those used by Claessen and Olsson[193]. Furthermore, on substitution of allenic methyl by a *t*-butyl group no isomerization took place with either of the two reagents. These differences were tentatively explained by steric factors and reduction potentials.

As previously mentioned, the stereochemical studies performed by Okamura and coworkers[18] on the metallation of chiral allenes (*R*)- and (*S*)-**8**–**10** seemed to indicate that alkyl-substituted allenic anions are configurationally unstable. On the other hand, several other reports describe evidence in support of configurationally stable allenic anions, including alkyl substituted substrates. For example, steroidal allenic sulfoxide **123** is almost instantaneously converted to the desulfurized allene **126** on treatment with MeLi at −70 °C (4 equivalents of CH_3Li, THF, 10 min)[105]. The formation of **126** has been explained by the intermediacy of tetra-coordinated intermediate **124**, which undergoes C—S bond cleavage to form the allenyl anion **125**, which is probably protonated by methyl phenyl sulfoxide and affords allene **126** stereospecifically with retention of configuration.



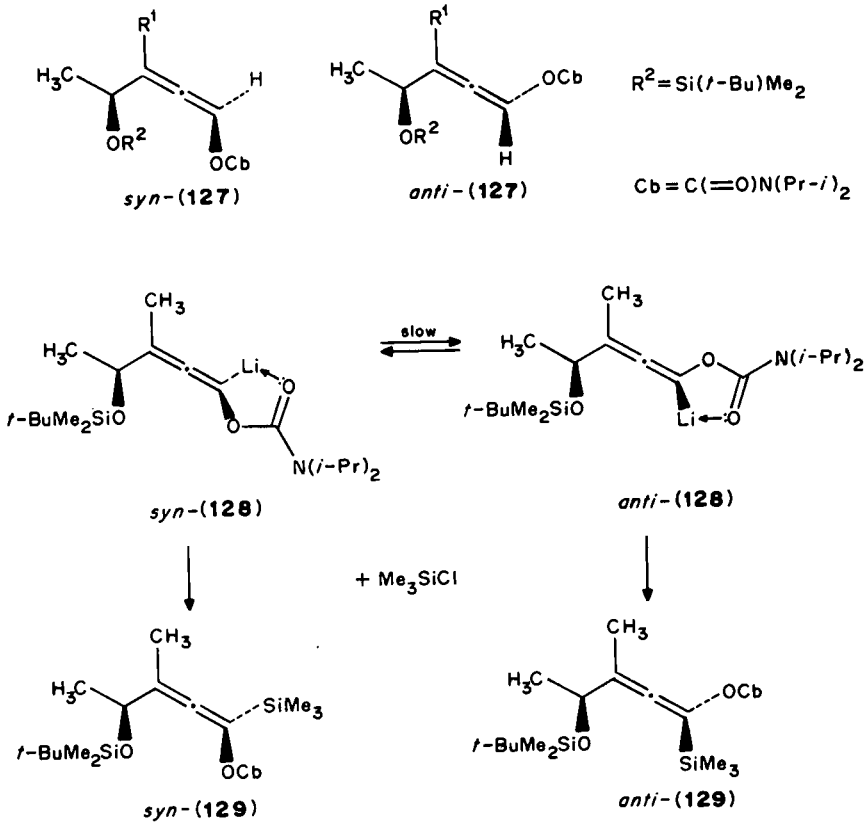


(123) (124) (125)



(126)

Another more recent example of a configurationally stable metallated allene is the case of the titanated γ-methoxy-γ-methylallene **75** discussed above[141]. Trapping of configurationally stable allenic carbanions generated from certain 4-oxy-substituted 1-lithio-1,2-alkadienyl carbamates has been reported by Hoppe and Gonschorrek[195]. These authors have found that when diastereomerically pure 4-(*t*-butyldimethylsilyloxy) allene (*syn*-**127**) was lithiated (BuLi, ether, 20 min, at −78 °C) and the reaction mixture quenched with Me_3SiCl, a 3:1 mixture of diastereomers, *syn*- and *anti*-**129**, was obtained in 70% yield. In contrast, when the allenyl lithium derivative **128** was generated by 1.5 equivalents of LDA in the presence of 2.2 equivalents of Me_3SiCl (THF, hexane, 2 h at −78 °C), diastereomerically pure *syn*-**129** was obtained. From these results the authors concluded that lithiated allenes **128** have considerable configurative stability, and their epimerization via inversion of the allenic stereo centers is a slow process[195].

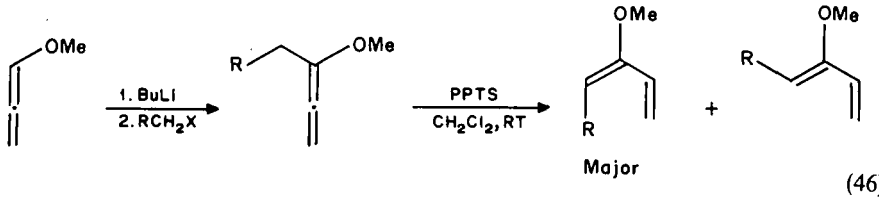


III. ALLENE–DIENE REARRANGEMENTS

The increasingly sophisticated applications of Diels–Alder strategies to the synthesis of complex molecules or highly functionalized ring systems have prompted the development of various hetero-substituted 1,3-dienes for use in such cycloadditions[196,197]. The ready access to functionalized allenes, as reflected in the previous section, and the facility of the

1,2→1,3-diene isomerization of appropriately substituted allenic substrates under various conditions, renders this approach of considerable synthetic potential. Several examples are described below.

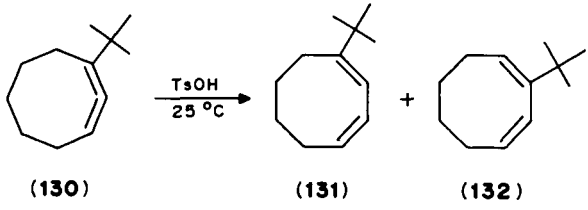
A new method for the preparation of *E*-1-substituted 2-methoxybutadiene by a two-step sequence involving initial alkylation of the carbanion derived from methoxyallene, followed by isomerization to the 1,3-diene with pyridinium *p*-toluenesolfonate (PPTS), is shown in equation 46[198].

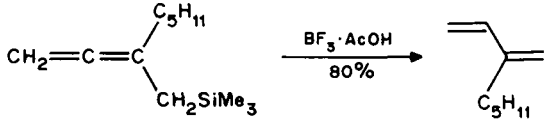


(46)

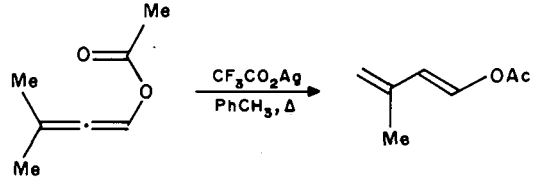
Recently, Price and Johnson[199] reported that unlike the parent cyclic allene, which can be observed by NMR ay −60 °C but dimerizes at ambient temperature, 1-*t*-butyl-1,2-cyclooctadiene (**130**) did not dimerize even on prolonged standing at room temperature. However, brief treatment of kinetically stable cyclic allene **130** with *p*-toluenesulfonic acid or potassium *t*-butoxide in DMSO gave dienes **131** and **132**. This rearrangement is undoubtedly facilitated by relief of strain.

Some other acid-catalyzed allene–diene rearrangements include isomerization of 1-*p*-anisyl-1,2-hexadiene to *trans,trans*-1-*p*-anisyl-1,3-hexadiene[83], the protodesilylation of (α)-(trimethylsilyl)allenes to conjugated dienes (equation 47)[200], the silver trifluoroacetate catalyzed isomerization of γ,γ-dimethylallenyl acetate (equation 48)[201,202] and the bromine-induced isomerization of γ,γ-dimethylallenyl aryl sulfones shown in equation 49[203].

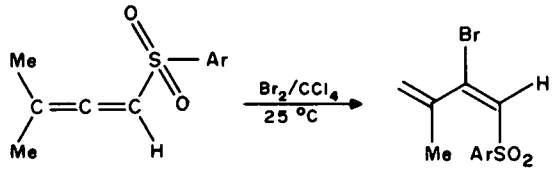




(47)



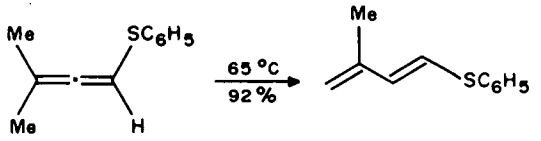
(48)



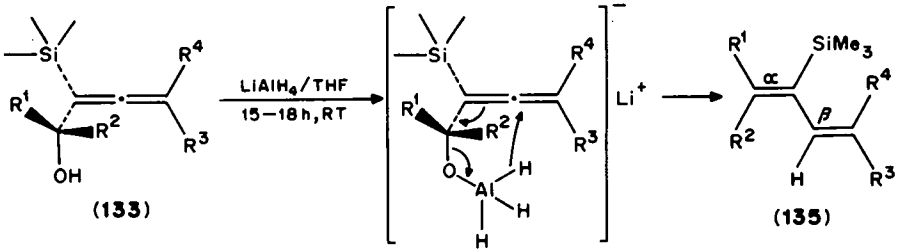
(49)

The thermally induced [1, 3] hydrogen shift of γ,γ-dimethylallenyl phenyl sulfide shown in equation 50[118] and a similar thermal rearrangement of allenic carboxylates, has also been reported[204].

The remarkable facility of a allene–diene rearrangements in certain cases may be illustrated by the isomerization of γ,γ-dimethylallenic dithioacetals to conjugated ketene dithioacetals upon silica gel chromatography[205]. Recently, a variety of 2-(trimethylsilyl)-1,3-butadienes (**135**)[206] have been prepared by reductive rearrangement of readily available trimethylsilyl-substituted α-allenic alcohols (**133**)[207,208]. Introduction of a bulky trimethylsilyl group at the internal carbon positions of dienes has been shown to greatly enhance their diastereoselection in intramolecular Diels–Alder reactions[209], and the alkenylsilane moiety formed also in intermolecular reactions masks numerous latent groups[210].



(50)



A highly stereocontrolled synthesis of (2*E*,4*Z*)-dienoic esters by thermal rearrangement of β-allenic esters in nonpolar solvents such as benzene and xylene in the presence of 5–10 equivalents of alumina has also been reported, and adapted to the total synthesis of several natural products[211].

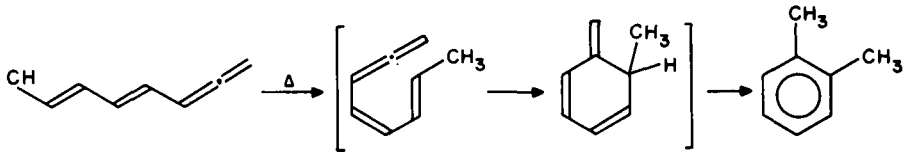
IV. PERICYCLIC REACTIONS

A. Electrocyclic

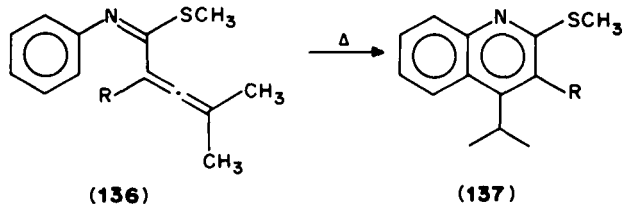
The isomerization of 1,2,4,6-octatetraene to *o*-xylene during pyrolysis at 490 °C was reported by Hopf and coworkers[22], and has been suggested to proceed by a *trans* to *cis*

isomerization of the C4—C5 double bond in the starting material followed by a six-electron electrocyclization (equation 51). The synthesis of quinoline derivatives such as **137** can also be achieved by the thermal electrocyclization of conjugated enallenes (equation 52)[212]. The allenyl thiocarboximidate **136** is readily available by addition of γ,γ-dimethylallenyllithium to phenyl isothiocyanate, followed by iodomethane.

Subsequently, several other electrocyclizations of conjugated allenyldienes were reported[213–216]. Of special interest are the elegant studies by Okamura and coworkers[214–216] in this area, as well as their general observation that unlike nonallenic 1,3,5-heptatrienes[217] which may undergo [1,7] sigmatropic hydrogen shift faster than electrocyclization, conjugated allenyldienes undergo spontaneous electrocyclization during formation, with only few exceptions. For example, the putative allenyldienes **140**, which are generated at low temperature by either S_N2' attack of mixed organocuprates with propargyl benzoates **138** or by [2,3] sigmatropic rearrangement of the corresponding benzenesulfenate **139**, undergo spontaneous six-electron electrocyclization to the drimatrienes **141** in good yield.

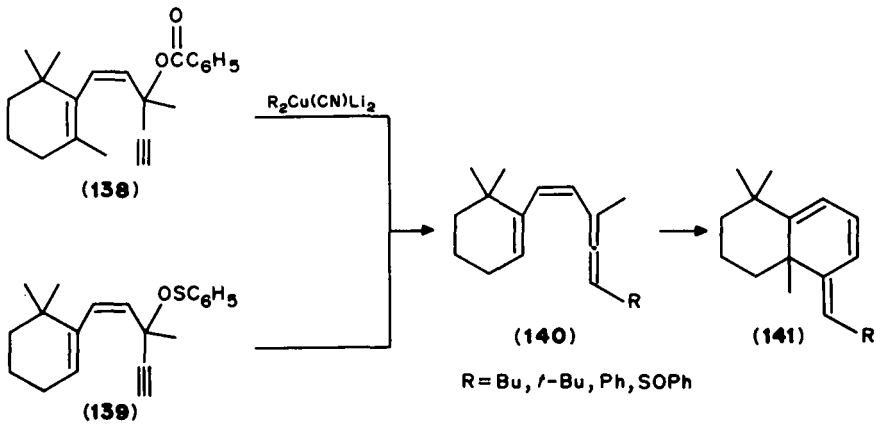


(51)

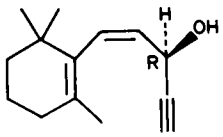


(52)

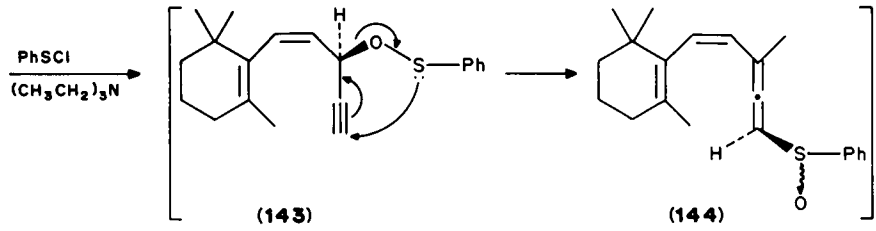
(136) (137)



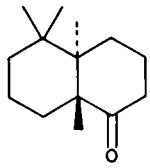
Through careful stereochemical studies an apparently unprecedented stereospecific tandem center → axis → center chirality transfer process has also been demonstrated for these rearrangements[215]. For example, reaction of optically active *cis*-propargyl alcohol **142** (84% ee) with benzenesulfenyl chloride afforded sulfoxide **145** (and its sulfur diastereomer **145'**), which was shown to have retained its stereochemical integrity (84% ee) during its formation, via [2, 3] sigmatropic rearrangement of ester **143** to sulfoxide **144** and electrocyclization of the latter to the final product. Conversion of optically active sulfoxides **145** and **145'** to the well-known ketone **146** established its absolute configuration. This remarkable center → axis → center chirality transfer was actually predictable by the known stereospecificity of both the [2, 3] sigmatropic rearrangement[218,219] and the disrotatory six-electron electrocyclization[220].



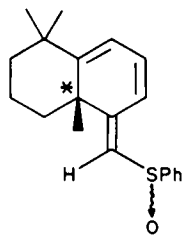
(142)



(143) **(144)**

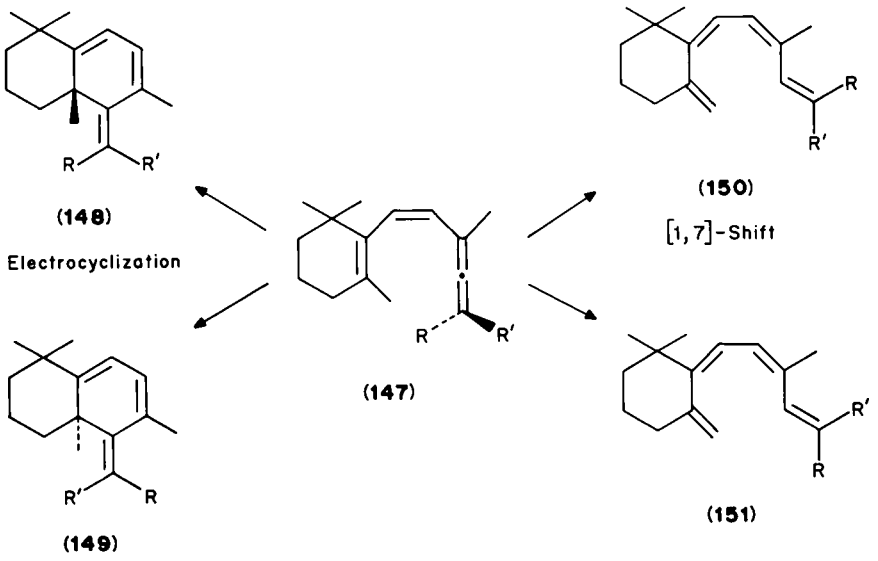


(146)



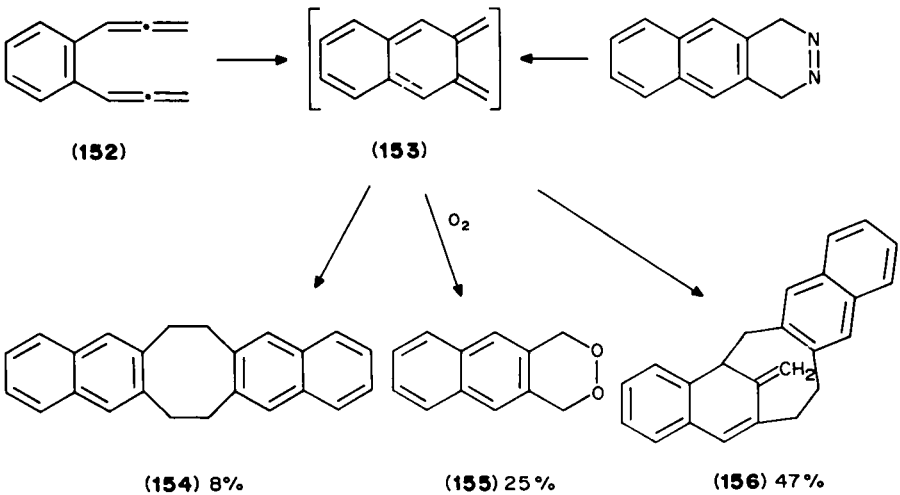
(145)

Very recently, a detailed study of the relative facility of [1, 7] hydrogen shifts versus disrotatory thermal electrocyclization in tetrasubstituted allenyldiene sulfoxides **147** has been published by the same authors[216]. This study has shown that for **147**, where R, R' = Me, Ph(S)O or R, R' = Et, PhS(O), electrocyclization to **148** and **149** is preferred even though these decalin systems appear highly sterically congested. However, introduction of both a *t*-Bu and PhS(O) group at the allene terminus in **147** diverts it entirely to the [1, 7] hydrogen shift pathway, and introduction of an isopropyl and PhS(O) group represent the

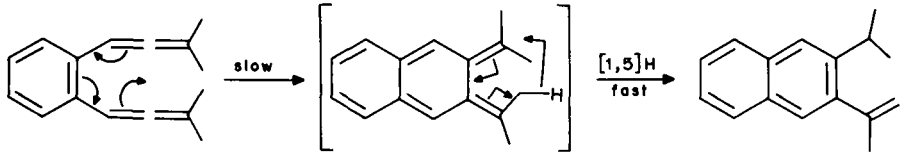


crossover point between the two processes investigated. Furthermore, the sulfoxide group has been found to influence both the stereochemical mode of electrocyclic ring closure as well as the [1,7] sigmatropic hydrogen shift.

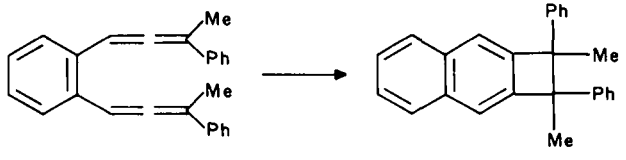
Rearrangements involving internal and external dimerizations of π and heteroatom substituted diallenes have already received considerable attention prior to the beginning of last decade[8,9]. In continuation of previous reports on the rearrangements of *o*-diallenylbenzene (**152**), the structure and conformational isomerism of the major product (**156**) has been reported by Sondheimer and coworkers[221]. The reaction is believed to involve six-electron electrocyclization and formation of 2,3-naphthaquinodimethane (**153**) which can be trapped by oxygen to give the cyclic peroxide **155**[222].



In contrast to the γ-unsubstituted bisallene **152**, *o-bis*-(γ,γ-dimethylallenyl) benzene (**157**) has been found to undergo rearrangement quantitatively at 30 °C to 2-isopropenyl-3-isopropylnaphthalene (**159**)[223]. A kinetic study of the rearrangement indicated only negligible solvent and isotopic effects. Based on these results a two-step mechanism has been suggested in this case too, involving formation of the quinodimethane intermediate **158** in the first rate-determining step, followed by a fast [1, 5] hydrogen shift in the second step. Interestingly, unlike bis-allene **157**, *o-bis*-(γ-methyl-γ-phenyl) benzene (**160**) undergoes a formal [2 + 2] cycloaddition to the cyclobutanonaphthalene derivative **161**, apparently by a diradical mechanism, which might be less congested than the corresponding quinodemethane intermediate[224]. Some unusual thermal rearrangements of *o-bis*-(but-1-en-3-ynyl) benzenes and some of their silylated derivatives, by at least two different mechanistic modes, depending on the substituents at the acetylenic termini, have also been reported[225].



(157) (158) (159)

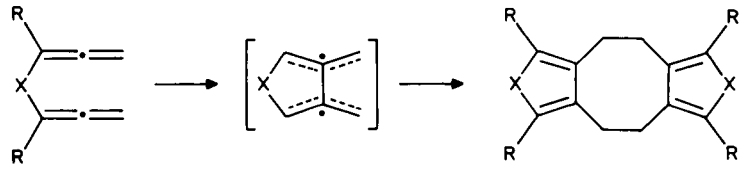


(160) (161)

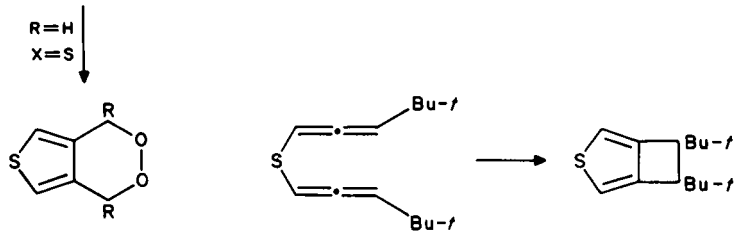
The thermal behaviour of heteroatom bridged diallenes generally parallels the behavior of the *o*-dialenylbenzenes described above. Thus, the bisallenes **29a–d**, obtained by carefully controlled base-catalyzed isomerization of the corresponding 4-heterohepta-1, 6-diynes at 0 °C or below, undergo dimerization at room temperature or above to the respective dimers **163a–d** by a process in which the rate-determining step is first order[37]. When thermolyses were conducted in the presence of oxygen, then cyclic peroxides such as **164** were formed, and when solutions of bis-γ-*t*-butylallenyl sulfide **165** were allowed to stand at 20 °C, 6,7-di-*t*-butyl-3-thiabicyclo[3,2,0]hepta-1,4-diene (**166**) was obtained. All these rearrangements are believed to proceed by a bis-allylic biradical intermediate **162**[37,226]. Such biradicals have often been discussed as reactive intermediates in thermal dimerizations of allenes[227].

Similar to the rearrangement of bisallene **157** to **159**, and in contrast to the heterobridged bisallenes **29a–d**, bis-γ,γ-dimethylallenyl selenide undergoes cycloaromatization to 3-isopropenyl-4-isopropylselenophene quantiatively at room temperature and is believed to proceed by a two-step mechanism, involving a quinodimethane intermediate analogous to **158**[223].

In continuation, the same authors[228] have also investigated the thermal behaviour of allenyl ethynyl sulfides and selenides. Sulfides **167** have thus been found to display a high thermal reactivity, undergoing cyclization to the corresponding thiophenic derivatives **169**, together with the thiophenic dimers such as **170–172**. In contrast, the analogous

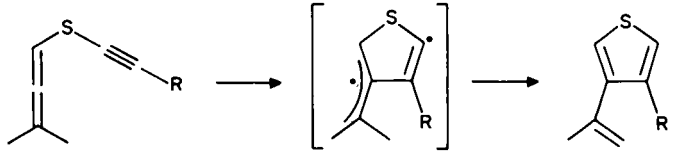


(29a–d) (162) (163a–d)

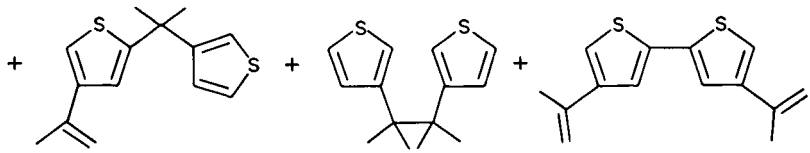


(164) (165) (166)

selenides are generally unreactive. The reaction exhibits a remarkable solvent effect. In isopropanol, only monomeric products are observed and the yield is greatly improved. An intramolecular free radical mechanism, involving the diradical intermediate **168**, was suggested on the basis of observed dimerization, solvent effect, deuterium labeling and a kinetic study of the reaction. The difference in reactivities between the analogous sulfides and selenides has been attributed to the varying ability of the respective heteratoms to stabilize the radical intermediate[228].



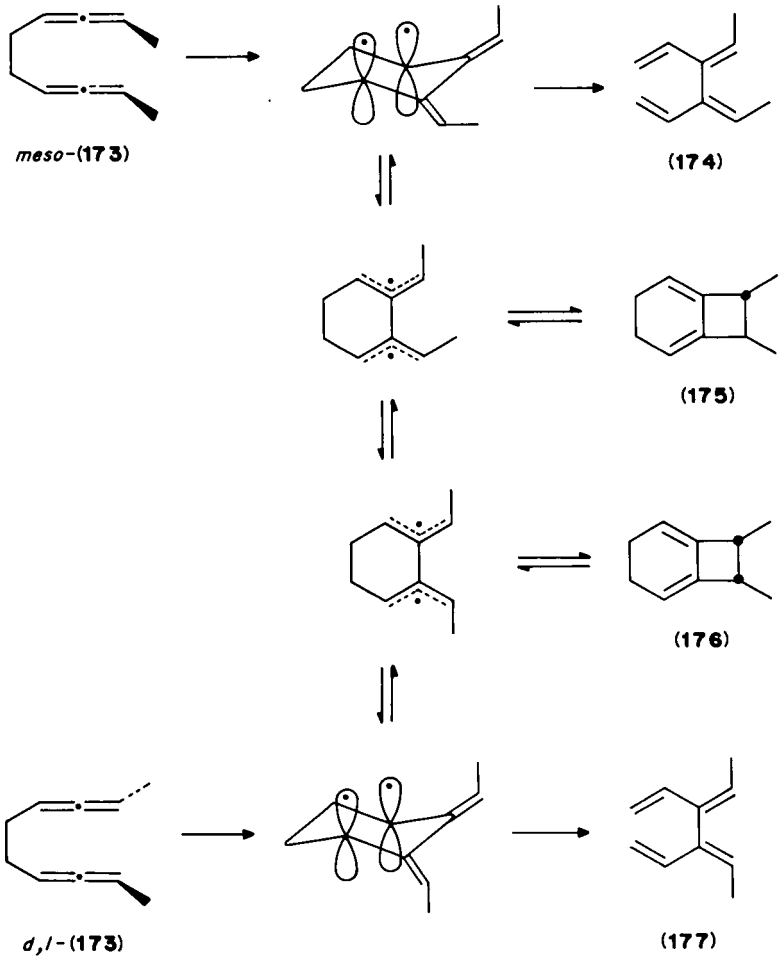
(167) R=H, Me, Et, Ph (168) (169)



(170) (171) (172)

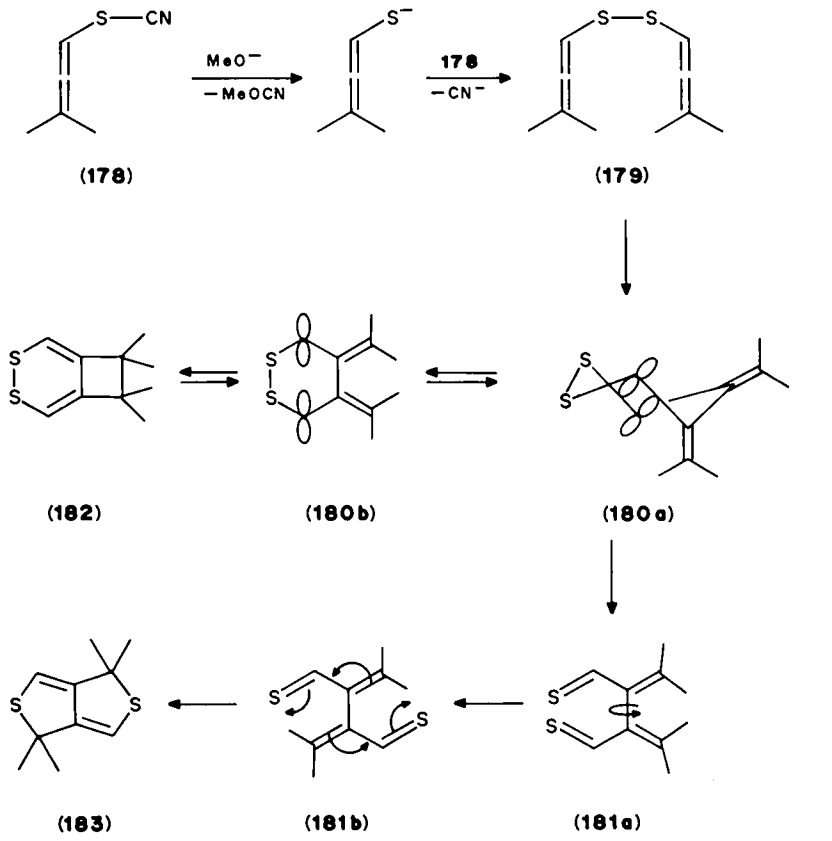
The thermal rearrangement of ethano bridged diallenes has also been studied[229]. Thus thermolysis of 2,3,7,8-decatetraene (**173**) at 300 °C yields a mixture of the four products **174–177**. The reaction is believed to involve a set of rapidly equilibrating twisted and planar bis-allylic diradical intermediates.

A bis-allylic biradical intermediate has also been suggested for the rather surprising one-step synthesis of the novel 1,1,4,4-tetramethyl-1*H*,4*H*-thieno[3,4-*c*]thiophene (**183**) and analogous selenophene by the action of lithium methoxide on γ,γ-dimethylallenyl

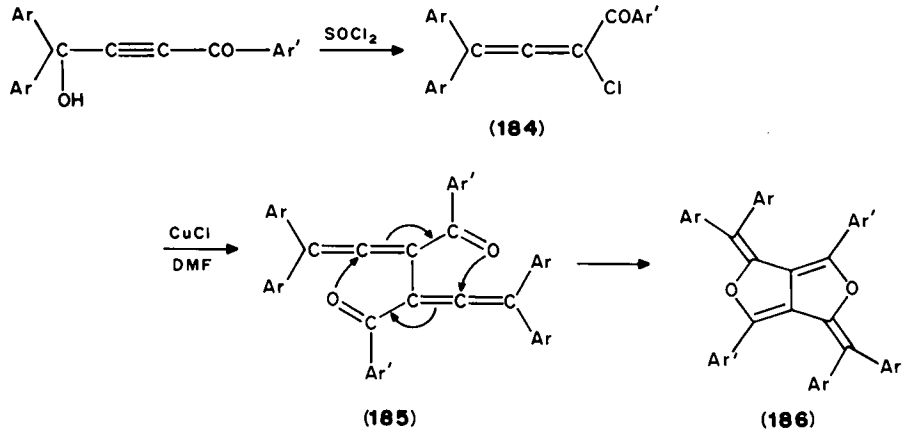


thiocyanate and selenocyanate respectively[230]. Both compounds are believed to be formed by the same multistep mechanism as illustrated in Scheme 2, for the formation of **183**. The failure to detect the bisallenyl disulfide **179** or the conjugated dienic dithial intermediate **181a** is hardly surprising in view of their known instability. Similarly, the absence of the 1,2-dithiin **182** in the present work may reflect the considerable steric and ring strain expected for this structure, as well as the low thermal stability of 1,2-dithiins in general. Rotation around the central C—C bond of **181a** by 180° brings the molecule into the requisite conformation **181b** for the operation of a double intramolecular Michael-type addition to give the observed product **183**, as indicated by the arrows in **181b**.

A similar double intramolecular Michael-type addition has also been suggested to occur during the recently reported exothermic coupling of α-chloro-α-aroyl-γ,γ-diarylallenes (**184**) to 3,7-dioxa-2,6-diaryl-4,8-bis(diarylmethylene)bicyclo[3.3.0]-octa-1,5-dienes (**186**), on treatment with CuCl in DMF at room temperature[231]. The reaction is believed to proceed by the conjugated diallene **185** which undergoes cyclization as indicated by the arrows.

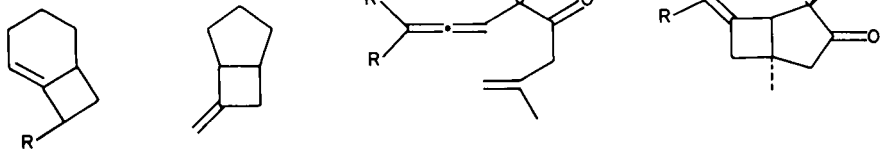

MeO⁻
−MeOCN
178
−CN⁻
(178)
(179)
(182)
(180b)
(180a)
(183)
(181b)
(181a)

SCHEME 2


SOCl₂
(184)
CuCl
DMF
(185)
(186)

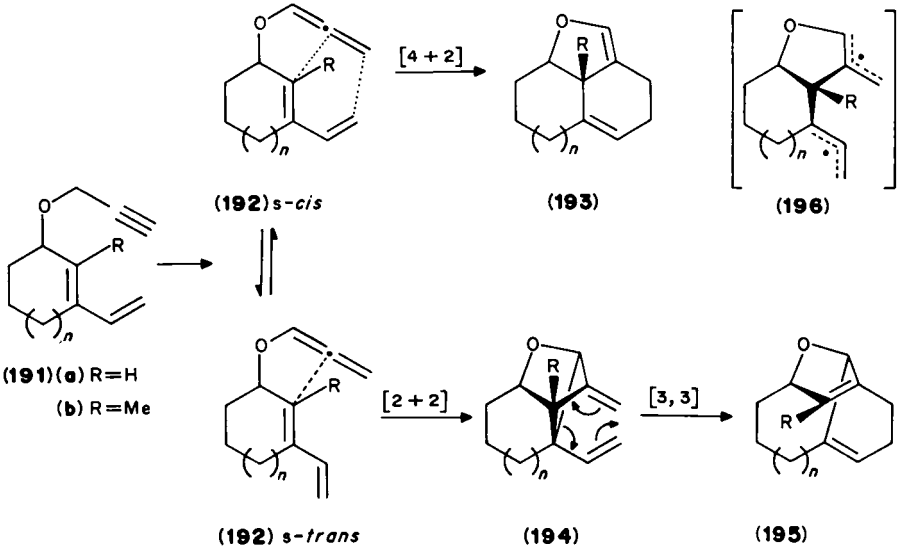
B. Intramolecular [2 + 2] Cycloadditions

Thermal and photochemical intramolecular [2 + 2] cycloadditions have received considerable attention during the last decade due to their mechanistic interest and synthetic utility. For example, competing intramolecular [2 + 2] cycloaddition and ene reaction has been reported by Huntsman and coworkers[232]. These authors observed the formation of 8-methyl-bicyclo[4.2.0]oct-1-ene (**187a**) and a mixture of both bicyclic hydrocarbons **187b** and **188** during pyrolysis of 1,6,7-nonatriene and 1,2,7-octatriene, respectively, at 400 °C in a flow system. A similar rearrangement has been used by Skattebøl and Stenstrom[233] for their improved synthesis of the aggregation pheromone (±) lineatin. The key reaction of this synthesis involved thermal intramolecular ene–allene cyclization of compound **189** to **190** at 490 °C.



(187) (a) R=Me (b) R=H **(188)** **(189)** **(190)**

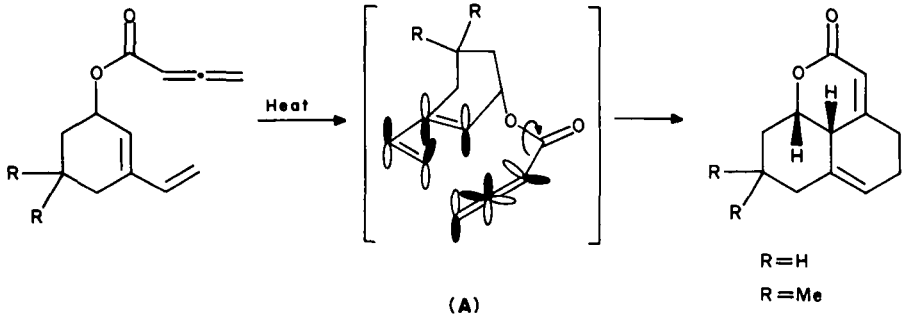
Extensive studies of both intramolecular [2 + 2][234–237] and [2 + 4][238–241] cycloadditions involving allenes have been performed by Kanematsu and coworkers, and some interesting contrasts have been described in the competition between these two processes[234–237]. For example, while the thermal treatment of the propargyl ether **191a** (R = H) with *t*-BuOK at 83 °C led to a smooth formation of Diels–Alder adduct **193** via the allenyl ether intermediate **192**[240], similar treatment of **191b** (R = Me) led to the formation of the novel bicyclo[5.3.1] undecane skeleton **195**[234]. This remarkable one-step synthesis



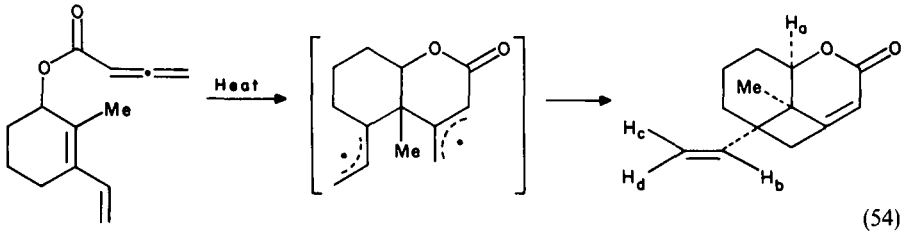
(191) (a) R=H (b) R=Me **(192)** s-*cis* **(193)** **(196)** **(192)** s-*trans* **(194)** **(195)**

has been explained by successive [2 + 2] cycloaddition of the initially formed allenyl ether **192** to yield **194**, and [3,3] sigmatropic rearrangement of the latter with preferential cleavage of the sterically most compressed C_2—C_3 bond to give **195**. The remarkable change of reaction mechanism has been attributed to the steric effects of the C-2 substituent (R). The bulky R could sterically disfavor the s-*cis* conformation of **192** required for the [4 + 2] reaction leading to **193**. On the other hand, the [2 + 2] cycloaddition of **192** has been considered to occur by the sterically less demanding stepwise mechanism via the diradical intermediate **196**.

A similar switching of the reaction pathway from [4 + 2] to [2 + 2] intramolecular cycloaddition has also been observed with various allene mono[235,236] and dicarboxylates[237] as a result of conformational differences in the transition state, as illustrated by equations 53 and 54. A discussion of the periselectivity of these reactions in terms of orbital overlap requirements of the ester linkage in the transition state[236] supported by theoretical calculations[237] has also appeared.

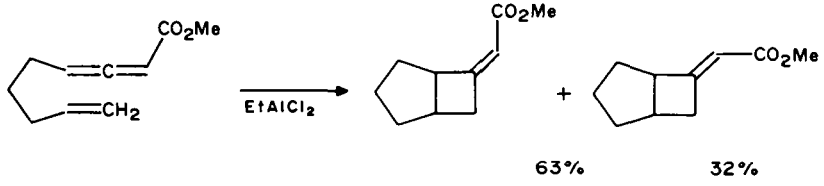


(53)



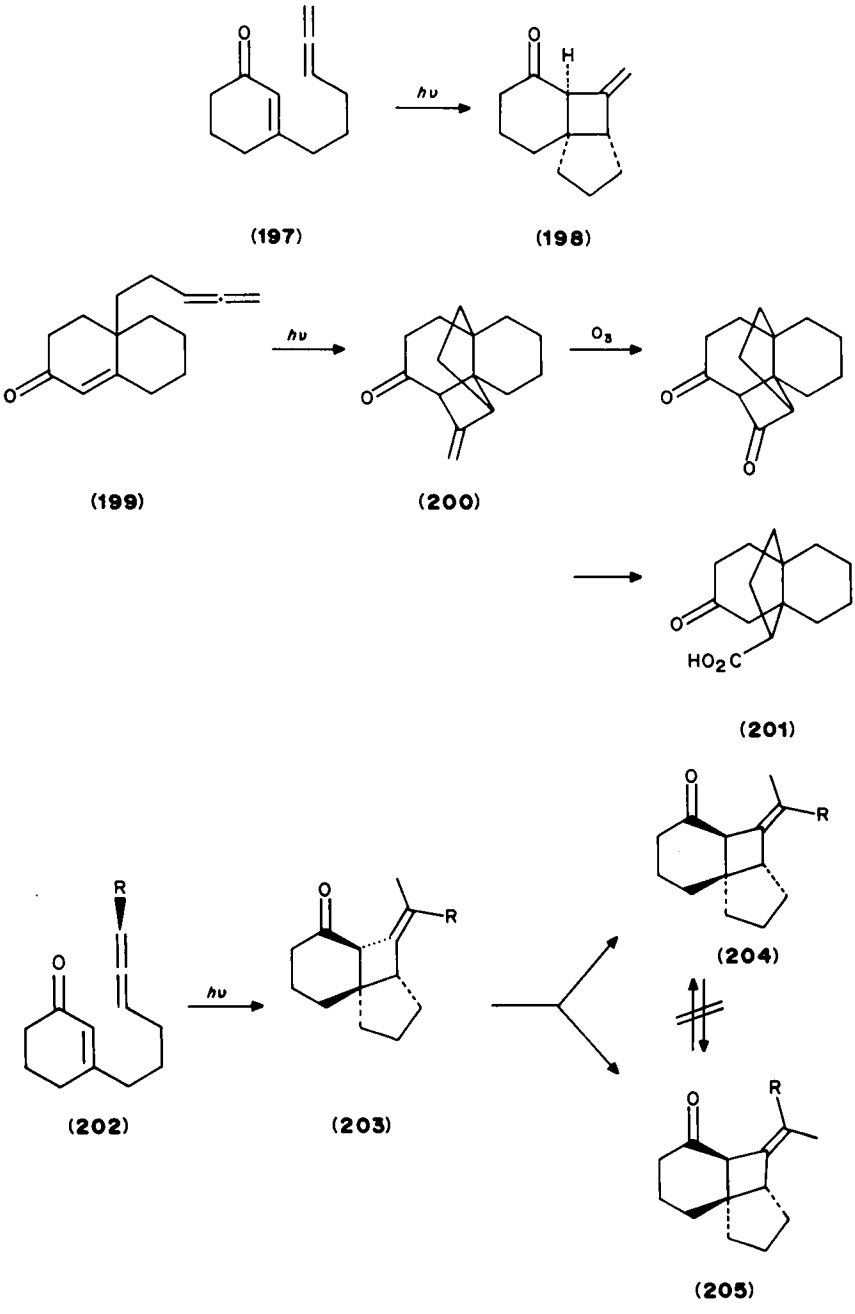
(54)

Interestingly, while the intramolecular [2 + 2] cycloaddition of the allenecarboxylate requires a temperature of 145 °C, the Lewis acid catalyzed intramolecular [2 + 2] cycloaddition shown in equation 55 proceeds at room temperature in CH_2Cl_2 in almost quantitative yield[242].



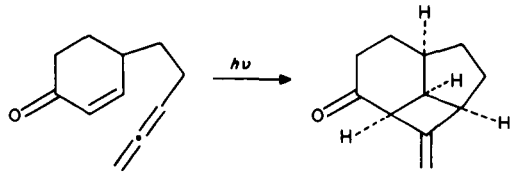
(55)

Intramolecular [2 + 2] photocycloadditions, generally of 3- and 4-(allenic-substituted)-2-cycloalken-1-ones, have been the focus of considerable synthetic attention during the

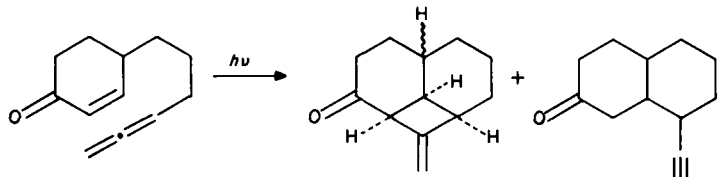


last decade[243–253], especially in the groups of Becker and Dauben. For example, irradiation of the 3-allene substituted 2-cyclohexen-1-one (**197**) resulted in a single product (**198**) in quantitative yield[243]. The synthetic potential of the reaction was shown in the synthesis of the [4.4.3]propellane **201**. Irradiation of allene **199** yielded a single adduct **200**, in excellent yield. Ozonolysis followed by acid treatment of the latter gave the keto acid [4.4.3]propellane **201**[243]. The observation that irradiation of the 1,3-disubstituted allene **202** afforded a 1:1.1 ratio of the two isomeric adducts **204** and **205** was suggested as evidence that the reaction proceeds by the 1,4-diradical intermediate **203** with formation of the first bond at the β carbon of the conjugated enone[244].

Some detailed studies by Dauben and coworkers[246–249] on the the effects of ring size, length of side-chain and temperature on the regioselectivity of the intramolecular [2 + 2] photoaddition of 4-(allenic-substituted)-2-cycloalken-1-ones has shown that the ring size of the cycloalkenone is important, but a simple rule of selectivity based on the side-chain length cannot be formulated. Thus, irradiation of the 1,6-unsaturated enone **206** with three carbon atoms separating the unsaturations gave the cycloadduct **207** as the sole product. On the other hand, five products were formed in the irradiation of the 1,7-unsaturated homolog **208**, with products **209**, **210** as the major products.

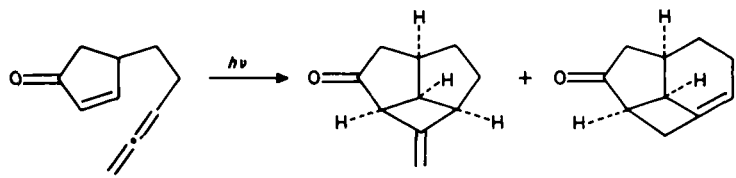


(206) **(207)**

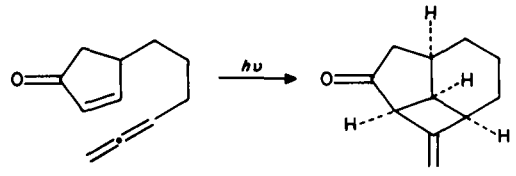


(208) **(209)** **(210)**

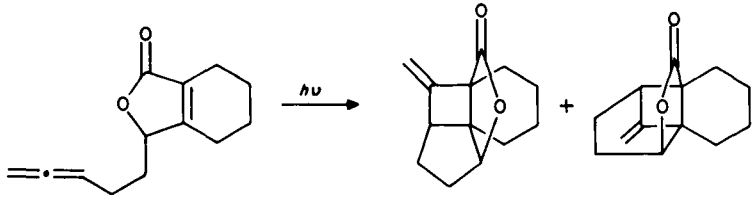
In contrast with these results, the intramolecular photocycloaddition of the analogous 1,6- and 1,7-unsaturated-cyclopentenones **211** and **214** shows an opposite effect. Thus, irradiation of **211** gave a 3:1 mixture of the expected cycloadduct **212** to the bridgehead olefin **213**, obtained by bonding of the central allenic carbon to Cβ rather than to Cα. The irradiation of **214** gave the 'straight' product **215** as the sole product. The synthetic utility of these reactions for the synthesis of the triquinane skeleton[247], decipiane diterpenoids[246], sequiterpene lactone precursors[251] and some fused tricyclic lactones such as **217**, **218**[250] has also been reported.



(211) **(212)** **(213)**



(214) (215)

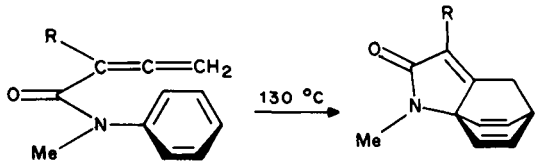


(216) (217) (218)

C. Intramolecular [4 + 2] Cycloadditions

As already demonstrated in the previous section, intramolecular cycloadditions of allenes constitutes a versatile method for the stereocontrolled synthesis of variously functionalized polycyclic compounds. In particular, the intramolecular Diels–Alder reactions of allenes fully enjoy the merits of their unique structure and proceed with extraordinary ease. The enhanced interest in intramolecular Diels–Alder (IMDA) reactions of allenes is apparantly also influenced by the widespread interest in IMDA reactions in general, which is reflected in the large number of reviews[254–257] on this subject, published in the past decade.

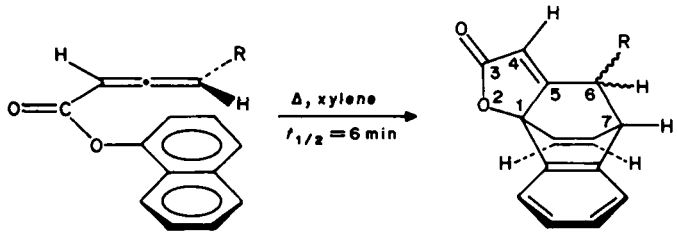
An unusual and apparantly unprecedented case of IMDA reaction in which a monosubstituted benzene ring assumes the diene function was reported by Himbert and Henn[258]. These authors have observed the isomerization of allene-carboxanilides **219** to give the tricyclic products **220** in boiling xylene (equation 56). Subsequently, the same[259,260] and other authors[261–264] have observed the occurrence of the same process also for related allenic systems such as carboxylates and phosphonates, and the dependence of the reaction rate on substitution and nature of aromatic system. For example, phenyl allenecarboxylates rearranged to the corresponding tricyclic lactone with a half-life of 23.6 h in refluxing xylene, while the [4 + 2] cycloaddition of the corresponding 1-naphthyl ester occurs with a half-life of only 6 min under the same conditions



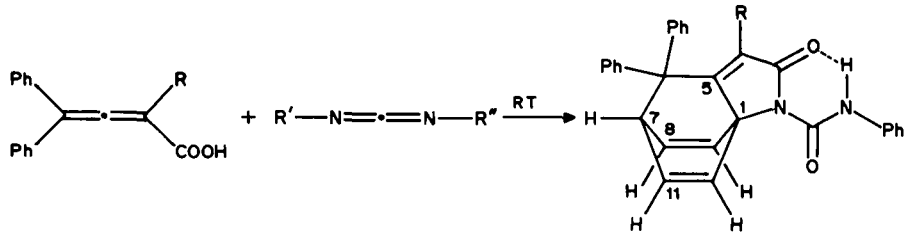
(219) (220)

R=H, Me, or SiR'_3 (56)

(equation 57)[260]. Furthermore, γ,γ-diphenyl-α-methylallenecarboxylic acid has been reported to add at room temperature under neutral conditions to diphenyl, di-α-naphthyl or pyridyl(cyclohexyl)carbodiimides to give the corresponding tricyclo[5.2.2.0^{1,5}]undeca-4, 8, 10-trien-3-ones **221a–c** (equation 58)[263] and involving an IMDA reaction of allenic acylurea intermediates.



(57)



(a) R′=R″=C_5H_{11}

(b) R′=R″=Ph

(c) R′=R″=1-naphthyl

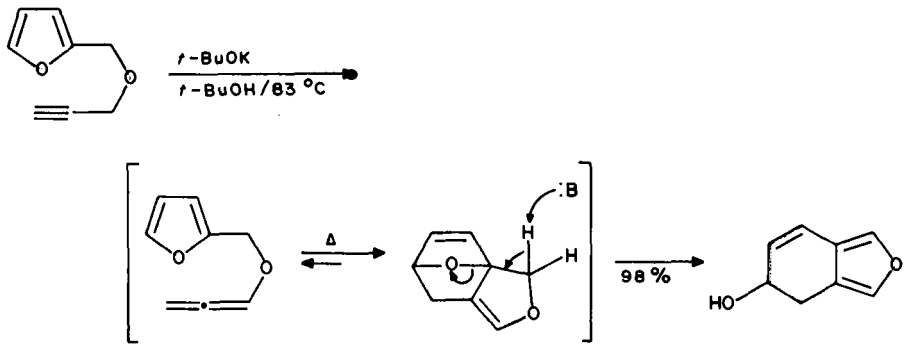
(221 a–c)

(58)

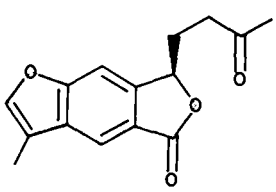
A number of interesting and useful IMDA reactions of allenes has been recently published by Kanematsu and coworkers[234,237–241,265], some of which have already been mentioned in the previous section (e.g. **191a** → **193** and equation 53). Another example is the novel bicycloannulation via tandem vinylation and intramolecular Diels–Alder reaction of five-membered heterocycles, which proceeds in almost quantitative yields (equation 6) and was used for a new synthesis of the phototherapeutic agents psoralen and azapsoralen[238].

Subsequently, the same group[239] developed a novel ring transfer reaction of furans to fused furans by tandem IMDA reaction and base-catalyzed ring opening of the adducts (equation 59) and a new synthesis of tricyclic fused lactone systems such as **193**, which are essential building blocks of a large number of naturally occurring terpenoid compounds. This methodology was recently applied for the first total synthesis of (+)-4-oxo-5, 6, 9, 10-tetradehydro-4, 5-secofuranoeremophilane-5, 1-carbolactone (**221**)[265] using an optically active starting material.

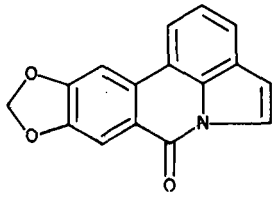
The allene IMDA strategy has also been applied by the same group[241] to an efficient and versatile one-step synthesis of the tetrahydroindole ring system. Thermal IMDA of various dienamides **222**, followed by dehydrogenation of the adduct as outlined in equation 60, afforded the expected indole **223**. A new approach to pyrrolophenanthridone alkaloids and a total synthesis of hipadiene (**224**), using allene IMDA reactions, has also been published[266].



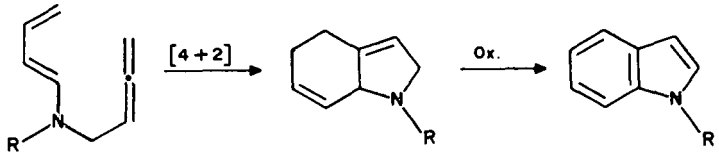
(59)



(+)-(221)

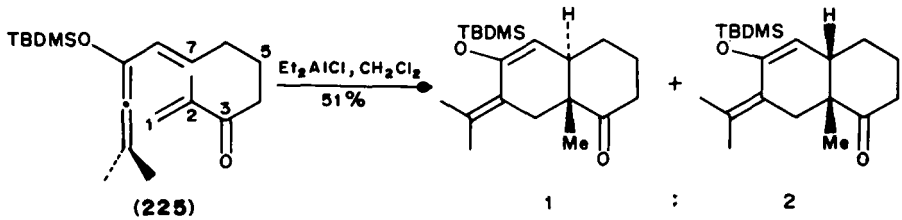


(224)

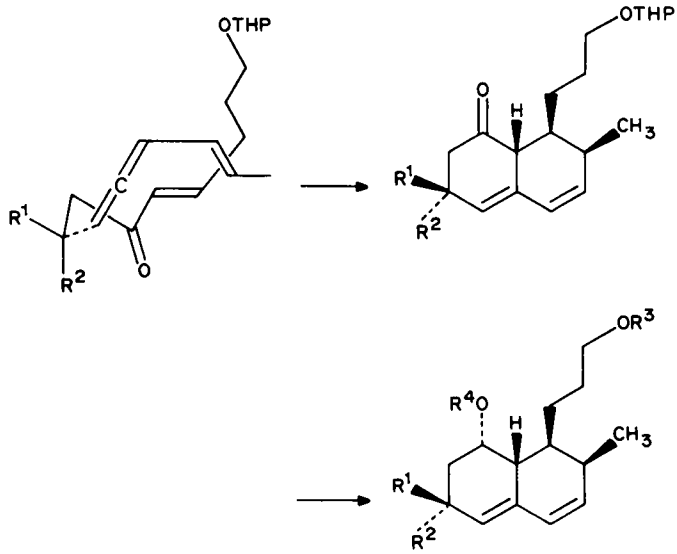


(222) (223) (60)

A number of IMDA reactions involving conjugated vinylallenes has also been investigated[267–271]. For example, vinylallenes acting as dienes and possessing an internal dienophile-activating group such as **225** showed enhanced *cis/endo* selectivity when the IMDA reaction was carried out in the presence of a Lewis acid (equation 61)[170,267]. These reactions have also been used for the efficient synthesis of the hexahydronaphthalene moieties **226** and **227**, of the potent sterol biosynthesis inhibitors (+)-meviolin and (+)-compactin, respectively (equation 62)[268–271]. This is a remarkable demonstration of the



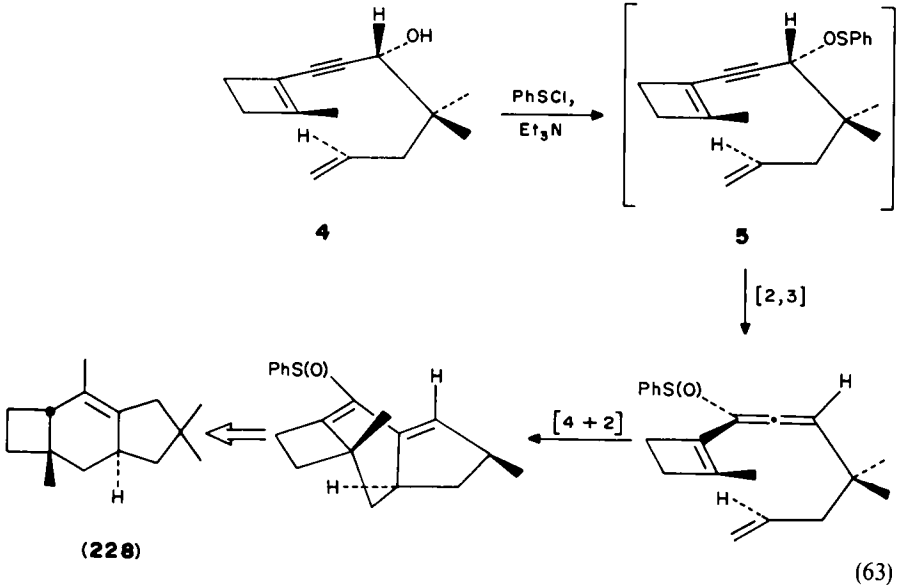
(225) 1 : 2 (61)



(62)

(226) R^3=THP, R^4=H

(227) R^3=H, R^4=(S)-CCH(CH_3)C_2H_5 (O)



(228)

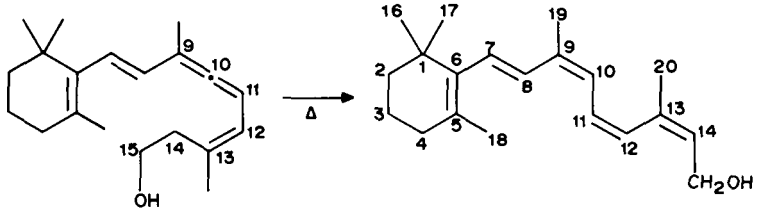
(63)

ability of Diels–Alder reactions in general to generate simultaneously up to four chiral centers in a highly stereoselective and largely predictable fashion. In another recent application, Gibs and Okamura[272] have demonstrated the use of a completely stereoselective vinylallene IMDA reaction as the key step in an exceptionally concise enantioselective synthesis of (+)-sterpurene (**228**), the parent member of a novel class of sesquiterpenes and the metabolites of which are considered to cause the silver leaf disease (equation 63). A biosynthetic proposal involving an intramolecular Diels–Alder reaction has also been made[273].

D. Sigmatropic Rearrangements

1. [1,5] and [1,7] Hydrogen shifts

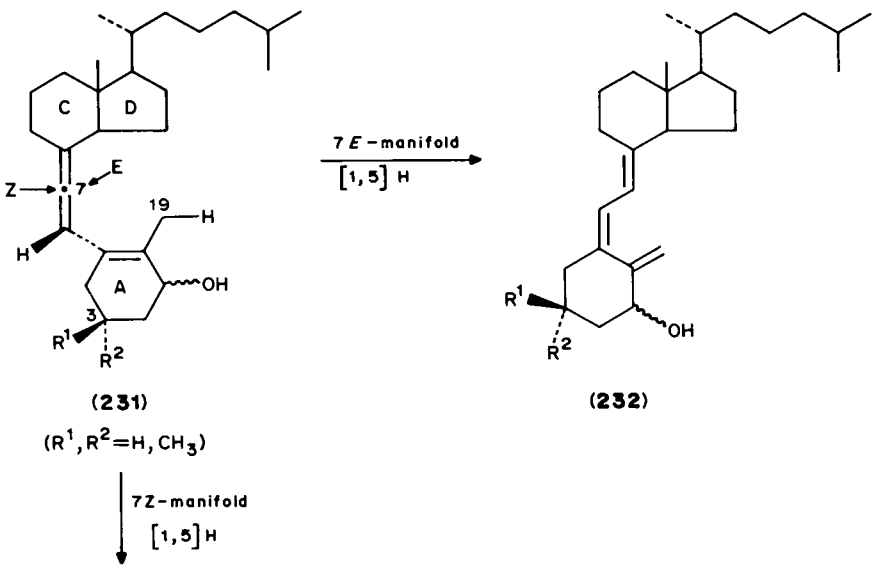
Thermal [1, 5] hydrogen shifts sometimes accompanied by [1, 7] hydrogen shifts have previously been shown to occur readily for a variety of π-conjugated allenes, including vinyl allenes[9]. These reactions, especially [1, 5] hydrogen shifts, have been applied extensively and most efficiently in some novel and elegant syntheses of a variety of calciferols (vitamin D analogues)[16,94,96,181–183,274–277] and retinoids[98,278–282] by Okamura and coworkers. These authors have also performed detailed mechanistic and stereochemical studies of the [1, 5] and [1, 7] hydrogen shifts, and an excellent review by Okamura has recently appeared[17]. Consequently, these important contributions are only briefly illustrated here by equation 64 and Scheme 3 below. For example, the novel and highly hindered 9-*cis*, 11-*cis*, 13-*cis*-retinal **230** is obtained, together with two other geometric isomers, by [1, 5] hydrogen shift of the allenic retinol **229** on heating at 69 °C for two hours[278]. Another example is the efficient construction of the 1, 3, 5-hexatriene moiety of the 1-hydroxy-vitamin D system **232**[16,94–96,181–183]. As shown in Scheme 3, the thermal suprafacial [1, 5] hydrogen shift of vinylallene **231** from C19 → C7 may proceed by two competing pathways. One pathway leads to the desired 7*E* manifold **232**, whereas the other pathway leads to the 7*Z* manifold **233**, which is not observed due to subsequent spontaneous antarafacial [1, 7] hydrogen shifts. Interestingly, the major factor which influences the migration preference is the relative orientation of the C1 hydroxyl group in the A ring[96], while substitution at C3 of the same ring by a methyl[182] or *gem*-dimethyl[95] has no significant effect on this migration. However, replacing the C3 carbon of the A ring with a sulfur atom has a significant effect. Thus, while the β-hydroxy allene **231** ($R^1 = R^2 = H$) leads to the 7*E* vitamin **232** ($R^1 = R^2 = H$) as the major product, in the case of the 3-thia analog, it is the epimeric 1α-hydroxy allene which leads to the corresponding 7*E* vitamin. This has been attributed to additional π-system perturbation by the allylic sulfur[183].



(64)

(229) **(230)**

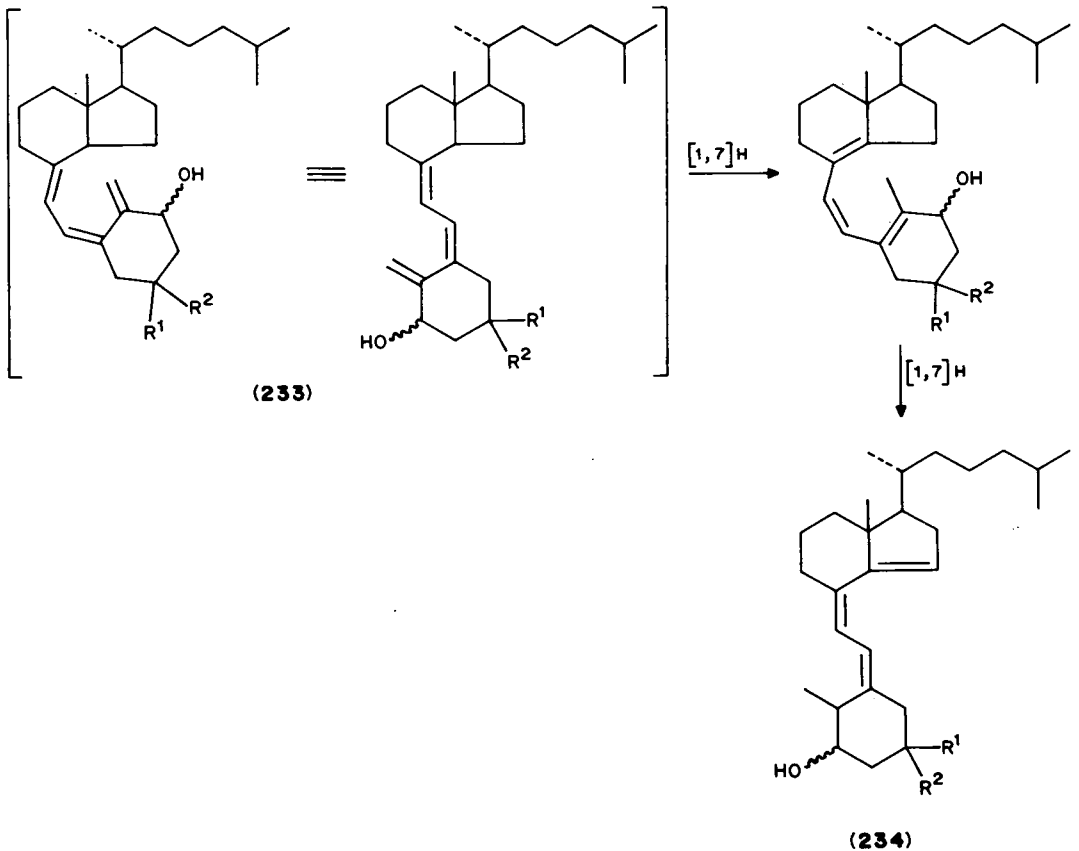
Very recently, Okamura and coworkers[283,284] have also described a more general study of substituent effects on the thermal [1, 5] sigmatropic hydrogen shifts of vinylallenes. Thus, vinylallenes **235** undergo rearrangement readily at 40 °C to a mixture of the two



(231)

$(R^1, R^2 = H, CH_3)$

(232)



(233)

(234)

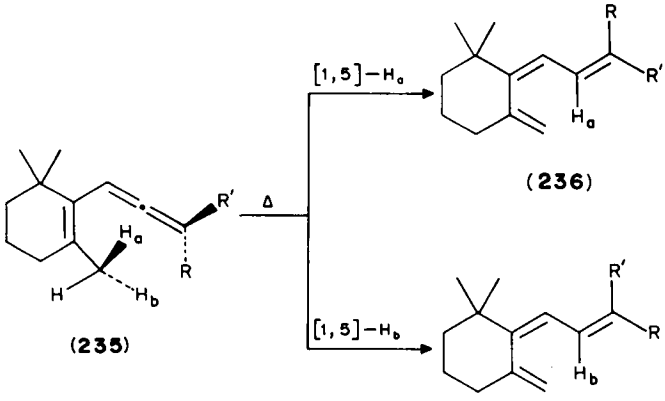
SCHEME 3

triene stereoisomers **236** and **237**, as a function of various allene end groups (**235a–i**). The presence of the phenylsulfinyl group (**235a–e**) at the allene terminus was found to have a profound effect on both the rate of reaction and control of π-facial geometric stereoselection in these triene syntheses. In the series **235a–e**, the bulkier the R group the greater the observed selectivity (3/1 to 98/2 favoring **237a–e**). The kinetic results for **235f–i** and **235a** (both diastereomers) indicate that their relative rates for [1, 5] hydrogen shifts parallel the electron-withdrawing nature of the substituent (SO_2Ph) > SOPh > SPh > H or *t*-Bu), but only the sulfoxide group affects π-facial selectivity significantly. Studies of kinetic isotope effect reveal results similar to those for classical nonallenic systems. For example, a large k_H/k_D of 12.8 for **235g** could be calculated, very similar to the value of 12.2 previously reported for the parent *cis*-1, 3-pentadiene, consistent with a highly symmetrical transition state in a connected process.

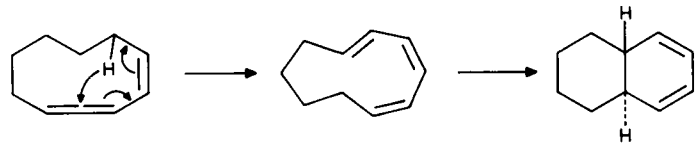
As previously mentioned (Section III.A), the question of competition between [1, 7] hydrogen shifts and six-electron electrocyclization in 1-allenyl-1, 3-dienes has also been addressed by Okamura and coworkers[214–216]. Several other studies on [1, 5] sigmatropic shifts of allenic systems have appeared in recent years[149,285–288]. For example, Minter and coworkers[285] have reported some interesting rearrangements for cyclic vinyl and cyclopropylallenes as shown in equations 65 and 66. Pyrolysis of cyclic vinylallene **238** in hexane at 100 °C for three hours gave *trans*-bicyclo[4.4.0]deca-2, 4-diene (**240**) in quantitative yield. The reaction was interpreted as a two-step process involving the intermediacy of *trans, cis, cis*-1, 3, 5-cyclodecatriene (**239**), which undergoes electrocyclic closure. The conformation preference of **238** and the restrictions of orbital symmetry combine to provide complete stereochemical control, while related open-chain analogs give mixed stereochemistry[285]. The same authors have shown that thermolysis of a mixture of cyclic cyclopropylallene **241** and its diastereomer produced one stereochemically pure product from **241**, while the diastereomer fails to rearrange under the same conditions. Again the conformation of the ring system coupled with orbital symmetry restrictions provide an explanation. Thus isomer **241** is aligned for [1, 5] hydrogen shift to generate the *trans, cis, cis* triene **242**, which can form the tricyclic product **243** by intramolecular Diels–Alder reaction. The analogous [1, 5] shift for the diastereomer would produce the *trans, trans, trans* isomer of **242**, which is more highly strained.

2. *[2, 3] Sigmatropic rearrangements*

One of the best studied and most useful [2, 3] sigmatropic rearrangements involving allenes is the rearrangement of propargylic sulfenates to allenic sulfoxides (equation 67) discovered by Braverman and Stabinsky[289] over twenty years ago. The considerable popularity enjoyed by these remarkably facile rearrangements which occur spontaneously at room temperature or below with complete stereospecifity is certainly due to their synthetic utility. This has been demonstrated in a variety of preparations of allenic sulfoxides[290–300], including the preparation of vinylallenes[17,97,214–216,272,283,284,297] which are useful intermediates in organic synthesis in general[301] and natural polyenes such as vitamins A and D in particular[17]. To cite Okamura[272], 'in our experience, the pericyclic transformations (e.g., the sulfenate ester–sulfoxide rearrangement) of chiral propargyl alcohols to chiral allenes represent the most reliable approach for achieving complete enantioselectivity in the preparation of allenes'. However, since these rearrangements have been recently reviewed by the present author[218] they are not further discussed here. The same applies to the analogous [2, 3] sigmatropic rearrangements of propargylic sulfinates to allenic sulfones (equation 68)[302] and the double [2, 3] sigmatropic rearrangements of propargylic sulfoxylates to diallenic sulfones (equation 69)[303], first discovered by the present author as well and recently reviewed in another chapter on rearrangements involving sulfones[304]. The rearrangement of propargylic sulfoxides[218] and selenoxides[27]



	R	R′
(a)	H	SOPh
(b)	Me	SOPh
(c)	Et	SOPh
(d)	*i*-Pr	SOPh
(e)	*t*-Bu	SOPh
(f)	H	H
(g)	H	*t*-Bu
(h)	H	SPh
(i)	H	SO_2Ph



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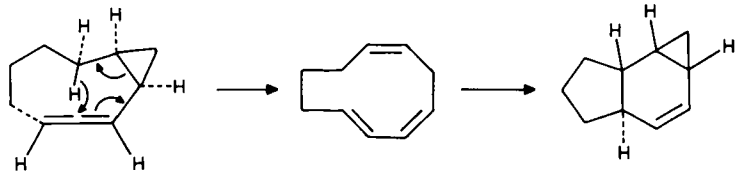
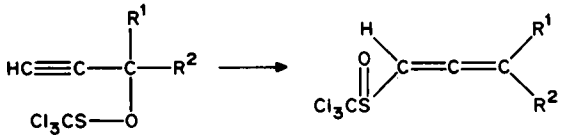


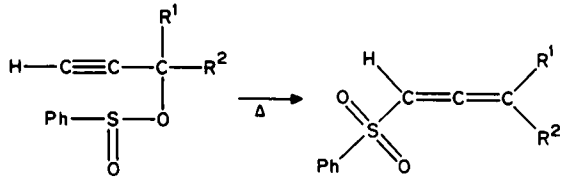
(66)

to allenic sulfenates and selenanates, respectively, and a very recent application of the rearrangement shown in equation 68 to a stereocontrolled synthesis of a vitamin D metabolite[305] have also been described.

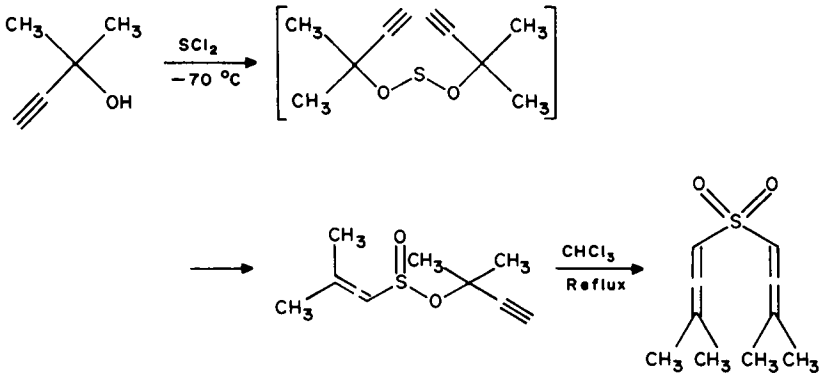


(67)

(a) $R^1=R^2=H$
(b) $R^1=H$; $R^2=Ph$
(c) $R^1=R^2=Me$



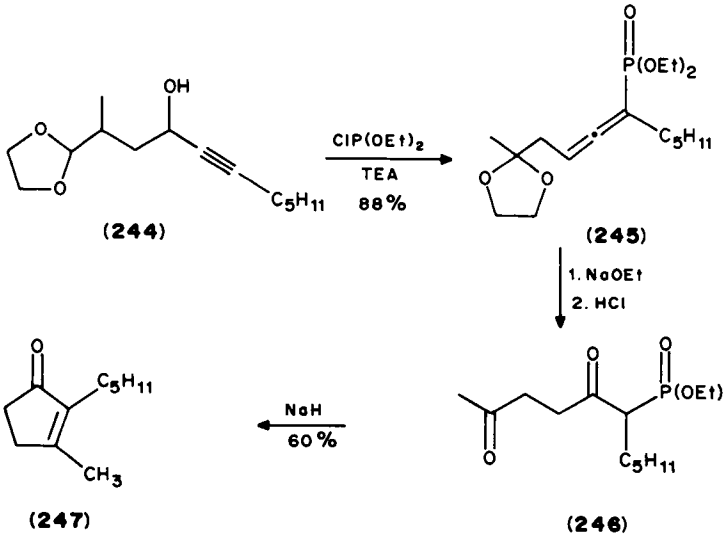
(a) $R^1=R^2=Me$
(b) $R^1=R^2=H$
(c) $R^1=H, R^2=Me$
(d) $R^1=H, R^2=Ph$
(e) $R^1=Me, R^2=Ph$

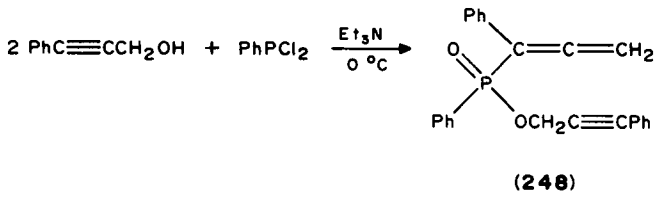


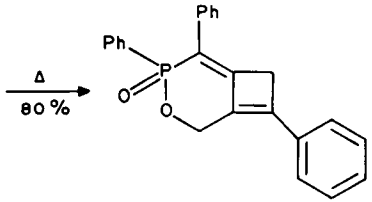
(69)

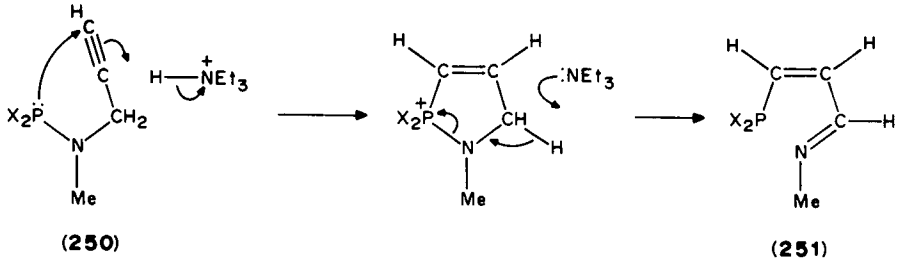
Another well-known [2, 3] sigmatropic rearrangement is the rearrangement of various trivalent propargyloxy phosphorous compounds to allenic products which, like the [2, 3] sigmatropic rearrangement of propargylic sulfenates to allenic sulfoxides, occurs spontaneously on treatment of propargyl alcohols with the appropriate trivalent phosphorous chloride in the presence of triethylamine[306–311] (e.g. **244** → **245**)[307]. An application of this rearrangement in a new synthesis of dihydrojasmone (**247**) by sequential addition of sodium ethoxide to allenic phosphonate **245**, hydrolysis of the enol intermediate and base-catalyzed cyclization of the resulting 1,4-diketone **246** has also been described[307]. Interestingly, the phosphinate ester **248**, obtained by reaction of γ-phenylpropargyl alcohol with dichlorophenylphosphine at 0 °C, is unstable at room temperature and on standing transforms into a yellow strongly fluorescing crystalline isomer whose X-ray analysis indicated structure **249**[309]. This unexpected reaction was suggested to occur by a concerted intramolecular [2 + 2] cycloaddition of the latter.

Another unexpected spontaneous rearrangement is the rearrangement of N-methyl-N-propargylaminodiethylphosphine (**250**) to N-methyl-Z, -3-diethylphosphino-2-propenal imine (**251**). The weaker P—N bond, compared to the P—O bond, could be the reason why the P—N bond is cleaved here, whereas the C—O bond is cleaved in the oxy analogs to give allenic products[312].


OH
C_5H_{11}
(244)
$ClP(OEt)_2$
TEA
88%
$P(OEt)_2$
C_5H_{11}
(245)
1. NaOEt
2. HCl
$P(OEt)_2$
C_5H_{11}
(246)
NaH
60%
C_5H_{11}
CH_3
(247)

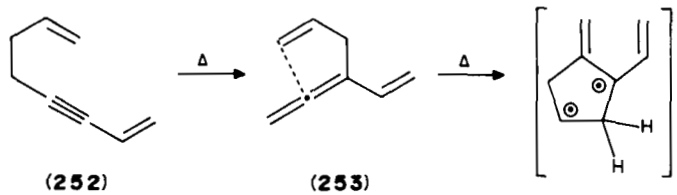

2 PhC≡CCH2OH + PhPCl2
Et3N
0 °C
Ph
C=C=CH2
P
Ph
OCH2C≡CPh
(248)


Δ
80%
Ph
Ph
P
O
O
(249)

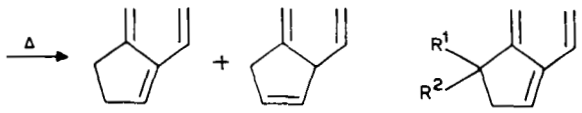

H
C
C
X_2P
CH_2
N
Me
H—NEt3
(250)
H
C=C
H
X_2P
CH
N
Me
:NEt3
H
(251)
H
C=C
H
X_2P
C—H
N
Me

3. Cope-type rearrangements

a. Open-chain 1-en-5-ynes. A review on intramolecular pericyclic reactions of acetylenic compounds has appeared[313]. Some novel thermal rearrangements providing cross-conjugated polyolefins (dendralenes) have been recently reported by Hopf and coworkers[314–316]. For example, in a multistep rearrangement which affords the cyclic dendralenes **255**, 1,7-octadien-3-yne (**252**) undergoes thermal isomerization via a [2,2] sigmatropic rearrangement to give the (isolable) allene **253**, which via diradical **254** and 1,2-hydrogen shifts stabilizes to the dendralene **255** (44%) or the triene **256** (52%)[315]. 6-Methyl derivatives of **252** lead to the expected methyl products **257**[315]. Subsequently the



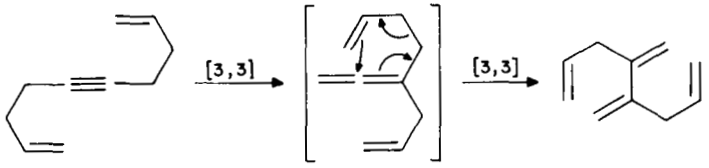
(252) **(253)** **(254)**



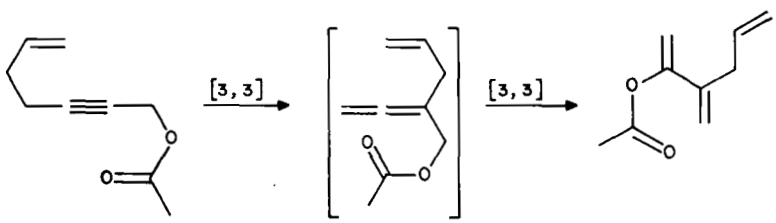
(255) **(256)** **(257)**

$R^1=R^2=CH_3$

same authors[317] have reported the thermal rearrangements shown in equations 70 and 71, each one of which involves a double Cope rearrangement and affords 2,3-disubstituted 1,3-butadiene.



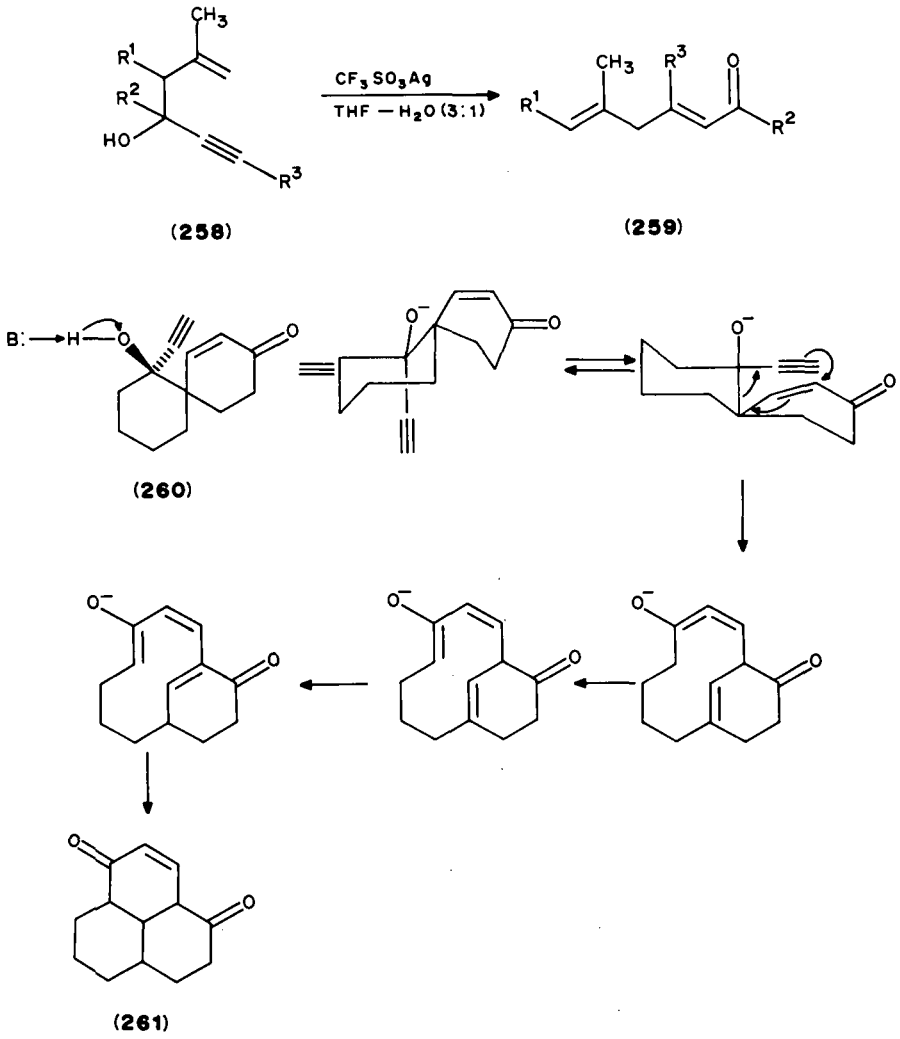
(70)



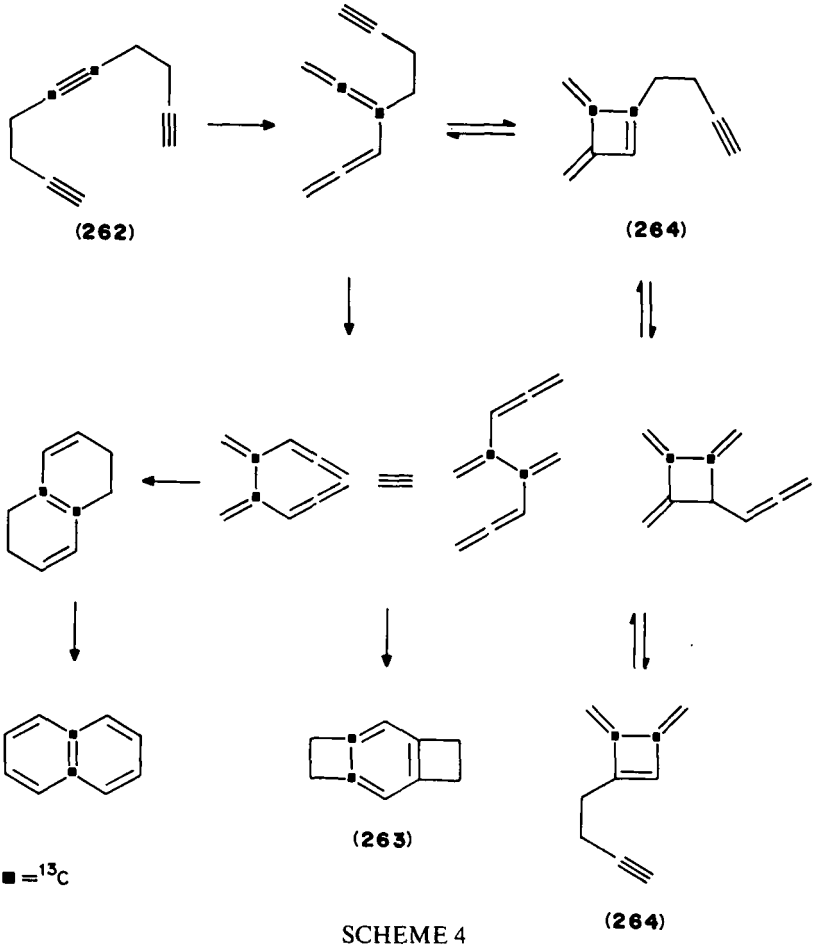
(71)

Several studies of acetylenic oxy-Cope and anionic oxy-Cope rearrangements have also been described[318–321]. For example, variously substituted enynols **258** have been

smoothly converted into α,γ-dienones **259** by treatment with one molar equivalent of silver triflate in aqueous THF at 20–60 °C[320]. Treatment of the spiro acetylenic carbinol **260** with KH/DME at room temperature for two hours afforded the tricyclic diketone **261** in 55% yield[321]. The reaction is believed to involve an anionic oxy-Cope rearrangement in tandem with an isomerization and an intramolecular Michael addition.



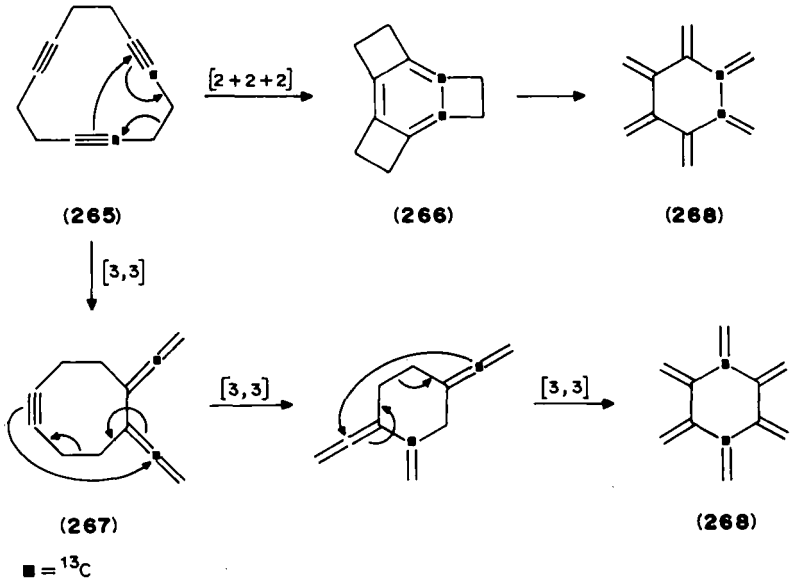
b. Cyclic and acyclic 1,5,9-triynes. Dower and Vollhardt[322,323] have found that flash or flow pyrolysis of 1,5,9-decatriyene (**262**) furnishes the linear 1,2:4,5-dicyclobutenobenzene **263** in addition to naphthalene (flash) or the dimethylenecyclobutene **264** (flow). The results were explained by a mechanism initiated by two consecutive [3,3] sigmatropic rearrangements (Scheme 4). This mechanism was supported by labelling experiments.



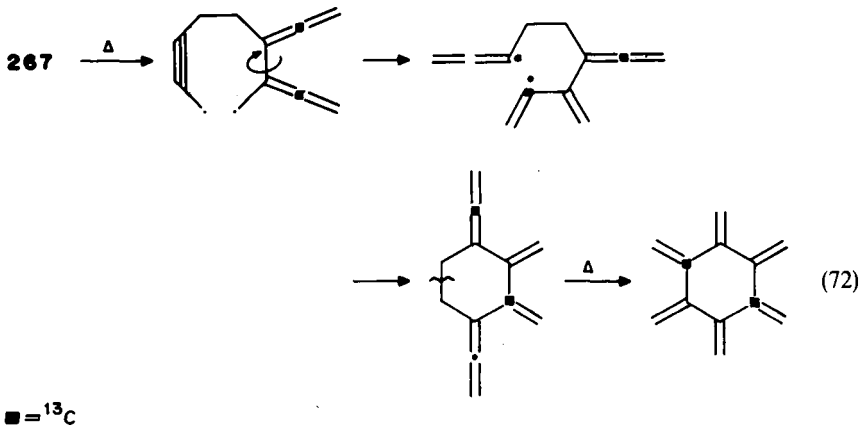
SCHEME 4

A similar mechanism has been advanced by the same authors[323] for the remarkable gas-phase thermal rearrangement of 1,5,9-cyclodecatriyene (**265**) to hexaradialene (**268**)[324,325]. In this case too, labelling experiments have been used to reject an alternative symmetry-allowed [2 + 2 + 2] cycloaddition pathway and involving the intermediacy of tricyclobutabenzene (**266**), a stable molecule[326] (Scheme 4a). While agreeing to the first [3,3] sigmatropic shift in Scheme 4a, and on the basis of the studies on thermal rearrangements of exocyclic allenes (*vide infra*), Hopf[327] has suggested an alternative mechanism for the conversion of the postulated intermediate **267** to **268** (equation 72).

c. 1,2,6-Trienes. Several studies on the thermal [3,3] sigmatropic rearrangement of both cyclic and acyclic 1,2,6-trienes have been described during the past decade[58,73,328–332]. Thus, 1-chloro-1-(cycloheptatrien-7-yl)-3,3-diphenylallene (**269**) undergoes valence tautomerization at room temperature to the corresponding norcaradiene **270** and is isomerized to a 1:1 mixture of the bicyclo[3.2.2]nonatriene derivative **271** by a Cope rearrangement of the norcaradiene system and an intramolecular Diels–Alder of the cycloheptatriene system.



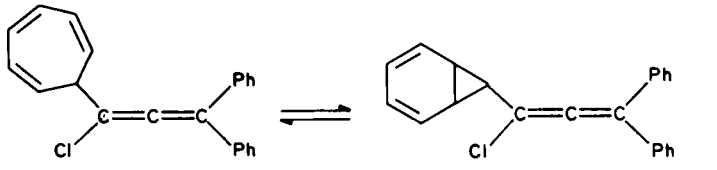
SCHEME 4a



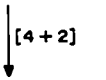
(72)

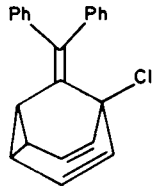
α-Ethylenic β-allenic alcohols undergo [3, 3] sigmatropic rearrangement on heating to γ-dienic aldehydes and ketones in moderate yields[73], while *trans*-1, 2, 6-cyclononadiene **273** has been regarded as a transient precursor of 2, 3-divinylcyclopentene (**274**)[328]. The gas-phase pyrolysis of *syn*-7-(1, 2-butadienyl) bicyclo[2.2.1]hept-2-ene (**275**) above 160 °C afforded trienes **276** as an approximate mixture of *E* and *Z* diastereomers, whereas the *anti* epimer of **275** was found to be thermally stable[329,330]. These results were interpreted as supporting a concerted pathway for this rearrangement. The photolysis of *syn*-allene **275** paralleled its thermal behaviour by affording *E* and *Z* trienes **276** as the only products[331].

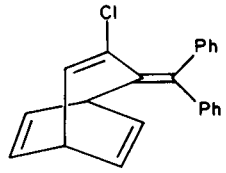
In continuation to previous studies, Roth and coworkers[333] performed a detailed study of the mechanism for the thermal and quantitative gas-phase rearrangement of 1,2,6,7-octatetraene (**277**) to bicyclo[4.2.0]octa-1,5-diene (**278**) and divinylbutadiene (**279**) and



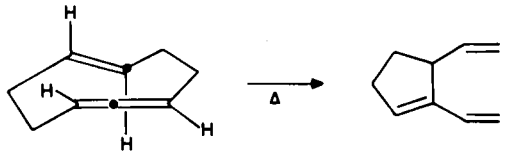
(269) (270)



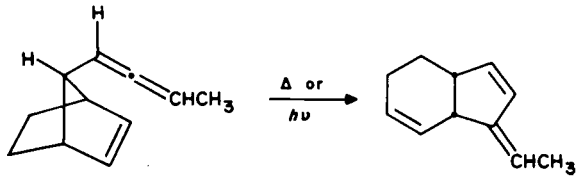




(272) (271)

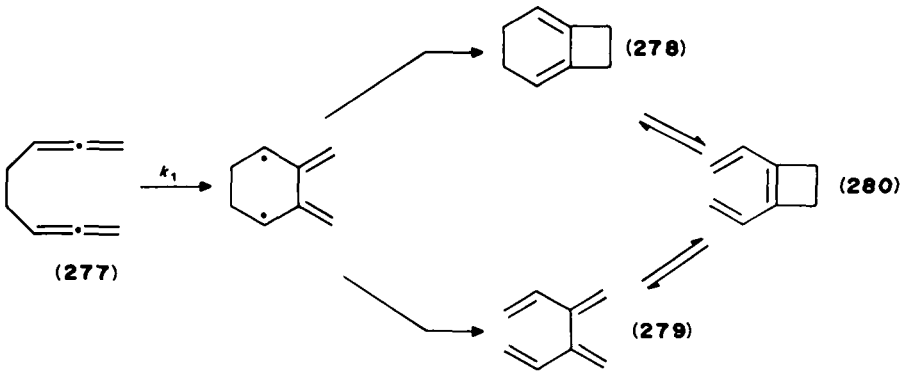


(273) (274)



(275) (276)

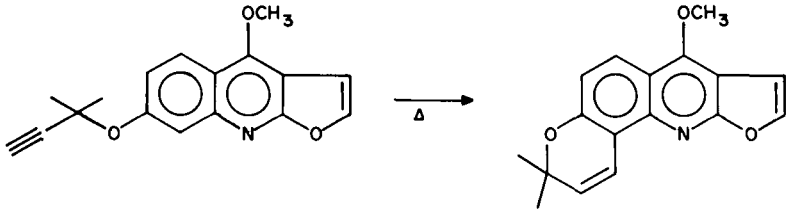
their interconversion by way of **280**, using kinetic and other quantitative methods. For the Cope-type rearrangement **277** → **279**, the competition of concerted and nonconcerted reaction paths has been demonstrated by trapping experiments with sulfur dioxides. As previously mentioned[229] the similar thermal behavior of the related 2, 3, 7, 8-decatetraene (**173**) has been suggested to proceed by a bisallyl biradical mechanism. The synthesis of allenic amino acids by an aza-Cope rearrangement has also been reported[334].



4. Claisen-type rearrangements

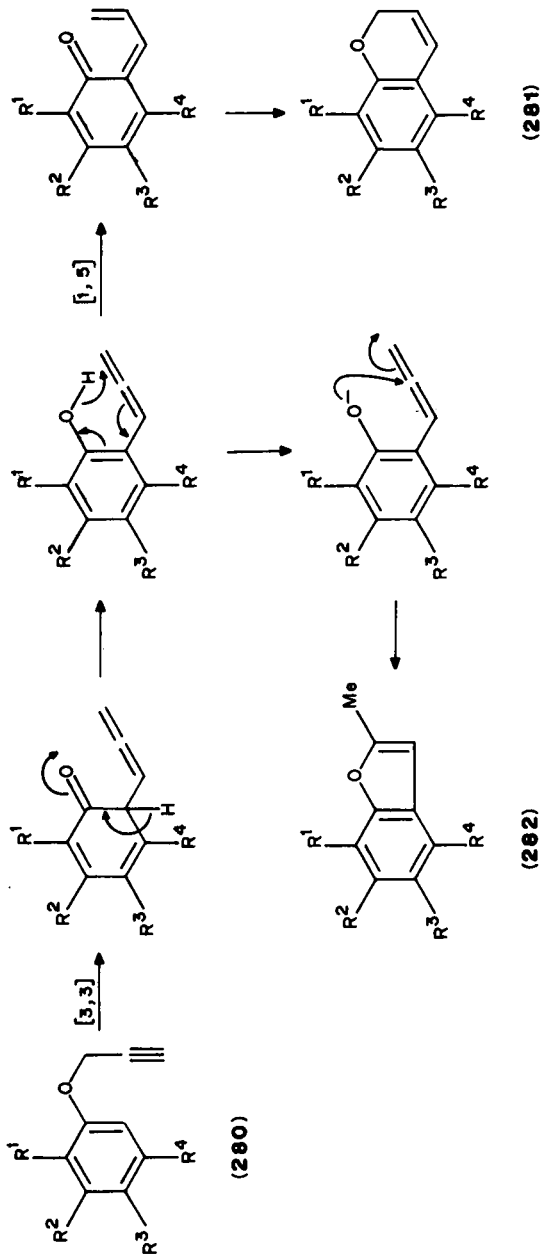
A variety of [3, 3] sigmatropic rearrangements of propargyl and thiopropargyl ethers have been reported during the last decade, some of which have also been included in a general review on catalysis of the Cope and Claisen rearrangements by Lutz[335].

a. Aryl and heteroaryl/propargyl ethers. The well-known Claisen rearrangement of aryl propargyl ethers[9] has continued to attract considerable attention[336–352]. For example, a remarkable substituent effect has been observed in the Claisen rearrangement of aryl propargyl ethers (**280**)[337,338]. In polyethylene glycol at 220 °C, ethers containing electron-donating groups yield (2*H*)-benzopyrans **281** and those containing electron-withdrawing groups yield 2-methylbenzofurans **282**. The results were explained by the enhanced acidity of the latter substrates (Scheme 5). Consistent with these results is the thermal rearrangement of pentafluorophenyl propargyl ether in *N*, *N*-diethylaniline to 2-methyl-5, 6, 7, 8-tetrafluorobenzofuran[339]. The Claisen rearrangement of the propargyl ether **283** in refluxing acetone was the key step in a synthesis of the novel alkaloid Dutadrupine (**284**)[340].



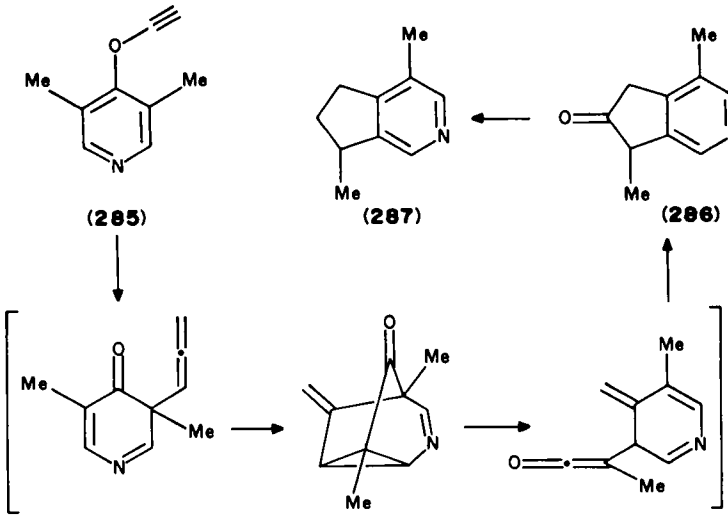
(**283**) (**284**)

Several studies of the Claisen rearrangement of various heteroaryl propargyl ethers have also been reported[341–346]. For example, unlike phenyl propargyl ethers, but similar to 2, 6-dimethylphenyl propargyl ether, the thermal rearrangement of propargyl 4-(3, 5-dimethyl)pyridyl ether (**285**) afforded 3, 7-dimethyl-5-azaindan-2-one (**286**) which was subsequently transformed to racemic actimidine **287** by Huang–Minlon reduction. In this case, Claisen rearrangement of **285** is followed by an intramolecular Diels–Alder reaction due to the inability of the primary product to undergo tautomerization and aromatization (equation 73)[341]. Similarly, the initial Claisen rearrangement of 2, 4-di (N-arylamino)-1, 3, 5-triazin-6-yl propargyl ethers is accompanied by further prototropic and sigmatropic

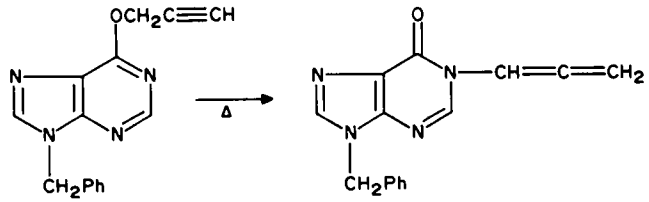


SCHEME 5

shifts[343,344], while 9-benzyl-6-propargyloxy purine undergoes normal thermal O→N Claisen rearrangement either neat or in refluxing *o*-dichlorobenzene (equation 74)[342]. Some unusual spontaneous Claisen rearrangements at room temperature or below of putative propargyl oxazole ethers have recently been observed and applied for the transfer of chirality from optically active propargyl N-aryl-C-phenylglycinates to α-branched ketones (Scheme 6)[346] and for an elegant synthesis of α-allenic α-amino acids[81,345]. The latter are potential inhibitors of vitamin B_6 linked decarboxylases.

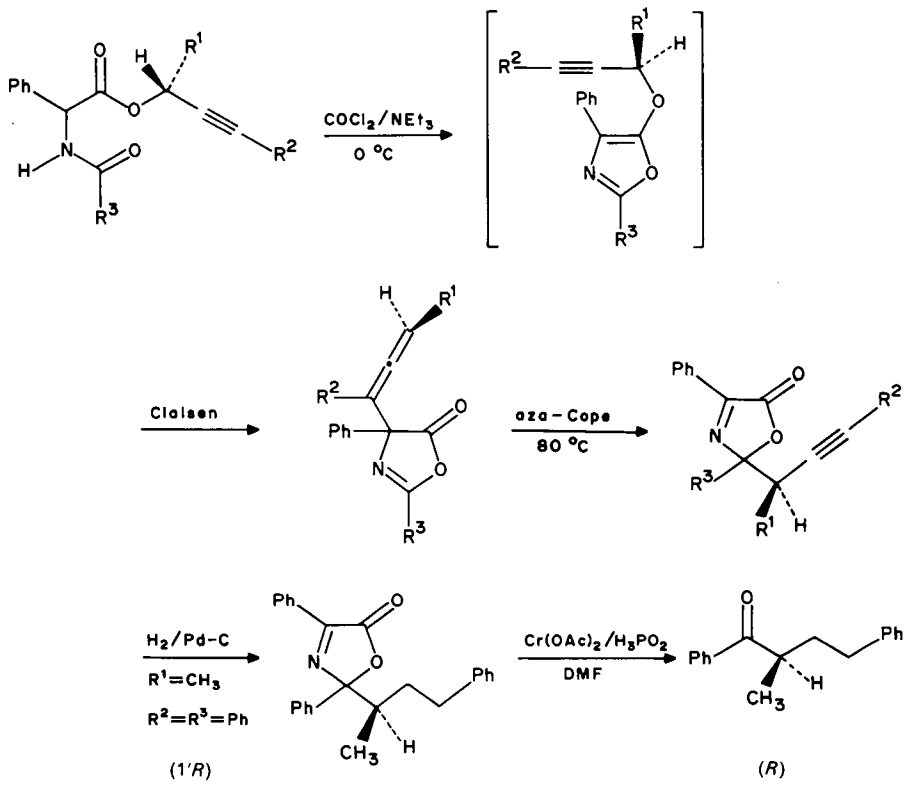


(73)

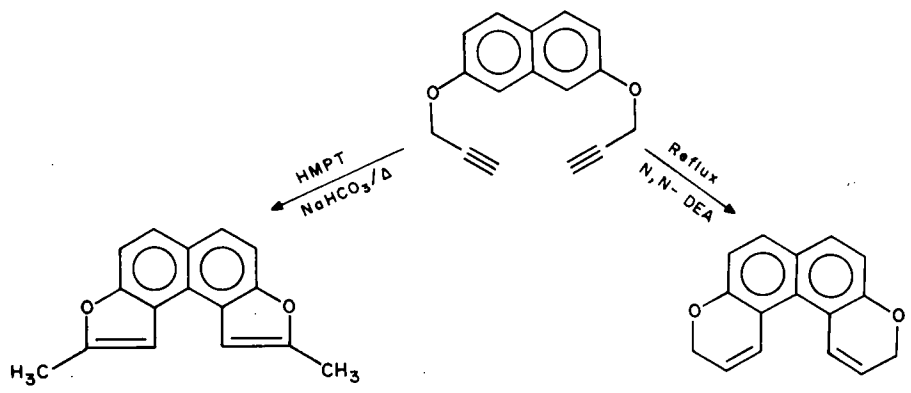


(74)

Some double Claisen rearrangements of various bis-propargyl aryl ethers have been reported by Balasubramanian as well as other workers[347–350]. One type of such rearrangements is the regiospecific rearrangement of bis propargyl ethers of naphthalene which yields naphthodipyrans when refluxed in *N,N*-diethylaniline (DEA) and naphthodifurans in HMPT in the presence of sodium bicarbonate as expected (equation 75)[347]. The other type of double Claisen rearrangement is the thermal[348,349] and acid-catalyzed rearrangement of 1,4-diaryloxy-2-butynes (**288**) to either 11a-methylpterocarpans **290** or the isomeric benzofuro(3,2-*b*)benzofuran **291** and benzofuro(2,3-*b*)benzofuran **292**, depending on reaction conditions. A ^{1}H-NMR study has provided conclusive evidence for the involvement of two sequential Claisen rearrangements and the intermediacy of **289** in the thermal conversion of **288** into **290** (Scheme 7)[348]. Charge acceleration of Claisen rearrangements by Lewis acids is well known[9]. Thus, catalysis by silver tetrafluoroborate was observed in the rearrangement of **288** to **289** or **290**, depending on reaction time (0.5–1 equivalent of $AgBF_4$, CH_2Cl_2, 25 °C)[350]. At the end of one hour the expected 2*H*-

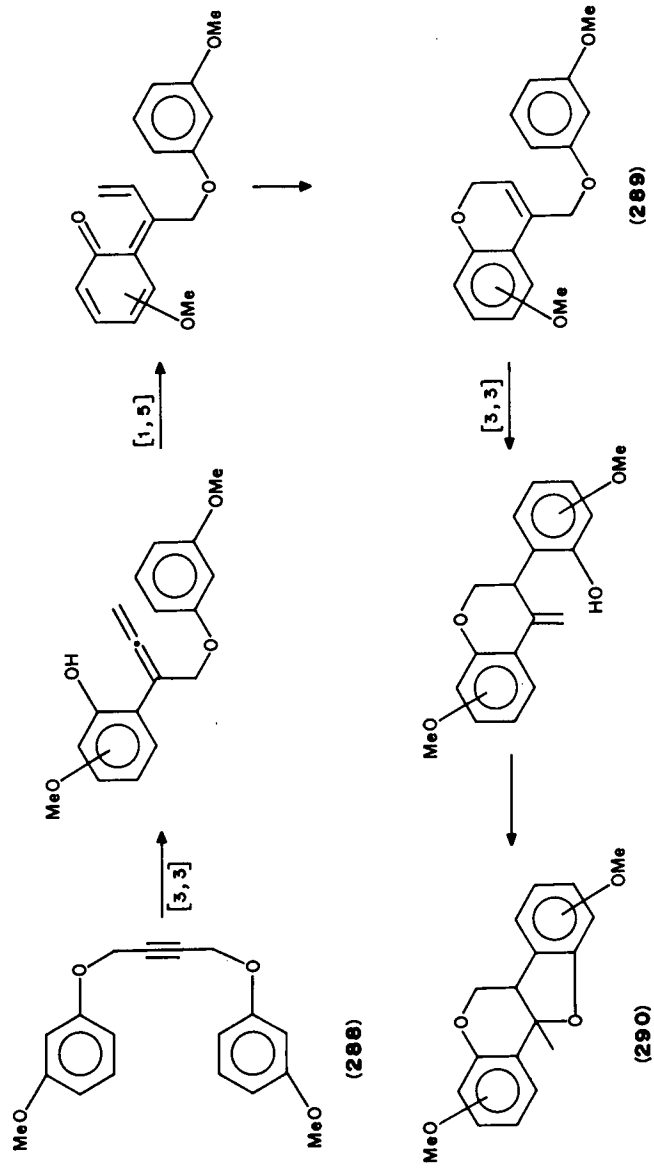


SCHEME 6

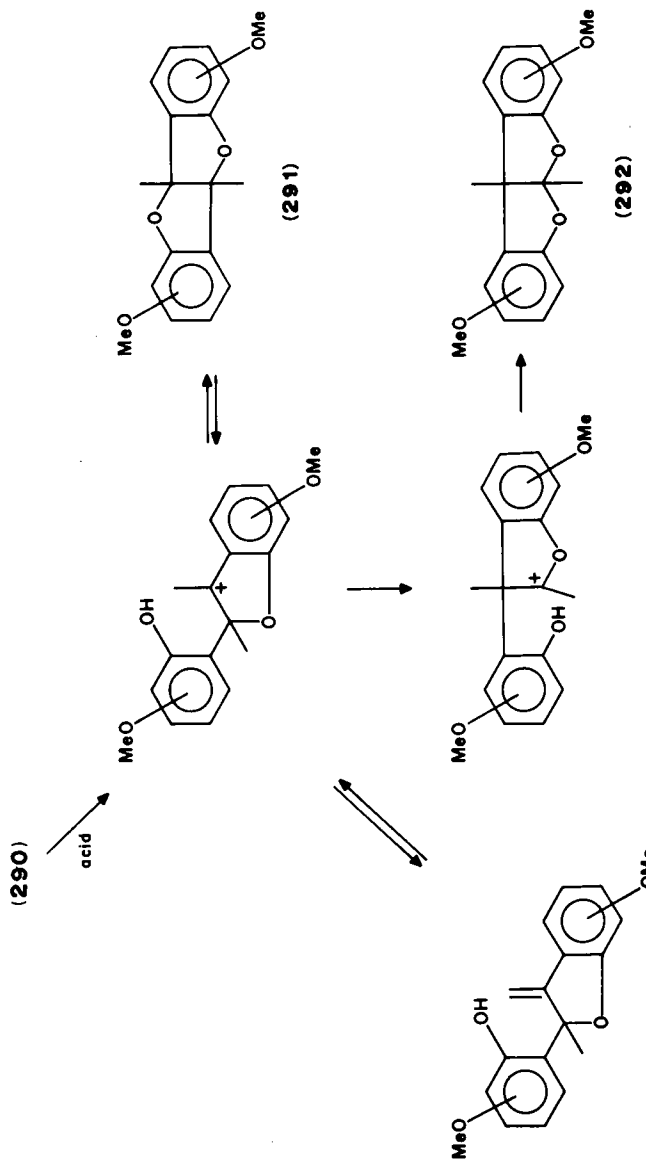


(75)

chromene derivative **289** was isolated in 55% yield; after 24 hours, the reaction gave 87% of **290** (R = 4-Me). The propargyl bis-ether **288** can also be converted selectively to **289** with mercuric trifluoroacetate, while the use of $AlCl_3$ in CH_2Cl_2 for several hours leads to the

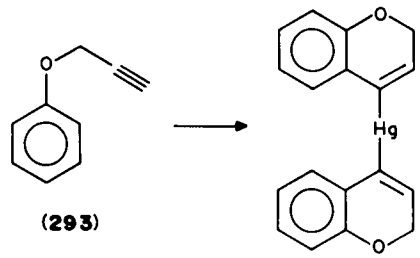


SCHEME 7 (*continued on next page*)



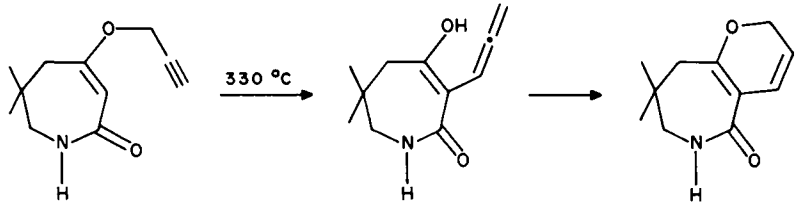
SCHEME 7 (*continued*)

formation of product **292**[350]. The same authors[351] have shown that if the acetylenic terminus is unsubstituted, the reaction takes a more complex course to give mercury derivatives of rearranged substrates, e.g. **293** → **294** [75% yield, $Hg(CF_3CO_2)_2$, CH_2Cl_2, 25 °C, 2 h, then $NaBH_4/OH^-$].



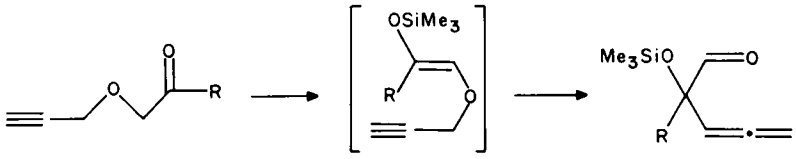
(293) **(294)**

b. Propargyl vinyl ethers, acetals, etc. The utility of the Claisen rearrangement of propargyl vinyl ethers in the synthesis of natural products has been demonstrated. For example, caprolactame **295** rearranges on heating to the allene **296**, which cyclizes to **297**, known for its activity as a central nervous system compound[353]. α-Propargyloxy ketones **298** afford α-allenyl-α-trimethylsiloxy aldehydes **300** upon treatment with chlorotrimethylsilane and triethylamine in dimethylformamide. This conversion presumably involves Claisen rearrangement *in situ* of intermediate enol silyl ether **299**[354]. In a one-pot procedure, the α-siloxy aldehydes **300** were hydrolyzed to α-hydroxy aldehydes with methanol solution and a trace of *p*-toluenesulfonic acid, and then oxidatively cleaved with periodate to give the corresponding allenyl ketones. A related process is the highly diastereoselective synthesis of 2-hydroxy-3,4-alkadienoic acids by the ester enolate Claisen rearrangement of propargyl glycolates, shown in equation 76[355].

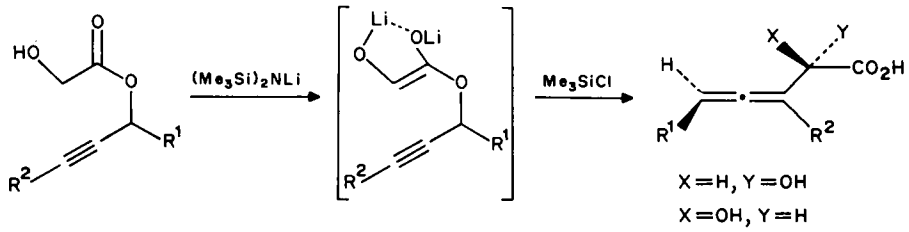


(295) **(296)** **(297)**

In the so-called *ortho* ester Claisen rearrangement[9], β-allenyl esters[356] or amides[357] are obtained when propargyl alcohols are heated with an *ortho* ester or 'amide acetal', respectively, in the presence of an acid catalyst. This stepwise reaction involves ester interchange, dealcoholation and Claisen rearrangement and is illustrated by conversion of the optically active propargyl alcohol (*R*)-(+)-**301** with excess ethyl orthoacetate in the presence of a catalytic amount of propionic acid at 110 °C for 7 h, to give the optically active allene (*R*)-(−)-**302**, $[\alpha]_D^{22}$ −47.0°, in 88% yield[356]. The success of this chirality transfer reaction was revealed by its later conversion into methyl (*R*,*E*)-2,4,5-tetradecatrienoate (**303**) with optical rotatory power greater than that of the natural pheromone. An efficient synthesis of various 3,4-bis(methylene)hexanedioic esters starting from 2-butynediol and using a double Claisen orthoester rearrangement has also been reported (equation 77)[358].

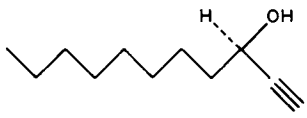


(298) (299) (300)

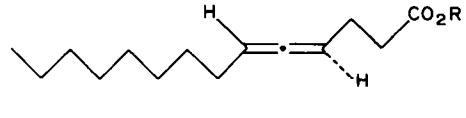


X=H, Y=OH
X=OH, Y=H

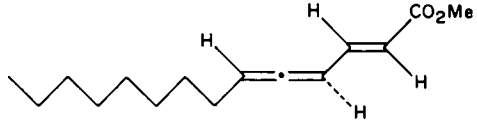
(76)



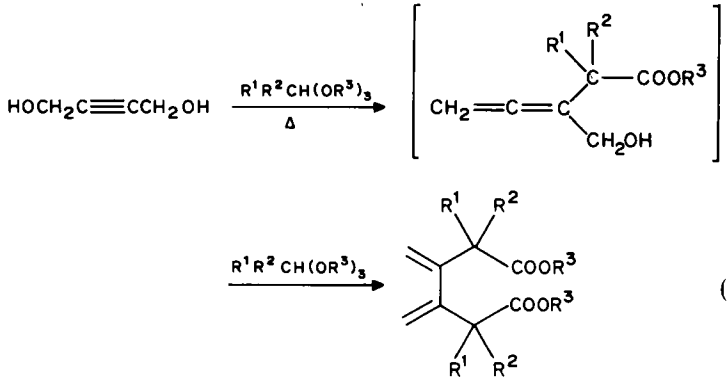
(*R*)-(+)-(**301**)



(*R*)-(−)-(**302**)

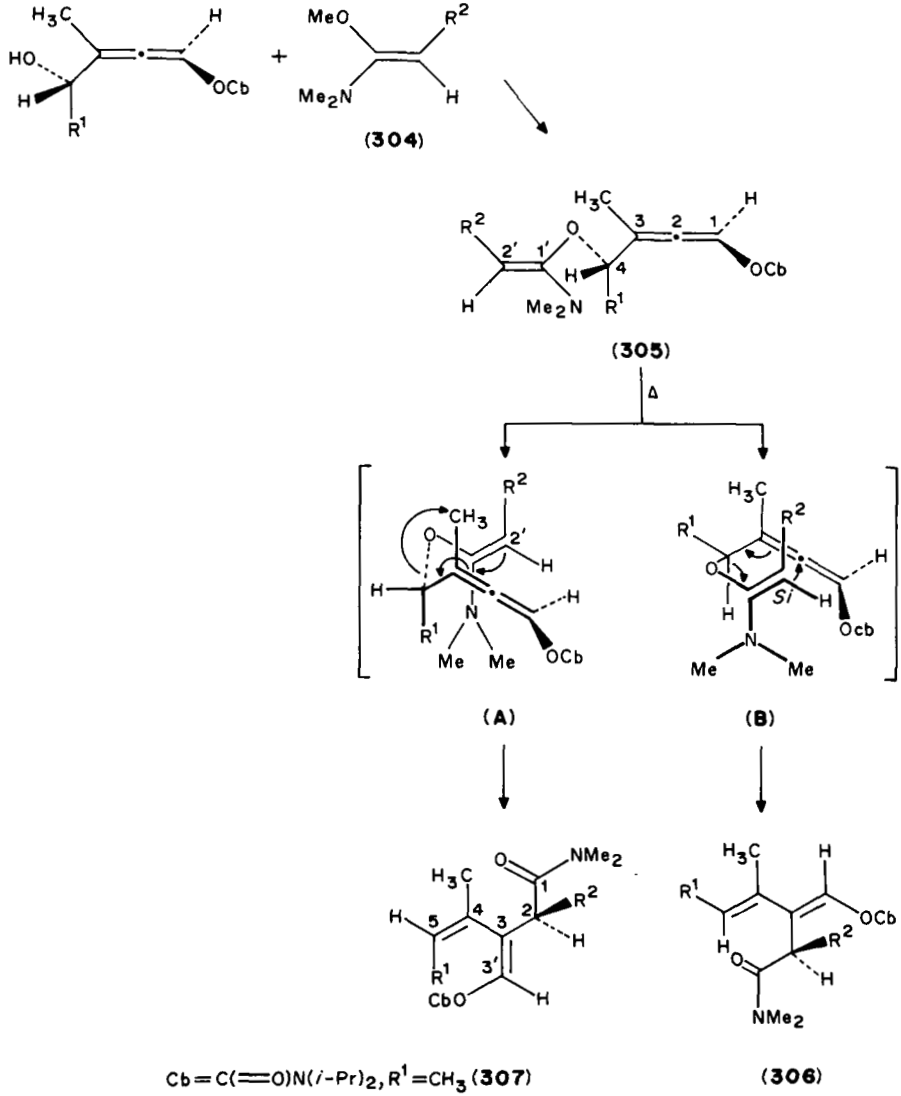


(*R,E*)-(−)-(**303**)



(77)

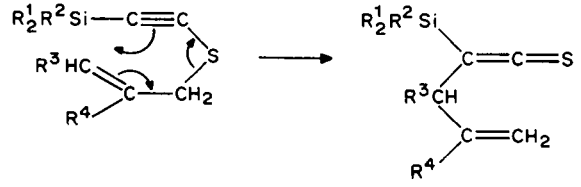
Following their report on a highly regio- and stereoselective synthesis of diastereomerically pure allenes such as **83**[142-144], Hoppe and coworkers[359,360] have investigated the amide Claisen rearrangement of these alcohols. In principle, a chiral allene like **83** and a ketone N, O-acetal **304** ($R^2 \neq H$) should react to give the *Z*-configurated intermediate **305**, whose [3, 3] sigmatropic rearrangement can proceed via four stereotopically different transition states. Which route is actually followed is revealed by the product. The chair-like transition states **A** and **B** lead to **306** (2*S*, 3*Z*, 4*Z*) and **307** (2*R*, 3*E*, 4*E*), respectively, whereas the boat-like transition states should lead to their enantiomers (Scheme 8)[359].



SCHEME 8

Using optically active chiral allenic substrates, the authors have demonstrated that the rearrangement proceeds via the transition state **B** in which R′ takes a pseudo-equatorial position and avoids the 1,3-diaxial interaction with the NMe_2 group present in the **A** transition state. This synthesis provides a simple and general entry to highly substituted diastereomerically pure 1,3-alkadienes of the type **306** in only two steps and demonstrates the occurrence of 1,4-chirality transfer in allene Claisen rearrangements[359]. More recently, a highly stereoselective synthesis of functionalized tetra- and penta-substituted 1,3-butadienes by allene Claisen rearrangements has been reported by the same authors[360].

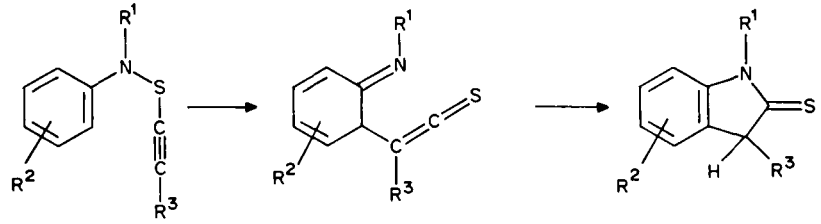
c. Thio-Claisen rearrangements. Schaumann and coworkers[361,362] have observed a facile thio-Claisen rearrangement of allyl silylethynyl sulfides **308** to allyl(silyl)thioketenes **309**. The sulfides are readily prepared by sequential treatment of trimethylsilylacetylene with BuLi, sulfur and an appropriate allyl bromide. A study of the substituent effects in the allylic group has revealed that electron-withdrawing groups at the β-position of the allyl residue favor the reaction while at the γ-carbon they show the opposite effect. For substituents on the triple bond, the sequence silyl > alkyl > alkylthio is valid. The results were rationalized in terms of a zwitterionic intermediate or a highly polarized transition state for the rearrangement[362]. The products can be converted to thioamides on reaction with primary or secondary amines[362].



(308) **(309)**

(a) $R^1=R^2=Me$; (b) $R^1=R^2=Et$; (c) $R^1=Me$, $R^2=t\text{-}Bu$

A closely related [3,3] sigmatropic rearrangement is the thermal rearrangement of *N*-aryl-1-alkyne-sulfenamides **310** to indoline-2-thiones **312**[363]. The sulfenamides are obtained by reaction of bromomagnesium benzeneamides with 1-alkynyl thiocyanates and are believed to rearrange first to intermediate thioketenes **311**, followed by cyclization to the observed products.



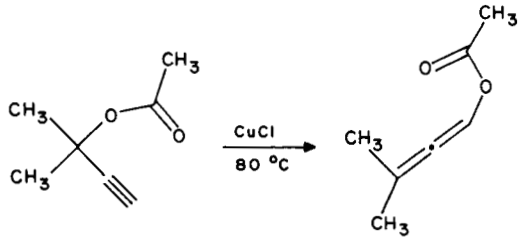
(310) **(311)** **(312)**

5. Propargyl ester–allenyl ester rearrangements

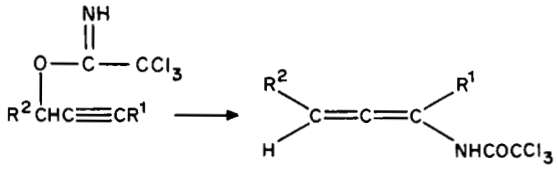
Although cuprous chloride has had only limited uses as a catalyst for [3,3] sigmatropic rearrangements[335], it was found superior to $AgBF_4$ in the rearrangement of α,α-

dimethylpropargyl acetate (**313**) to γ,γ-dimethylallenyl acetate (**314**)[201,202]. A quantitative yield of the product was obtained with the former catalyst in boiling benzene, while with the latter catalyst the yield was only 60%.

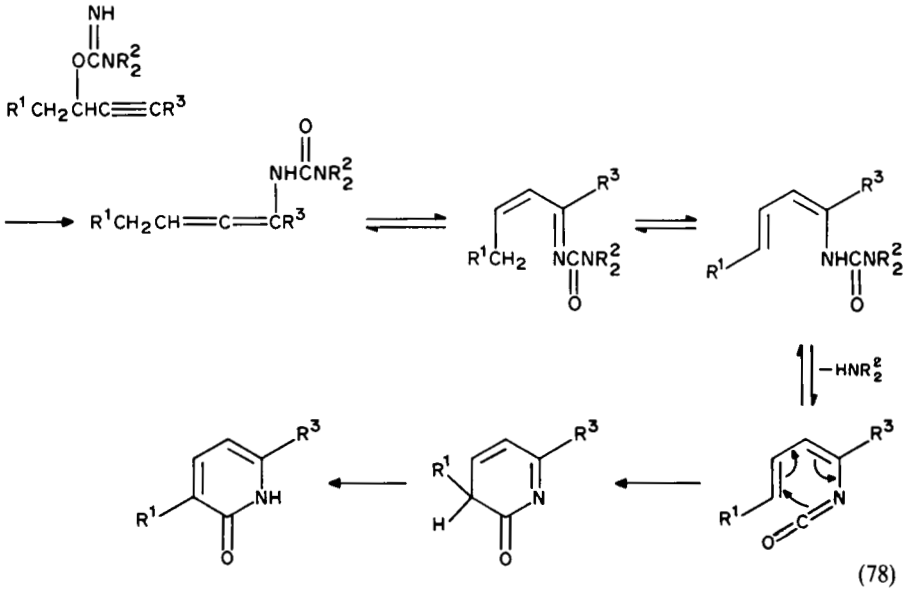
In a related study, it has been shown that propargylic trichloroacetimidates **315** undergo rearrangement in refluxing xylene for several hours to the allenic trichloroacetamides **316**[364,365]. Similar [3,3] sigmatropic rearrangements have been proposed to initiate the multistep thermal rearrangements of propargylic pseudoureas to 6-substituted 2-pyridones by the same authors (equation 78)[366,367].



(**313**) (**314**)



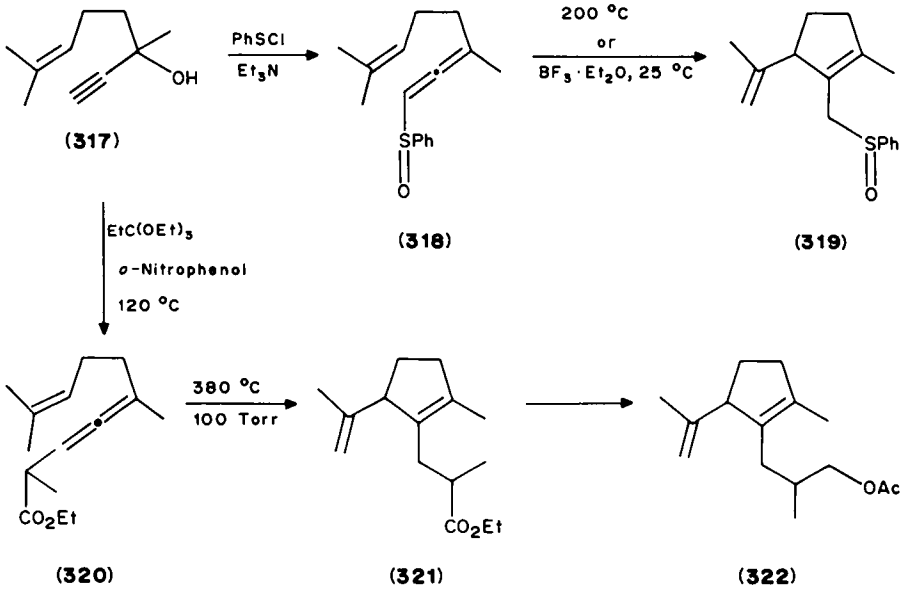
(**315**) (**316**)



(78)

6. Ene and retro-ene reactions

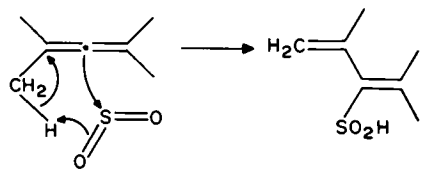
The ene reaction usually involves the thermal reaction of an olefin containing an allylic hydrogen (ene) with an electron-deficient multiple bond (enophile). A general review on the scope, limitations and utility of intramolecular ene reactions[368] and a review on Lewis-acid catalyzed ene reactions[369] have been published during the past decade. For the same period, one of the early examples of intramolecular ene reactions involving allenic enophiles[370] is the quantitative cyclization of the allenic sulfoxide **318**, easily prepared from **317**, to the doubly functionalized cyclopentene derivative **319**. A striking rate enhancement of this reaction can be achieved by Lewis acid catalyses. Another example is an industrial process which involves thermolysis of β-allenic ester **320**, also readily prepared from **317**, to give cyclopentene **321**, which is then converted into the odorant **322**[371].



(317) (318) (319) (320) (321) (322)

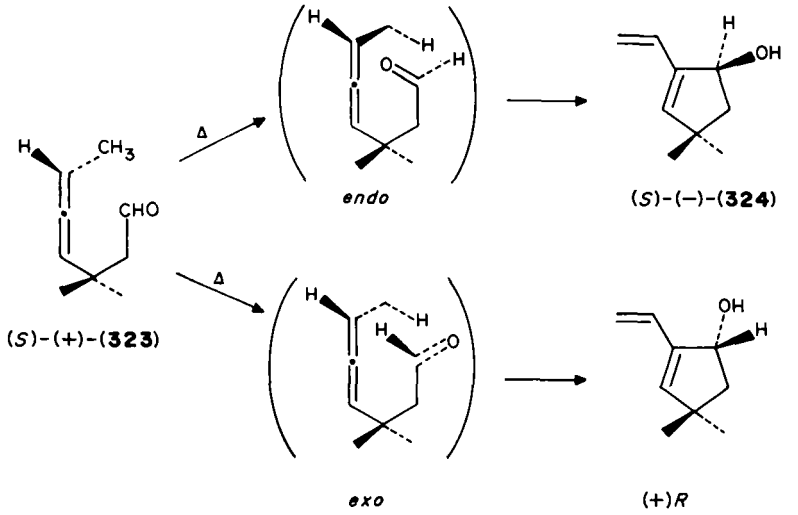
In the presence of suitable enophiles, alkylallenes are highly reactive substrates also as ene partners, by virtue of the energetically favorable bond reorganizations that such reactions entail. For example, 2,4-dimethyl-2,3-pentadiene in liquid sulfur dioxide undergoes ene addition with the solvent at low temperatures and affords 3-(2,4-dimethyl-1,3-pentadienyl)sulfinic acid (equation 79)[372].

A variety of substituted cyclopentenols are easily accessible by intramolecular hetero-ene reactions in which γ-allenic carbonyl compounds are submitted to thermolysis and the



(79)

carbonyl group acts as the heteroenophile (equation 80)[373]. The yields of cyclized products are better when the carbon α to the allenic linkage is substituted. Thermolysis of an optically active γ-allenic aldehyde proceeds with transfer of axial chirality into central chirality. Starting from (*S*)-(+)-γ-allenic aldehyde **323**, (*S*)-(−)-cyclopentenol **324** was obtained (optical yield 36%). This result is consistent with a concerted pathway involving an *endo* or *exo* oriented interaction. The '*endo*' approach, in which the allenic and aldehyde protons are far from each other in the transition state, seems to be the favored conformation[374]. A similar conversion of δ-allenic aldehydes into cyclohexenols has also been reported by Bertrand and coworkers[375].

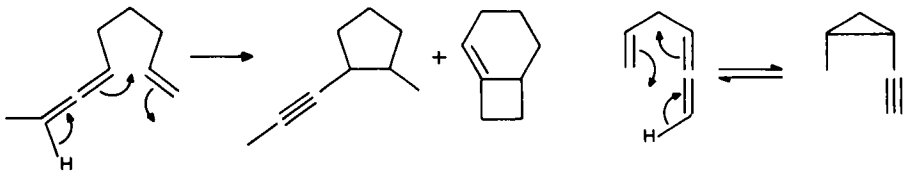


(80)

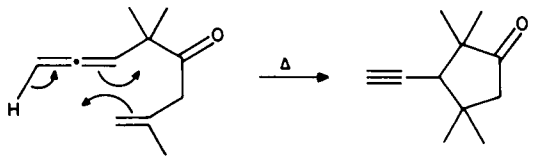
An unusual intramolecular ene reaction in which the allenyl group acts as an ene partner was recently described by Huntsman and coworkers[232]. For example, the pyrolysate of 1,6,7-monatriene **325** at 390 °C in a flow system contained two major products in the ratio of 60:38, identified as **326** and **187b**. The formation of **187b** involves one of the anticipated intramolecular [2 + 2] cycloaddition processes, while the formation of **326** involves transfer of allenic hydrogen as shown by the arrows. Interestingly, the 1,5-homodienyl shift (**327**⇌**328**) proposed by Berson and coworkers[287a] to account for isotopic labelling patterns observed in the pyrolysis of 6-methyl-5-hepten-1-yne is analogous to the present reaction. The transformation of **328** to **327** was previously observed by Dalacker and Hopf[287b]. Another process similar to the conversion of **325** to **326** is the thermal rearrangement of allenic ketone **329** to acetylenic ketone **330** reported by Skattebøl and Stenstrom[233].

Similar to the retro-ene reaction[9], a thermal hetero retro-ene reaction is also possible. For example, the rearrangement of β-hydroxyacetylenes in both the cyclic (equation 81)[376] and acyclic[313] series has provided a general method for the synthesis of allenes and a comprehensive mechanistic investigation in the latter has been described[313].

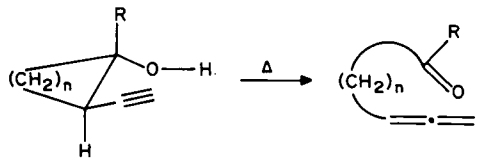
Retro-ene reactions have also been observed during flash vacuum thermolysis of 1,2-cyclonona- and 1,2-cyclodecadienes which yield terminal enynes and enedienes as primary products (equations 82 and 83)[377]. A concerted mechanism in which the allene is strongly bent but not yet planar has been proposed for these rearrangements.



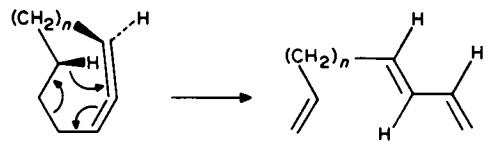
(325) (326) (187b) (327) (328)



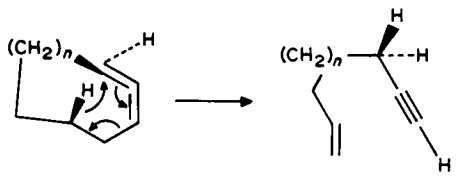
(329) (330)



(81)

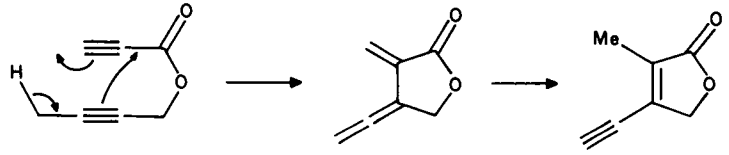


(82)



(83)

Propargylic hydrogens can also act as ene partners. Thus, Dreiding and coworkers[378] have found that gas-flow thermolyses of propargyl propiolate **331** affords methylene-vinylidene-butanolide **332** by way of an intramolecular ene reaction, followed by a second ene reaction to butenolide **333**, the observed product.

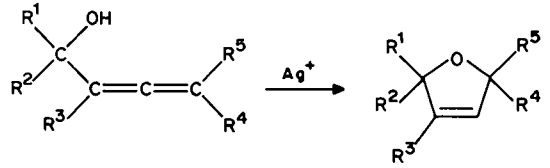


(331) (332) (333)

V. ACID- AND BASE-CATALYZED CYCLIZATIONS

A. Acid-catalyzed Cyclizations

An impressive number of heterocyclic systems have been prepared from allenic starting materials, and occasionally from allenic intermediates. The electrophilic cyclization of allenic alcohols provides a convenient route to five- and six-membered oxygen heterocycles and depends on the relative positions of the two functionalities. Thus, for example, Olsson and Claesson have achieved the synthesis of 2,5-dihydrofurans and 5,6-dihydro-2*H*-pyrans by silver(I) catalyzed cyclization of variously substituted α- and β-allenic alcohols, under mild conditions (equations 84 and 85)[379]. Similar cyclizations of various



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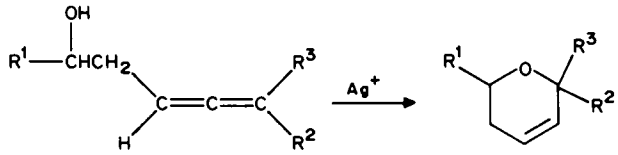
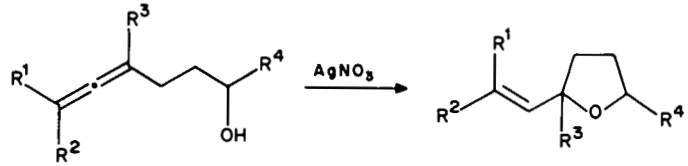


(85)

α- and β-allenic alcohols have been subsequently observed by other workers as well[24,167,354,380–383]. On the other hand, γ-substituted allenic alcohols have been shown to undergo cyclization to 2-vinyltetrahydrofurans and δ-allenic alcohols yield 2-vinyltetrahydropyrans, under the action of silver nitrate or mercuric trifluoroacetate, in aqueous acetone at room temperature (equations 86 and 87)[383,385]. Similarly, the cyclization of the allenic β-ketoester **334** to furan derivative **335** under the action of catalytic amounts of yellow mercury(II) oxide and *p*-toluenesulfonic acid should proceed by the same mechanism[386]. The silver(I) catalyzed cyclizations of α-, γ- and δ-allenic amines parallels the rearrangement of the corresponding alcohols and afford 3-pyrroline[387], 2-vinylpyrrolidine and 2-vinylpiperidine[388] derivatives, respectively.

The electrophilic cyclization of several other functionalized allenes has also been described. For example, cyclization of β-allenic oximes in the presence of a catalytic amount of $AgBF_4$ leads to 4,7-dihydro-1,2-oxazepines[389]. β,γ-Unsaturated δ-lactones (**338**) are obtained in practically quantitative yield on treatment of β-allenic carboxylic acids (**336**) with boron trifluoride, and are believed to involve the bridged complex **337** as



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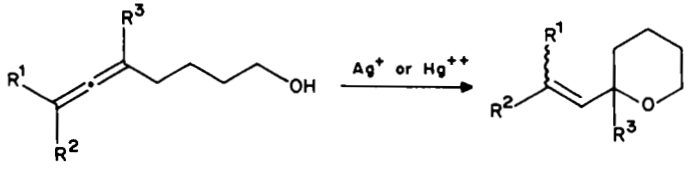

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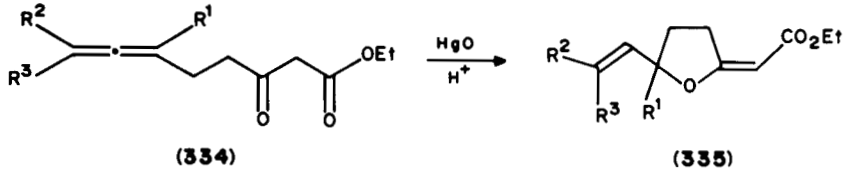
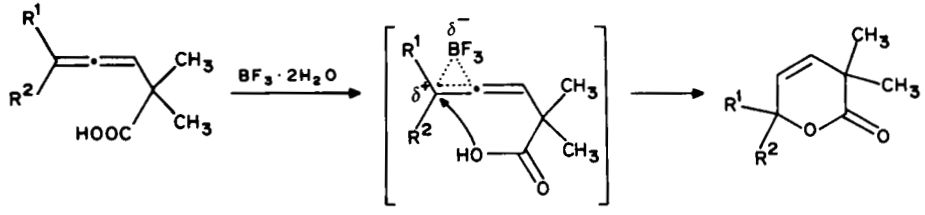
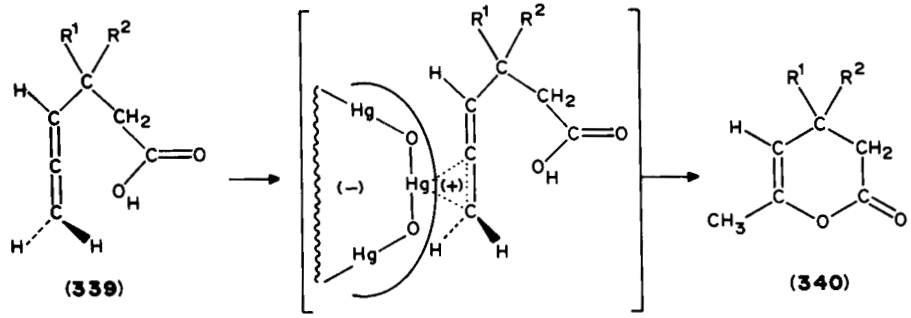


(334) (335)



(336) (337) (338)

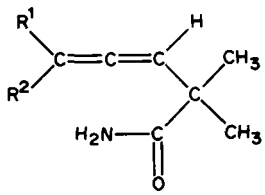


(339) (340)

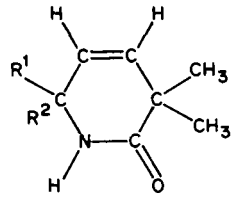
an intermediate[390]. The latter, which is susceptible to nucleophilic attack by the carboxyl oxygen, is stabilized by alkyl substitution at the δ carbon of **336**. More recently, the same authors[391] have found that unlike β-allenic acids **336**, γ-allenic carboxylic acids **339**, unsubstituted at the terminal double bond, undergo quantitative cyclization in the presence of a catalytic amount of yellow mercury(II) oxide, and afford γ,δ-unsaturated-δ-lactones (**340**), that is, by bonding of the carboxyl oxygen at the central allenic carbon instead of the terminal one.

Interestingly, while the silver ion catalyzed cyclization of β-allenic amides **341** leads to 3,6-dihydro-2(*H*)-pyridones (**342**)[392] as expected, the exocyclic α-allenic amide **343** leads to the spiro butenolide **344**, i.e. by attack of oxygen rather than nitrogen on the developing carbenium ion intermediate[357], on treatment with aqueous formic acid.

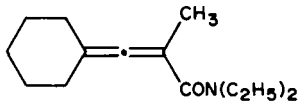
Allenephosphinic and phosphonic acids as well as their esters, which are easily prepared by reaction of propargylic alcohols with phosphorous halides (Section IV.D.2), undergo facile electrophilic cyclizations to various 2-oxo-1,2-oxaphosphol-3-enes (e.g. equation 88)[393]. This reaction, which represents one of the most efficient preparations of this type of heterocycles, has been intensively studied in recent years[394–400] and thoroughly reviewed by Angelov[400], a major contributor in the area. The reader is therefore referred to this source.



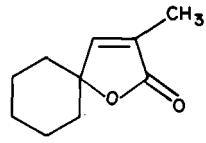
(**341**)



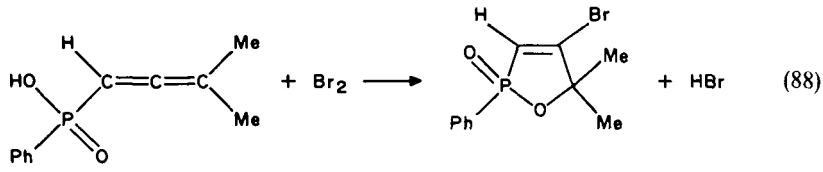
(**342**)



(**343**)



(**344**)

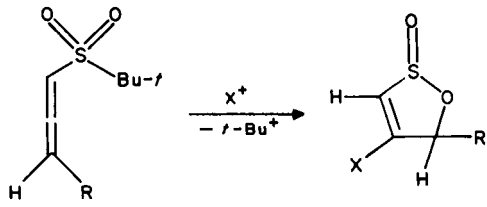


(88)

Another acid-catalyzed allene cyclization which has been recently reviewed is the electrophilic fragmentation cyclization of mono- and diallenic sulfones to α,β-unsaturated γ-sultines (equation 89)[304]. A stereochemical study of this unexpected sulfone to sulfinate transformation revealed that the reaction is stereoselective and provided a convenient method for the preparation of optically active γ-sultines of known absolute configuration[401]. A recent review on cyclic allenes also includes electrophilic rearrangements of cyclic allenes[402].

B. Base-catalyzed Cyclizations

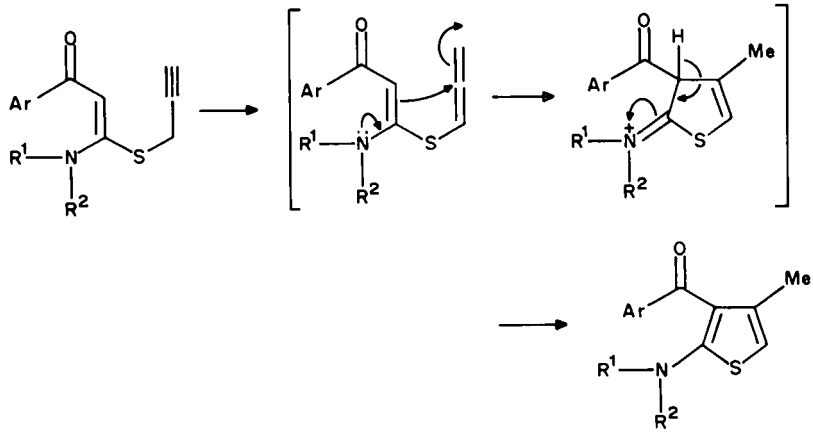
Although not as extensively studied as the acid-catalyzed cyclizations, base-catalyzed cyclizations of certain functionalized allenes have also been studied in the past decade and



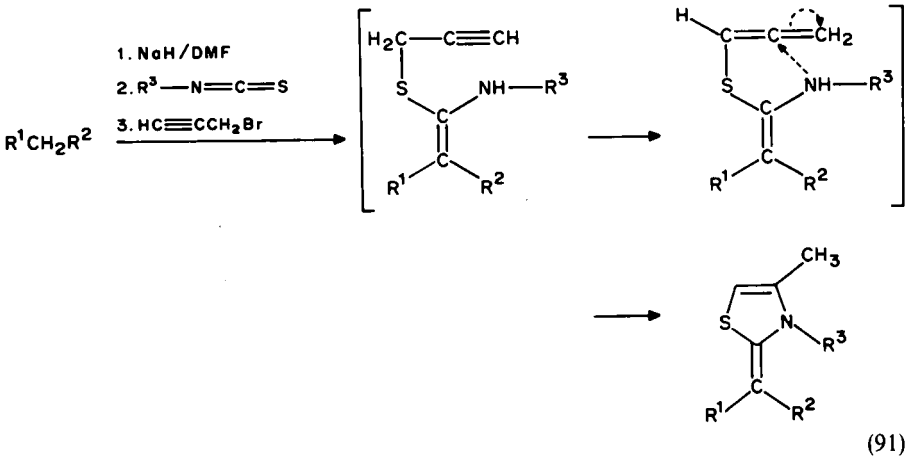
(89)

(*R*)-(−)

		$[\alpha]_D^{20}$ deg
R=Me	X=Br, R=Me	+ 16.9
R=*t*-Bu	X=Br, R=*t*-Bu	+ 15.6
	X=MeS, R=Me	+ 23.7
	X=MeS, R=*t*-Bu	+ 15.9

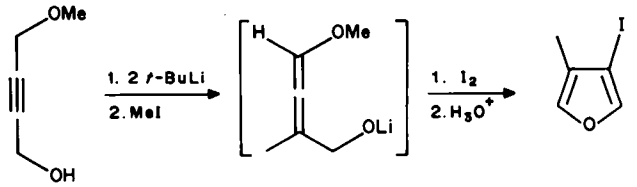


(90)

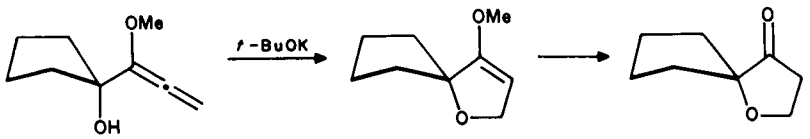


(91)

found useful in the synthesis of five-membered heterocycles such as substituted thiophenes (equation 90)[403], thiazoles (equation 91)[404], furans (equation 92)[170] and dihydrofurans (equation 93)[133,134]. The last application is of particular interest, since it provided an elegant approach to the synthesis of the first primary helical molecules of the tetrahydrofuran ring system: polyoxapolyspiroalkanones **350**. The adduct **345** between cyclopentanone (a starting block) and α-lithio-α-methoxyallene, on treatment with *t*-BuOK in *t*-BuOH containing 18-crown-6, heated at reflux for 15 hours, gave the spiroannulation product **346**. Acid hydrolysis of the latter afforded spirodihydrofuranone **347** in 82% overall yield. Repetition of this spiroannulation procedure on **347** affords **348**, which can be sequentially converted to beautifully crystalline cyclopentyl[3]helixane **349** and [4]helixane **350**, by the same process.

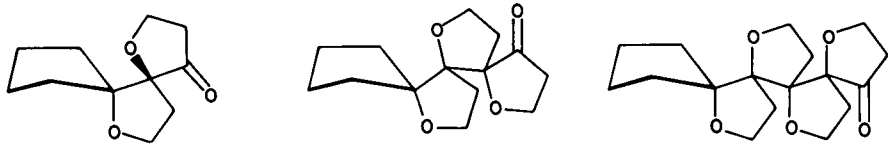


(92)



(93)

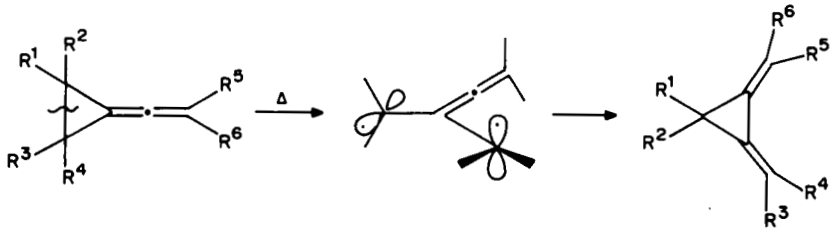
(345) (346) (347)



(348) (349) (350)

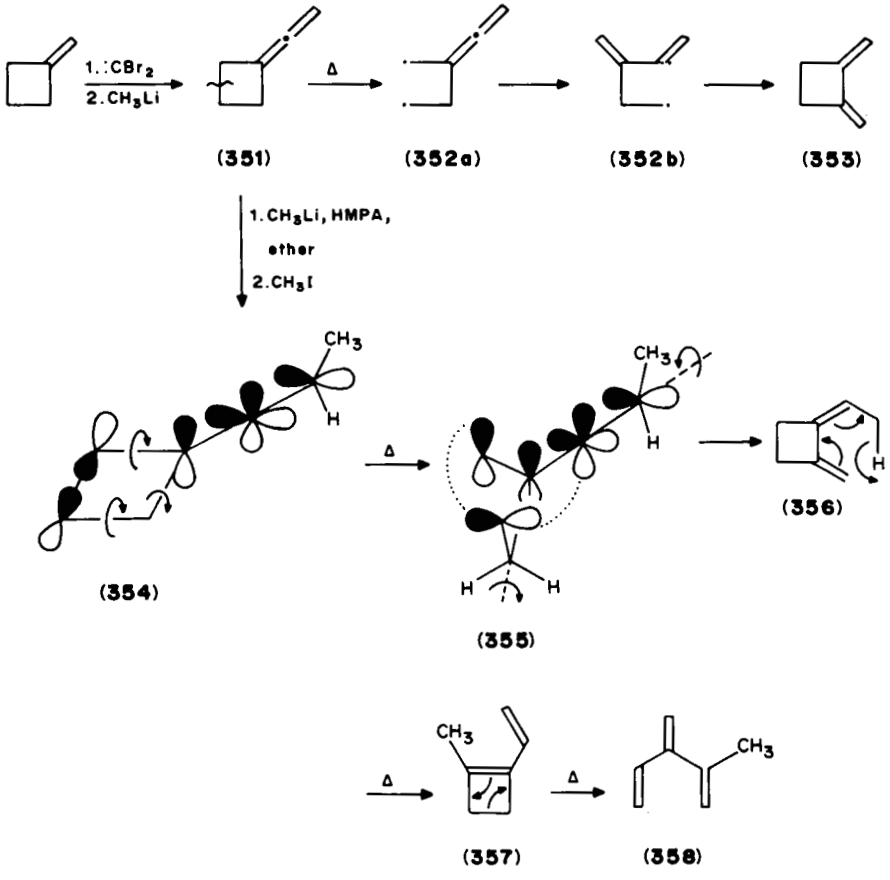
VI. REARRANGEMENTS OF ALKENYLIDENECYCLOALKANES

In continuing previous studies on the well-known thermal isomerization of alkenylidenecyclopropanes to dimethylenecyclopropanes, which is believed to proceed via an orthogonal trimethylenemethane diradical (equation 94)[9], Hopf and coworkers[327] have carefully investigated the thermal rearrangement of several other exocyclic allenes in a high-temperature flow system in order to establish the effect of ring size on this reaction. Since many exocyclic allenes are known today[405] or may be prepared by routine methods[4], the allene–diene interconversion was expected to provide a novel, general access to 1,2-bismethylenecycloalkanes. Furthermore, substrates with more than one exocyclic allene group could conceivably isomerize to polymethylene cycloalkanes related to radialenes. These aims have indeed been achieved by these authors, but not without exceptions.

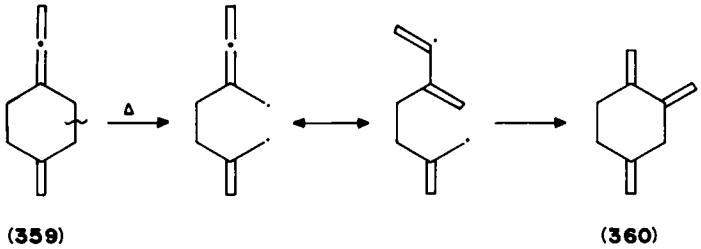


(94)

Thus, at 600 °C vinylidenecyclobutane **351** rearranges cleanly to 1,2-bis-methylenecyclobutane (**353**) by an allene–diene isomerization. The methylallene **354** behaves analogously although the primary product **356** does not survive under the same reaction conditions, and the isolated cross-conjugated triene **358** is a product of a 1,5-hydrogen shift followed by an electrocyclic ring-opening reaction. These rearrangements are also believed to proceed by a free radical mechanism involving biradicals **352** and **355** as intermediates.

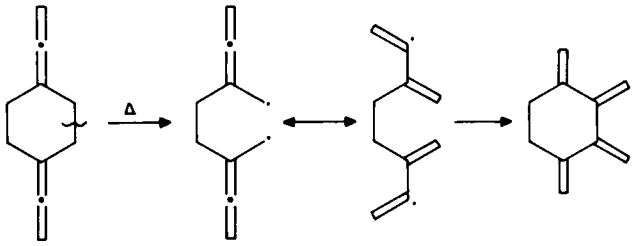


In contrast to the strained vinylidenecyclopropane and cyclobutane, vinylidenecyclopentane and cyclohexane are completely stable under the condition used for the pyrolysis of **351** and only at much higher temperatures do they yield aromatic products such as toluene and *o*-xylene, respectively. On the other hand, the allene–diene isomerization is observed again when a C—C bond is doubly activated by an allene and methylene group as in **359** or by two allene moieties as in **361**: at 500 °C 1,2,4-trimethylenecyclohexane (**360**) and 1,2,3,4-tetramethylenecyclohexane (**361**), respectively, are obtained in good yield. These isomerizations were also suggested to occur by a diradical intermediate mechanism (equations 95 and 96).



(95)

(359) **(360)**



(96)

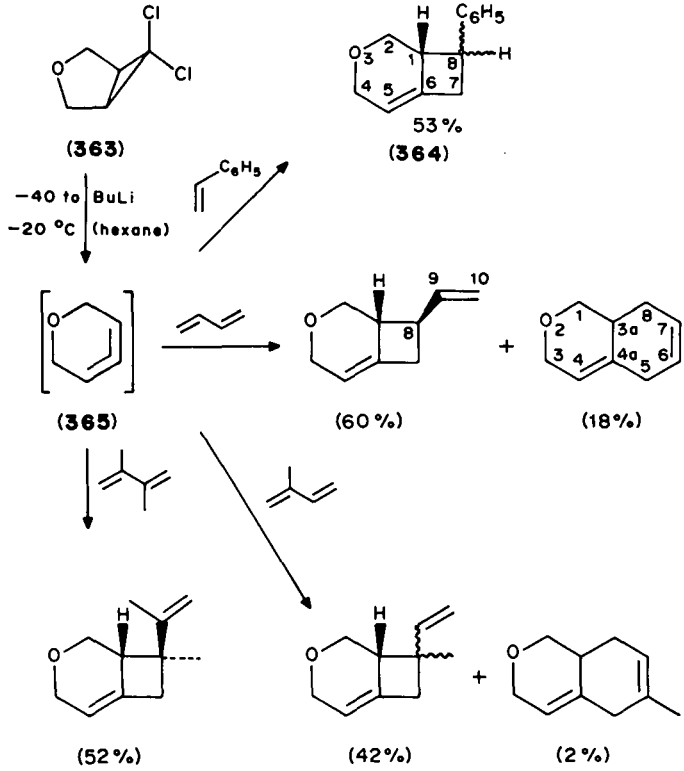
(361) **(362)**

The same authors have also suggested that the **361** → **362** isomerization may constitute a model reaction for the interconversion of 1,5,9-cyclodecatriyne (**265**) into [6]radialene (**268**) studied by Vollhardt and coworkers[325], and proposed the modified mechanism shown in equation 72. While both groups agree that the rearrangement is most likely initiated by a [3,3] sigmatropic isomerization converting **265** into the bisallene **267** (Scheme 4a), they object to the following Cope-rearrangement steps that were assumed to lead to the final product because of severe steric restrictions. The ^{13}C-labeling studies reported by Vollhardt[325] are in full agreement with the mechanism shown in equation 72.

VII. MISCELLANEOUS REARRANGEMENTS

A comparison of the list of contents of the Huntsman review[9] with that of the present review indicates the absence of several topics from the latter. One such topic is oxidative cyclization involving epoxidation of allenes to the so-called allene oxides which, in certain cases like vinylallenes, rearrange spontaneously to conjugated cyclopentenones[9]. Interestingly, no further relevant documentation of this topic appears except for the comprehensive review by Chan and Ong[406] on the chemistry of allene oxides published in 1980. More recently, a review on the chemistry of the related allene episulfides has also been published,

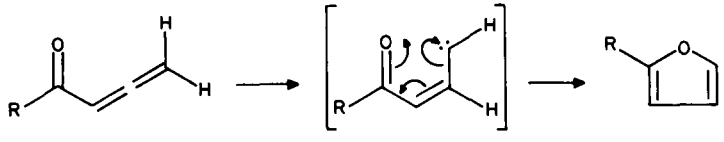
by Ando[407]. Another subject which has previously enjoyed considerable attention is homoallenic participation in the solvolyses or nitrous acid deaminiation of β-allenic tosylates and amines, respectively[9]. A full account by Dulcere and Santelli[408] on the nitrous acid deamination of β-allenic amines seems to be the only publication on this subject in recent years. On the other hand, photochemical rearrangements of allenes have continued to be the focus of considerable mechanistic and synthetic interest during the last decade as well, and some photochemical rearrangements have already been mentioned in the present review (Section IV.B). However, since a comprehensive review by Johnson[7] on the photochemistry of cumulenes was recently published, the subject is not further discussed here. Similarly, rearrangements involving carbene intermediates have also continued to attract considerable attention, particularly with regard to the application of the well-known cyclopropylidene-to-allene rearrangement in the synthesis of strained cyclic allenes. However, since three extensive reviews on cyclic allenes have recently appeared[402,409,410] this subject is also omitted here, except for indicating some of the recent reports[411–416] published since 1986, when the last review appeared. An illustration of some of these reports is shown in Scheme 9. Treatment of 6,6-dichloro-3-oxabicyclo[3.1.0]hexane **363** with BuLi at −40 to −20 °C generates 1-oxa-3,4-cyclohexadiene (**365**) via a cyclopropylidene-to-allene rearrangement, and is trapped



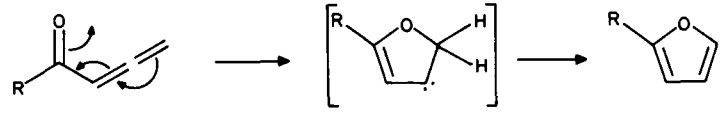
SCHEME 9

with activated alkenes to yield the corresponding cycloaddition products[411]. The preparation and reactivity of **365** are similar to that of 1,2-cyclohexadiene, also investigated by Christl and Schreck[412], and regarded as the most highly strained of the previously known monocyclic allenes.

Several rearrangements, not easily classified under the previous substitles, are described below. Huntsman and Yin[417] have investigated the thermal rearrangement of allenyl ketones in a flow system and observed conversion of 3,4-pentadien-2-one into 2-methylfuran at 520 °C in 72% yield. Two possible mechanisms have been considered for this rearrangement by the authors as shown in equations 97a and 97b. Both mechanisms involve a vinylcarbene intermediate and a [1,2] hydrogen shift and differ only in the timing of these steps.



(97a)



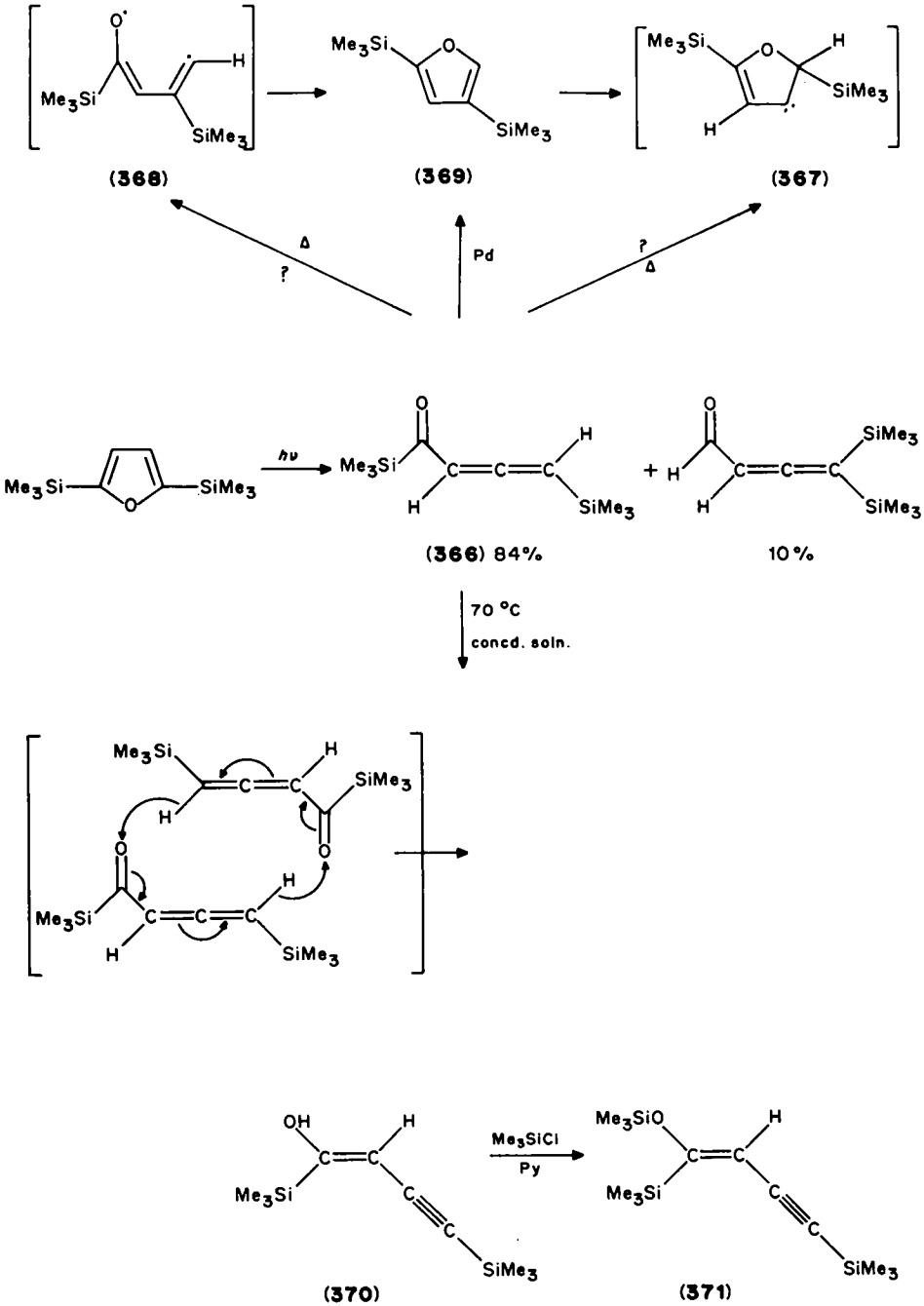
(97b)

R=CH$_3$

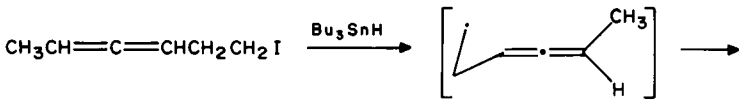
Interestingly, a similar mechanism to that shown in equation 97b has been considered by Barton and Hussmann[418] for the quantitative rearrangement of bis(trimethylsilyl) ketone **366** into 2,4-bis(trimethylsilyl) furan **369** on heating a dilute benzene solution at 150 °C for 30 minutes. However, the authors considered this cyclization geometrically unlikely and suggested that the reaction is initiated by a 1,2-silyl migration in **366** to afford diradical **368**, which closed to **369**. Surprisingly, heating very concentrated solutions of **366** resulted in quantitative formation of enol **370**, which on quenching afforded silyl enol ether **371** in high yield. The concentration dependence of the enolization of **366** to **370** was suggested to occur via a bimolecular process and a possible concerted 12-electron pathway as shown in Scheme 10. Allenyl ketone **366** itself is obtained by an extraordinary photorearrangement of 2,5-bis(trimethylsilyl) furan along with γ,γ-bis(trimethylsilyl) allenyl aldehyde as a byproduct.

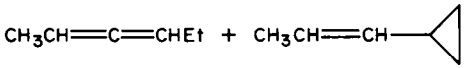
A free radical induced cyclization of allenes has been reported by Crandall and coworkers[419]. Several homoallenyl radicals have been generated by the reaction of the corresponding iodides with Bu_3SnH and found to produce small amounts of vinylcyclopropanes in addition to allene hydrocarbons, establishing that homoallenyl radicals cyclize to isomeric 1-cyclopropylvinyl radicals (equation 98).

The mass spectral fragmentation of ω-functionalized allenes has also been investigated and collision-induced dissociation spectra have been used in structural elucidation of $C_4H_5X^{+\cdot}$ ions, formed by chlorine or hydroxyl group migration in a McLafferty-type rearrangement of the molecular ion (equation 99)[420,421].



SCHEME 10





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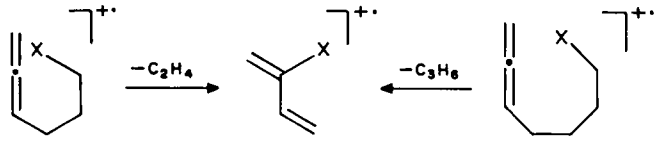

(99)

Isomerization of phenylpropadiene to 1-phenyl-1-propyne upon electrochemical reduction at mercury cathodes in dimethylformamide has been recently observed by Peters and coworkers[422].

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The Chemistry of Double-bonded Functional Groups
Edited by S. Patai

CHAPTER **15**

1,1-Diarylalkenes

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I. INTRODUCTION

1, 1-Diarylalkenes are a unique group of alkenes. The *gem*-diaryl arrangement confers this character on them. They are susceptible to a wide range of addition reactions, the driving force for which is the ability of the aryl groups to stabilize an anionic, cationic or radical centre. Thus they are involved in reactions not normally associated with alkenes without electron-withdrawing groups, *e.g.* conjugate addition and diazo coupling reactions.

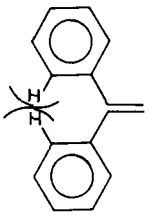
The steric interaction between the aryl groups prevents planarity of these molecules, inhibits polymerization and is in part responsible for the rearrangement, with aryl migration, of 2, 2-diarylvinyl carbanionic and carbocationic species. Because of this inhibition towards polymerization, they have been extensively employed as models for investigating the initiation steps of cationic polymerization. This steric effect also accounts for the recently observed kinetic stability of the acid enol: 2, 2-bis(pentamethylphenyl)ethene-1, 1-diol[1].

1, 1-Diarylalkenes undergo a wide range of cycloaddition reactions with dienes and 1, 3-dipolar ions. The steric hindrance presented by the *gem*-diaryl grouping is more than offset by its ability to stabilize a full or partial change in the transition state.

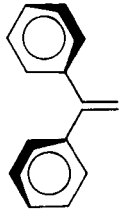
The 1, 1-diarylalkenes have not been reviewed previously.

II. STEREOCHEMISTRY

The conformation of 1, 1-diarylalkenes has been investigated intensively. In particular, the degree of twisting of the aryl groups out of the plane of the vinyl group has attracted attention[2–4]. A wide range of spectroscopic techniques has been employed to elucidate this point. In 1, 1-diphenylethylene (**1**) it is not possible for both phenyl rings to be coplanar because of steric interactions between the *ortho* hydrogens[5]. This effect has been observed



(1)



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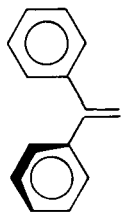


(3)

in other cross-conjugated 1, 1-diaryl compounds such as benzophenones[6], benzophenone oximes[7], thiobenzophenones[8] and tetraphenylcumulenes[9].

Coates and Sutton[10] concluded from dipole moment studies that the two rings are rotated 30° out of the plane of the double bond in the most stable conformation **2**. The loss of resonance energy prevents a larger angle of rotation[11]. Both a 38° and 40° angle of rotation for the two rings have been detected by Casalone and Simonetta[12] in their X-ray crystallographic study of 1, 1-di-(*p*-nitrophenyl)ethylene. The slight distortion from C_2

symmetry, which they have observed, is probably a consequence of crystal forces. The crystal structure of 1,1-diphenylethylene has not been reported[13].

Because of the similarity between the UV spectrum of 1,1-diphenylethylene, λ_{max} 224 and 251 nm in 95% ethanol, and that of styrene, Jones[14,15] proposed the planar-orthogonal conformation **3**. However, a more detailed investigation of the UV spectra of 1,1-diarylethylenes by Suzuki[16] has led to the conclusion that both rings are twisted out of the plane of the double bond. ^{1}H NMR studies have led to the same conclusion[17,18]. A single NMR signal is observed for the two vinyl protons of 1,1-diphenylethylene, even at −90 °C. In addition, it is noted is these studies that the electronic effect of *para* substituents on the conformation of 1,1-diarylethylenes is small[17,18].

The C_2 symmetry 1,1-diphenylethylene and 1,1-diphenyl-2,2-dideuterioethylene has also been determined from the polarization of the Raman spectra of the pure liquids[19]. Gustav and Boelke[20] have confirmed this and determined the angle of torsion as 34.5°. Schmid and Topson[3], from a Raman intensities study, have deduced a 44–47° angle. This conclusion compares favourably with 43.5°, a value calculated by Suzuki[21] from UV spectra. A new molecular orbital based technology for the rapid and accurate calculation of bond lengths has been applied to both 1,1-diphenylethylene and tetraphenylethylene[22]. Studies of 1,1-diphenylethylene, using fluorescence spectroscopy, have also confirmed C_2 symmetry[23,24].

The IR spectrum of 1,1-diphenylethylene[4,13] is also consistent with C_2 symmetry. Thus, two bands: the out-of-plane CH mode involving the ethylenic hydrogens at 900 cm^{-1} and the double-bond torsional mode at 685 cm^{-1}, allow the question of the molecular geometry of diphenylethylene to be firmly settled as C_2 symmetry[13].

III. SYNTHESIS

Many of the synthetic methods outlined below are general for the synthesis of terminal alkenes. It seems that the synthesis of 1,1-diphenylethylene is a favourite objective for testing the efficiency of a new synthetic method. This is largely because the product is normally stable towards polymerization and the carbonyl compound employed, benzophenone, is an efficient reactant which is neither prochiral nor enolizable.

A. 1,1-Diarylalkenes

1. *Grignard reagents*

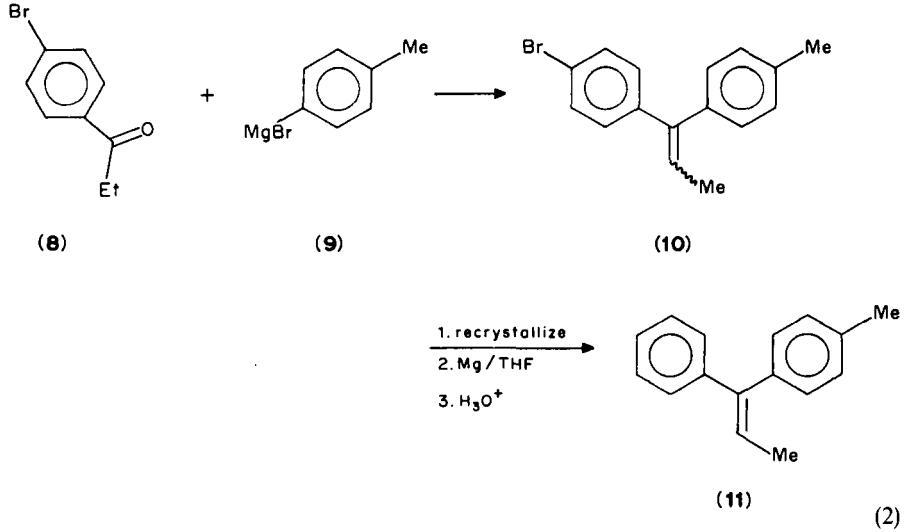
Most 1,1-diphenylalkenes and their nuclear substituted derivatives are readily accessible by dehydrating the corresponding alkanols **6**[25,26] (equation 1). Alternatively,

$$\underset{(4)}{RCH_2CO_2Et} + \underset{(5)}{2ArMgBr} \longrightarrow \underset{(6)}{RCH_2C(OH)Ar_2} \xrightarrow{H^+} \underset{(7)}{RCH{=}CAr_2} \qquad (1)$$

the intermediate alkanol **6** may be synthesized by treating the corresponding benzophenone with methylmagnesium iodide[27] or, if the aryl groups are dissimilar, by reaction of the corresponding acetophenone with the appropriate arylmagnesium halide[17]. When either one or both aryl groups bear a nitro substituent, these methods have been found to be unsuccessful[28].

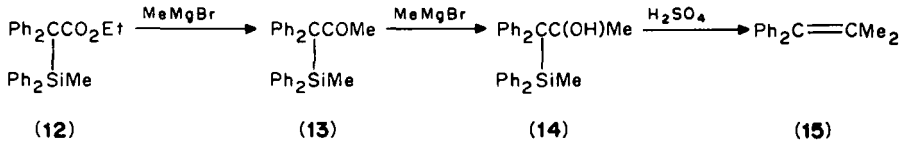
1,1-Diarylpropenes are prepared by a Grignard reaction between the appropriately substituted propiophenone and bromobenzene[5]. The resulting carbinol has been dehydrated in the course of distillation and, in some cases, by refluxing with iodine in ethanol. Normally, *E* and *Z* isomers of 1,1-diarylpropenes are separable by GLC. However, 1-*p*-

tolyl-1-phenylpropenes could not be separated by this method; instead, van der Linde, Veenland and de Boer[5] synthesized the corresponding *p*-bromobenzene derivative. This crude product could then be separated into its *E* and *Z* isomers by recrystallization and subsequent debromination (equation 2). 1, 1-Diaryl-2-methylpropenes have been similarly prepared from substituted isobutyrophenones and phenymagnesium bromide, followed by dehydration of the resulting carbinol[5].



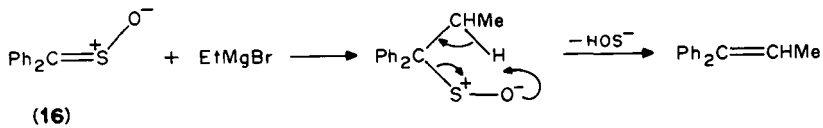
(2)

More recently, α-silylesters have been employed in the synthesis of 1, 1-diarylalkenes. Although yields are variable, the method readily allows for the synthesis of alkenes in which all four groups differ. In addition, the intermediate carbinol **14** is converted to alkene under mild conditions[29] (equation 3). It has been noted that Grignand reagents, for



(3)

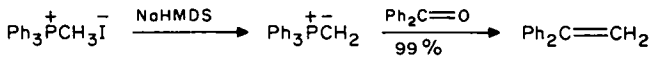
example ethylmagnesium bromide, react with thiobenzophenone *S*-oxide (diphenylsulphine) **16** with the formation of 1, 1-diphenylpropene[30]. In some other cases, sulphoxides and sulphides are formed. The products are the result of competition between electron transfer and proton abstraction reactions (equation 4).



(4)

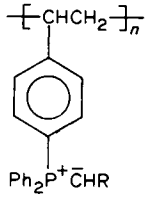
2. Wittig reagents

Both sodium dimsylate and sodium hexamethyldisilazide are effective bases in the Wittig reaction as, for example, that outlined (equation 5)[31]. However, with triphenylphosponium methylide **18** very low yields of alkene are obtained in its reaction with nitrobenzophenone[28].



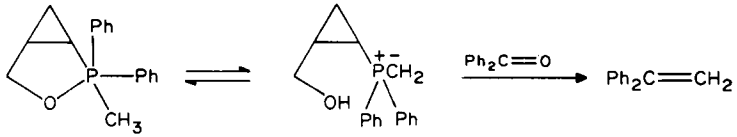
(17) (18) (5)

A development in this area is the preparation of insoluble polymeric phosphorane resins. The derived Wittig reagents **19** (R = H, Me and Ph) react efficiently with aldehyde and ketones. For example, **19** (R = H) reacts with benzophenone to give 1,1-diphenylethylene in 93% yield. The reaction mechanism has been shown to resemble closely that in solution[32].



(19)

An interesting alternative to the methylide **19** is 2,2-dihydro-2-methyl-2,2-diphenyl-3,4-methano-1,2-oxaphospholane (**20**). This reagent, which is in equilibrium with the ylide **21**, is an effective methylenating agent which requires neither base nor solvent (equation 6)[33].



(20) (21) (6)

3. Modified Wittig reagents

A number of modifications to the Wittig reaction have been developed. Horner's modification[34,35] using triethyl phosphonoacetate has been the only efficient method for the synthesis of 1-(*m*-nitrophenyl)-1-phenylethylene[28].

Phosphono-bis-*N*,*N*-dimethylamide **22** is a useful alternative reagent[36], since it can be metallated with butyllithium and then treated with benzophenone (equation 7). Alternatively, **23** can be alkylated, again metallated and then treated with benzophenone. This is a general route to 1,1-diphenylalkenes.

The phospho derivatives **25**[37], **26**[38] and **27**[39] have been employed as alternatives to **22**. However, the intermediate alkoxide derived from each requires somewhat different work-up conditions. A high yield of 1,1-diphenylethylene has been obtained from each reagent.

$$H_3CPO(NMe_2)_2 \xrightarrow[-80\ ^\circ C]{BuLi} LiCH_2PO(NMe_2)_2 \xrightarrow{Ph_2C{=}O} Ph_2C(OH)CH_2PO(NMe_2)_2 \xrightarrow[\Delta]{C_6H_6} Ph_2C{=}CH_2 \quad (7)$$

(22) (23) (24)

$MePS(OMe)_2$ (25) $MePPh(S)NMe_2$ (26) $MeP(O)(OMe)_2$ (27)

Wittig reactions can be carried out[40] with the ylide **28** if it is pure and salt free[41,42]. Thus with benzophenone, tetraphenylallene and diphenylethylene are formed quantitatively (equation 8). The ylide **29** reacts somewhat differently (equation 9). When benzophenone is

$$3Ph_2C{=}O + 2Ph_3\overset{+}{P}\overset{-}{C}HSiMe_3 \longrightarrow Ph_2C{=}CH_2 + Ph_2C{=}C{=}CPh_2 + 2Ph_3PO + (Me_3Si)_2O \quad (8)$$

(28)

$$3Ph_2C{=}O + 2Me_3\overset{+}{P}\overset{-}{C}HSiMe_3 \longrightarrow 2Ph_2C{=}CH_2 + Me_2P(O)CH{=}CPh_2 + Me_3PO + (Me_3Si)_2O \quad (9)$$

(29)

treated with the phosphonate **30**, 1,1-diphenylethylene is obtained. The reaction is considered to occur via the Wittig reagent **31** formed by C→O 1,3-trimethylsilyl migration (equation 10)[43]. A combination of chloromethyltrimethylsilane and triphenylphosphine has been shown to form the basis of an improved synthesis of 1,1-diphenylethylene[44].

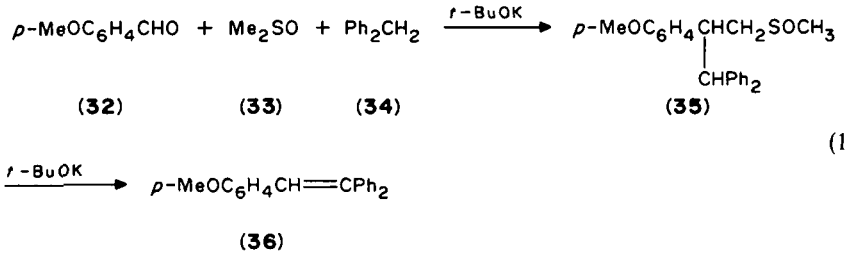
$$Me_3SiCH_2P(O)(OMe)_2 \longrightarrow \overset{-}{C}H_2\overset{+}{P}(OMe)_2OSiMe_3 \xrightarrow{Ph_2C{=}O} Ph_2C{=}CH_2 \quad (10)$$

(30) (31)

4. α-Sulphoxyl and α-sulphonyl carbanions

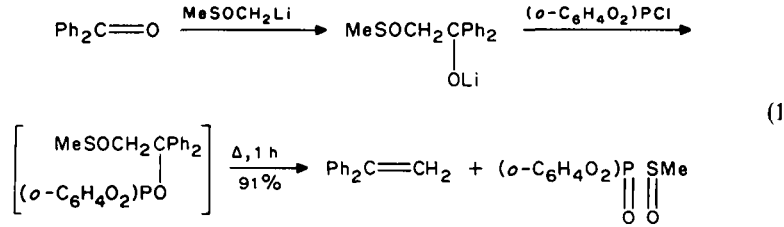
The 1,1-diphenylalkene **36** is formed in the reaction between *p*-methoxybenzaldehyde and diphenylmethane under basic conditions[45]. The reaction is catalyzed by the dimsylate anion. Evidently, aldol condensation is followed by conjugate addition of Ph_2CH^- to give **35**. Prolonging the reaction time or increasing the concentration of base improves the yield of **36** (equation 11).

A related synthetic method applicable to non-enolizable aldehydes and ketones, e.g.



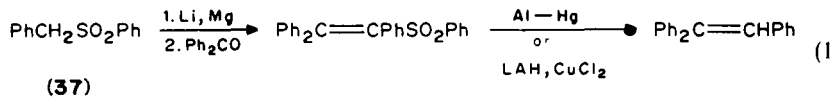
(11)

benzophenone, involves aldol addition of the dimsylate anion in THF[46]. *o*-Phenylene phosphorochloridite is added and the intermediate heated. 1,1-Diphenylethylene is formed in 91% yield (equation 12).



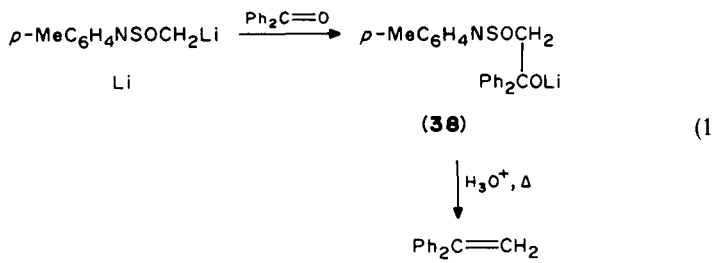
(12)

The anion of the sulphone **37** also condenses readily with benzophenone[49]. Hydrogenolysis to the 1,1-diphenylalkene is effected both by aluminium amalgam and by LAH in the presence of copper(II) chloride (equation 13). Alternatively, the sulphenamide group can



(13)

be employed to act with a methyl group. *N*-Methanesulphinyl-*p*-toluidine dianion reacts with benzophenone[47,48]. The adduct **38** when heated decomposes to 1,1-diphenyethylene (96%) (equation 14).



(14)

5. α-Silyl carbanions

The anion of trimethylsilylmethane **39** reacts with benzophenone to give 1,1-diphenylethylene in 53% yield[50] (equation 15). Similarly, α-lithio-α-trimethylsilylmethane **41**, obtained by cleavage of the thio derivative **40**, reacts smoothly with benzophenone to

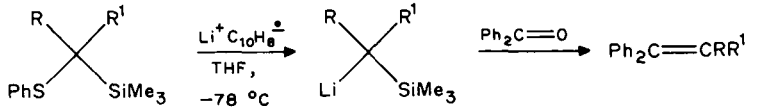
$$(Me_3Si)_2CH_2 \xrightarrow[HMPT]{NaOMe} Me_3SiCH_2Na$$

(39)

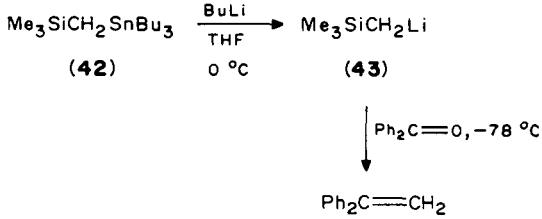
$$\downarrow Ph_2C{=}O$$

$$Ph_2C{=}CH_2 \longleftarrow [Ph_2C(ONa)SiMe_3] \qquad (15)$$

give 1,1-diphenylethylene[51] (equation 16). This reaction has been extended to the synthesis of a series of 1,1-diphenylethylenes in good yield (R^1 = H, R^2 = H, Me, Bu, Ph). Transmetallation of (trimethylsilyl)methyl tributylstannane (**42**) with butyllithium occurs quantitatively[52]. The resulting lithium carbanion **43** reacts in good yield with benzophenone (equation 17).

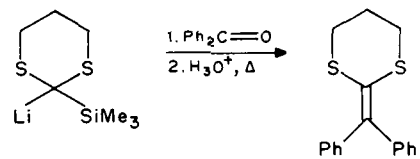


(40) **(41)** (16)



(42) **(43)** (17)

1,1-Diphenylethylidene (1,3-dithiane) **45** has been synthesized in the first reported reaction of a metallo-1,3-dithiane with benzophenone or indeed any ketone (equation 18). The reaction employs the trimethylsilyl stabilized anion **44** in a one-pot reaction[54]. In (2-

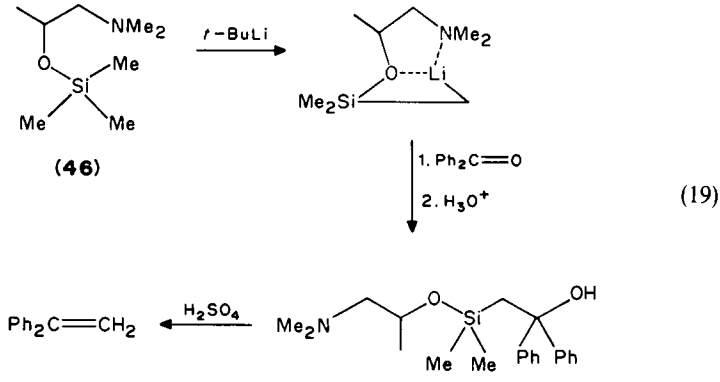


(44) **(45)** (18)

aminoalkoxy)trimethylsilane **46** the trimethylsilyl group is activated by two heteroatoms. It undergoes efficient metallation with *t*-BuLi. Benzophenone is methylenated in 83% overall yield with this reagent[53] (equation 19).

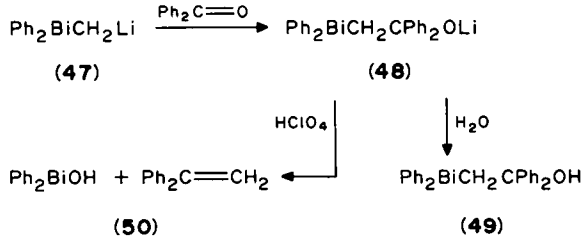
6. α-Bismuth carbanions

Bis(diphenylbismuth)methane has been prepared in 53% yield for the first time from Ph_2BiBr and Na in liquid ammonia with dichloromethane[55]. It is transmetallated with



(19)

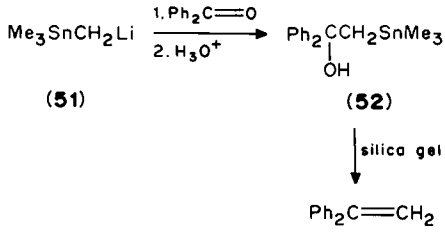
phenyllithium to the thermolabile carbanion **47**. The latter reacts with benzophenone. The intermediate **48** is hydrolyzable either to 1, 1-diphenylethylene or to the stable carbinol **49** (equation 20).



(20)

7. α-Trimethylstannyl carbanions

The lithiostannane **51** reacts smoothly with benzophenone[56]. The resulting carbinol **52** is readily converted to 1, 1-diphenylethylene in the presence of silica gel (equation 21).

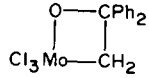


(21)

8. Organometallic carbenoids

bis-Cyclopentadienyltitanium chloride, Cp_2TiCl, reacts[57] with $(IZn)_2CH_2$ to give the methylenating agent, $Cp_2TiCH_2 \cdot ZnCl_2$. This, the Tebbe reagent, reacts with benzophenone to give 1, 1-diphenylethylene, in 93% yield. Pine and coworkers[58] have found that Cp_2Ti with chloromethyl dimethylalane is a useful methylenating agent. It reacts with benzophenone rapidly in THF at 0 °C to give 1, 1-diphenylethylene in 97% yield. Kauffmann and coworkers[59,60] have found that a number of tungsten and molybdenum

derivatives, e.g. $Cl_2Mo(O)(THF)_2$, react with methyllithium in THF at $-70\,^{\circ}C$ with the formation of the corresponding carbenoid, in this instance $Cl_3Mo{=}CH_2$. This reacts *in situ* with benzophenone to give the intermediate molybdaoxetane **53**, which is then hydrolyzed to 1,1-diphenylethylene.



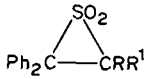
(53)

9. Dimesitylalkylboranes

Deprotonated dimesitylalkylboranes $(2,4,6\text{-}Me_3C_6H_2)_2BR$ (R = Me, Et, octyl) condense[61] with benzophenone. Elimination of lithium dimesitylborinate yields the corresponding 1,1-diphenylalkene, prepared in 75% yield by this route.

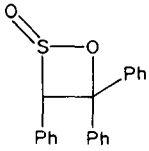
10. Extrusion

A new route to 1,1-diarylalkenes has been developed by Meyers and coworkers[62]. They find that addition of KOH to sulphones, $Ph_2CHSO_2CHRR^1$, in *t*-BuOH-CCl_4, results in the formation of 1,1-diphenylalkenes (R = Me, R^1 = H, Me; R = R^1 = Ph) in > 96% yield. The mechanism involves the transient thiirane 1,1-dioxides **54**.



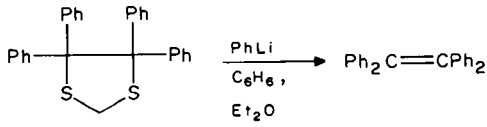
(54)

β-Sultines **55** are intermediates in a sulphur analogue of the Wittig olefin synthesis[63]. In some instances, these intermediates have been isolated as, for example, **55**. They are normally thermally labile. On heating, **55** extrudes SO_2 with the formation of 1,1,2-triphenylethylene, in 75% yield.



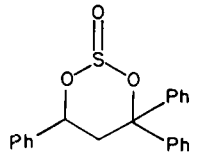
(55)

Extrusion of sulphur occurs readily from the appropriate dithiolane[64], e.g. **56** (equation 22). In a similar type reaction, the chair isomer of 2-oxo-1,3-dioxathiane **57** fragments in a Grob-like manner in polar solvents[65] (equation 23). The other, twist boat, isomer is unreactive.



(56)

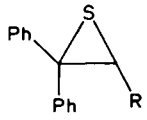
(22)



(57)

$$\xrightarrow{\Delta} Ph_2C{=}CH_2 + PhCHO + SO_2 \qquad (23)$$

The episulphides (**58**; R = H, Me) slowly (24 d) extrude sulphur by interaction with thiobenzophone[66]. Yields of 1,1-diphenylalkenes are excellent. The other product **59**, a thiocarbonyl *S*-sulphide, is a new class of 1,3-dipole (equation 24).

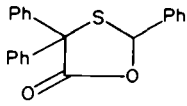


(58)

$$+ Ph_2C{=}S \xrightarrow[Et_2O]{25\ ^\circ C} Ph_2C{=}CHR + Ph_2C{=}S^+{-}S^- \qquad (24)$$

(59)

An example of twofold extrusion is provided by the high yielding (95%) synthesis of triphenylethylene by heating 2,4,4-triphenyloxathiolan-5-one **60** with tris(diethylamino)phosphine (equation 25)[67].



(60)

$$\xrightarrow[\Delta]{P(NEt_2)_3} Ph_2C{=}CHPh \qquad (25)$$

11. Coupling

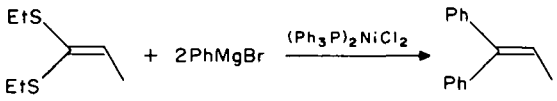
It has been noted that phenyl diazonium salts PhN_2X (X = Cl, BF_4, PF_6) undergo a Pd-catalyzed coupling reaction with 2-trimethylsilylstyrene **61**[68] (equation 26). However, the reaction is not regiospecific. A synthetically useful reaction is the facile substitution of vinyl

$$PhCH{=}CHSiMe_3 \xrightarrow{[PhPd]^+BF_4^-} Ph_2C{=}CH_2 + PhCH{=}CHPh \qquad (26)$$

(61)

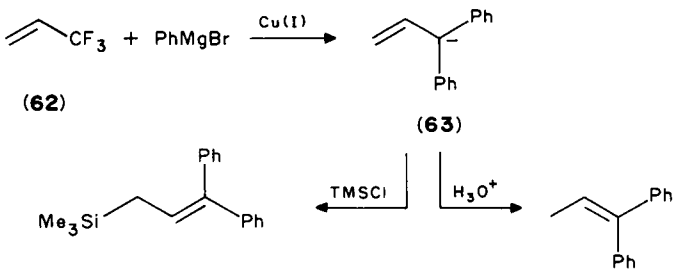
thioethyl groups by aryl groups. This reaction is effected by the Grignard reagent in the presence of a catalytic low-valent Ni species. 1,1-Diphenylpropene has been prepared in 72% yield by this route[69] (equation 27).

An interesting, if synthetically limited, reaction involves the Cu(I) catalyzed coupling



(27)

between 3, 3, 3-trifluoropropene **62** and phenylmagnesium bromide[70]. The anion **63** is first formed, in addition to other products. 1, 1-Diphenylpropene is isolated in 31% yield (equation 28).

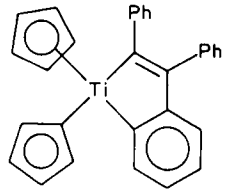


(28)

12. Other methods

An old but convenient route to 1, 1-ditolylethylene and 1, 1-dixylenyl-ethylene is based on the reaction of toluene and *o*-xylene, respectively, with pyruvic acid in concentrated sulphuric acid[70a].

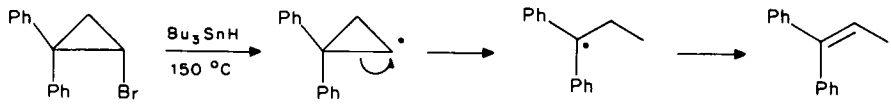
In a modification of the Masai–Rausch reaction, diphenylacetylene is found[71] to react with phenyllithium in the presence of titanocene dichloride. Triphenylethylene is formed in good yield *via* the titano cycle **64**.



(64)

In the first reported thermal generation of 2-substituted 1, 1-dimethyl-1-silaethenes[72], both 1, 1-dimethyl-1-silapropene, $Me_2Si{=}CHMe$, and 1, 1-dimethyl-1-sila-2-phenylethene, $Me_2Si{=}CHPh$, have been observed to react with benzophenone, *via* a four-centered pseudo-Wittig mechanism. The products are 1, 1-diphenylpropene and triphenylethylene, respectively.

An unusual route to 1, 1-diphenylpropene is provided[73] by the reaction of 1, 1-diphenyl-2-bromocyclopropane **65** with tributyltin hydride at 150 °C (equation 29). The ring opening **66** is undoubtedly assisted by the ability of the phenyl groups to stabilize the resulting radical[67].



(65) (66) (67)

(29)

B. 1,1,2-Triphenylethylene

Most methods outlined above are applicable to the synthesis of triphenylethene. Included here are a number of reactions which lead specifically to this alkene.

1. *Phenyldiazonium chloride*

β,β-Diphenylacrylic acid and phenyldiazonium chloride couple with the formation of triphenylethene[74] (equation 30).

$$Ph_2C{=}CHCO_2H + PhN_2Cl \longrightarrow Ph_2C{=}CHPh + HCl + CO_2 + N_2 \quad (30)$$

2. *Rearrangement*

1,1,1-Triphenyl-2-chloroethane is solvolyzed with a concerted 1,2-phenyl migration[75]. The anionic analogue of this reaction has also been established[76]. When the same substrate **68** is treated with amylsodium at 35 °C, triphenylethene is formed (equation 31).

$$\underset{\textbf{(68)}}{Ph_3CCH_2Cl} \xrightarrow[H_2O]{HCO_2H} Ph_2\overset{+}{C}CH_2Ph \xrightarrow{-H^+} Ph_2C{=}CHPh \quad (31)$$

C. Tetraphenylethene

1. *Coupling of diphenyldihalomethane*

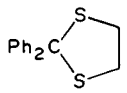
Diphenyldichloromethane **69** couples in boiling benzene in the presence of copper bronze[77], copper(I) chloride in DMSO at 100 °C[79] or sodium in liquid ammonia[78]

$$\underset{\textbf{(69)}}{Ph_2CCl_2} \longrightarrow Ph_2C{=}CPh_2 \quad (32)$$

(equation 32). Alternatively, tetraphenylethylene can be prepared from the dibromide, prepared *in situ*, by interaction with sodium iodide[80] (equation 33).

$$2\,Ph_2CH_2 \xrightarrow[2.\ NaI]{1.\ Br_2} Ph_2C{=}CPh_2 \quad (33)$$

In a formally related reaction, benzophenone dithioglycolate **70** reacts in 97% yield, with tungsten hexacarbonyl[81] (equation 34).



$$\xrightarrow{W(CO)_6} Ph_2C{=}CPh_2 \quad (34)$$

(70)

D. Conjugated α, α, ω, ω-Tetraphenyl Alkapolyenes

1. Grignard reagents

Diethyl succinate reacts with phenylmagnesium bromide to give the diol **71**, which is readily dehydrated to 1, 1, 4, 4-tetraphenyl-1, 3-butadiene[82] (equation 35). This latter diene

$$EtO_2CCH_2CH_2CO_2Et + 4PhMgBr \longrightarrow Ph_2C(OH)(CH_2)_2CPh_2OH \xrightarrow{SOCl_2} Ph_2C{=}CHCH{=}CPh_2 \quad (35)$$

(71)

can be prepared also by heating the vinyl Grignard **73** with the corresponding vinyl nitrile **72** (equation 36)[83].

$$\underset{\textbf{(72)}}{Ph_2C{=}CHCN} + \underset{\textbf{(73)}}{Ph_2C{=}CHMgBr} \xrightarrow{\Delta} Ph_2C{=}CHCH{=}CPh_2 \quad (36)$$

The *bis*-Grignard of butadiyne **74** reacts with benzophenone[84]. The resulting diol **75** is hydrogenated to the diene-diol **76** and finally converted to the triene **77** with P_2I_4 (equation 37).

$$\underset{\textbf{(74)}}{BrMgC{\equiv}CC{\equiv}CMgBr} \xrightarrow{2Ph_2C{=}O} \underset{\textbf{(75)}}{Ph_2C(OH)(C{\equiv}C)_2CPh_2(OH)} \xrightarrow{H_2, Pd} \underset{\textbf{(76)}}{Ph_2C(OH)(CH{=}CH)_2CPh_2OH} \xrightarrow{P_2I_4} \underset{\textbf{(77)}}{Ph_2C{=}CHCH{=}CHCH{=}CPh_2} \quad (37)$$

2. Vinyl bromides

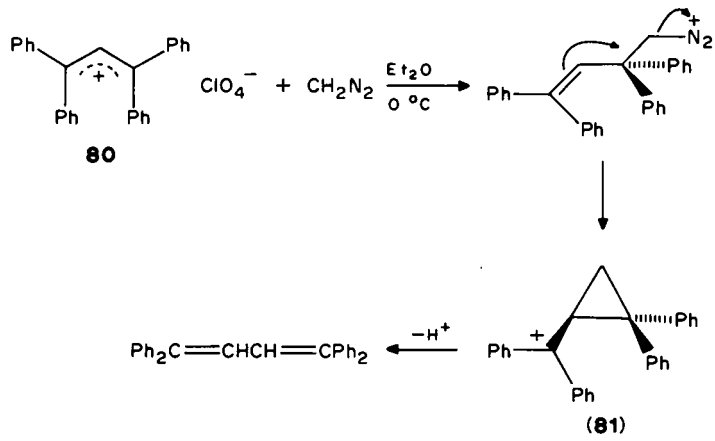
When 1, 1-bis(*p*-hydroxyphenyl) vinyl bromide **78** in the presence of a catalytic quantity of HBr is heated alone or with the corresponding diarylmethane, 1, 1, 4, 4-*tetra*(*p*-hydroxyphenyl)-1, 3-butadiene **79** is formed[85,86] (equation 38).

$$\underset{\textbf{(78)}}{(p\text{-}HOC_6H_4)_2C{=}CHBr} \underset{HBr + Ar_2CH_2}{\overset{HBr}{\rightleftharpoons}} \underset{\textbf{(79)}}{(p\text{-}HOC_6H_4)_2C{=}CHCH{=}C(C_6H_4{-}OH\text{-}p)_2} \quad (38)$$

3. Methylene insertion

Methylene insertion occurs in the reaction between 1, 1, 3, 3-tetraphenyl propenyl perchlorate **80** and diazomethane. The mechanism involves formation and ring opening of

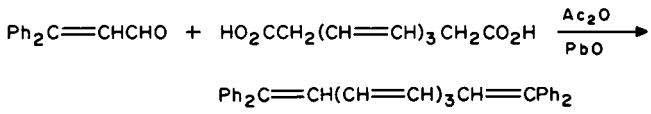
the cyclopropylcarbinyl carbocation **81**[87] (equation 39). This interpretation is consistent with an earlier finding, that diphenyl(2,2-diphenylcyclopropyl)carbinol is converted to 1,1,4,4-tetraphenylbutadiene in acid[88].



(39)

4. Condensation

Condensation of 3,3-diphenylpropenal with dicarboxylic acids of type $HO_2CCH_2(CH{=}CH)_nCH_2COOH(n = 0,1,2,\cdots)$ occurs in the presence of acetic anhydride and lead monoxide as, for example, when $n = 3$ (equation 40)[89].



(40)

IV. REACTIONS

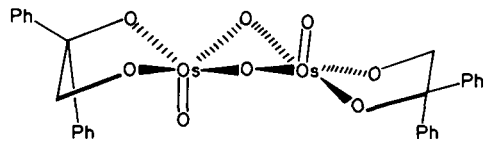
A. Oxidation

1. Without cleavage

a. Peracids. Diphenylethylene is smoothly converted to the epoxide when treated with peracetic acid at 25 °C. The reaction occurs four times faster than with styrene[90]. Tetraphenylethylene is epoxidized with perbenzoic acid in chloroform[91] and also with chromic acid in acetic acid[91]. Under the latter conditions, some benzophenone and phenyl triphenylmethyl ketone, by pinacolic rearrangement, are also formed[91].

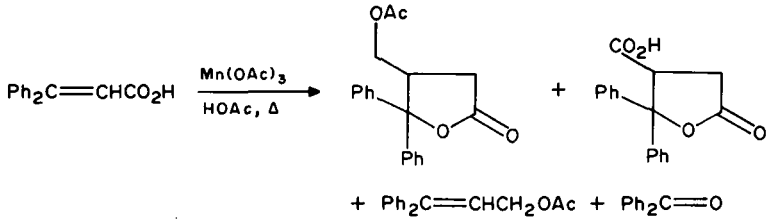
b. Osmium tetroxide. Casey[92] has investigated diol formation from the reaction of osmium tetroxide and diphenylethylene. He has shown that the intermediate dimeric Os(IV) ester has the structure **82** and not the oxametallocyclobutane structure which had been previously proposed[93].

c. Manganese(III). 1,1-Diphenylethylene is oxidized by $Mn(OAc)_3$ in acetic acid. γ,γ-diphenyl-γ-butyrolactone is formed in 71% yield[94,95]. The mechanism involves the



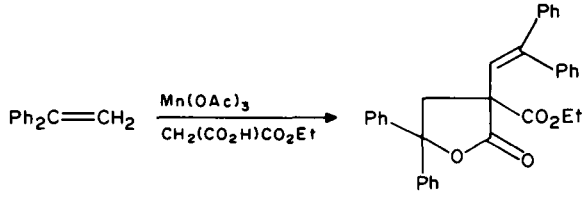
(82)

$^{\bullet}CH_2COOH$ radical. The reaction pathway of the analogous reaction of 3,3-diphenylacryclic acid is more complex (equation 41).



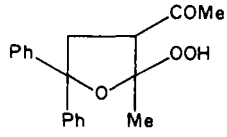
(41)

Similar products are formed with $Mn(OAc)_3$ when malonic acid is employed[96], in the absence of acetic acid. However, when the half ester of malonic acid is used the lactone **83** is formed (equation 42). A radical mechanism is suggested[96]. Oxidation of 1,1-diphenylethylene with *tris*(2,4-pentanedionato)manganese(III) in refluxing acetic acid results in the formation of the hydroperoxide **84** in 89% yield[97].



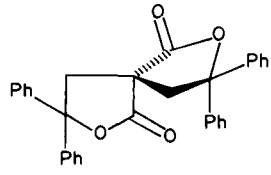
(42)

(83)



(84)

When 1,1-diphenylethylene is treated with $Mn(OAc)_3$ and malonic acid in refluxing acetic acid, a high yield of the spiro-bis-lactone **85** is obtained[98,99]. With malonamide and $Mn(OAc)_3$, 1,1-diphenylethylene is converted to a mixture of the butenolide **86** and spiro-bis-lactone **85**[100]. However, pyrrolones **87–89** are formed when the more reactive 1,1-bis-(*p*-methoxyphenyl)ethylene is the reactant[100]. In this case the pathway is considered to involve oxidation to a carbocation intermediate (equation 43).



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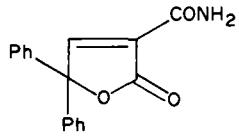

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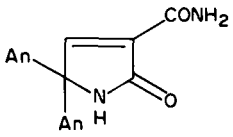

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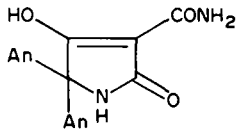
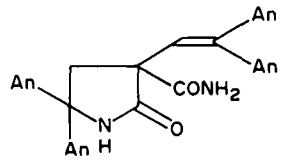
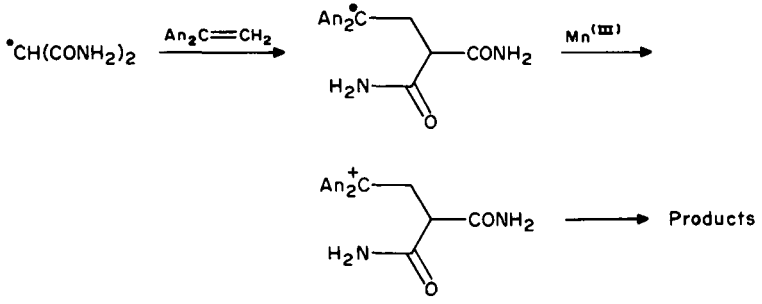


(88)



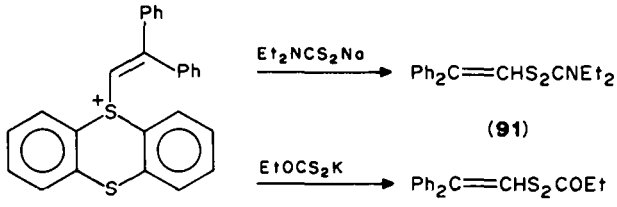
(89) An = *p*-$MeOC_6H_4$



(43)

d. Cobalt(III) acetate. 1,1-Diphenylethylene is oxidized by $Co(OAc)_3$ in wet acetic acid to the corresponding glycol monoacetate in moderate yield. The reaction proceeds through a Co co-ordinated intermediate[101]. This investigation has been extended to the homologues, 1,1-diphenyl-propene, -butene and -3-methylpropene[102].

e. Electrochemical. The electrochemical oxidation of thianthrene in the presence of 1,1-diphenylethylene produces the vinylsulphonium ion **90**, which undergoes addition–elimination to yield the vinyldithiocarbamate **91** and the xanthate **92** (equation 44)[103].



(90) (91) (92)

(44)

1,1-Diphenylethylene is oxidized in methanol mainly to the dimethyl ether of the corresponding 1,2-glycol in the absence of the supporting electrolyte at a platinum grid lying on a cation exchange membrane[104].

f. Miscellaneous. 1,1-Diphenylethylene and 1,1,2-triphenylethylene are converted to the corresponding 1,2-diols when treated with phenyliodine(III) *bis*(trifluoroacetate), $PhI(OCOCF_3)_2$[105]. Yamamoto and coworkers[106] have investigated the oxidation of 1,1-diphenylethylene with hydroperoxides, *e.g.* **93**. Addition of the benzoyl radical to the alkene followed by termination with a hydroxyl radical results in the ketocarbinol **94**.

$PhCOCH(OMe)OOH$ $PhCOCH_2C(OH)Ph_2$

(93) **(94)**

1,1-Diphenylethylene reacts with trichloroacetic acid in the presence of $CuCl_2$. α,α-Dichloro-γ,γ-diphenyl-γ-butrolactone is formed[107].

It has been noted that the rhodium carbonyl complex $[RhCl(CO)_2]_2$ reacts with 1,1-diphenylethylene under hydroformylation conditions (120–180 °C, 1500–3000 psi H_2/CO). 3,3-Diphenylpropanaldehyde is formed in 85% yield, together with 1,1-diphenylethane. In contrast, the cobalt carbonyl, $Co_2(CO)_8$, under the same conditions leads to 5% yield of aldehyde and 95% 1,1-diphenylethane. It is considered that the Co-catalyzed reaction follows a free radical pathway, while the rhodium reaction involves the conventional olefin insertion into a metal–hydride bond[108].

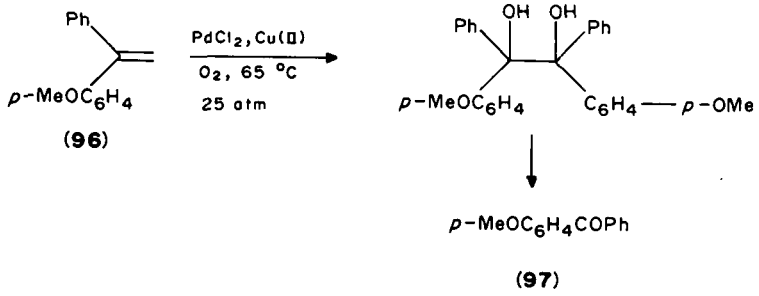
2. With cleavage

The classical Barbier–Wieland procedure (equation 45) for decreasing the length of a chain involves oxidative cleavage by acid dichromate or $NaIO_4$–RuO_4, usually in good yield[109]. It has been applied to the problem of steroidal side-chain modification[110].

$$\begin{array}{l} RCHCO_2Et \xrightarrow{PhMgBr} RCH_2C(OH)Ph_2 \\ \qquad\qquad\qquad\qquad\qquad\quad \Big\downarrow H_3O^+ \\ RCO_2H + Ph_2C{=}O \xleftarrow{CrO_3} RCH{=}CPh_2 \\ \qquad\qquad\qquad\qquad\qquad\quad \textbf{(95)} \end{array} \qquad (45)$$

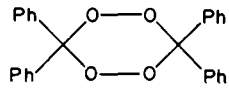
There are now a wide range of reagents suitable for cleaving 1,1-diarylalkenes; these include: peroxouranium oxide[111,112], peroxydisulphate in acetic acid[113], $H_2CrOCl_5 \cdot 2,2^1$-bipyridyl[114], pyridinium chlorochromate[115], and exposure of the alkene to light and air when absorbed on silica, neutral or basic alumina or florisil[116]. 1,1-Diphenylethylene is converted into benzophenone and 1,1-diphenylethane at high temperature, by entering the interlamellar spaces in a synthetic fluorolectorite[117].

1,1-Diarylalkenes are oxidized to ketones by oxygen in the presence of Pd(II) catalysts in a reaction similar to the Wacker process[118]. 1,1-Diphenylethylene gives a mixture of benzophenone and benzyl phenylketone. The *p*-methoxy derivative **96** yields only the benzophenone **97** (equation 46).



(46)

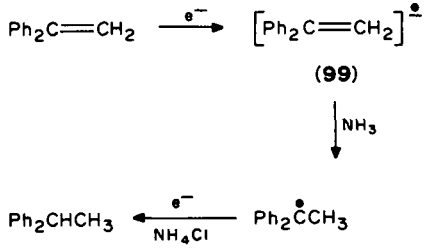
Ozonolysis of tetraphenylethylene leads to the formation of the tetraoxane **98**, which has been isolated[119].



(98)

B. Reduction

Catalytic hydrogenation of 1,1-diphenylalkenes catalyzed by palladium, palladized barium sulphate or nickel[120] is a well established[121] reaction. Sodium in ethanol[122] or in liquid ammonia[123] has also been employed to effect the same transformation. The mechanism of the latter reaction has been studied by Wooster's group[123] and has been considered to involve a 1,2-dianion intermediate. However, a pathway involving rapid protonation of the anion radical **99** is more probable[124] (equation 47). Some 1,1,4,4-tetraphenylbutane is also formed. This finding mitigates against a dianion mechanism and proves the intermediacy of the anion radical **99**. Ammonia is sufficiently acidic (pK_a 35) to protonate **99**.



(47)

Tetraphenylethylene acts as an electron acceptor from sodium naphthalenide. It forms a blue-coloured radical anion **100**, which does not dimerize but disproportionates into the dianion and alkene[125]. With excess sodium naphthalenide, conversion to the dianion **101** is complete (equation 48).

Lithium aluminium hydride reduces 1,1-diphenylalkenes in ether solvents at 65–150 °C[126]. Tetrahydrofuran is more effective than ether. *o*-Methoxy and *o*-dimethylamino groups accelerate the reaction, probably by coordinating onto the lithium cation (equation 49). When present in THF, anisole methylates the intermediate carbanion and the corresponding 2,2-diarylpropane is formed (equation 50).

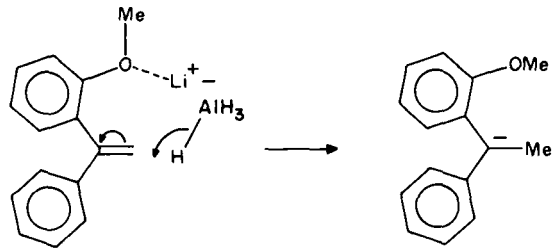
$$2\,Ph_2C{=}CPh_2 \xrightarrow[-70\ ^\circ C]{C_{10}H_8^{\bullet-}Na^+} 2\,Ph_2\bar{C}\dot{C}Ph_2$$

(100)

$$\Updownarrow \qquad (48)$$

$$Ph_2CHCHPh_2 \xleftarrow{H_3O^+} Ph_2\bar{C}\bar{C}Ph_2 + Ph_2C{=}CPh_2$$

(101)

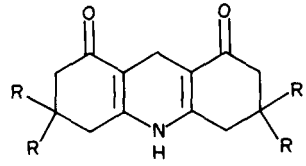


(49)

$$Ar_2MeC^- + MeOPh \longrightarrow Ar_2CHMe_2 + PhO^- \qquad (50)$$

A number of organometallic reagents are now available for the homogeneous reduction of 1,1-diphenylalkenes, for example $HCo(CO)_4$ in methylene chloride[127], $Co_2(CO)_8$ or $Co_2(CO)_6(PBu_3)_2$ under phase transfer conditions in the presence of 48–50% aqueous fluoboric acid[128], lithium triethylborane[129] and PhYbI in THF–HMPA–MeOH[130].

1,1-Diarylalkenes are reduced efficiently with diimide[131] and also with an equimolar amount of acridan **102** (R = H, Me) in the presence of trifluoroacetic acid[132].

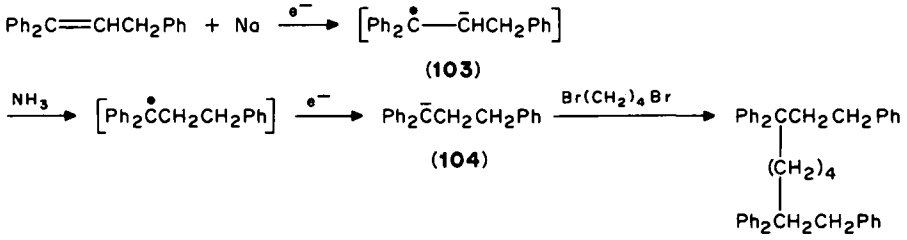


(102)

C. Reductive Alkylations

The early observations of Wooster and Ryan[133] have been extended by Murphy and Hauser[134] and involve the addition of two gram atoms of Na or K to 1,1-diphenylalkenes in liquid ammonia. The red-orange carbanions, *e.g.* **104**, are alkylated with alkyl halides[134] and 2-aminoethyl chlorides[135] in good yield (equation 51).

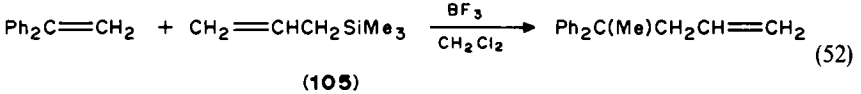
The mechanistic details have not been resolved. The initially formed reaction mixture, which is black, may contain not only the 1,2-dicarbanion, which rapidly undergoes ammonolysis, but also the anion radical in equilibrium with the dicarbanion and olefin. However, no direct evidence for the intermediacy of the dianion has been formed, *e.g.* a 1,2-dialkylation product. A reasonable alternative pathway involves sequential



(51)

ammonolysis—electron addition of the anion radical **103** to the monoanion **104**. Lerflaten and Parker[136] have noted in a cyclic voltammetric study of the reduction of 1,1-diphenylethylene that the initially formed anion radical is first protonated irreversibly.

A more recent alternative method of reductive allylation of 1,1-diphenylethylene involves the attack by the silane **105** on 1,1-diphenylethylene in the presence of boron trifluoride at room temperature[137] (equation 52).



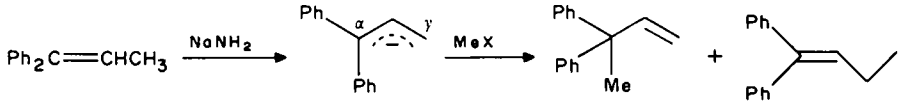
(52)

(105)

D. Metallo-1,1-diphenylpropenes

1. Alkylation

The anion formed in the reaction of 1,1-diphenylpropene and 1,1-diphenylbutene with sodium amide in liquid ammonia reacts readily with alkyl halides. Murphy and coworkers[138] have noted that the orientation of the methylation of 1,1-diphenylpropenylsodium **106** correlates well with the order of hardness of the leading group, X: $OTs > SO_4 > Cl > Br > I$. The harder the leaving group, the greater the proportion of the α-product **107** (equation 53). However, α-methylation only is observed in the case of 1,1-diphenybutenylsodium.

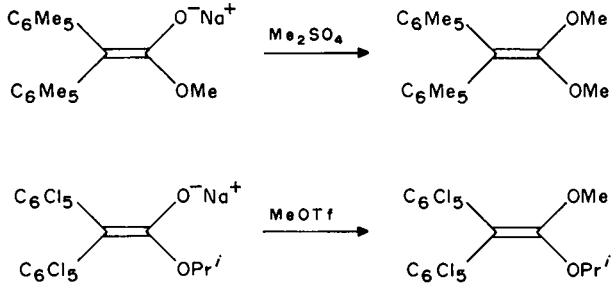


(106) **(107)**

(53)

The orientation of alkylation of both a range of 1,1-diphenylallyl anions and alkylating agents has been investigated[139,140]. The results are consistent with the Principle of Least Motion. The one exception, 1,1,3-triphenylpropenylsodium, undergoes alkylation exclusively at the γ-position, probably as a result of an interplay between steric and electronic effects. An alternative rationale[141] based on the Hammond postulate also predicts predominant electrophilic attack at the centre of greater negative charge (α-position). However, this theory does not explain the anomalous behaviour of 1,1,3-triphenylpropenylsodium with alkyl halides.

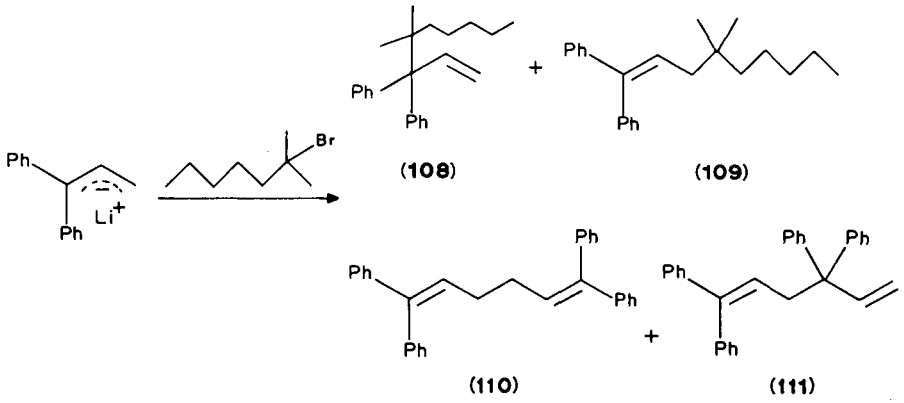
Extreme examples of the steric effect of fully substituted aryl groups is presented by O'Neill and Hegarty[142]. They investigated the enolates of methyl bis(pentamethylphenyl)acetate and isopropyl bis(pentachlorophenyl)acetate. Methylation with either dimethyl sulphate or methyl triflate occurs exclusively at oxygen, for steric reasons. No C-alkylation is observed (equation 54).



(54)

These results in general correlate with those of Rappoport[143], who has investigated the effect of substitution on keto–enol equilibria.

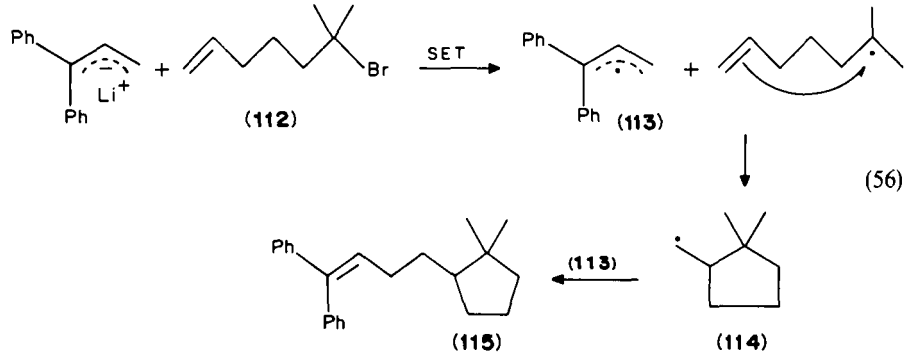
Nojima and coworkers[144] have carefully investigated the reaction of 1,1-diphenylpropenyllithium and other phenylallyllithium substrates with *tert*-alkyl bromides. Two conjoint mechanisms operate: a slow α-attack by a polar, not necessarily S_N2, mechanism and γ-attack by a single electron transfer (SET) mechanism. The SET pathway is indicated by: (a) the results of reaction of 2-bromo-2-methylheptane (equation 55). In addition to the α- and γ-alkylation products **108** and **109**, the γ,γ- and α,γ-dimers **110** and **111**, are also formed. (b) The α:γ-alkylation ratio is dramatically increased by the addition of 1,4-cyclohexadiene, a radical scavenger. (c) When the 6-bromohexene **112** is employed, the cyclized product **115** is formed in addition to the normal products (equation 56).



(55)

2. Aldol condensation

1,1-Diphenylallyl anions $[Ph_2C{=}CH{=}CHR]^- M^+$ (R = H, CH_3, Ph) react[145] with a range of aldehydes and ketones with exclusive formation of the γ-product, **116**. No



(56)

$Ph_2C{=}CHCHRC(OH)R^1R^2$

(116)

evidence has been found for an initial α-attack with subsequent rearrangement to the more stable γ-product. The metal cation is important. A condensation product from the 1, 1, 3-triphenylpropenyl anion is isolable only when the lithium counter ion is employed, probably due to the greater ability of lithium to co-ordinate to oxygen.

3. *Carboxylation*

1, 1-Diphenylallyl anions, prepared by treatment of the parent alkene with a metal amide in liquid ammonia, are carbonated by replacing the ammonia with dry ether and treating with carbon dioxide. The efficiency of this overall process is in part dependent on the metal cation $K^+ > Na^+ > Li^+$ [146]. The orientation of carbonation parallels that of the aldol condensation[145]. For example, the γ-carboxylic acid **117** is formed exclusively

$$Ph_2C{=}CHCH_2Ph \xrightarrow{KNH_2} [Ph_2C{=}CH{=}CHPh]^-K^+ \xrightarrow[2.\ H_3O^+]{1.\ CO_2} Ph_2C{=}CHCH(Ph)CO_2H$$

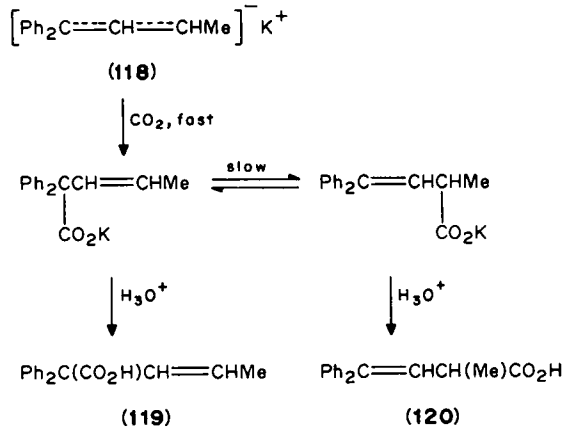
(117) (57)

(equation 57). One exception is 1, 1-diphenylbutenylpotassium (**118**). When this anion is carbonated and then quenched after fifteen minutes, an approximately 1:1 mixture of the regioisomeric acids **119** and **120** is isolated (equation 58). When the reactants are permitted to stand ten hours before quenching, the γ-regioisomer **120**, exclusively, is obtained. This result suggests the rapid formation of the α-product followed by a slow rearrangement to the γ-isomer, prior to neutralization.

E. Dimerization

1. *Carbocationic pathway*

1, 1-Diphenylethylene has been used by several authors in model systems of cationic polymerization. The basic reactions of 1, 1-diphenylethylene parallel those of other monomers but, at least in the initial stages of reaction, only a reversible dimerization



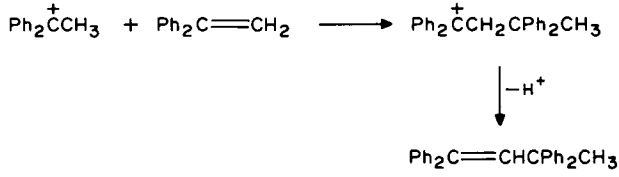
(58)

occurs. The early kinetic studies of Evans and coworkers[147–149] have been confirmed and extended by Sigwalt[150,151] and by Bywater and Worsfold[152] using dilatometry and UV spectroscopy at low temperature. The forward and reverse linear dimerization reactions in benzene, catalyzed by trichloroacetic acid, have been studied[152]. Formation of the monomeric ion $Ph_2C^+CH_3$ involves trichloroacetic acid and 1,1-diphenylethylene in a molar ratio of 3:1. One mole of acid contributes the proton and two moles solvate the carbocation[152].

A two-fold depression of the freezing point occurs[147,153] in sulphuric acid, consistent with equation 59. This solution absorbs strongly at 431 nm, that is, with a λ_{max} similar to that exhibited by Ph_3C^+. Dimerization occurs subsequently. With sulphuric acid at 30 °C in CH_2Cl_2, the charge transfer complex $Ph_2C{=}CH_2 \cdot SO_3$ has also been detected[154].

$$Ph_2C{=}CH_2 + H_2SO_4 \rightleftharpoons Ph_2\overset{+}{C}CH_3 + \bar{H}SO_4 \tag{59}$$

A high yield of the linear dimer, 1,1,3,3-tetraphenyl-1-butene, is obtained from 1,1-diphenylethylene when treated with aluminium chloride[155], stannic chloride[156] or during the acid-catalyzed dehydration of 1,1-diphenylethanol[157] (equation 60). With iodine in

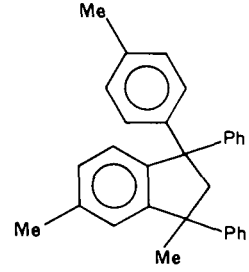


(60)

acetic acid, the dimer 1,1,3,3-tetraphenyl-1-butene reverts to 1,1-diphenylethylene. Similarly, 1,1-bis(4-methoxyphenyl)ethylene dimerizes in the presence of mineral acids and trichloroacetic acid and the dimer reverts to the monomer with chlorine or iodine but gives the dibromo dimer with bromine[158].

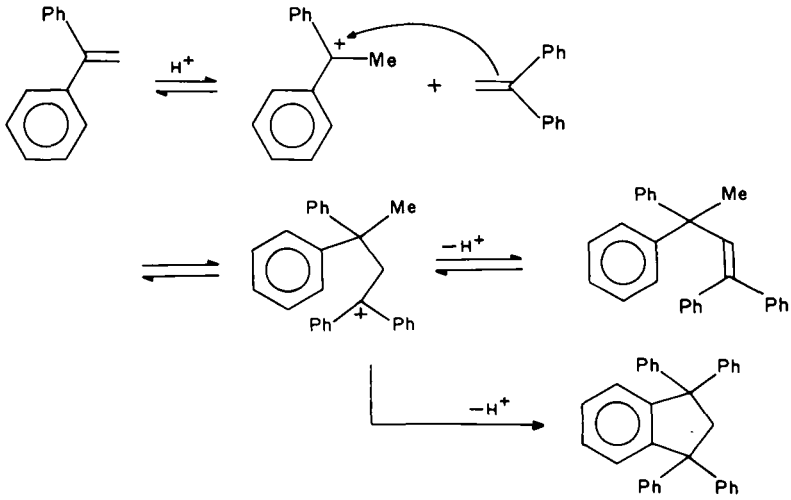
1,1-Diarylethylenes $ArCPh{=}CH_2$ (Ar = Ph, *o*-MeC_6H_4, *p*-MeC_6H_4, *p*-xylyl) dimerize[159] at 25–90 °C in benzene or toluene containing $H_3PO_4 \cdot BF_3$. Both linear and cyclic dimers are formed. For example, from *p*-$MeC_6H_4CPh{=}CH_2$ both dimers **121** and **122** are formed. The extent of reaction decreases with increasing *o*-substitution. Thus when Ar = mesityl, no dimerization is observed.

p-$MeC_6H_4CPh{=}CHC(CH_3)CPhC_6H_4$-Me-$p$
(121)



(122)

The rate of cyclization of the linear dimer is affected by the nature of the Lewis acid, $TiCl_4$–$HCl > SnCl_4$–HCl[152]. The mechanism suggested is as outlined[152] (equation 61).

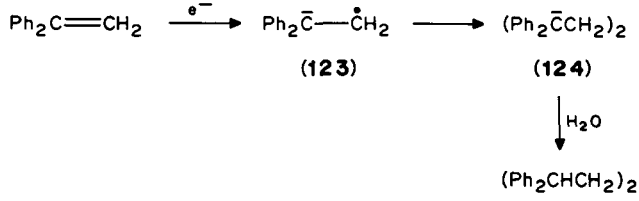


(61)

At $-30\,°C$ the yield of carbocation is very low relative to the concentration of the catalysts $AlCl_3$ or $TiCl_4$[160]. In triflic acid, however, a stop-flow system has been required to study cyclodimerization of 1,1-diphenylethylene. The linear dimer is not detected[161].

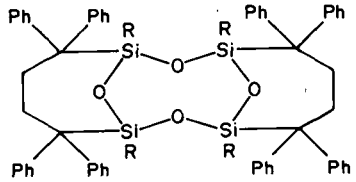
2. *Radical anion pathway*

Electrolytic reduction of 1,1-diphenylethylene in HMPTA gives a magenta-coloured solution of the bis-carbanion **124**. Addition of water quantitatively yields 1,1,4,4-tetraphenylbutane[162] (equation 62). These results are consistent with dimerization of the initially formed radical anion[123].



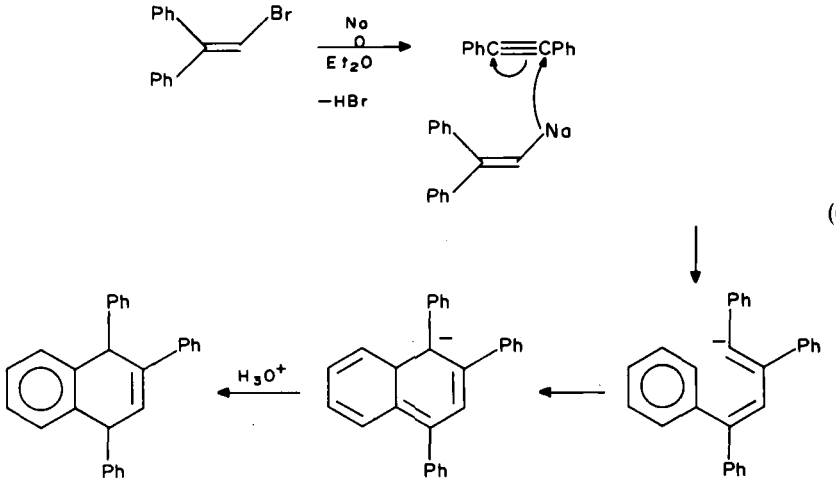
(62)

Both lithium naphthalenide in THF and BuLi in hexane induce immediate formation of the radical anion **123**, which rapidly and quantitatively dimerizes. These observations form the basis of a convenient titrimetric method for determining lithium naphthalenide[163] and BuLi[164], since the red diphenylethylene dimer can be titrated against standard 2-butanol in toluene. This dianion also reacts with trichlorosilanes $RSiCl_3$ (R = H, Me, C_6H_5). The tricyclic siloxane **125** is formed[165].



(125)

1, 1-Diphenyl-2-bromoethylene when treated with sodium in ether is converted to 1, 4-dihydro-1, 2, 4-triphenylnaphthalene[166]. Although the mechanism has not been proved, it is considered to involve an initial Fritsch–Buttenburg–Wiechell rearrangement to tolan[167,168] (see Section IV.I.3) followed sequentially by nucleophilic attack by the vinylsodium and electrocyclic ring closure (equation 63). Formation of dimer does not seem to involve direct metal-catalyzed cyclodimerization of tolan, since tolan reacts with lithium although probably via a related reaction pathway, to give 1,2,3-triphenylnaphthalene[169,170].



(63)

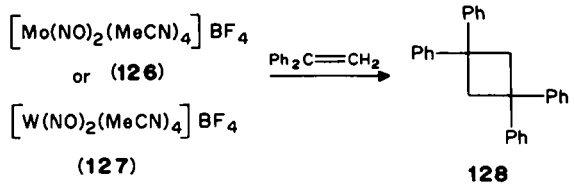
3. Radical pathway

Hydrogen atoms produced by microwave discharge in a mixture of hydrogen and helium at 2 torr result in a reaction with 1, 1-diphenylethylene. 1, 1-Diphenylethane and 2, 2, 3, 3-tetraphenybutane are formed, consistent with a radical mechanism[171] (equation 64).

$$Ph_2C{=}CH_2 \rightarrow Ph_2CHCH_3 + Ph_2C(CH_3)C(CH_3)CPh_2 \qquad (64)$$

4. Involving organometallic regents

2,2-Dibromo-1,1-diphenylethylene dimerizes to 1,1,4,4-tetraphenylbutatriene in the presence of tetrakis-triphenylphosphine Ni(0)[172]. 1,1-Diphenylethylene undergoes head-to-tail cyclodimerization with the formation of **128** in the presence of either the molybdenum or tungsten complexes **126** and **127**[173] (equation 65). On the other hand, the Pd complex **129** catalyzes[174] the formation of the indane **130** (equation 66). This product is a common Lewis acid catalyzed cyclodimerization product (Section IV.E.1). A carbocation mechanism which does not involve participation of the allyl group is proposed[174].



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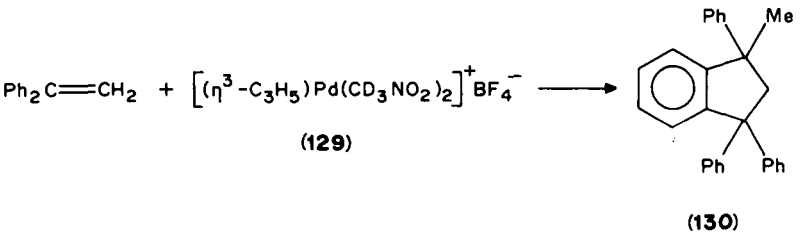


(66)

F. Addition and Addition–Elimination Reactions

1. π-Complexes

The immediate formation of coloured solutions accompanying the mixing of tetranitromethane with various unsaturated organic compounds was reported as early as 1909[175,176]. The colours are indicative of the formation of charge transfer complexes[177]. The charge transfer band, λ_{max} 450 nm, disappears with a half life of 120 min in the case of 1,1-bis(*p*-methoxyphenyl)ethene[178]. In the dark, the charge transfer solution of 1,1-diphenylethylene and tetranitromethane is stable for days[179].

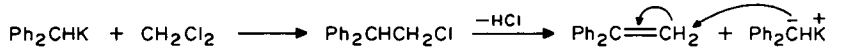
The dimeric 1,1-diphenylethylene platinum(II) complex **131** is prepared[180] either by heating a solution of 1,1-diphenylethylene with chloroplatinic acid in acetic acid or by irradiating these reactants in acetone with light. The monomeric π-complex is stabilized by pyridine, **132**. A Te(IV) complex with diphenylethylene originally assigned a π-complex structure has now been recognised as having the σ-bonded structure **133**[181].

$[Ph_2C{=}CH_2 \cdot PtCl_2]_2$ (131) $Ph_2C{=}CH_2 \cdot PtCl_2 \cdot py$ (132) $(Ph_2C{=}CH)_2TeCl_2$ (133)

2. Conjugate addition

The conclusion[182] that the reaction of sodium diphenylmethide with methylene chloride followed a two-fold alkylation pathway to give 1,1,3,3-tetraphenylpropene has been corrected by Kofron and Goetz[183]. They have shown that the product is formed by conjugate addition to the 1,1-diphenyl ethylene formed *in situ* (equation 67). Conjugate

addition of potassium diphenylmethide to the homologous 1,1-diphenylalkenes does not occur due to the inhibiting effect of allylic anion **134** formation by proton transfer (equation 68). The effect is not steric, since Morton and Wohlers[184] had already shown that increasing the size of the 1,1-diphenylmethide does not inhibit conjugate addition. Thus pentylsodium adds to 1,1-diphenylethylene in pentane. This anion can add to a further molecule of 1,1-diphenylethylene. Apparently, oligimerization does not proceed further. These anions are carboxylated with carbon dioxide to 2,2-diphenyloctanoic acid and 2,2,4,4-tetraphenyldecanoic acid, respectively (equation 69). Lithio phenyltrimethylsilylmethyl sulphide (**134**) also undergoes smooth addition to 1,1-diphenylethylene with subsequent intramolecular displacement of thiophenylate anion to yield the cyclopropane (**135**)[185] (equation 70).



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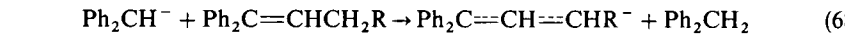

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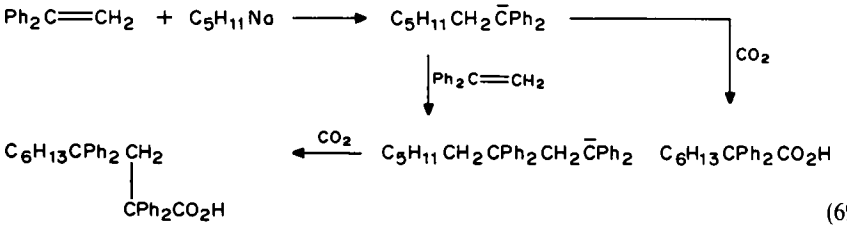

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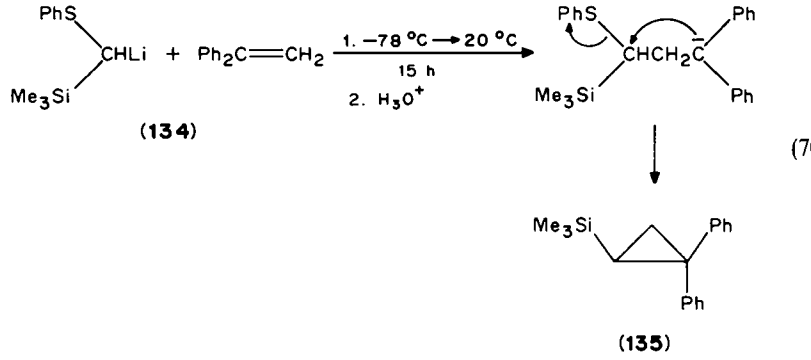


(70)

3. *Miscellaneous*

A wide range of mainly electrophilic addition and/or addition–elimination reactions are presented in Table 1. However, points of exceptional interest only will be discussed.

The reactions in entries 2, 4 and 16 have also been applied to higher homologues of 1,1-diphenylethylene. Entry 5: mild reduction of this alkene in acid medium leads to the formation of 2,2-diphenylacetaldehyde. This method has been applied to the synthesis of a range of 2,2-diarylacetaldehydes. Entry 6: polar addition of nitrosyl chloride results in the

TABLE 1. Addition and addition–elimination reactions of 1,1-diphenylethylene

Entry	Reagents	Final product	Reference
1	(i) Et_2AlCl (ii) H_2O_2	Ph_2CHCH_2OH	186
2	N_2O_4	$Ph_2C(OH)CH_2NO_2$	187, 188
3	HNO_3, HOAc	$Ph_2(ONO_2)CH_2NO_2$	188
4	$C_5H_{11}ONO$, HOAc	$Ph_2C{=}CHNO_2$ $Ph_2C(OH)CH_2NO_2$	189
5	HNO_2	$Ph_2C{=}CHNO_2$	190
6	NOCl	$Ph_2CClCH(Me)NO_2$	191
7	$C(NO_2)_4$	$Ph_2C{=}CHNO_2$, $Ph_2CCH_2NO_2$ | $C(NO_2)_3$	179
8	MeS(O)SMe, $(CF_3CO)_2O$	$Ph_2C{=}CHSMe$	192
9	PhSCl	$Ph_2C{=}CHSPh$	193
10	$HC{\equiv}CCH_2OH$, NBS	$Ph_2C(CH_2Br)OCH_2C{\equiv}CH$	194
11	$(EtO)_2P(O)NBr_2$, BF_3	$Ph_2C(CH_2Br)N(Br)$ | $P(O)(OEt)_2$	195
12	PhN_3, CF_3CO_2H	$Ph_2C(CH_3)NHPh$	196
13	HN_3, $TiCl_4$	$Ph_2C(CH_3)N_3$	197
14	HCON(Me)Ph, $POCl_3$	$Ph_2C{=}CHCHO$	198
15	Ph_2N_2Cl, $CuCl_2$	$Ph_2C{=}CHPh$	199–201
16	*p*-$NO_2C_6H_4N_2Cl$, HOAc	$Ph_2C{=}CHN{=}NC_6H_4NO_2$-*p*	202
17	1,3-bis[4-vinyl-naphthalene]propane	[3,3]paracyclo(1,4) naphthalenophanes	204
18	$(COBr)_2$	$Ph_2C{=}CHCOBr$	205
19	$(COCl)_2$	$Ph_2C{=}CHCOCl$	206, 207
20	$COCl_2$	$Ph_2C{=}CHCOCl$	208
21	$SOCl_2$	$Ph_2C{=}CHSOCl$	208
22	$TeCl_4$	$(Ph_2C{=}CH)_2TeCl_2$	208

formation of the normal adduct $Ph_2CClC(NO)CH_3$. Nitric oxide, from decomposition of excess nitrosyl chloride, then oxides this intermediate to the final nitro product. Entry 7: addition of a catalytic quantity of ferrocene or exposure to a 100-W medium-pressure Hg lamp induces rapid reaction of the coloured charge transfer complex **136**. The mechanism is an $^{\bullet}NO_2$ radical-induced chain reaction (equation 71). Entry 8: the most probable pathway is considered to involve addition of $MeS(O)COCF_3$, generated *in situ*. The resulting ester $Ph_2C(OCOCF_3)CH_2SMe$ then undergoes elimination of CF_3CO_2H. Entry

$$Ph_2C{=}CH_2{\cdot}C(NO_2)_4 \longrightarrow Ph_2C{=}CH_2 + {}^{\bullet}NO_2$$

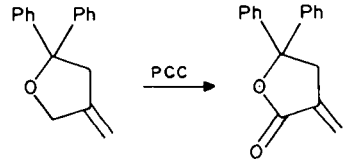
(136)

$$\longrightarrow Ph_2\dot{C}{-}CH_2NO_2$$

$$\xrightarrow{C(NO_2)_4} O_2NCH_2\overset{+}{C}Ph_2 + \bar{C}(NO_2)_3 + {}^{\bullet}NO_2$$

$$\longrightarrow O_2NCH{=}CPh_2 + O_2NCH_2\underset{\displaystyle C(NO_2)_3}{\overset{\displaystyle |}{C}}Ph_2 \qquad (71)$$

10: treatment of propargyl ether with either a Co(I) complex or Bu_3SnH[210] leads to the radical induced formation of the methylene tetrahydrofuran **137**, which is oxidizable with pyridinium chlorochromate (PCC) to the α-methylene butyrolactone **138** (equation 72). Entry 11: *in situ* reduction of the adduct with $NaHSO_3$ leads to the *N*-(β-bromomethyl)phosphoramidate, which is readily cleaved to 1,1-diphenyl-2-bromoethylamine hydrochloride in 42% overall yield. Entry 15: 1,1-diphenylethylene is arylated[199,200] under the conditions of the Meerwein reaction[201] to give triphenylethylene. Entry 16: both 1,1-diphenylethylene and 1,1-diphenylpropene couple with 4-nitrodiazobenzene in acetic acid[202]. In pyridine, arylation takes place at the same carbon atom. Electron-donating substituents in the *para* position facilitate coupling. In certain cases it is possible to isolate a crystalline intermediate **139**[203] (equation 73). Entry 17: 1,1-diphenylethylene is readily protonated by trifluoroacetic acid in benzene and induces cationic cyclodimerization with the bis-α-vinylnaphthyl substrate **140**. A similar reaction is observed with the *p*-vinylphenyl-α-vinylnaphthyl analogue of **140** (equation 74). Entry 19: the first formed adduct $Ph_2CClCH_2COCOCl$, loses CO and subsequently HCl *en route* to the final product $Ph_2C{=}CHCOCl$. Entry 21: the same final product is formed with phosgene as with oxalyl chloride, by thermal elimination of HCl from the initially

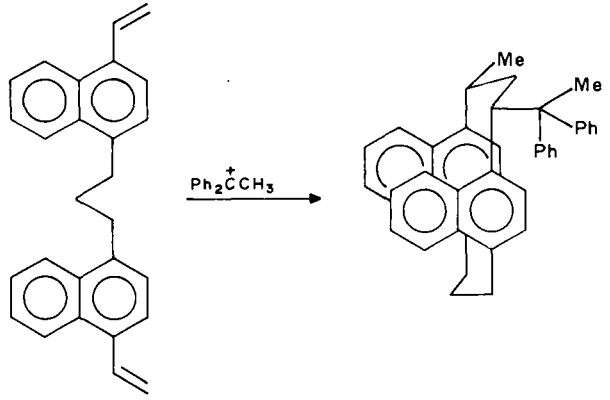


(137) (138) (72)

$$Ar_2C{=}CH_2 + Ar^1N_2X \longrightarrow [Ar_2CCH_2N_2Ar^1]^+X^-$$

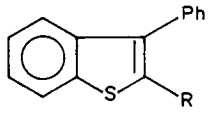
(139)

$$\longrightarrow Ar_2C{=}CHN{=}NAr^1 \quad (73)$$

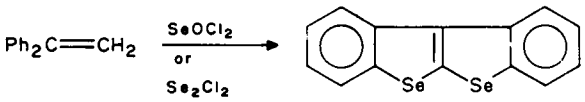


(140) (74)

formed adduct, Ph_2CClCH_2COCl. Entry 21: this reaction has been re-investigated[209]. It has been found that whereas 1, 1, 2-triphenylethylene does not react with thionyl chloride, 1, 1-diphenylethylene, -propene and -butene do react with the formation of the corresponding benzothiophen **141** in 50–60% yield. The mechanism of this reaction has not been determined. In a possibly related reaction, seleninyl chloride or diselenium dichloride each react to give the same product **142** with 1, 1-diphenylethylene[208] (equation 75). Entry 22: depending on conditions, either the σ-complex $(Ar_2C{=}CH)_2TeCl_2$, the corresponding vinyl chloride or, in typical behaviour towards Lewis acids, the linear or cyclic dimer of 1, 1-diphenylethylene, are formed.



(141)



(75)

(142)

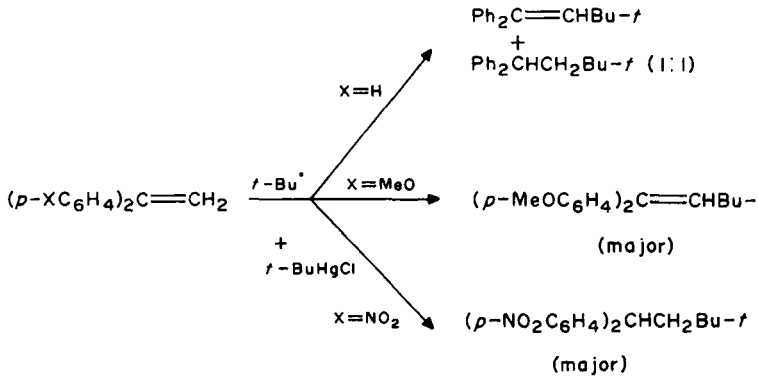
4. Radical

The results discussed in this section have been selected on the basis that the authors have formally undertaken the investigation of radical additions to 1, 1-diarylalkenes or used 1, 1-diarylalkenes to detect and trap radicals formed in a reaction.

Cadogan and coworkers[211] have shown that benzene diazonium acetate decomposes in solution to both benzene and phenyl radicals. Addition of 1, 1-diphenylethylene efficiently diverts reaction towards benzene by trapping the phenyl radicals. 1, 1, 2-Triphenylethane and 1, 1, 2-triphenylethylene, the products from disproportionation of the 1, 1, 2-triphenylethyl radical[212], are isolated. Following these lines and the work of McEwen[213] and Walborsky[214], Barton and coworkers[215] have tested for a radical mechanism and a competing radical pathway in a wide range of phenylation reactions involving Bi(V), Pb(IV), I(III) and Sb(IV) reagents. They have studied the effect of 1, 1-diphenyethylene on the phenylation of phenol. In all cases, the yield of phenylated phenol either improves or remains unchanged. They have thereby disproved mechanisms involving phenyl radical intermediates, in these phenylation reactions. They have also investigated[215] the efficiency of 1, 1-diphenylethylene as a phenyl radical trapping agent by heating it with benzene diazonium tetrafluoborate and copper(0) in DMF. 1, 1, 2-Triphenylethylene is isolated in 43% yield. Disproportionation is not evident.

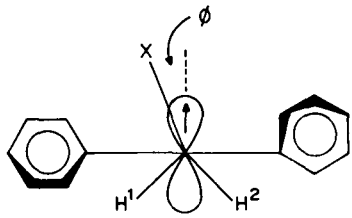
Russell and coworkers[216] have noted that *t*-butyl radicals, when photogenerated from excess *t*-butylmercury chloride, undergo radical addition to 1, 1-diarylethylenes. The product selectivity depends on the aryl substituents and reflects the donor or acceptor properties of the intermediate $t\text{-}BuCH_2{}^{\cdot}CAr_2$ in relation to alkyl mercurials (equation 76).

Lahousse, Merenyi and coworkers[217] have investigated the kinetics of addition of the isobutyronitrile radical to 1, 1-diarylethylenes. Hammett σ_p values have been employed and give the best correlation. It is concluded that rates with aryl donor substituents are determined by SOMO–HOMO interactions, whereas when acceptor substituents are present the rates are determined by SOMO–LUMO interactions. Giese and Meixner[218]



(76)

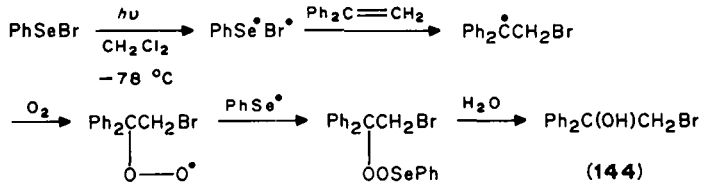
have studied the kinetics of addition of the cyclohexyl radical to 1,1-diarylethylenes. Correlation with Hammett σ values show that substituents at the non-attached vinyl carbon atom show mainly polar effects. Mesomeric and steric effects are minor. In a later study Giese[219] has compared the same reaction with that of styrene. The rate of reaction of 1,1-diphenylethylene is slower due to steric hindrance to co-planar orientation of the π system. From an ESR study of the *t*-BuO radical adducts of *p*-substituted 1,1-diarylethylene (t-$BuOCH_2C^{\cdot}Ar_2$) it is concluded[220] that the aryl rings are twisted with respect to each other, **143**, as in benzophenone ketyl.



(143)

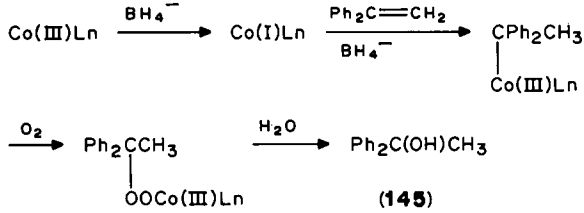
The phenylselenosulphate, p-$MeC_6H_4SO_2SePh$, photodecomposes to the phenylselenide and *p*-methylphenylsulphonyl radicals[221]. The latter react with 1,1-diphenylethylene (equation 77). A similar reaction is the photolysis of phenylselenyl bromide in 1,1-diphenylethylene in the presence of oxygen[222]. The α-bromo carbinol **144** is formed in addition to benzophone (equation 78).

$$p\text{-}MeC_6H_4SO_2SePh \xrightarrow{h\nu} p\text{-}MeC_6H_4SO_2^{\cdot} + PhSe^{\cdot}$$
$$\downarrow Ph_2C{=}CH_2$$
$$p\text{-}MeC_6H_4SO_2CH{=}CPh_2 \qquad (77)$$



(78)

Okamoto and Oka[223] have isolated the tertiary carbinol **145** in the reaction of 1,1-diphenylethylene with oxygen, sodium borohydride and bis-(dimethylglyoximato)chloro(pyridine)cobalt(III). The mechanism they suggest is outlined in equation 79.



(79)

When hydroperoxydiazenes $HOOCMe_2N{=}NCH_2R$ ($R = CF_3$, CH_2CN, CHMeCN, CH_2OMe, CH_2OPh) are thermolyzed (50–80 °C) in 1,1-diphenylethylene, hydroxyalkylation occurs[224] (equation 80). A radical intermediate is considered probable.

$$HOOCMe_2N{=}NCH_2CF_3 + Ph_2C{=}CH_2 \xrightarrow{\Delta} CF_3CH_2CH_2C(OH)Ph_2 \qquad (80)$$

5. *Halogenations*

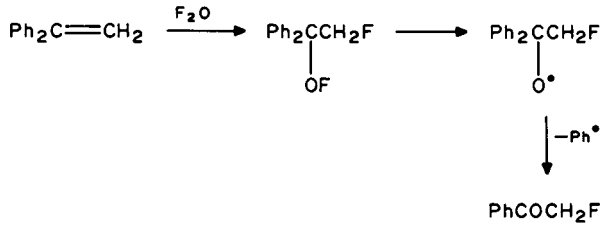
a. Fluorination. Fluorination of 1,1-diphenylethylene has been achieved using LTA–HF[225], $ArIF_2$[226] and F_2[227] at low temperature. The first two reagents cause skeletal rearrangement by phenyl migration (see Section IV.I.4) whereas use of molecular fluorine results in nuclear fluorination. Zupan and his group[228] have found that xenon difluoride in methylene chloride in the presence of HF or trifluoroacetic acid leads to the difluoride Ph_2CFCH_2F without any complications. Simple teflon apparatus only is required. Methyl iodine(III) difluoride, $MeIF_2$, which is prepared from xenon difluoride and excess methyl iodide, reacts with 1,1-diphenylethylene to yield 1,1-diphenyl-1-fluoro-2-iodo methane[229]. Bis(*sym*-collidine)iodine(II) tetrafluoroborate is the most recently developed reagent for iodofluorination[230].

Xenon difluoride in the presence of bromine yields the corresponding 1,1-diphenyl-1-fluoro-2-bromoethane[231]. The latter product has also been prepared by employing polymer-supported HF with NBS[232]. More recently caesium fluoroxysulphate has been developed[233]. It reacts with 1,1-diphenylethylene in methylene chloride to give 1,1-diphenyl-2-fluoroethylene (equation 81). This reaction, in the presence of nucleophiles, *e.g.* HF, MeOH or AcOH, leads to the formation of the *vic*-difluoride, methoxy fluoride or acetoxy fluoride, respectively.

$$CsSO_4F + Ph_2C{=}CH_2 \xrightarrow[\text{RT}]{CH_2Cl_2} Ph_2C{=}CHF \qquad (81)$$
$$24\ h$$

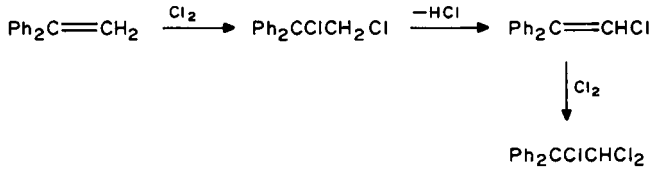
Oxygen difluoride, OF_2, is readily absorbed by 1,1-diphenylethylene in Freon 11 at −78 °C. Phenacyl fluoride is formed in 66% yield. The major by-product, apart from polymer, is biphenyl[234]. The mechanism is outlined (equation 82).

b. Chlorination. Chlorine, but not bromine or iodine, adds to tetraphenylethylene, to give the reactive 1,2-dichloride[235], which solvolyzes in methanol with concomitant pinacolone rearrangement and in boiling water with formation of tetraphenylethylene oxide[236]. Magerramov and coworkers[237] have investigated the formation of the 1,2,2-trichloride



(82)

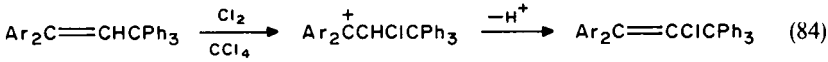
when 1,1-diphenylethylene is treated with chlorine. They have found that the vinyl chloride is formed first which then undergoes further addition of chlorine (equation 83).



(83)

A new binary-phase chlorination reaction between copper(II) chloride and 1,1-diphenylalkenes has been reported[238]. Thus 1,1-diphenyl-2-chlorobut-1-ene is formed in 93% yield within 3 h using this method. The rate of chlorination is enhanced by electron-donating groups but is retarded both by electron-withdrawing substituents on the aryl rings and by long-chain alkyl groups attached to the ethylenic residue. Two polymer-supported reagents have been prepared[239] by chlorinating a crosslinked polymer containing pyridinium iodide or *N*-methylpyridinium iodide residues. These reagents react with 1,1-diphenylethylene in various solvents with the formation of 1,1-diphenyl-1,2-dichloroethane and 1,1-diphenyl-2-chloroethylene. The ratio of these products is dependent on time, conditions, reagent and solvent.

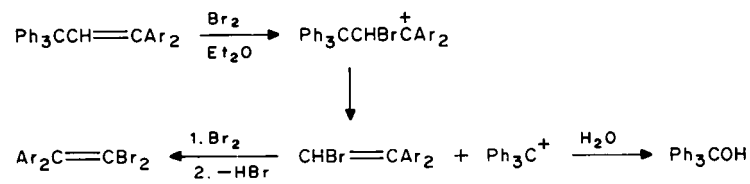
Chlorine, unlike bromine, reacts normally with $(p\text{-MeOC}_6H_4)_2C{=}CHCPh_3$[240] (equation 84).



(84)

c. Bromination. 1,1-Diphenylethylene and its homologues undergo facile addition reactions with bromine[241]. Addition of bromine in carbon disulphide or acetic acid occurs at room temperature; on warming, elimination of hydrogen bromide occurs with formation of 1,1-diphenyl-2-bromoethylene[242].

Pentaphenylpropenes $Ph_3CCH{=}CAr_2$ (Ar = 4-$MeOC_6H_4$) are cleaved by bromine with loss of the triphenylmethyl carbocation which is isolated as the carbinol[240] (equation 85). Additional evidence[240] for a mechanism involving a trityl carbocation leaving group is provided by the UV absorbtion spectrum of a solution of this alkene in a mixture of acetic acid and sulphuric acid. This spectrum λ_{max} 406, 429 and 516 nm is consistent with the formation of a mixture of trityl carbocations (λ_{max} 406 and 429 nm) and protonated 1,1-diarylalkenes (λ_{max} 516 nm) (equation 86).



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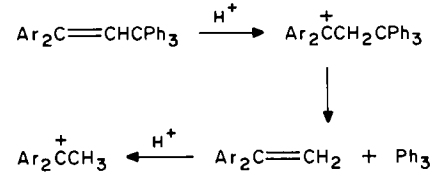


(86)

A detailed kinetic investigation of the bromination of mono-substituted 1,1-diphenylethylenes has been undertaken by Dubois, Hegarty and Bergmann[11,28]. They find that (a) molecular bromine is the only important electrophilic species, and (b) the rate constants for *meta*-substituted substrates correlate with $\rho = -3.57$ and for those with *para*-electron-donating substituents, the resonance susceptibility constants $R = 0.84$. This R value correlates well with that already determined[243] (0.81) from ^{1}H NMR shifts of the ethylenic protons of 1,1-diphenylethylenes and implies an angle of torsion $\Phi = 23°$ between the substituted phenyl ring and the plane of the ethylenic group in the transition state. This study has been extended to the kinetics of bromination of multiply substituted 1,1-diphenylethylenes. They postulate an unsymmetrical transition state in which one ring remains co-planar and in conjugation with the developing carbocation, the other ring lying out of this plane. An alternative model of the transition state in which both rings are equally inclined to the plane of the carbocation proves less exact[11]. A detailed investigation of the effect of nucleophilicity of the solvent on the rate of bromination of 1,1-diphenylalkenes has been reported by Ruasse and Lefebvre[244].

G. Allylic Bromination

The dibromide of 2-methyl-1,1-diphenyl-1-propene, on warming, readily loses one mole of HBr with the formation of the corresponding allylic bromide **146**[245] (equation 87). Bromination of 1,1-diphenylpropene with 1-bromo-3,5,5-trimethylhydantoin yields $Ph_2C{=}CHCH_2Br$ in 89% yield[246]. When the dibromides of 1,1-diphenylpropene and 1,1-diphenylbutene are irradiated with a sunlamp, the corresponding allylic bromide is obtained in good yield[247].

$$Ph_2C{=}CMe_2 \xrightarrow[CS_2]{Br_2} Ph_2CBrCBrMe_2$$
$$\xrightarrow[-HBr]{\Delta} Ph_2CBrCMe{=}CH_2$$
$$\longrightarrow Ph_2C{=}CMeCH_2Br \qquad (87)$$

(146)

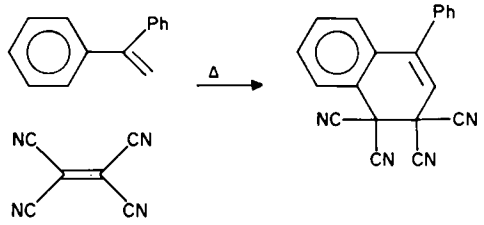
Incremona and Martin[248] in a careful study of the bromination of 1,1-diarylpropenes finally established the mechanism of allylic bromination with NBS[249], as one involving bromine radicals, with the NBS acting to provide a low steady-state concentration of bromine.

H. Cycloadditions

1. Diels–Alder

1,1-Diphenylethylene undergoes reversible cycloaddition to TCNE[250]. The kinetics of this reaction have been studied. Initially an electron donor–acceptor (EDA) complex is

formed, subsequent to which cycloaddition occurs (equation 88). There is evidence for some charge separation in the transition state. A similar reaction is observed between TCNE and cyclopropylidene derivatives **147** (X = H, OMe)[251] (equation 89). In this instance the initially formed cycloadduct **148** is unstable and is transformed to the stable 1-arylnaphthalene **149**. A cycloaddition reaction between dicyanoacetylene and 1,1-diphenylethylene occurs readily[252] (equation 90). However, some disproportionation of the first-formed product **150** leads to a complex reaction product mixture. 1,1-Diphenylethylene also reacts with dimethyl acetylene dicarboxylate (DMAD)[253]. The product **151** is formed, presumably by an initial cycloaddition followed by an ene reaction. A 2:1 structurally related compound **152** is formed in the reaction between 1,1-diphenylethylene and diethylazodicarboxylate[253].



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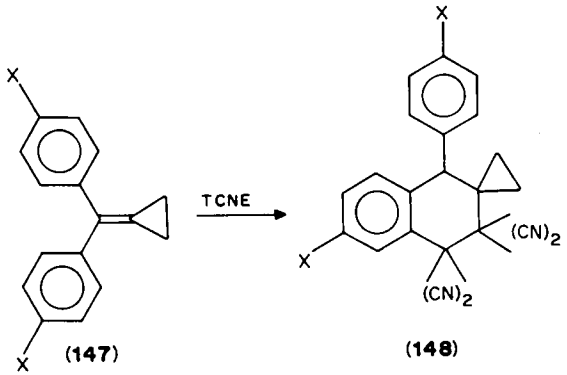

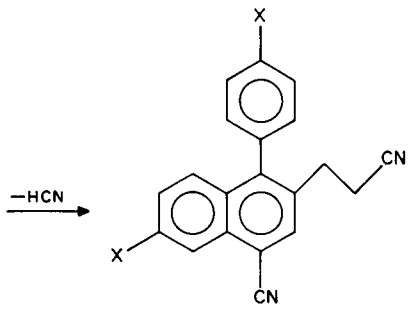

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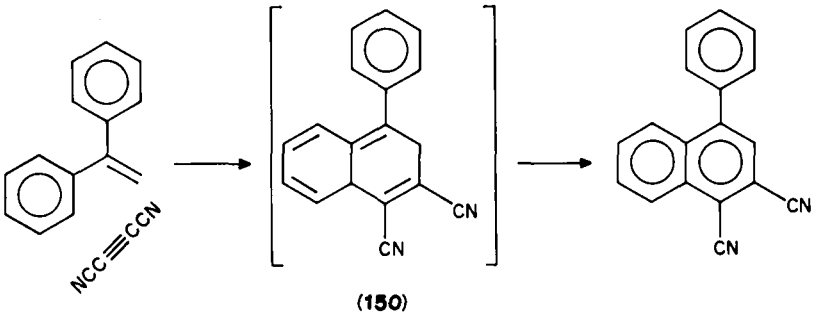

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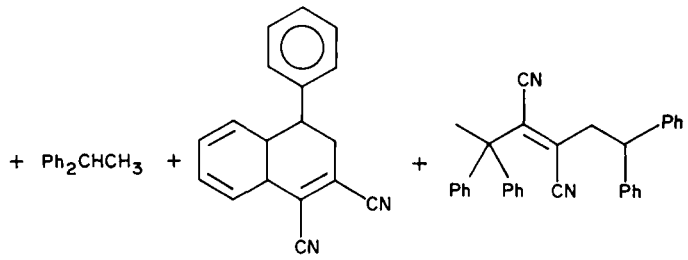

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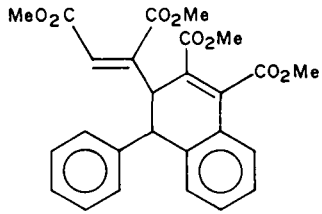

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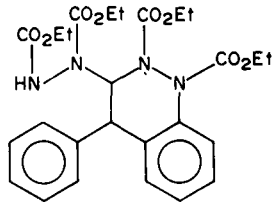

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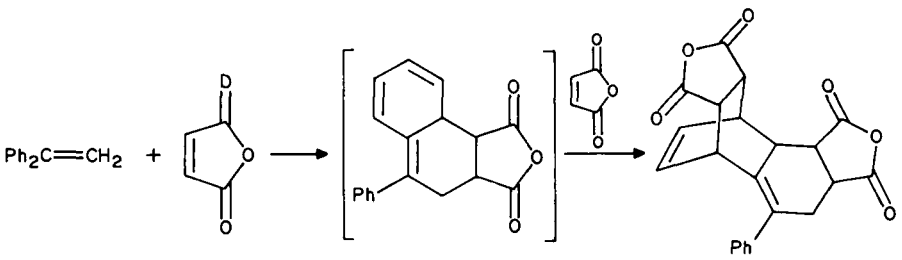
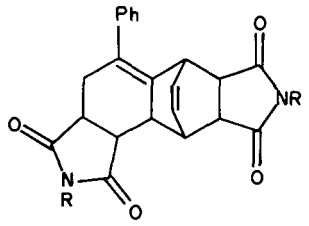


(153)

(91)

With maleic anhydride, 1, 1-diphenylethylene forms a Wagner-Jauregg[254] 1:2 cycloaddition product **153**[255] (equation 91). The formtion of analogous products has been reported with (carbomethoxy) maleic anhydride[256] and bis(carbomethoxy)maleic anhy-

dride[257]. However, citraconic anhydride does not react with 1,1-diphenylethylene[258]. Maleimide and *N*-alkylmaleimide lead to the Wagner-Jauregg product **154** with 1,1-diphenylethylene. *N*-(2-Naphthyl)maleimide in boiling nitrobenzene leads to the 1:1 dehydroadduct **155**[259].



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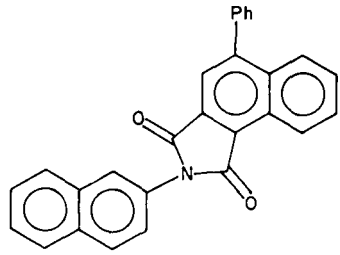
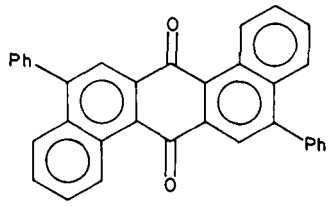


(155)

In boiling nitrobenzene a double cycloaddition of 1,1-diphenylethylene with benzoquinone occurs. It is dehydrogenated *in situ* to the quinone **156**[253]. Two moles of diphenylketene add directly to 1,1-diphenylethylene. The mechanism of formation of the product **157** has not been fully elucidated[260–262].



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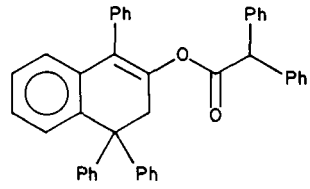
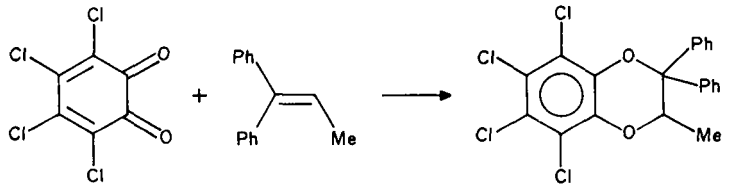


(157)

2. Heterodienes

Tetrachloro-*o*-benzoquinone undergoes thermal and photochemical cycloaddition to 1,1-diphenylpropene[263] (equation 92). The *o*-quinone methide functionality behaves similarly[264]. Thus 3,6-bis-(hydroxymethyl)catechol **158** when heated alone or in the presence of BF_3 reacts with 1,1-diphenylethylene to give the bis-adduct **159** (equation 93). *p*-Methoxyphenylmethylene malonaldehyde **160** also undergoes cycloaddition to 1,1-diphenylethylene in the presence of zinc iodide, in reasonable yield[265] (equation 94). Another example of a Diels–Alder reaction with inverse electron demand is provided by the nitrosoalkenes[266,267]. No indication of a dipolar intermediate has been found in the course of formation of the oxazines **161**, R = CO_2Et, Ph (equation 95). Selenooxazine **162** is formed in the reaction of 1,1-diphenylethylene with $PhSO_2N{=}Se{=}NCOPh$[268].



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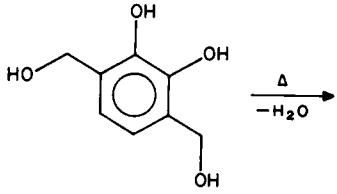

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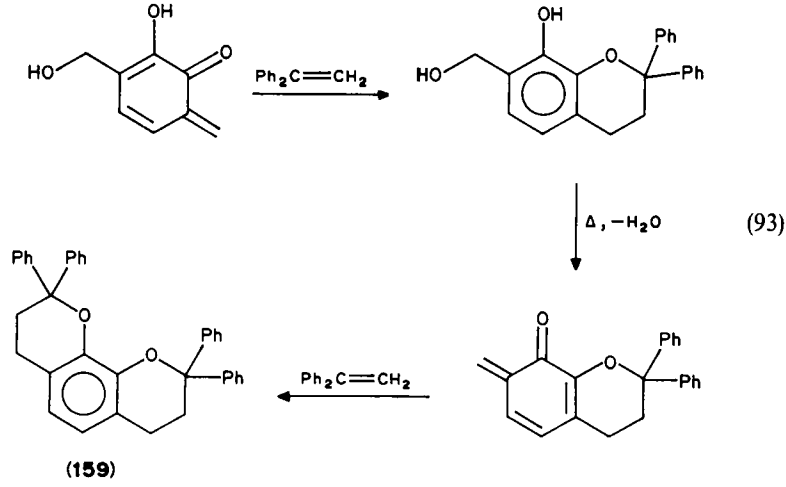

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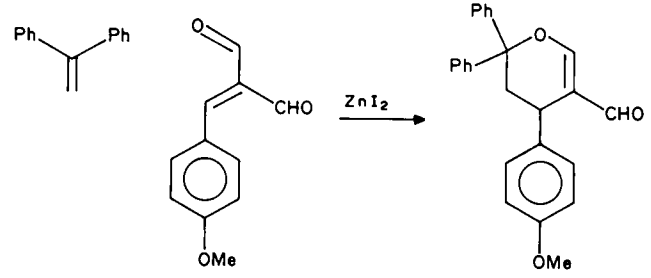
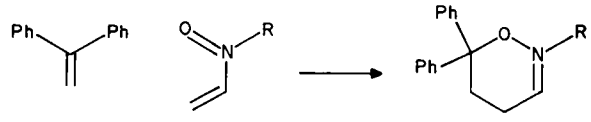
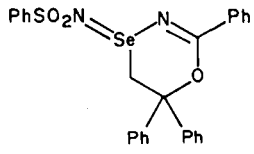


(160) (94)



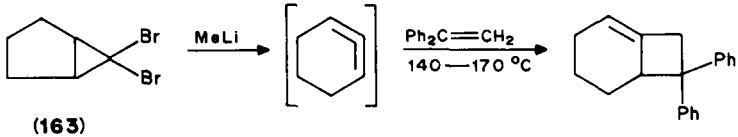
(161) (95)



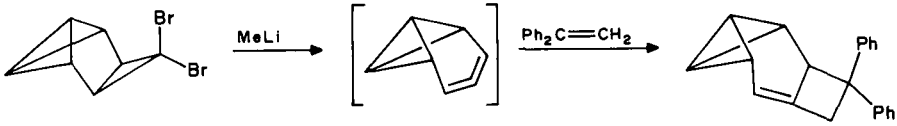
(162)

3. (2 + 2)π

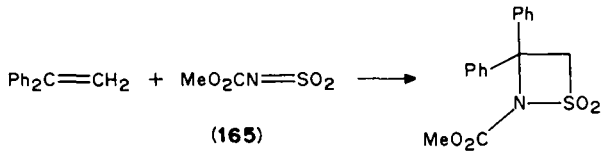
The 1,2-cyclohexadiene formed in the reaction of the dibromide **163** with methyllithium reacts with 1,1-diphenylethylene probably by a diradical pathway[269] (equation 96). The allene **164** undergoes a similar reaction[270] (equation 97). Methyl *N*-sulphonylurethane **165** undergoes (2 + 2) cycloaddition with 1,1-diphenylethylethylene. The 2-carbomethoxy-3,3-diphenyl-1,2-thiazetidine 1,1-dioxide **166** is formed in low yield[271] (equation 98).



(163) (96)



(164) (97)

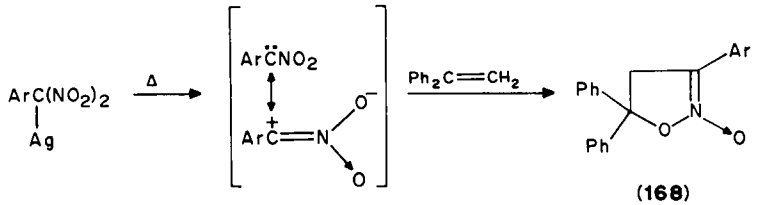


(165) (166) (98)

4. 1,3-Dipolar

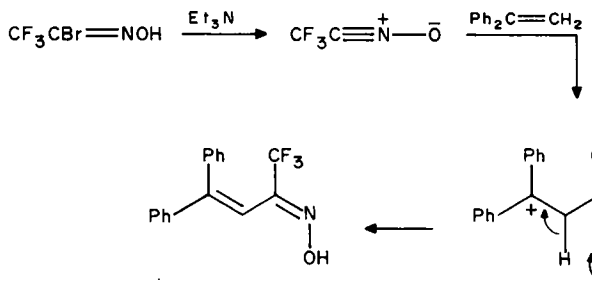
1,1-Diphenylethylene reacts with silver dinitroarylmethanes when heated to 100 °C in heptane[272]. The nitrocarbene **167** which is formed is considered to undergo cycloaddition. The reaction is regiospecific and the Δ^2-isoxazoline *N*-oxide **168** is the major product (equation 99). Attempted cycloaddition of trifluoracetonitrile oxide with 1,1-diphenylethylene failed[273]. The linear oxime **170** only is formed, probably by an intramolecular proton abstraction mechanism through **169** (equation 100).

Nitrones RN(O)CHR^1 (R = Me, Bu, $PhCH_2$, Ph_2CH, 4-MeC_6H_4; $R^1 = CO_2R$) react regiospecifically with 1,1-diphenylethylene. The isoxazolidenes **171** are formed[274].



(99)

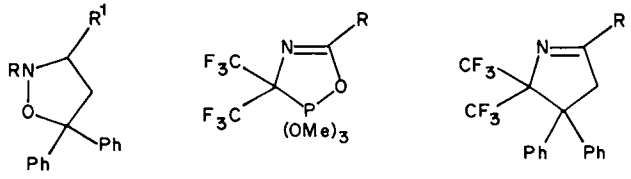
(167) (168)



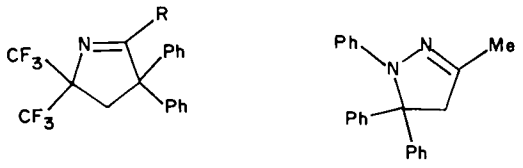
(100)

(170) (169)

The nitrile ylides $(F_3C)_2\overset{-}{C}\overset{+}{N}{\equiv}CR$ (R = Bu^t, Ph) have been prepared by thermolysis of the corresponding cyclic phosphate **172** and trapped with 1,1-diphenylethylene[275]. Both regioisomers **173** and **174** are formed. 1,1-Diphenylethylene has been used to trap *in situ* the *C*-alkylnitrilimine, $PhN\overset{-}{-}\overset{+}{N}{\equiv}CMe$, which has been prepared by the thermal elimination of $NaNO_2$ from $NaPhNN{=}CMe(NO_2)$ in boiling acetonitrile[276]. The cycloadduct **175** is formed regiospecifically, although in low yield.



(171) (172) (173)



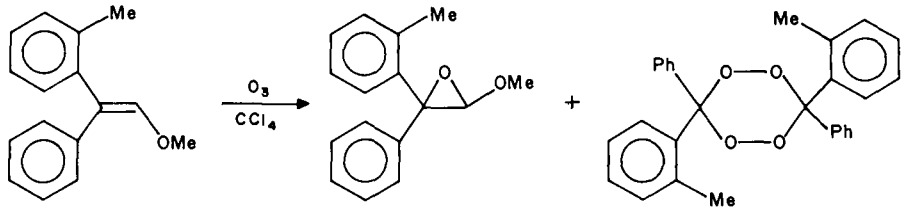
(174) (175)

When the ozonide **176** (R = C_5H_{11}, C_6H_5) is treated with $BF_3{\cdot}OEt_2$ in the presence of 1,1-diphenylethylene, the endoperoxide **177** is isolated at 32% yield. The results are consistent with the formation of a carbonyl oxide **178** followed by a (3 + 2)-cycloaddition

(176) (177)

(178)

reaction[277]. Ozonolysis of the vinyl ether **179** in carbon tetrachloride results in the formation of the epoxide **180** (64%) and the tetroxane **181** (11% yield)[278] (equation 101). Formation of the latter is consistent with the formation and dimerization of the carbonyl oxide, *o*-methylbenzophenone oxide.



(179) (180) (181)

(101)

5. Carbene and carbenoid

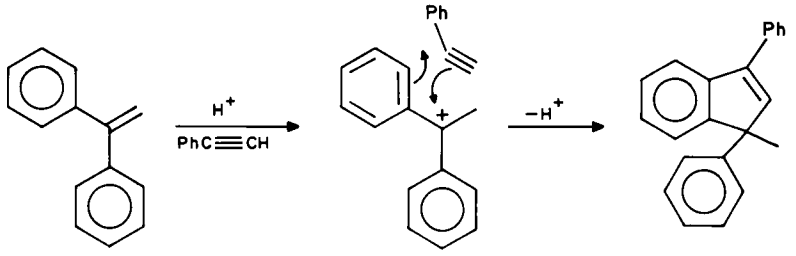
Whereas dimethylsulphonium methylide undergoes cycloaddition to 1,1-diphenylethylene. In reactions of 1,1-diarylalkenes, generation of dibromocarbene via *t*-dimethylsulphoxonium methylide does not react[279].

The haloform-strong base route to dihalocarbenes has been successfully applied to the synthesis of *gem*-dihalo-1,1-diphenylcyclopropanes by reaction with 1,1-diphenylethylene. In reactions of 1,1-diarylalkenes, generation of dibromocarbene via *t*-butoxide–bromoform in pentane[280] has been largely superceded by NaOH–haloform with the phase transfer catalyst benzyltriethylammonium iodide[281]. However, care must be exercised since halogen exchange may occur under these conditions[282]. A convenient and highly efficient new reagent for dichlorocarbene addition to 1,1-diphenylethylene is KOH–CCl_4 in *t*-BuOH–dimethylsulphone[283]. The relative reactivity of dichlorocarbene towards 1,1-diphenylalkenes decreases in the series $Ph_2C{=}CH_2 > Ph_2C{=}CHMe \gg Ph_2C{=}CMe_2$[284]. The efficient cycloaddition of carbethoxycarbene to 1,1-diphenylethylene by heating with ethyl diazoacetate has been patented[285]. The enantioselective analogue of the latter reaction has been achieved with 64–75% enatiomeric excess by employing chiral ligands in conjuction with Cu(II) acetate[286,287]. Helquist and coworkers have found that the complex $(\eta^5\text{-}C_5H_5)Fe(CO)_2CHMeSPh$ ethylidenates 1,1-diphenylethylene when treated with methylfluorosulphonate[288]. An unstable sulphonium salt is thought to be involved. Their original methylene transfer reagent[289] has now been

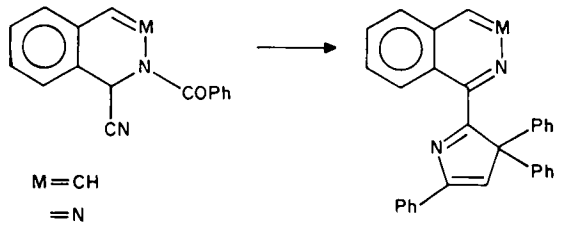
superseded[290] by the complex $Cp(CO)_2FeCH_2SMe_2BF_4$. It is stable and methylenates, e.g. 1,1-diphenylethylene, in high yield (86%).

6. *Miscellaneous*

Ryabov and Korobkov[291] have noted that phenylacetylene reacts with 1,1-diphenylethylene in orthophosphoric acid–BF_3. A carbocationic pathway is probable (equation 102). Both the isoquinoline[292] and phthalazine[293]. Reissert compounds undergo formal cycloaddition to 1,1-diphenylethylene in concentrated sulphuric acid (equation 103). The complex carbocationic reaction pathways have been carefully investigated.

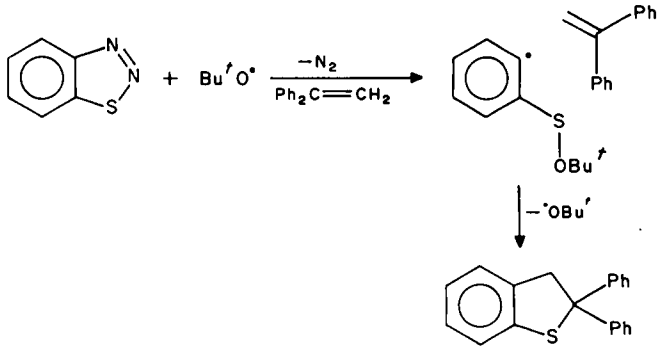


(102)

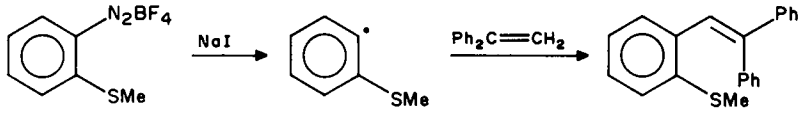


(103)

The radicophilic 1,1-diphenylethylene reacts with 1,2,3-benzothiadiazole in the presence of di-*tert*-butyl peroxide in a formal cycloaddition[294] (equation 104). When the sulphur is protected as in **182**, then formation of a cycloadduct is impeded and quantitative vinyl substitution ensues (equation 105). Tetraphenylporphyrin complexes of manganese or iron react with tosyliminoiodobenzene, PhINTs[295]. The complexed tosyl nitrene reacts with 1,1-diphenylethylene with the formation of *N*-tosyl-2,2-diphenylaziridine.



(104)



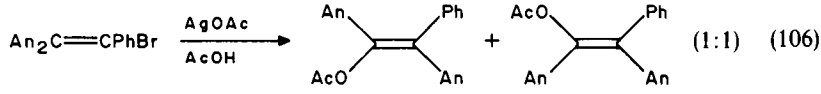
(182)

(105)

I. Rearrangements

1. β-Halotriarylethylenes

β-Bromo- and β-chloro-triarylethylenes undergo solvolysis to vinyl carbocations[296] which may undergo rearrangement[297] (equation 106).

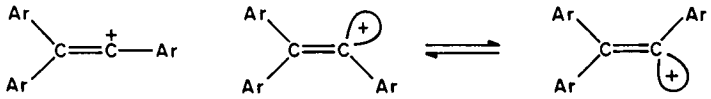


(106)

An = 4-MeOC$_6$H$_4$

This rearrangement has been investigated in great detail and has been reviewed[298–300]. The effect of the nature of the aryl migrating group and the aryl substituents at the migrating origin and migrating terminus have been summarized[301]. Rappoport[302] has also made extensive studies of the degenerate β-aryl rearrangement in solvolytically generated triarylvinyl cations, which had been first reported by Lee in 1974[303]. These systems have the advantage that the reactant and product ions are chemically identical, so that the intrinsic driving force for the rearrangement itself is reflected by the ease of rearrangement of the different ions. In general, these reactions are characterized by rearrangement, elimination and capture processes.

Solvolysis of α-anisyl-β,β-diphenylvinyl bromide in 80% ethanol containing either sodium acetate or thiolate ion is an S_N1 reaction[296]. The effect of β-aryl substituents on the rate of solvolysis is nearly additive[297,304,305]. From a study of the relative rates of solvolysis of geometrical isomers, aryl participation is considered unimportant[296,301]. The migratory aptitude of substituted aryl groups is the same as in saturated systems. The rearrangement is non-concerted. The first-formed carbocation can be trapped by bromide ion before it rearranges[301]. It has been difficult to differentiate between the linear form **183** and the rapidly equilibrating trigonal ions **184**. The former has found greater acceptance[301].

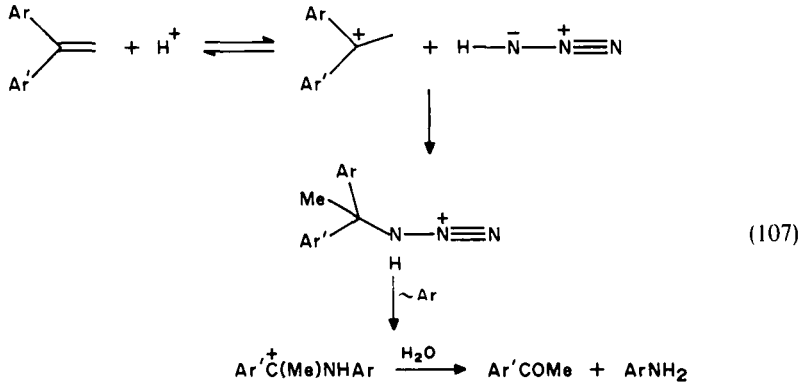


(183) (184)

2. Schmidt reaction

The Schmidt reaction has been applied to a series of unsymmetrical 1,1-diarylethylenes[306] (equation 107). The migratory aptitudes have been deduced from the relative yields of acetophenones. The results are those expected for a group migrating with

its pair of electrons: *p*-anisyl > *p*-tolyl > *p*-biphenyl > phenyl > *p*-chlorophenyl > methyl. Qualitatively, these results correlate with the migratory aptitudes found in the pinacol–pinacolone rearrangement of symmetrical pinacols[307].

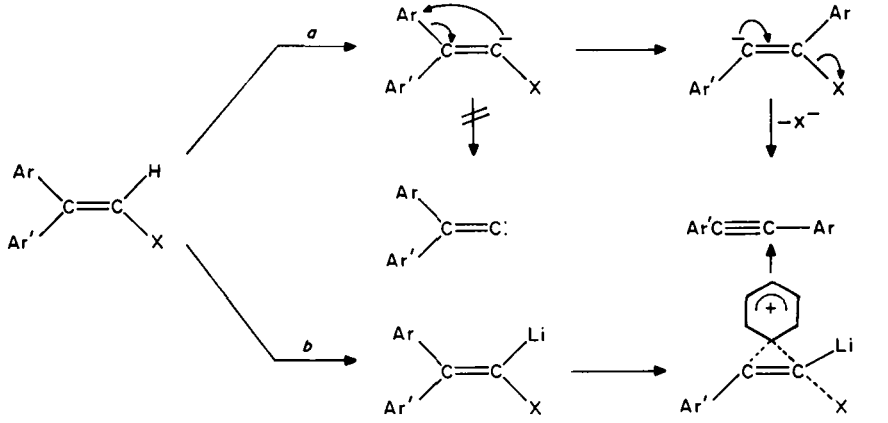


(107)

3. *Fritsch–Buttenburg–Wiechell rearrangement*

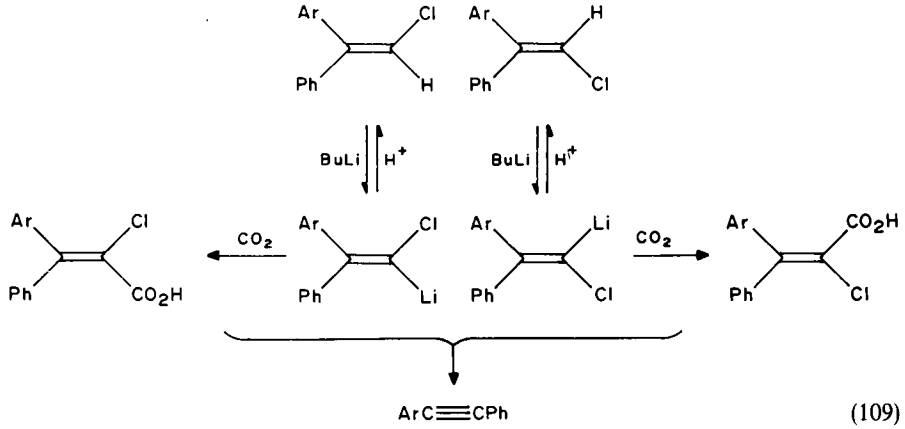
The rearrangement of 1, 1-diaryl-2-haloethylenes to diarylacetylenes with strong bases constitutes the Fritsch–Buttenburg–Wiechell rearrangement[168,308]. The order of reactivity is Br > I > > Cl[309]. Bases such as sodium amide, alkoxide and alkyllithiums are effective. The reaction is intramolecular and stereoselective, *i.e.* the aryl group *trans* to the halogen migrates preferentially[310]. Largely for this reason, a mechanism involving a free vinyl carbene, a species now known to undergo rapid rearrangement to the acetylene[311], is not considered acceptable. On the other hand, a concerted mechanism is not mandatory since vinyl carbanions can retain their configurations[312].

The mechanism seems to depend on the substrate. Two mechanistic pathways are considered[310] (equation 108). Mechanism *a* involves migration of the aryl group with its pair of electrons whereas mechanism *b* involves migration without the pair of electrons. The rate is affected by substituents: *p*-MeO > *p*-H > *p*-Cl and is consistent with mechanism *b*[310].

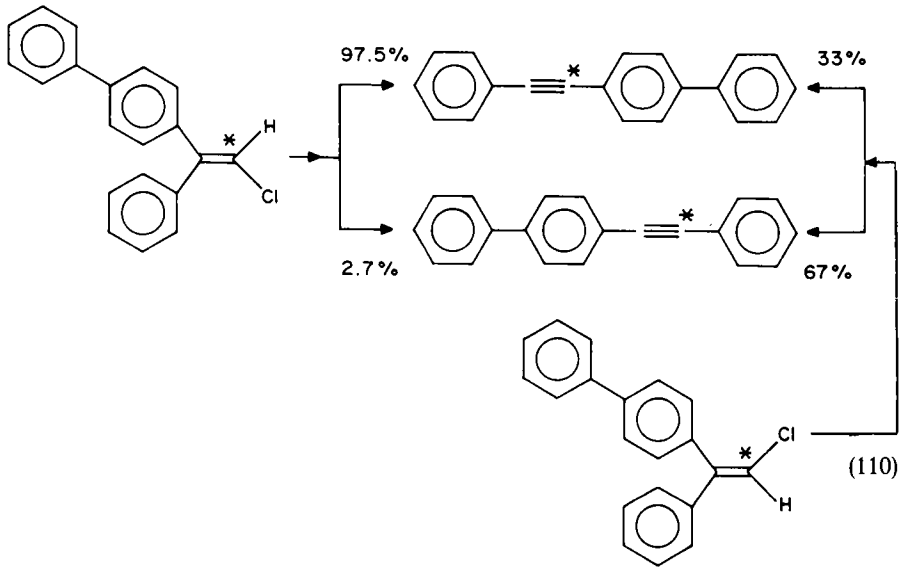


(108)

At least in some cases, the rearrangement is a two-step process and has been shown to involve a discrete vinyl carbanion[310]. Thus the *E* and *Z* isomers of 1-aryl-1-phenylvinyl chlorides (R = Cl, Ph, CH_3) have been investigated. Treatment with BuLi and carboxylation at − 110 °C has provided the corresponding acid with retention of configuration. At − 40 °C rearrangement occurs and, when carboxylated at this temperature, a mixture of carboxylic acid and acetylene is isolated[312] (equation 109). The reaction has been shown to be stereoselective by using a radiolabelled vinyl chloride[312,313] (equation 110). The rearrangement is inhibited by steric constraints. Thus, whereas **185** and **186** do not undergo rearrangement in the presence of phenyllithium, the next homologue **187** does[314] (equation 111). Some variants of this rearrangement have been observed[107]. This rearrangement has been much less intensively investigated than that of the triarylethylene halides (see Section IV.I.1).

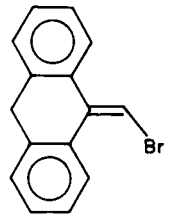


(109)

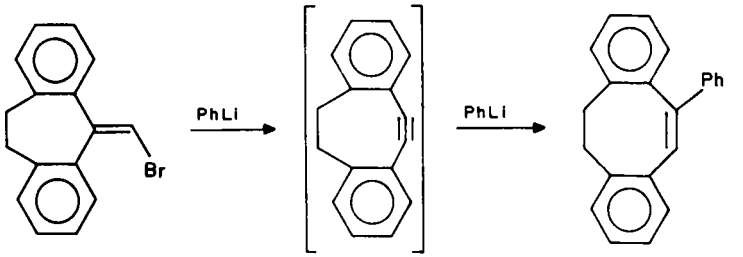


(110)

(185)



(186)



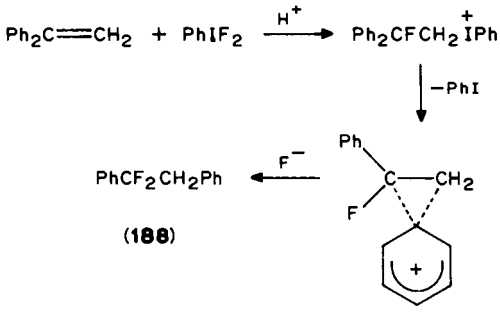
(187) (111)

4. Fluorination

Lead tetrafluoride, prepared in $CHCl_3$ by the reaction of liquid HF on $Pb(OAc)_4$, reacts with 1,1-diphenylethylene to give in moderate yield a crystalline difluoride[315] (equation 112). The product, then assumed to be 1,1-diphenyl-1,2-difluoroethane, has been established[316] as the rearranged difluoride **188**. Iodobenzene difluoride with an acid catalyst in dichloromethane also produces this product. The structure of **188** has been confirmed by ^1H and ^{19}F NMR. The mechanism is considered now to involve a phenonium ion[226] (equation 113).

$$Ph_2C{=}CH_2 \xrightarrow[0\ ^\circ C]{PbF_4} PhCF_2CH_2Ph \qquad (112)$$

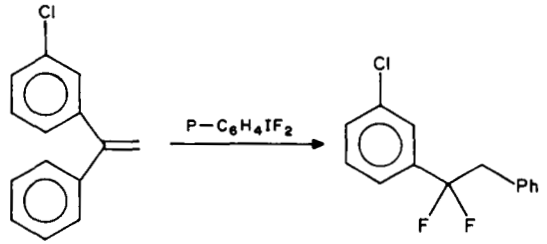
42 %



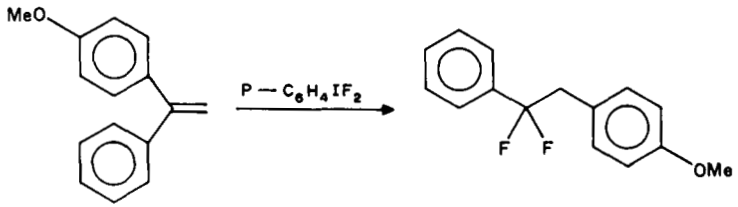
(188) (113)

Zupan[317] has employed a polymer-supported aryliodonium difluoride. Both 1,1-diphenylethylene and 1,1-diphenylpropene react with this reagent to give the correspond-

ing rearranged *gem*-difluoride. The rearrangement product depends on the aryl substituent (equations 114 and 115). A homogeneous recyclable fluorinating agent *p*-$F_2IC_6H_4CH_2COOH$ with HF is an effective alternative reagent for the synthesis of difluoride **188** from 1,1-diphenylethylene[318].



(114)

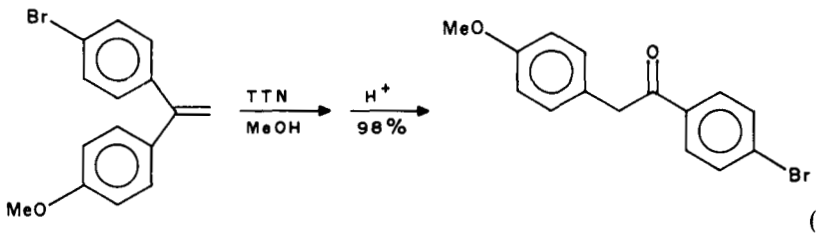


(115)

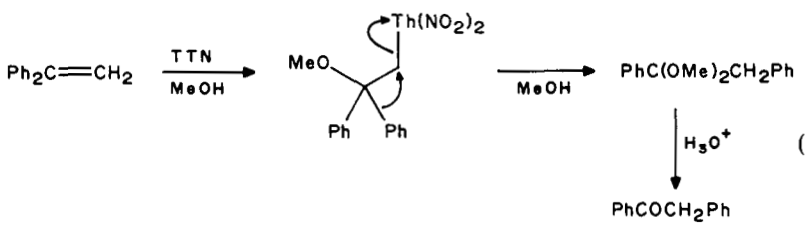
P=polymer support

5. Oxidative

1,1-Diphenylethylene undergoes oxidative rearrangement to deoxybenzoin in 95% yield when treated with thallium(III) nitrate (TTN)[319]. With substrates in which more than one substituent could theoretically migrate, rearrangement occurs cleanly to give the product expected on the basis of the relative migratory aptitudes within a carbocation (equation 116). The reaction is inhibited by steric effects: 1,1-diphenyl-2-methylpropene does not react[319]. The mechanism of the rearrangement is outlined (equation 117).

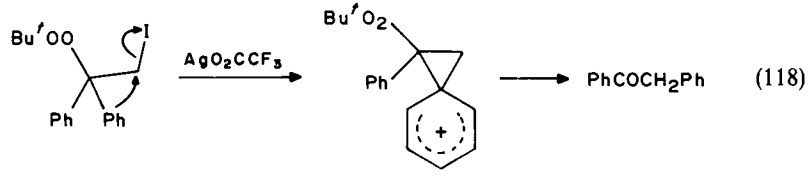


(116)



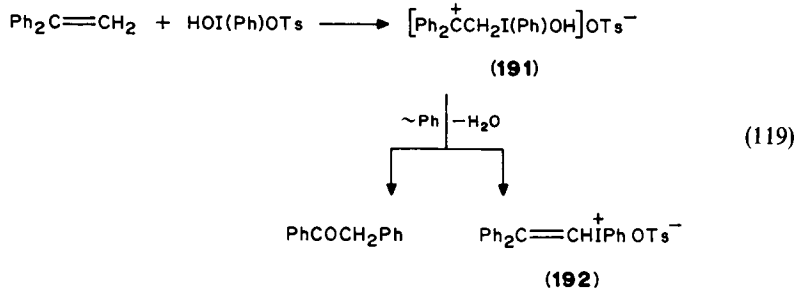
(117)

Bloodworth and his group[320] have investigated the solvolysis of the 1,1-diphenylethylene iodoperoxy derivative **189**. They have found no evidence in this case for a peroxonium ion intermediate. The phenonium ion **190** is formed and deoxybenzoin obtained in 72% yield (equation 118). From comparative studies, the migratory aptitudes are found to be Ph > *t*-BuOO > alkyl[320]. [Hydroxy(tosyloxy)iodo]benzene also effects the rearrangement of 1,1-diphenylethylene to deoxybenzoin in 65% yield[321]. The iodo(II) tosylate **192** is probably formed by loss of water from the common intermediate **191** (equation 119).



(118)

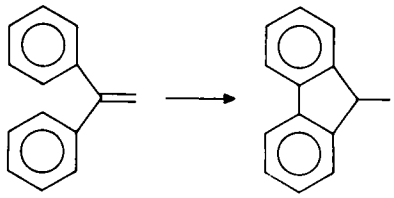
(189) **(190)**



(119)

6. *Miscellaneous*

Ryabov, Silin and Sycheva[322] have noted that 1,1-diphenylethylene isomerizes to 9-methylfluorene when heated in steam with an aluminium oxide containing catalyst at 350–425 °C (equation 120).



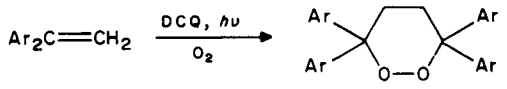
(120)

J. Photochemistry

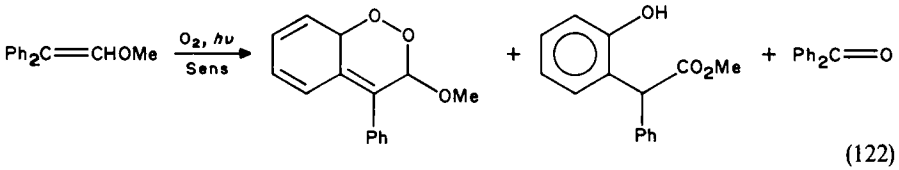
1. *Cycloadditions*

a. Oxygen. In the presence of 9,10-dicyanoanthracene sensitizer, 1,1-diarylethylenes undergo electron transfer photooxygenation in quantum yields of 3.1–15.1[323]. When the aryl groups are electron rich, *e.g.* Ar = *p*-$MeOC_6H_4$, 88% yield of product **193** is obtained

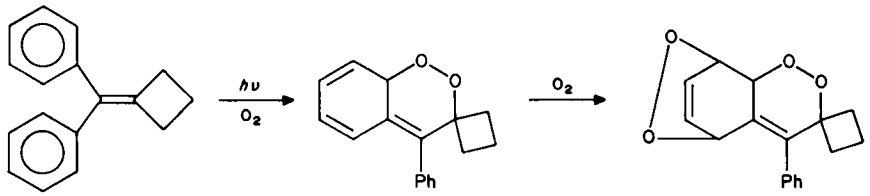
(equation 121). When electron poor, such as Ar = C_6H_5 or *p*-ClC_6H_4, the yields are low, 30% and 10% respectively. In contrast, 1,1-diphenyl-2-methoxyethylene undergoes photosensitized photoaddition to oxygen. A number of products are formed[324] (equation 122). The benzophenone is probably derived from a 1,2-dioxetane. The light-induced reaction of oxygen and diphenylmethylenecyclobutane **194** results in the bis-dioxin derivative[325] **195** (equation 123).



(193) (121)

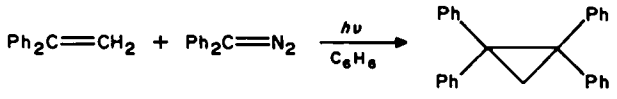


(122)

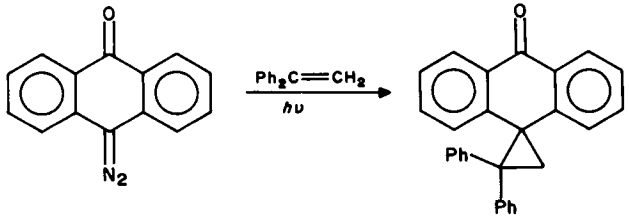


(194) (195) (123)

b. Carbenes. Photochemically generated diphenyl carbenes react with 1,1-diphenylethylene[326] (equation 124). Likewise the diazoanthrone **196**, when photolyzed with 1,1-diphenylethylene, provides the spiro cyclopropane **197** in 78% yield[327] (equation 125).

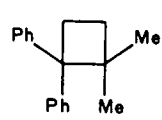


(124)

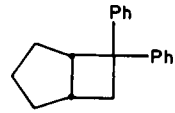


(196) (197) (125)

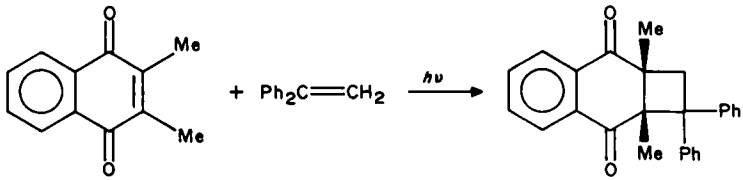
c. (2 + 2)π. The (2 + 2) cycloadducts **198** and **199** have been isolated from the xanthone-sensitized reaction of 1, 1-diphenylethylene with isobutene and cyclopentene, respectively[328]. The naphthoquinone **200** also undergoes cycloaddition[329] (equation 126). The attempted photosensitized (2 + 2) cycloaddition of 1, 1-diphenylethylene to the cyclopropene **201** in benzene has lead to the unexpected formation of **202**[330] (equation 127).



(198)

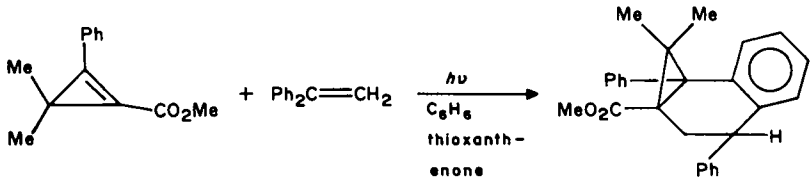


(199)



(126)

(200)

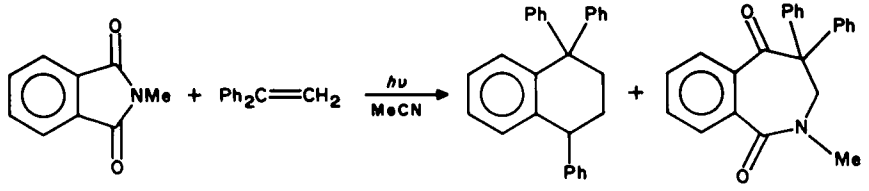


(201) (202)

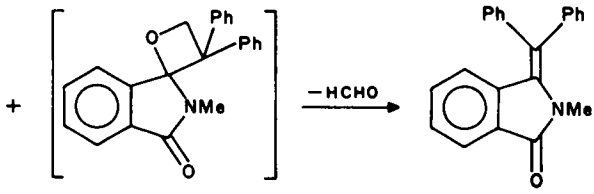
(127)

The photochemically induced cycloaddition of 1, 1-diphenylethylene to imides has been studied extensively by Kubo and coworkers. Cycloaddition arises from the triplet state of the imide and involves a biradical intermediate. This theory helps explain the regiochemistry and the diverse behaviour that is observed. Thus in the absence of sensitizer, *N*-methylphthalimide reacts via electron transfer with diphenylethylene[331]. The photodimer **203** as well as **204** and **206** are isolated. The latter is considered to arise from loss of formaldehyde from the (2 + 2)π cycloadduct **205** (equation 128). In methanol, however, no evidence for cycloaddition has been found[332]. The products are **207** and **208**. In the case of *N*-methylnaphthalene-2, 3-dicarboximide[333], photolysis in methanol leads to both the adduct **209** and the (2 + 2) cycloadduct **210**. Unexpectedly, the (2 + 2) cycloadduct **211** is formed in 67% yield from the interaction of 1, 1-diphenylethylene with *N*-methylnaphthalene-1, 8-dicarboximide in benzene[334] (equation 29).

Hemi-thioimide systems have been investigated. The predominant or exclusive reaction pathway normally involves overall (2 + 2) cycloaddition to the thiocarbonyl group. The thioimide **212** with 1, 1-diphenylethylene has been investigated by both Coyle and Rapley[335] in acetonitrile and Kanaoka and coworkers[336] in benzene. The former group

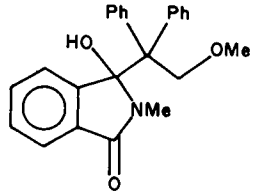


(203) (204)



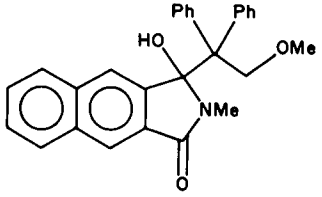
(128)

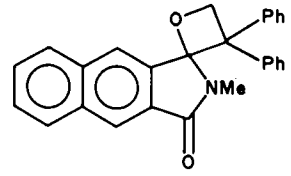
(205) (206)



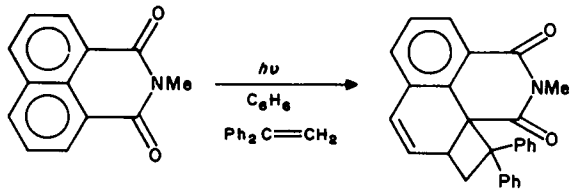
Ph_2CHCH_2OMe

(207) (208)





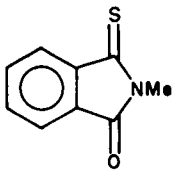
(209) (210)



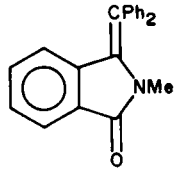
(129)

(211)

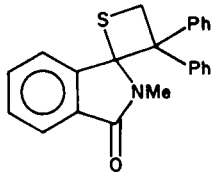
isolated diphenylemethylene isoindolone **213** in 62% crude yield but detected no thietane **214**. The latter group, however, isolated the thietane in 34% yield but none of the isoindolene. They suggest a triplet-derived biradical pathway involving the intermediate **215**.



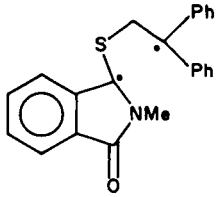
(212)



(213)

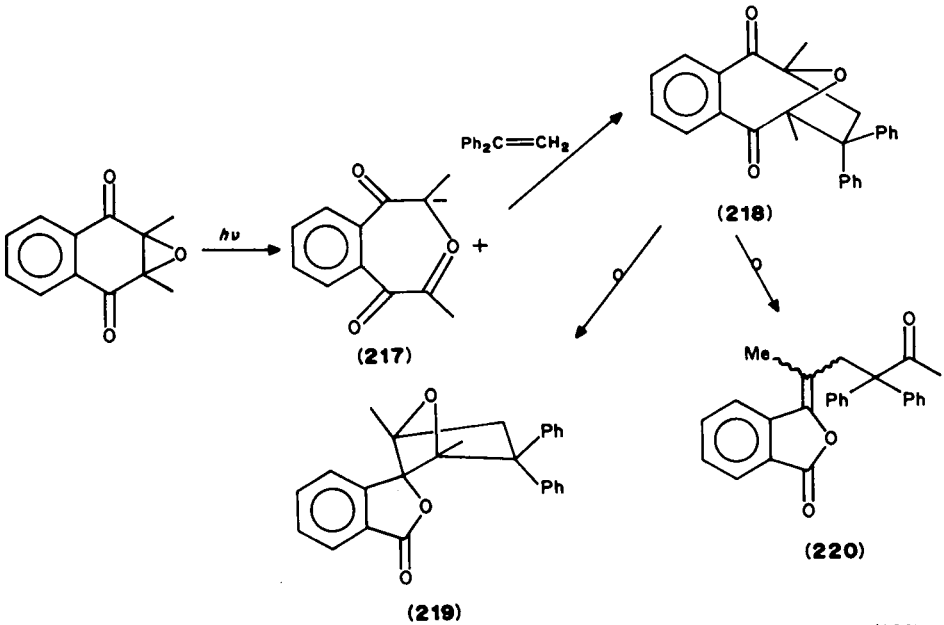


(214)



(215)

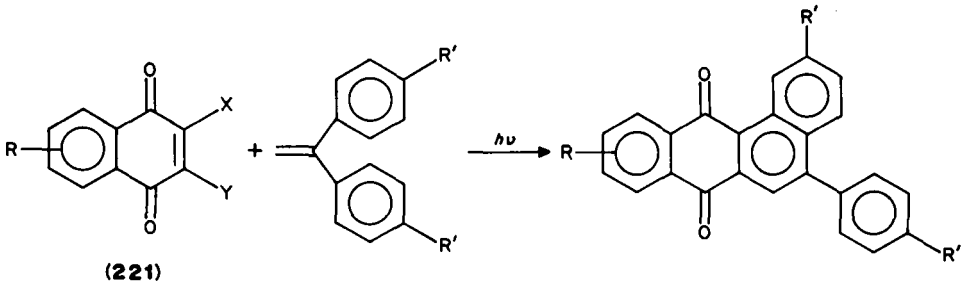
d. Carbonyl ylide. Maruyama and coworkers[337] have noted that the naphthoquinone epoxide **216**, which opens photochemically to the carbonyl ylide **217**, could be trapped by 1,1-diphenylethylene as the adduct **218**. Subsequent rearrangement leads to the isolable products **219** and **220** (equation 130).



(217) **(218)** **(219)** **(220)**

(130)

e. Miscellaneous. 1, 1-Diarylethylenes undergo photochemical reaction with naphthoquinones **221**[338] (equation 131). A range of benz[*a*]anthracene-7, 12-diones have been prepared regioselectively in this one-pot reaction, in low-to-medium yield. This reaction has been successfully extended to the quinoline-5, 8-diones[339] and to each of the methoxyl-substituted naphthoquinones. The reaction pathway has been elucidated[340] (equation 132).

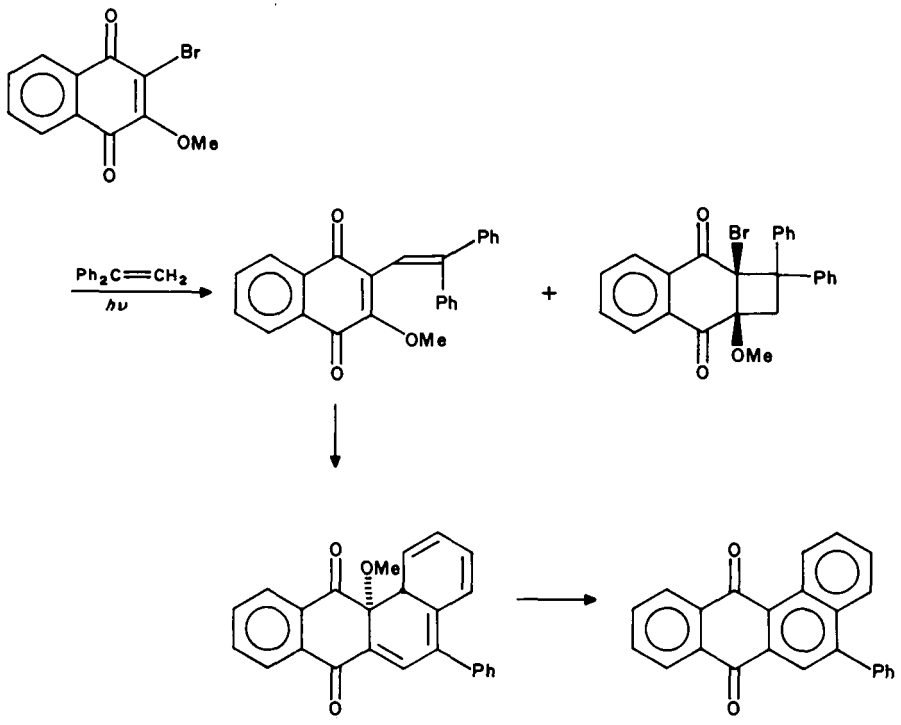


(221)

X=Cl, OMe
Y=Br, Cl

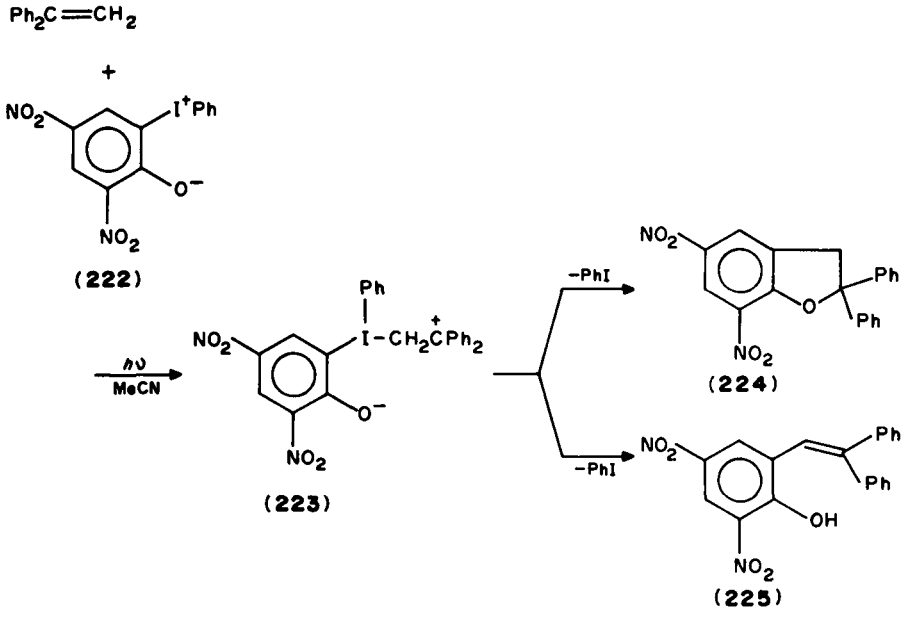
R=H
=OMe
=Me

(131)



(132)

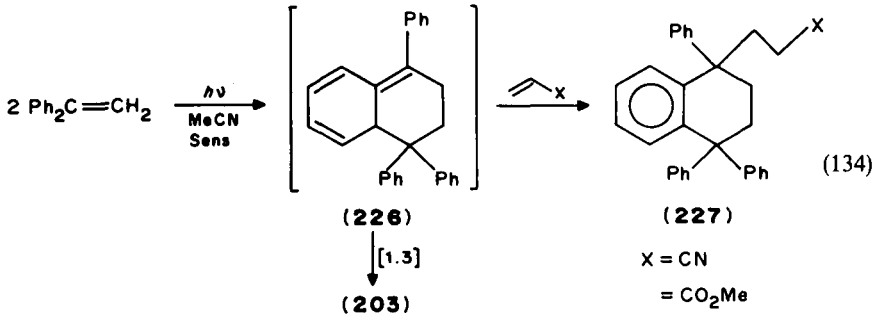
Spyroudis[341] has investigated the photolysis of 1,1-diphenylethylene with the stable zwitterion, 2,4-dinitro-6-phenyliodonium phenolate (**222**) in acetonitrile. The dihydrobenzofuran **224** and the triarylethylene **225** are formed. The mechanism involves the intermediate formation of the iodinane **223** (equation 133). Details of the subsequent reaction pathway remain to be clarified.



(133)

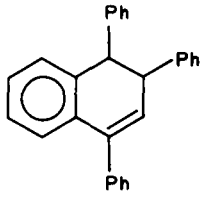
2. *Photodimerization*

The linear photodimerization of 1,1-diphenylethylene to 1,1,4,4-tetraphenylbuta-1,3-diene occurs in good yield in the presence of recoverable iodinated polystrene[342]. The photocyclodimerization results in the formation of **203**[343]. The intermediate triene **226** has been trapped with the electron-poor eneophiles, acrylonitrile and methyl acrylate (equation 134).

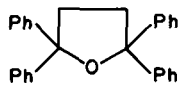


(134)

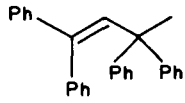
Cation radicals of hexamethoxydiphenyl amine, tetraphenyl-*p*-phenylenediamine or of phenothiazine initiate photochemical reaction of 1,1-diarylethylenes (Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$)[344]. As well as the cyclodimer **228**, the dimers **229** and **230** are formed. The mechanism involves initial photoinduced electron transfer from the ethene to the irradiated cation radical. The dicyanoanthracene photosensitized electron transfer reactions of 1,1-diarylethylenes have been comprehensively investigated by Mattes and Farid[345]. The wide range of products are derived from the cation radical of the β,β-dimer of 1,1-diarylethylene **231** and include the (2 + 2) dimer **232** and cyclodimer **203** and its dehydro-derivative.



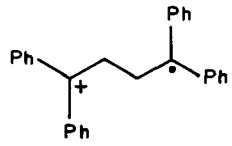
(228)



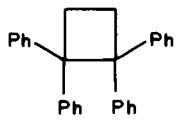
(229)



(230)



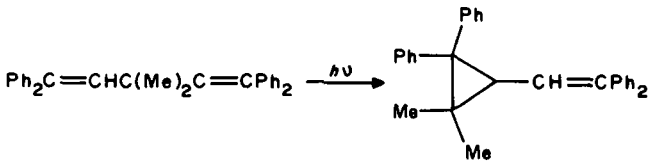
(231)



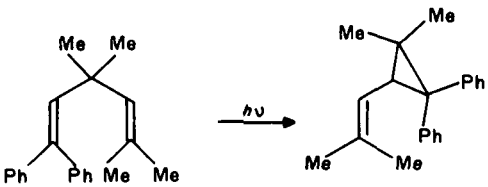
(232)

3. Rearrangement

a. Di-π-methane. 1,1,3,3-Tetraphenylpropene undergoes photochemical di-π-methane rearrangement[346] through the singlet excited state to 1,1,2,3-tetraphenylcyclopropane[347]. This rearrangement has been studied using 3-vinyl homologues of 1,1-diphenyl-1-propene, such as 3,3-dimethyl-1,1,5,5-tetraphenyl-1,4-pentadiene[346] (equation 135). When the diene is unsymmetrical, the reaction is regiospecific[348] (equation 136). The mechanism may be described by a diradical pathway[346,349].

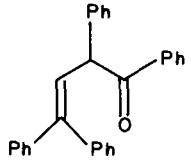


(135)

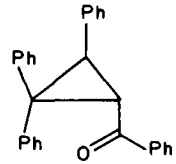


(136)

An example of the corresponding oxa-di-π-methane rearrangement has been reported wherein a 1,2-shift of the benzoyl group occurs. Direct irradiation of the 1,1-diphenyl-4-ketone **233** leads to the rearranged product **234** along with numerous products formed by α-cleavage and recombination. Labelled derivatives have been employed to establish the skeletal changes involved[350].

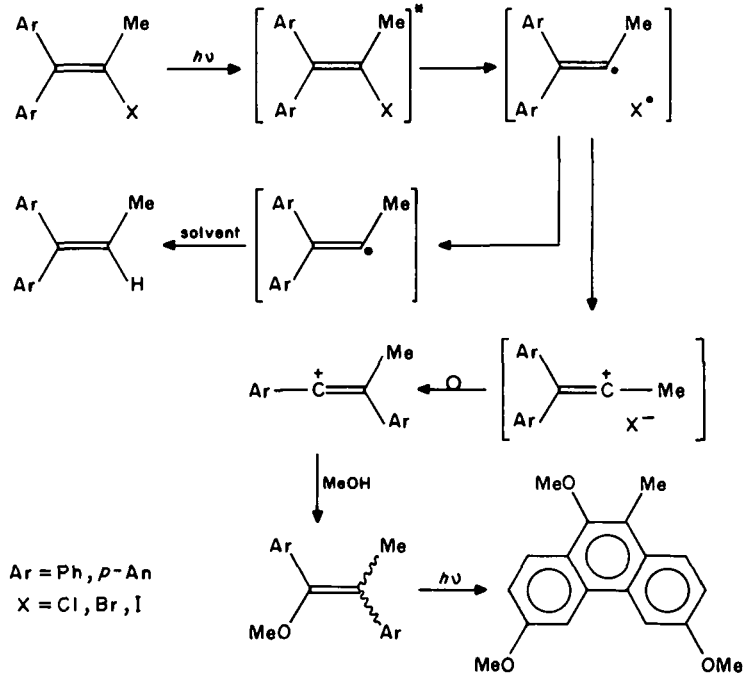


(233)



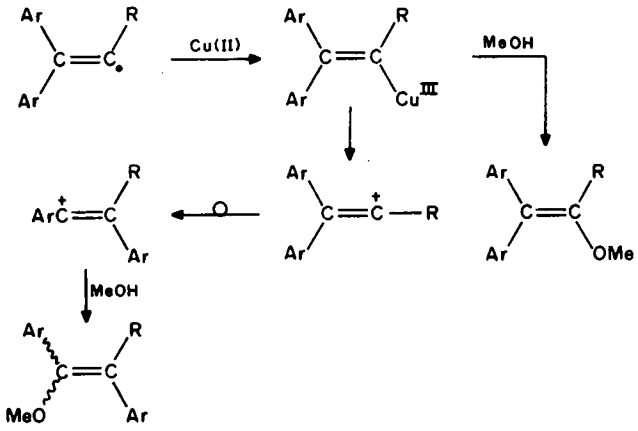
(234)

b. 1,1-Diaryl-2-haloethylenes. It has been of interest to compare and contrast the behaviour of photochemically produced carbocations with those solvolytically produced. Kitamura, Kobayashi and Taniguchi[351] have shown that β,β-diarylvinyl bromides undergo photochemical homolytic cleavage with subsequent electron transfer. The vinyl cations rearrange to the more stable ions as in solvolytically generated ions (equation 137). This group together with those of Lee and of Rappoport have combined to investigate the degenerate photoinduced β-aryl rearrangement of triphenyl, tri-*p*-tolyl and tri-*p*-anisylvinyl bromide in methanol and trifluorethanol[352]. They have largely confirmed their earlier findings, namely that photochemically and thermally generated ions follow semi-



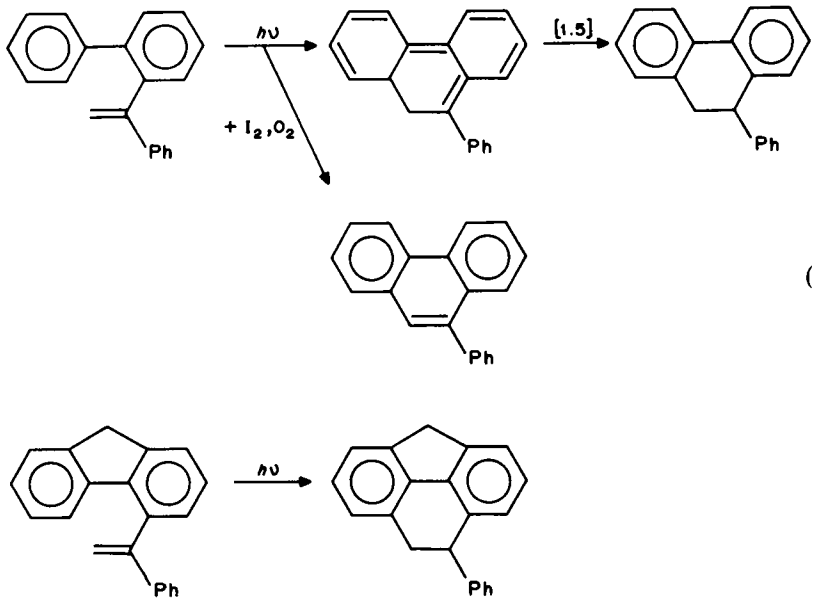
(137)

quantitatively the same pattern. Subsequently, Kitamura and coworkers[353] observed that Cu(II) salts dramatically improve the ratio of 1,1-diarylvinyl cation relative to vinyl radical produced photo-products. This novel effect is attributed to trapping of the free vinyl radical by the Cu(II) ions and their oxidation by the cupric salt (equation 138).



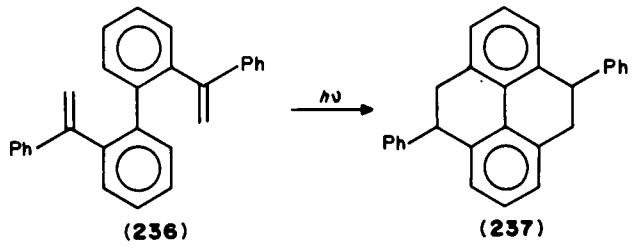
(138)

c. Electrocyclization. 1-Phenyl-1-(*o*-phenyl)phenylethylene and the fluorene derivative **235** undergo photocyclization to the corresponding dihydrophenanthrenes[354]. In the presence of I_2 and O_2 the corresponding aromatic product is formed (equation 139). The bis-vinylbiphenyl **236** undergoes photochemical cyclization to the tetrahydropyrene



(139)

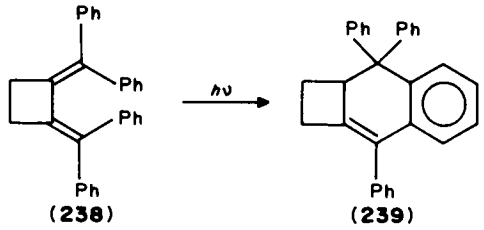
(235)



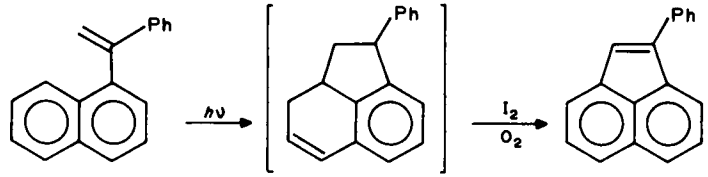
(236) (237) (140)

237[355] (equation 140). Similarly, the bis-benzhydrylidene cyclobutane **238** when irradiated at 365 nm rearranges to the tetrahydrocyclobuta[*b*]naphthalene **239**[356] (equation 141).

A rare example of five-membered ring formation has been observed in the photolysis of 1-naphthyl-1-phenylethylene **240** in the presence of O_2 and I_2 or Cu(II) bromide (equation 142). A number of related cyclizations have been reported[354,357].

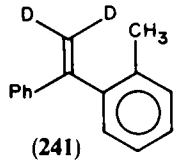


(238) (239) (141)

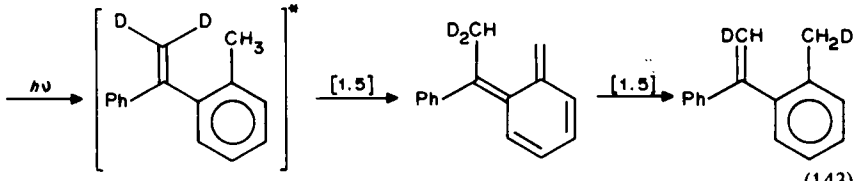


(240) (142)

d. Sigmatropic. The apparent similarity between the photoreactivity of 1,1-diphenylethylene[358] and photoenolization of benzophenone prompted this study[359]. Since phenyl tolyl ketone had been shown to undergo photoenolization, the ethylene **241** has been investigated and is found to undergo scrambling (equation 143).



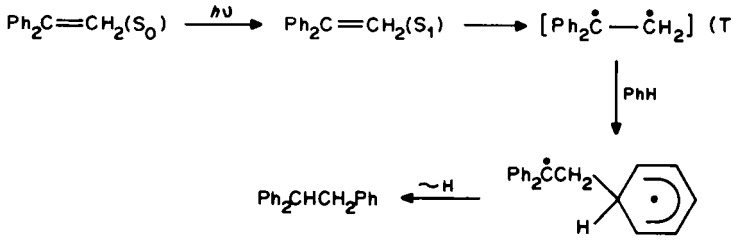
(241)



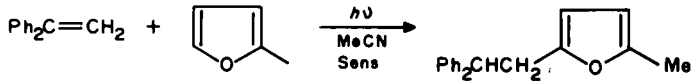
(143)

4. Photoarylation

Kawanisi and Matsunaga[360] have found that 1,1-diphenylethylene in the photoexcited triplet state may be considered a resonance stabilized diradical and reacts with benzene in an overall 28% conversion (equation 144). Mizuno and coworkers[361] have reported the novel photocrossed addition between diphenylethylene and the five-membered heteroaromatics, furans and 1-methylpyrrole, in the presence of 1-cyanonaphthalene in high yield (equation 145). The photoaddition occurs only if the reactants have similar oxidation potentials. No photoreaction occurs in non-polar solvents such as benzene or cyclohexane even in the presence of α-cyanonaphthalene sensitizer.



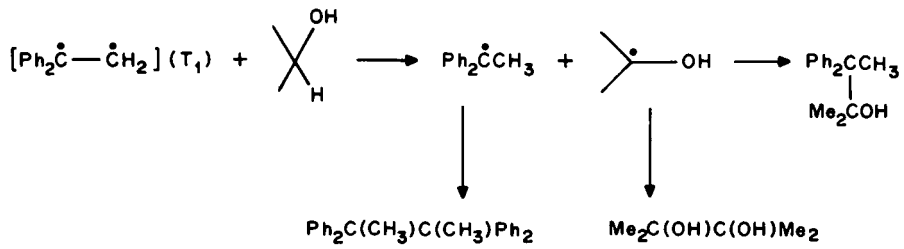
(144)



(145)

5. Photoreduction

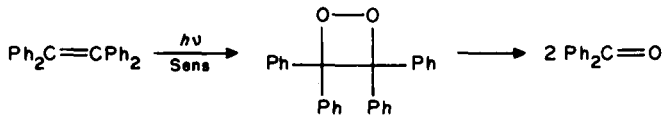
The apparent analogy between the chemistry of photoexcited diphenylethylene and benzophenone encouraged Rosenburg and Servé[362] to investigate the photoreduction of diphenylethylene in isopropanol. The mechanism of formation of the products is explained (equation 146).



(146)

6. Photooxidation

a. With cleavage. Tetraphenylethylene undergoes 9,10-dicyanoanthracene-sensitized photocleavage, probably through the dioxetane **242**[363] (equation 147). Similarly, 1,1-diphenylethylene[364,365] and a range of homologues[365] undergo cleavage in oxygen-saturated acetonitrile in the presence of the 9,10-dicyanoanthracene. The oxidation potentials and free-energy changes for the reaction have led to the conclusion that an



(147)

(242)

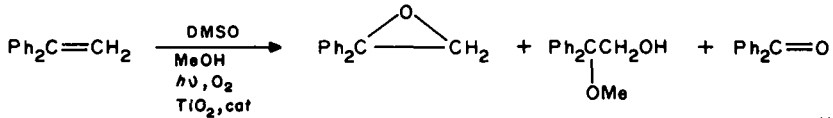
electron transfer mechanism is involved. Semiconductor photocatalyzed olefin to carbonyl oxidative cleavage has also been investigated[366]. Photooxidation of 1,1-diphenylethylene on TiO_2 in air-saturated MeCN has led to high yields of benzophenone (84%), together with low yields of 1,1-diphenylethylene oxide (14%) and 2,2-diphenylacetaldehyde (2%). The reaction is a near diffusion controlled electron transfer from the absorbed olefin to the photogenerated hole at the surface of the TiO_2 powder[367]. This is followed by a slower electron transfer equilibration of the competing olefin with the photogenerated radical cation. It is suggested that the method offers the synthetic chemist an advantageous route since the TiO_2 is cheap, may be filtered off, and organic solvents are found to be preferable[367].

b. Without cleavage. A range of 1,1-diarylalkenes, ArPhC=CHR (Ar = Ph, *p*-MeC_6H_4; R = H, Me) have been irradiated in the presence of Cu(II) and Fe(III) salts in methanol[368]. The dimethoxylated products **243** and the β,β-dimers **244** are produced. The formation of these products is attributed to the participation of olefin-derived cation radicals by electron transfer to the metal cation.

$ArPhC(OMe)CH_2OMe$ $[ArPhC(OMe)CH_2]_2$

(243) **(244)**

Kanno and coworkers[369] have found that the semi-conductors, TiO_2 or CdS, suspended in the reactant, catalyze the photooxidation of diphenylethylene. Reaction is initiated by electron transfer from the alkene to the photoexcited semiconductor. The overall reaction is outlined in equation 148. Electron-deficient photosensitizers 9,10-



(148)

$Ph_2C(OH)CH_2OMe$ Ph_2CHCH_2OMe

(245) **(246)**

dicyanoanthracene or 9-cyanoanthracene sensitize the photooxidation of 1,1-diphenylethylene[364]. The hydroxy ether **245** is formed in oxygen-saturated methanol and the ether **246** in nitrogen-saturated methanol. The ether **246** is also formed when phenanthrene is the photosensitizer[370]. Kinetic studies suggest that a key intermediate is the π-complex between 1,1-diphenylethylene and the cation radical of phenanthrene.

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The Chemistry of Double-bonded Functional Groups
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CHAPTER **16**

Fulvenes

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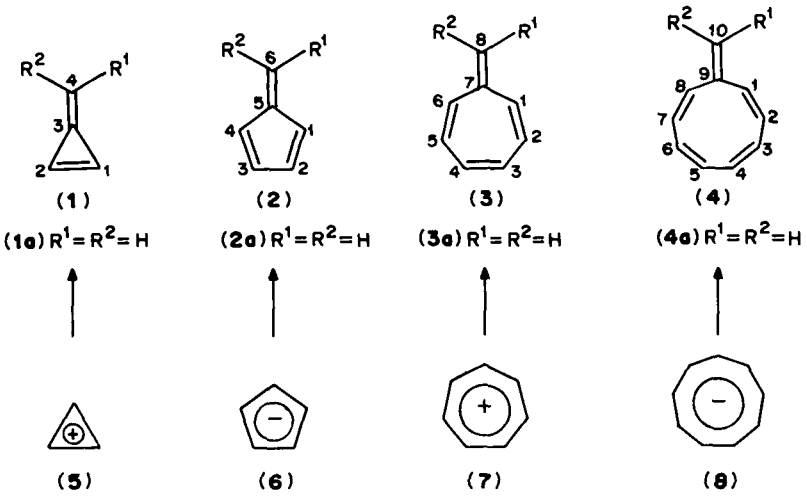
I. INTRODUCTION

Fulvenes are cyclic cross-conjugated molecules with an odd number of C atoms in the ring. According to the size of the ring skeleton they are named triafulvenes (**1**), pentafulvenes (**2**), heptafulvenes (**3**) and nonafulvenes (**4**). Although recent investigations clearly demonstrate that the parent compounds are characterized by typically olefinic properties, fulvenes have always intrigued organic chemists and theoreticians by virtue of their colour and their structural features.

Pentafulvenes (**2**) were the first fulvenes to be discovered in 1900[1], and the yellow colour of these compounds is responsible for the name of the whole family (lat. fulvus = yellow). After the spectacular synthesis of heptafulvene (**3**) in 1955[2] and the first syntheses of substituted triafulvenes (**1**) in 1964/65[3–6], it became usual to add the ring size as prefix to the name. The first simple member of the class of nonafulvenes (**4**) was isolated in 1969[7] (see Scheme 1).

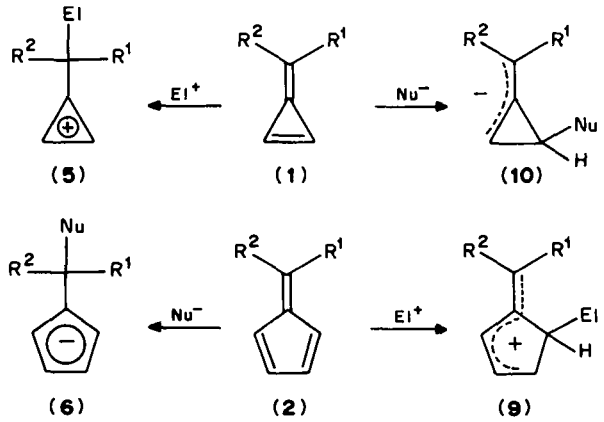
Compared with cyclic aromatic and open-chain olefinic molecules, some typical features of fulvenes should be mentioned. First, fulvenes **1–4** are easily available from appropriate 'Hückel-type' cations **5** and **7** and anions **6** and **8**. Obviously, in principle, similar sequences may be applied for triafulvenes (**1**) and heptafulvenes (**3**), starting with



SCHEME 1

cations **5** and **7**. On the other hand, successful procedures for pentafulvenes (**6** → **2**) may have a good chance for nonafulvenes as well (**8** → **4**).

Then it is remarkable that fulvenes are dipolar molecules. Although the dipole moment is small for the parent molecules **1** ($\mu = 1.90 D$[8]), **2** (0.44 D[9]) and **3** (0.48 D[10]) according to microwave results, it may be considerably larger for triafulvenes (**1**) and heptafulvenes (**3**) with electron-accepting substituents R^1 and R^2, or for pentafulvenes (**2**) with electron-donating substituents (see Scheme 1).

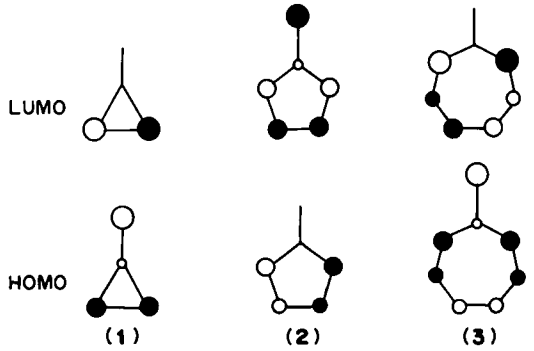


SCHEME 2

Most fulvenes easily react with electrophiles *and* nucleophiles. Looking at the energy of the hereby formed reactive intermediates, and considering Hammond's postulate, the reaction of pentafulvenes with nucleophiles (to give substituted cyclopentadienides) and that of triafulvenes with electrophiles (to give substituted cyclopropenylium salts) are easily understood. It is important to note, however, that electrophilic attack at C-1/C-4 of

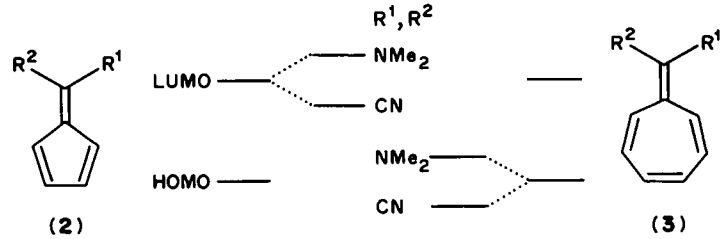
pentafulvenes (**2**) may give delocalized cations **9**, while nucleophilic attack at C-1/C-2 of triafulvenes (**1**) may give allylic anions of type **10**. So reactions of type **1** → **10** and **2** → **9** are possible too, especially if **9** and **10** are stabilized by appropriate substituents R^1 and R^2.

Even more insight into the reactive behaviour of fulvenes comes from frontier-orbital considerations[11,12]. Compared with benzene, its isomer pentafulvene (**2**) has a high-energy HOMO (*h*ighest *o*ccupied *m*olecular *o*rbital) and a comparably low-energy LUMO (*l*owest *u*noccupied MO). This accounts for the 'surprising' long-wavelength UV absorption of fulvenes, being responsible for the colour of these compounds. Furthermore, one of the frontier orbitals of every fulvene has a nodal plane through the exocyclic double bond, so that the energy of that MO remains nearly uninfluenced by exocyclic substituents R^1 and R^2. This applies to the HOMOs of **2** and planar **4** as well as the LUMOs of **1** and **3** (Scheme 3).



SCHEME 3. Hückel coefficients and frontier orbitals of fulvenes **1**, **2** and **3**

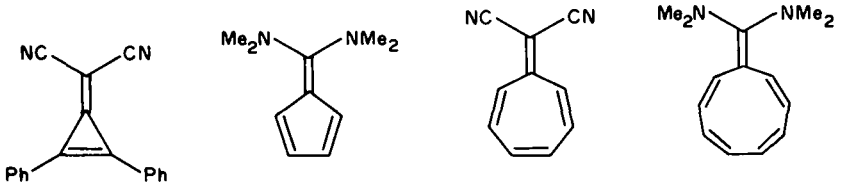
Considering the fact that − M substituents (like CN groups) are generally lowering the energy of frontier MOs while + M substituents (like NMe_2 groups) are raising the energy of frontier orbitals[11], the consequences for fulvenes are the following: In pentafulvenes (**2**) [and planar nonafulvenes (**4**)], NMe_2 groups are raising the energy of the LUMO, thus increasing the energy gap between HOMO and LUMO. On the other hand, CN groups are expected to lower the energy of the LUMO, to decrease the energy gap and to induce a bathochromic shift of the longest-wavelength UV absorption. In heptafulvenes (**3**) and triafulvenes (**1**) CN groups are lowering the energy of the HOMO, thus increasing the energy gap. On the other hand, NMe_2 groups are expected to raise the energy of the HOMO, to decrease the energy gap and to induce a bathochromic shift of the UV absorption (see Scheme 4).



SCHEME 4. Influence of exocyclic substituents on the energy of frontier orbitals (schematic)

Looking at the high-energy HOMO and the low-energy LUMO of parent fulvenes compared with aromatic systems, it is qualitatively understood that the thermal stability of unsubstituted fulvenes is very low: While the parent triafulvene (**1a**) and heptafulvene (**3a**) polymerize very easily at − 50 °C and 0 °C, respectively, pentafulvene (**2a**) undergoes an easy Diels–Alder dimerization reaction. On the other hand, the stability of nonafulvene (**4a**) is dramatically reduced by its easy valence isomerization to dihydro-benzofulvene.

Furthermore, since − M substituents like cyano groups are increasing the energy gap between HOMO and LUMO of triafulvene (**1**) and heptafulvene (**3**) while + M groups like dialkylamino groups have the same effect for pentafulvenes (**2**) and nonafulvenes (**4**), electronic substituent effects on thermal stability may be rationalized on a frontier-orbital basis. In fact, 4,4-dicyanotriafulvenes or 8,8-dicyanoheptafulvene are thermally much more stable than the parent triafulvene **1a** or parent heptafulvene **3a**, and the same is true for 6,6-dimethylamino-pentafulvene and 10,10-bis(dimethylamino)nonafulvene compared with the parent fulvenes **2a** and **4a** (see Scheme 5).



SCHEME 5. Fulvenes with increased thermal stability

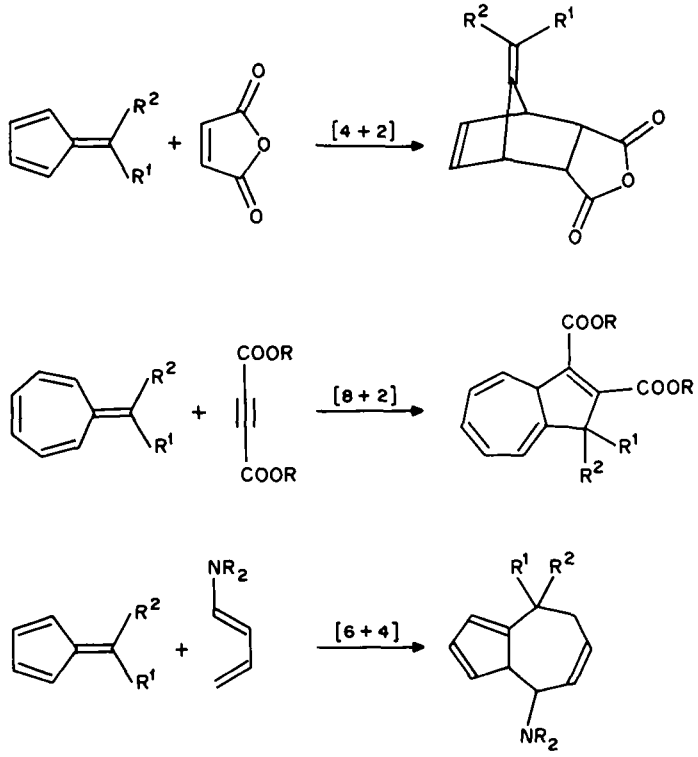
According to frontier-orbital considerations, *nucleophiles* (with a high-energy HOMO) are expected to have a strong binding interaction with the LUMO of fulvenes. Looking at the LUMO of pentafulvene (**2**) (see Scheme 3), it turns out that C-6 has the largest Hückel coefficient. So we may predict that nucleophiles will attack C-6 of pentafulvenes (and C-10 of planar nonafulvenes). If any reactions with triafulvenes (**1**) or heptafulvenes (**3**) take place, then, according to Scheme 3, it will be with the ring C atoms.

On the other hand, *electrophiles* (being characterized by a low-energy LUMO) are expected to have a strong binding interaction with the HOMO of fulvenes. According to the Hückel coefficients, they are predicted to attack the exocyclic C atoms of triafulvenes and heptafulvenes, while pentafulvenes are expected to react predominantly at C-1/C-4.

Frontier-orbital considerations give very useful predictions concerning *cycloadditions* as well. Since dienophiles with a low-energy LUMO (like tetracyano-ethylene or maleic anhydride) are expected to have strong binding interactions with the *HOMO* of fulvenes, the preferred route of pentafulvenes should be a [4 + 2]-cycloaddition (see Scheme 6). Because the Hückel coefficients at C-8/C-1 of heptafulvene are large, [8 + 2]-cycloadditions should be favoured in this case. [6 + 4]-cycloadditions of pentafulvenes are expected if the LUMO of **2** becomes important, e.g. in the reaction with 1-dialkyl-aminobutadiene, which is characterized by a high-energy HOMO.

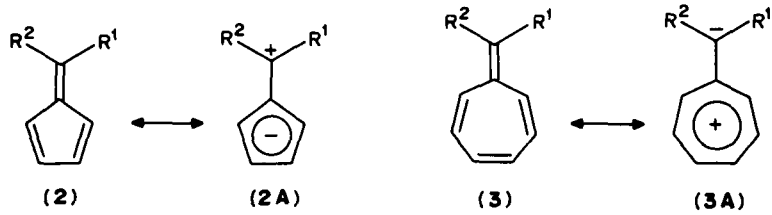
Hence in general we have two classes of fulvenes with respect to their synthesis, reactivity and spectroscopic properties (and especially substituent effects on spectra) as well. Thus, triafulvenes (**1**), heptafulvenes (**3**), hendecafulvenes,... with 3-, 7-, 11-membered rings and a total of 4, 8, 12,... π electrons belong to one class, and pentafulvenes (**2**), nonafulvenes (**4**), tridecafulvenes,... with 5-, 9-, 13-membered rings and a total of 6, 10, 14,... π electrons to another.

Based on their dipole moments as well as on their reactivity patterns, fulvenes **1**–**4** could occupy an intermediate position between open-chain olefinic and aromatic compounds[14]. Exocyclic substituents R^1, R^2 might increase the dipolar character and favour 'aromatic



SCHEME 6. Typical cycloaddition reactions of fulvenes[2,12,13]

substitution' over 'olefinic addition', thus increasing the aromatic character of fulvenes, as indicated in the VB notation of Scheme 7. Prominent examples are 6-dimethylaminopentafulvene (**2**, $R^1 = NMe_2$, $R^2 = H$) and 8, 8-dicyanoheptafulvene (**3**, $R^1 = R^2 = CN$)[14]. This means that aromaticity of fulvenes has to be discussed, especially in relation to prominent X-ray, MW and NMR data.



SCHEME 7

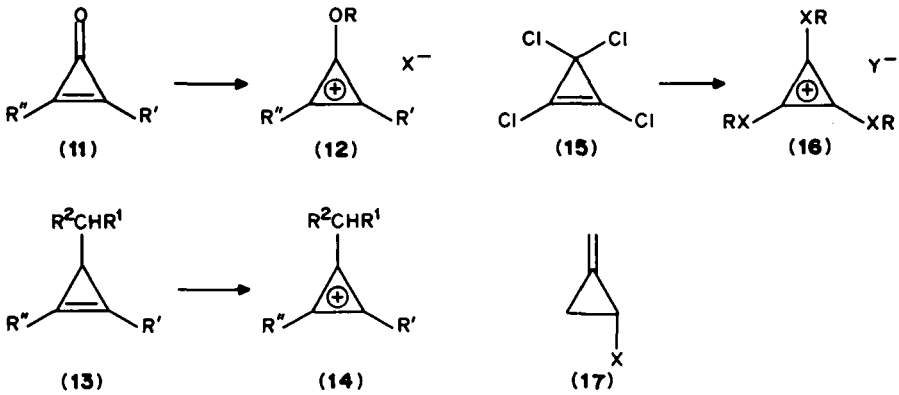
This review will deal with the synthesis, reactions and spectroscopic properties of carbocyclic fulvenes **1–4** and will be restricted to non-annelated compounds (compounds not fused to benzenoid rings). It will not include metalorganic complexes of fulvenes, and the synthesis of metallocenes (especially of ferrocenes) from fulvenes will only be briefly mentioned. The numbering system used here is that of *Chemical Abstracts* (see Scheme 1).

Review articles of the same topic have been published earlier[15-18], Yates' contribution[17] being very complete and instructive concerning non-annelated pentafulvenes. Very recently, fulvenes have been included in a Houben-Weyl volume dealing with carbocyclic π-electron systems[19-22]. Because of that, only a relatively brief survey of the synthetic sequences will be given, especially as far as pentafulvenes are concerned.

II. SYNTHESIS OF FULVENES

A. Synthesis of Triafulvenes

It follows from the introduction that synthetic sequences for triafulvenes (**1**) will be related to those for heptafulvenes (**3**), mainly because in both cases the energy of cyclopropenylium cations **5** and tropylium cations **7** is comparably low. This makes these cations **5** and **7**, and substituted cations, ideal intermediates for syntheses. In fact, most classical procedures for triafulvenes (**1**) start with compounds from which substituted cyclopropenylium cations are easily generated. These are cyclopropenones **11** which are easily O-alkylated or acylated to give alkoxy- and acyloxy-cyclopropenylium salts **12**; or substituted cyclopropenes **13** which may be transformed into cyclopropenylium salts **14** by hydride abstraction (see Scheme 8).



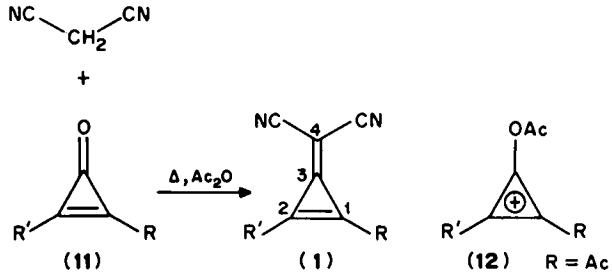
SCHEME 8

For 1,2-diheterosubstituted triafulvenes, tetrachlorocyclopropene (**15**) is an ideal starting material for triheterosubstituted cyclopropenylium salts **16**. Recently, different synthetic methodologies have been developed for the synthesis of parent triafulvene (**1a**), key intermediates being methylenecyclopropanes **17** bearing a potential leaving group.

1. From cyclopropenones

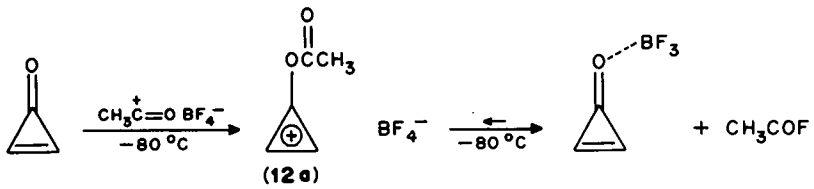
Highly substituted and electronically stabilized triafulvenes of type **1** are formed by condensation of substituted cyclopropenones **11** (R, R' = alkyl or aryl) with CH-acidic methylenes like malononitrile in the presence of acetic anhydride (see Scheme 9). In some cases β alanine is added as a catalyst. By this method, the first stable triafulvenes were isolated[3,4,23] using high reaction temperatures and in most cases with moderate yields. Therefore only highly substituted and/or electronically stabilized triafulvenes are available in this way. Bulky substituents favour nucleophilic attack at the carbonyl group of the cyclopropenone[24]. It is mechanistically resonable to assume that substituted

acetoxycyclopropenylium salts **12** are formed as intermediates, being attacked by the deprotonated nucleophile.



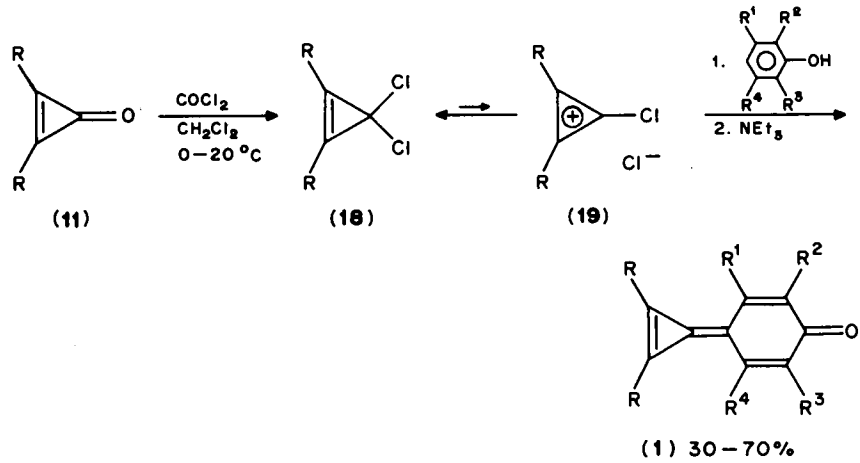
SCHEME 9

A low-temperature version would be the acylation of cyclopropenones with the easily available acetyl fluoroborate[25]. This has been tried with the parent cyclopropenone[26] and fails due to the instability of **12a** even at $-80\,^{\circ}C$[27] (see Scheme 10).



SCHEME 10

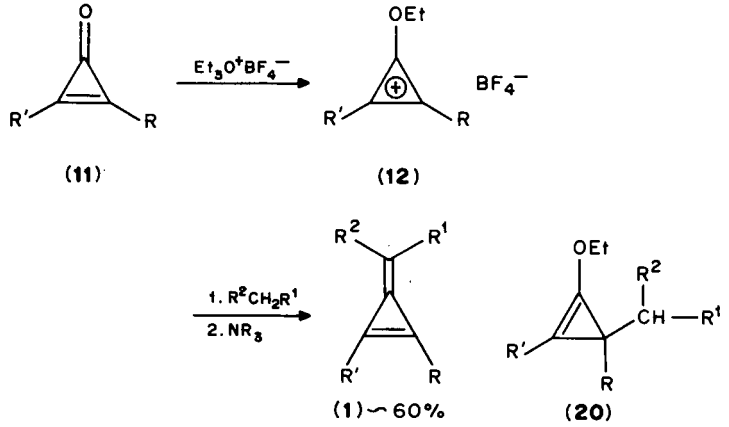
An interesting modification is the acylation of cyclopropenones with phosgene to give 3,3-dichlorocyclopropenes, which react with nucleophilic phenols under reflux[28–30]. Once again cyclopropenylium salts **19** may be the reactive intermediates (Scheme 11).



SCHEME 11

In summary, acylation of cyclopropenones followed by reaction with a nucleophile is limited so far to the synthesis of highly substituted triafulvenes. Some prominent examples are given in Table 1.

A second widely applied sequence consists in an alkylation of substituted cyclopropenones, giving alkoxycyclopropenylium salts **12** in good yields[36] (Scheme 12). Provided that cyclopropenones **11** with bulky substituents are applied and reaction conditions are carefully controlled[37], stabilized triafulvenes **1** are isolated by reacting the alkoxycyclopropenylium salt **12** with acidic methylene compounds in the presence of an amine. Otherwise side-products of type **20** are observed which often rearrange under ring opening[37,38]. Although the preparative restrictions are basically the same as in the acylation sequence (Scheme 9), reaction temperatures are considerably lower and the yields are higher. Furthermore, intermediates **12** may often be isolated or spectroscopically observed. Some typical examples are listed in Table 2. Substituted pentatriafulvalenes have been prepared by the same sequence[36,41–43].



SCHEME 12

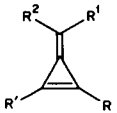
Although tried very early[5], the Wittig reaction is of limited use for the synthesis of triafulvenes[44]. This is mainly due to the fact that strong nucleophiles react with cyclopropenones preferentially through Michael addition[24], very often followed by rearrangement of the cyclopropene intermediates. So instead of the desired 4-benzoyl-1,2-diphenyltriafulvene, mainly pyrone **21** (R″ = Ph) is isolated (Scheme 13). The highest triafulvene yields are obtained at room temperature[44]. Similarly, the attempted synthesis of 4-cyano-4-phenyl-1,2-diphenyltriafulvene failed as well[45].

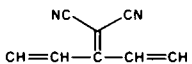
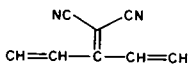
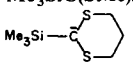
It has been shown very recently[46] that Peterson olefination of methylated cyclopropenones **12** is an interesting synthetic alternative for triafulvenes, although nucleophilic attack at C-1/C-2 or even at the methyl group may take place too. In two cases products of type **20** have been isolated besides the desired triafulvenes **1** (Table 1[46]), but they may be rearranged to triafulvenes (Scheme 13).

2. *From cyclopropenes through cyclopropenylium salts*

Substituted cyclopropenes **13** without a leaving group X may be used for the synthesis of triafulvenes as well. They are easily prepared by various methods, e.g. by carbene additions to olefins or by reaction of cyclopropenylium salts with nucleophiles, although sometimes

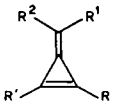
TABLE 1. Selected triafulvenes prepared by acylation of cyclopropenones as well as by the Wittig reaction and Peterson olefination



R^1	R^2	R	R′	Nucleophile	Conditions/ remarks	Yield (%)	Ref.
CN	CN	Ph	Ph	$CH_2(CN)_2$	Ac_2O, Δ	5	3
CN	CN	Ph	Ph	$CH_2(CN)_2$	$Ac_2O(BF_3)$, Δ	23	23
CN	COOEt	Ph	Ph	$CNCH_2COOEt$	Ac_2O(β-Alanin), Δ	15	31
CN	$COCH_2COOH$	Ph	Ph	$CNCH_2COOH$	Ac_2O, Δ	28.5	32
CN	CN	Pr	Pr	$CH_2(CN)_2$	Ac_2O, Δ	18	4
CN	CN	*t*-Bu	*t*-Bu	$CH_2(CN)_2$	Ac_2O (β-Alanin), Δ	37	33
CN	COOEt	*t*-Bu	*t*-Bu	$NCCH_2COOEt$	Ac_2O(β-Alanin), Δ	42	33
CN	CN	Pr	Me	$CH_2(CN)_2$	Ac_2O(β-Alanin), Δ	8	30
CN	$COOCH_3$	Pr	Me	$NCCH_2COOMe$	Ac_2O, E/Z-mixture	6	30
		Ph	Ph	$PhCH(CN)_2$	Ac_2O, Δ	72	34, 35[a]
		*p*-An	*p*-An	$PhCH(CN)_2$	Ac_2O, Δ	85	35[a]
CO_2Et	H	Ph	Ph	$Ph_3P{=}CHCOOEt$	Wittig	10–20	5
CO_2Me	H	Ph	Ph	$Ph_3P{=}CHCO_2Me$	Wittig	13	35
$SO_2C_6H_5$	$SiMe_3$	Ph	Ph	$(Me_3Si)_2\bar{C}SO_2Ph$	Peterson	70	46
$SO_2C_6H_4CH_3$	SMe	Ph	Ph	$Me_3Si\bar{C}(SMe)SO_2Tol$	Peterson	26	46
$S{-}CH_2CH_2CH_2{-}S$		*t*-Bu	*t*-Bu		Peterson	26	46

[a]For more *o*- and *p*-quinocyclopropenes see Reference 35.

TABLE 2. Selected triafulvenes prepared by nucleophilic addition to alkoxy cyclopropenylium salts[a]



R^1	R^2	R	R′	Yield (%)	Ref.
COMe	COMe	Ph	Ph	80	37
COPh	COMe	Ph	Ph	63	37
COPh	COEt	Ph	Ph	62	37
CONHPh	COMe	Ph	Ph	78	37
CONHPh	COPh	Ph	Ph	79	37
COPh	COH	Ph	Ph	74	37
COOEt	COOEt	Ph	Ph	58	37
COMe	COMe	Ph	H	*b*	39
COMe	COPh	Ph	H	*b*	39
CONHPh	COPh	Ph	H	*b*	39
O O ‖ ‖ $CCH_2C(CH_3)_2CH_2C$		Ph	Ph	22	36
$2,4\text{-}(NO_2)_2C_6H_3$	H	Ph	Ph	2	36
$p\text{-}NO_2C_6H_4$	COOMe	Ph	Ph	49	36
$p\text{-}NO_2C_6H_4$	COPh	Ph	Ph	31	36
COC_6H_5	COMe	$p\text{-}XC_6H_4$	$p\text{-}XC_6H_4$	51–82	40
COC_6H_5	COR	Ph	Me	49–91	40

[a]For more triafulvenes prepared in the same way see especially References 36–40.
[b]No yield has been reported.

in relatively poor yields. The interesting point is that hydride abstraction of allylic hydrogen may be realized with reagents such as triphenylcarbenium tetrafluoroborate to give substituted cyclopropenylium salts **14** whose α hydrogen is easily eliminated by tertiary amines. However, despite their availability, hydride abstraction **13** → **14** very often turns out to be not as easy as in the example of Scheme 14[47]. Some examples are listed in Table 3. The method is of more importance for penta-triafulvalenes[49–52].

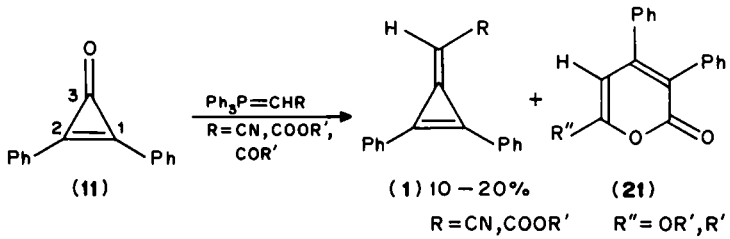
3. *From heterosubstituted cyclopropenylium salts*

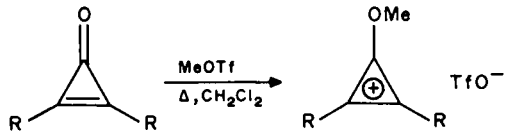
Triheterosubstituted cyclopropenylium salts **16a, b** are available from tetrachlorocyclopropene by treatment with $AgBF_4$ (to give trichlorocyclopropenylium fluoroborate)

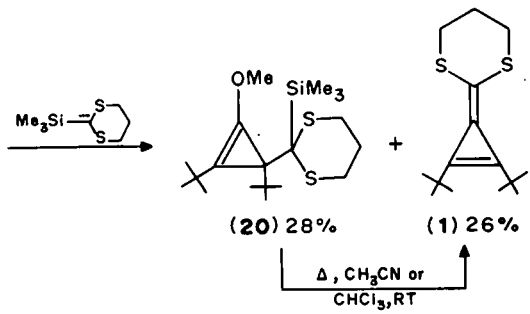
TABLE 3. Selected triafulvenes prepared by hydride abstraction from cyclopropenes

R^1	R^2	R	R′	Reagents	Yield (%)	Ref.
COOEt	H	Ph	Ph	$Ph_3C^+BF_4^-/NaHCO_3 + H_2O$	75	6
Ph	Ph	Ph	Ph	$Ph_3C^+BF_4^-/NEt_3$	95	47
	H	Ph	Ph	$Ph_3C^+ClO_4^-$ in CH_3CN	*a*	48

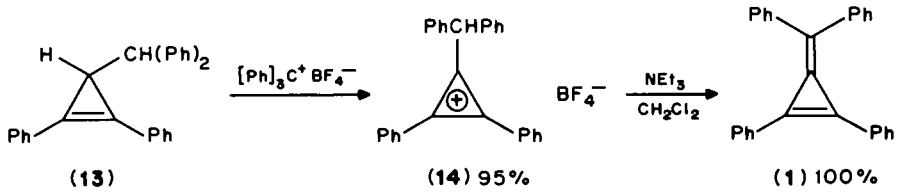
[a]No yield has been reported.





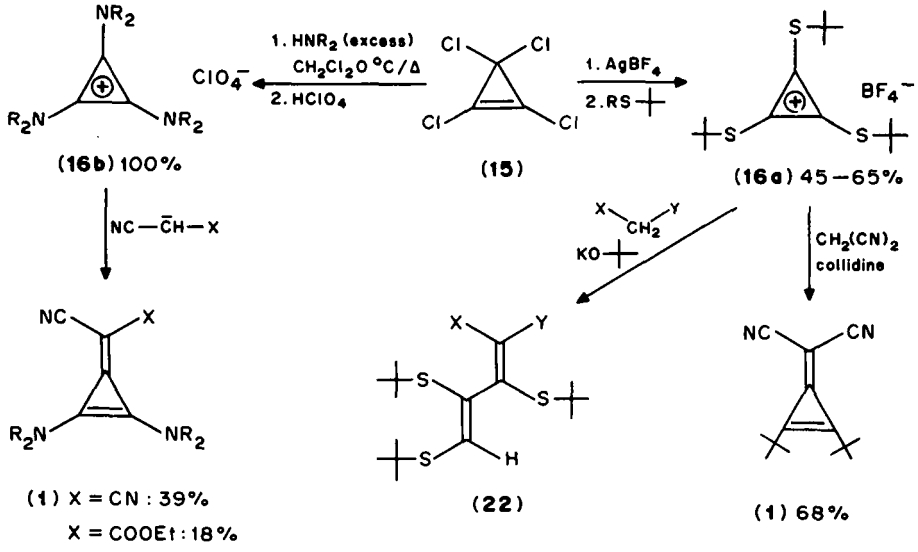


SCHEME 13



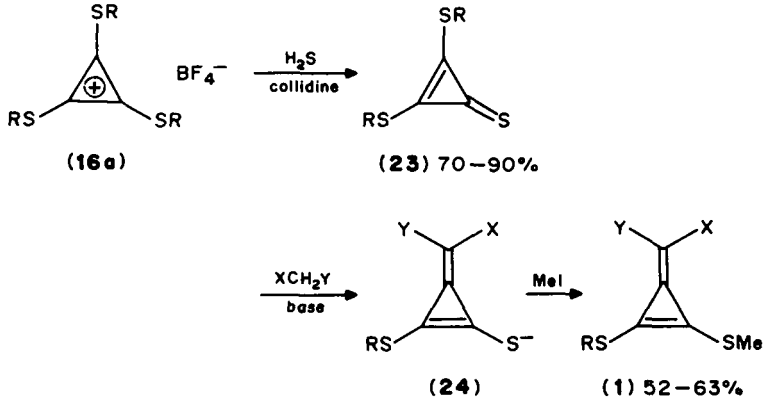
SCHEME 14

followed by chloride extrusion realized by an excess of nucleophiles like R_2NH or RSH[53–55] (see Scheme 15). The following addition–elimination sequences **16a, b** → **1** need carefully controlled conditions since otherwise rearrangements under ring opening may occur. So if **16a** is reacted with malononitrile in the presence of potassium-*t*-butoxide, then substituted butadienes **22** are isolated[54].



SCHEME 15

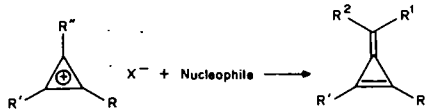
The undesired rearrangement **16a** → **22** may be avoided if dialkylthiocyclopropene **23** is prepared first (see Scheme 16). Now the envisaged Michael addition–elimination sequence (**23** → **24**) followed by alkylation (**24** → **1**) gives electronically stabilized triafulvenes of type **1** with good yields[54]. Sequences similar to the reaction **16** → **1** or **23** → **1** have been thoroughly studied in view of the synthesis of stabilized penta-triafulvalenes[55,56].

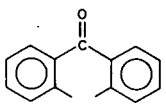
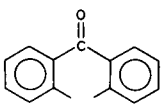
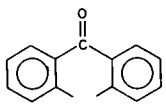


SCHEME 16

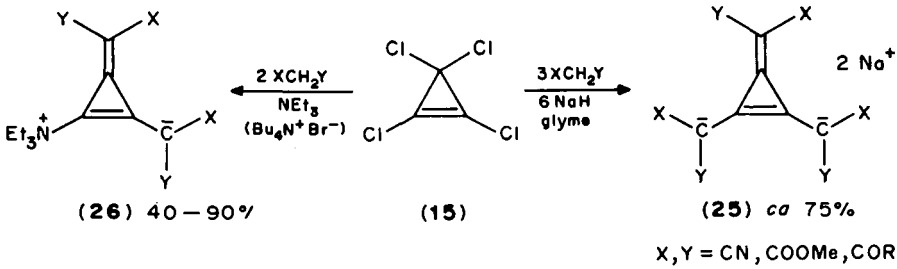
Finally, tetrachlorocyclopropene has been used as starting material for the synthesis of highly delocalized and electronically stabilized intensively coloured triafulvene-bis(carbanions) **25** and zwitterions **26**[57,58] (see Scheme 17; Table 4).

TABLE 4. Selected triafulvenes prepared from heterosubstituted cyclopropenylium salts



R^1	R^2	R	R′	R″	X	Nucleophile (base)	Yield (%)	Ref.
CN	CN	Pip[a]	Pip	Pip	ClO_4	$CH_2(CN)_2$	39	53
CN	COOEt	Pip[a]	Pip	Pip	ClO_4	$CNCH_2COOEt$	18	53
H	H	$N(i\text{-}Pr)_2$	$N(i\text{-}Pr)_2$	Me	ClO_4	(BuLi)	75	53
CN	CN	SBu-*t*	SBu-*t*	SBu-*t*	BF_4	$NCCH_2CN$(collidine)	68	54
COOMe	COOMe[b]	SR	SR′	SR″	ClO_4	$MeOOCCH_2COOMe$	52	54
CN	COOMe[b]	SR	SR′	SR″	ClO_4	$NCCH_2COOMe$	63	54
CN	CN[b]	SR	SR′	SR″	ClO_4	$NCCH_2CN$	59	54
		Ph	Ph	Cl	Cl[c]	9-anthrone	88	28,29
		Pr	Pr	Cl	Cl[c]	9-anthrone	99	29
		Pr	Me	Cl	Cl[c]	9-anthrone	55	30

[a]Pip = piperidine.
[b]Prepared through thione, nucleophilic attack and S-alkylation.
[c]Starting with dichlorocyclopropene.

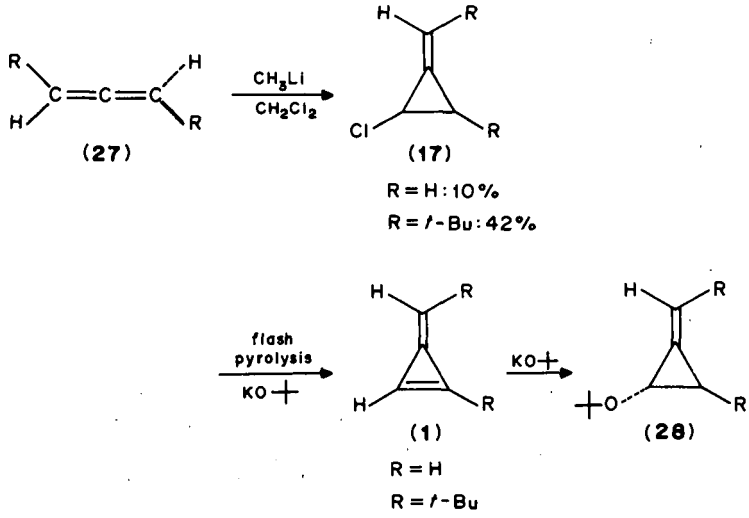


SCHEME 17

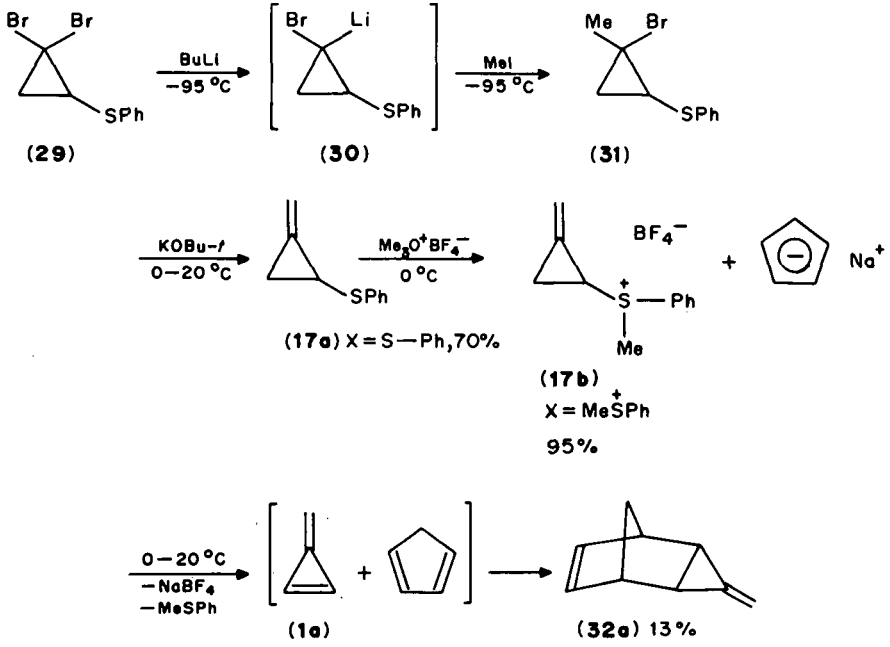
4. By HX elimination from substituted methylenecyclopropanes

Method 1–3 make use of highly substituted cyclopropenones, cyclopropenes and cyclopropenylium salts. Precursors of that type are not suited for the synthesis of the parent triafulvene. For this, two different synthetic approaches have been developed recently, each taking into account the pronounced thermal instability of the parent system.

Potential precursors **17** of the parent triafulvene (**1a**) and of alkyltriafulvenes are available by addition of chlorocarbenes to allenes **27** (Scheme 18) and to haloethylenes, respectively. Early elimination experiments with strong bases resulted in the isolation of 1-alkoxy-2-methylenecyclopropanes **28** and gave first hints that triafulvenes might have been formed as reactive intermediates[59–61]. These hints were substantiated by spectroscopic evidence of 1-halo-2,4-di-*t*-butyltriafulvene[62] as well as of 1,4-di-*t*-butyltriafulvene[63]. Very recently, the parent triafulvene **1a** could be generated by flash-vacuum pyrolysis of 1-chloro- and 1-bromo-2-methylenecyclopropane over chromosorb/potassium *t*-butoxide and trapped in a matrix at low temperature[64,65].



SCHEME 18



SCHEME 19

In an alternative approach to **1a** (see Scheme 19), trifunctional cyclopropanes of type **29**[66] are reacted with BuLi at −95 °C to give lithium derivatives **30**, which are easily methylated (**30** → **31**). After elimination of HBr (**31** → **17a**), the phenylthio substituent is transformed into a leaving group (**17a** → **17b**). Elimination of the leaving group with cyclopentadienide gives **1a** and cyclopentadiene in close proximity to each other and allows trapping of **1a** as a [4 + 2]-cycloaddition product **32**[67].

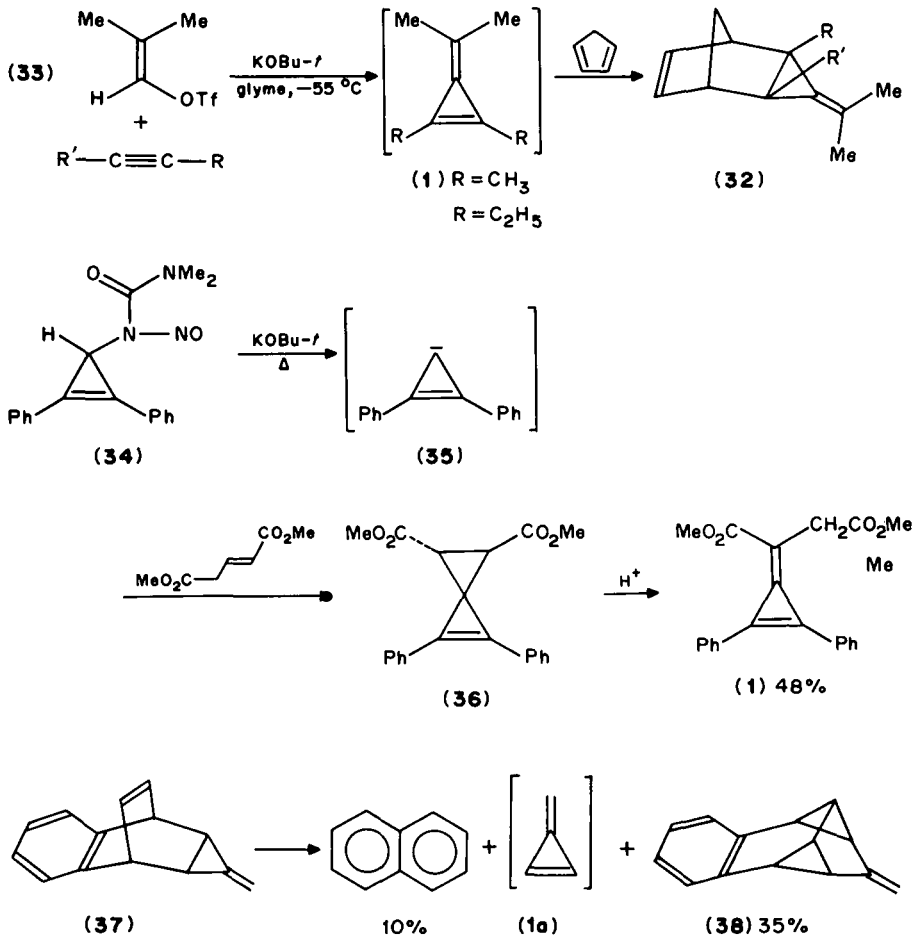
5. *Miscellaneous*

The following attractive triafulvene syntheses have sporadically been applied without obtaining the broad scope of methods 1–3 (Scheme 20):

(a) The first electronically *not* stabilized triafulvenes **1** (R = Me) and **1** (R = Et) have been generated by treatment of a mixture of triflate **33** and of dimethyl- or diethyl-acetylene with strong bases at low temperature. Subsequent trapping with cyclopentadiene gave cycloaddition products **32**[68,69]. An attempted generalization of the method failed, because alkylidene carbenes are reacting with potassium *t*-butoxide too[68].

(b) Attempts to trap the cyclopropenyl carbene **35**, generated by thermolysis of **34** in the presence of bases with dimethyl fumarate, resulted in the unexpected formation of triafulvene **1**[70] instead of the expected spiro compound **36** which was isolated later on[71]. Similar reactions have been observed with dimethyl maleate and fumarodinitril[72].

(c) Another general concept for the synthesis of parent triafulvenes and fulvalenes consists in retro-Diels–Alder reactions of precursors like **37** which produce stable aromatic compounds besides unstable fulvenes or fulvalenes. Attractive precursors **37** for that plan, which has been successfully applied to cyclopropenes[73], may be prepared by carbene additions to barrelene or benzobarrelene. Unfortunately, gas-phase pyrolysis of



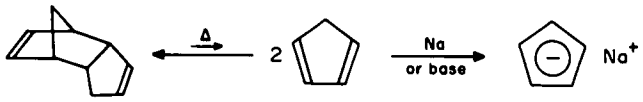
SCHEME 20

precursors **37** is dominated by the rearrangement **37** → **38**, so that only minor amounts of parent **1a** and of naphthalene are observed[74].

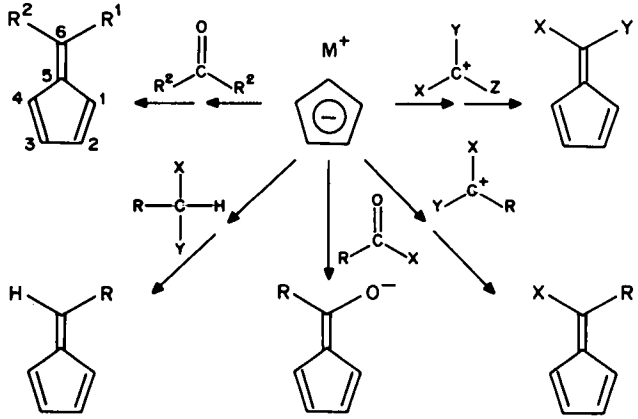
B. Synthesis of Pentafulvenes

Pentafulvenes **2** are the most intensively investigated cross-conjugated molecules. There exist a large number of pentafulvene syntheses, and their reactivity pattern is well known today. A very complete review covering the literature up to 1967 has been published[17] and, very recently, fulvene syntheses have been thoroughly reviewed[20]. Therefore, it will *not* be the goal of this chapter to give a compilation of all the synthetic methods or of all the pentafulvenes prepared so far. It seems to be more important to cover the general synthetic methods of wide scope, to discuss their advantages and limitations and to disclose similarities with fulvenes of different ring size.

Although pentafulvenes may be prepared by cyclization of open-chain systems[20], the main starting material for simple pentafulvenes is cyclopentadiene, which is easily available as cracking product, may be stored as the Diels–Alder dimer from which it is easily generate, and it has a comparatively high acidity (pK_a *ca* 15[75]). Deprotonation is performed either by strong bases or by alkali metals to give cyclopentadienide which is a good nucleophile (see Scheme 21). All important procedures consist in a reaction of cyclopentadienes or cyclopentadienides with various electrophiles (Scheme 22).

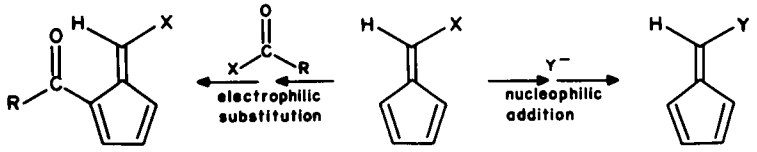


SCHEME 21



SCHEME 22

Furthermore, since pentafulvenes themselves are reactive dipolar and easily polarizable molecules[76], being attacked by electrophiles preferably at C-1 and by nucleophiles preferably at C-6 (see later), pentafulvenes bearing appropriate substituents are easily transformed into substituted pentafulvenes as well (Scheme 23).

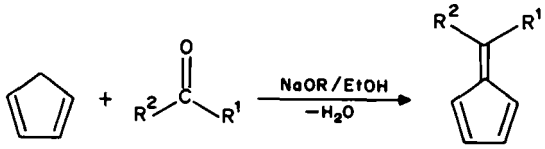


SCHEME 23

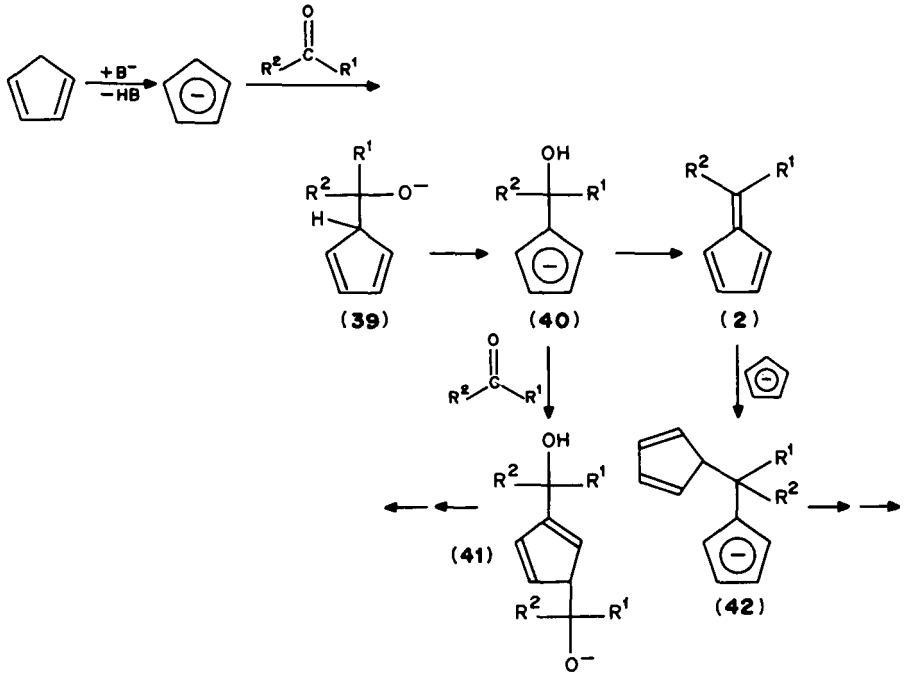
1. Base-induced condensation of cyclopentadienes with aldehydes and ketones

The most widely used pentafulvene synthesis developed by Thiele in 1900[1] consists in condensation of cyclopentadiene with aldehydes or ketones in the presence of NaOEt,

NaOH or KOH in alcohol (Scheme 24). The base has two functions: to deprotonate cyclopentadiene (the pK_a values of alkohols and cyclopentadiene being similar) and then to catalyze dehydration which is realized by deprotonation of substituted cyclopentadienes **39** as well (Scheme 25).



SCHEME 24. Thiele synthesis

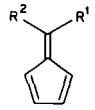


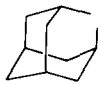
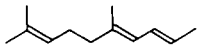
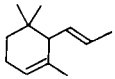
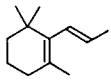
SCHEME 25

By-products are mainly obtained by electrophilic attack of the carbonyl compound at the intermediate cyclopentadienides, e.g. **40** → **41**[77,78], as well as by nucleophilic attack of cyclopentadienides at C-6 of the fulvene, e.g. **2** → **42**, as shown by a GC analysis of by-products of 6-methylfulvene[79] (Scheme 25). Side-reactions become much more important for sterically less shielded 6-monosubstituted pentafulvenes. Accordingly the Thiele synthesis gives good yields (Scheme 26) for aliphatic and alicyclic ketones, medium yields for diaryl ketones or alkyl aryl ketones, but in most cases very low yields for aliphatic aldehydes, and is most widely used for the synthesis of 6, 6-disubstituted pentafulvenes, as shown in Table 5*.

*If conditions are set so that Cannizarro reaction may be prevented and that the fulvene precipitates during formation, then the yields of 6-arylfulvenes may be raised up to 70%[80].

TABLE 5. Selected 6,6-disubstituted pentafulvenes prepared according to Thiele[a]



R^1	R^2	Yield (%)	Ref.
CH_3	CH_3	50–70	89
C_2H_5	CH_3	75	90
hexyl	CH_3	44	91
nonyl	CH_3	73	90
—$(CH_2)_4$—		48	92
—$(CH_2)_5$—		45	92,93
—$(CH_2)_6$—		66	94
$(CH_2)_4$—CH=CH— 	CH_3	41	95
		75	96
	CH_3	38	97
	CH_3	76	97
	CH_3	80	97
		30	98
Ph	C_6H_5	56	99
p-ClC_6H_4	p-ClC_6H_4	43	100
p-BrC_6H_4	p-BrC_6H_4	47	100
p-An	p-An	21	100
p-$NO_2C_6H_4$	p-$NO_2C_6H_4$	25	100

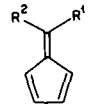
[a]For a more complete compilation see References 17 and 20.

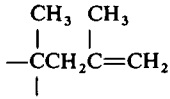
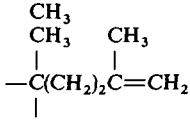
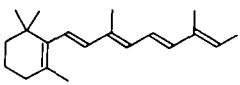
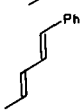
On the other hand, the procedure is not suitable for simple 6-alkyl-[79] and 6-vinylfulvenes[81]. As soon as aldehydes are sterically more shielded, e.g. by substituents in the α-position, or electronically stabilized, then considerably better yields are obtained, because side-reactions of type **40** → **41** and **2** → **42** of Scheme 25 are slowed down. The best examples* are collected in Table 6.

The yields obtained by Thiele synthesis may be dramatically improved, especially for 6-alkylpentafulvenes, if strong bases are replaced by secondary amines. While first

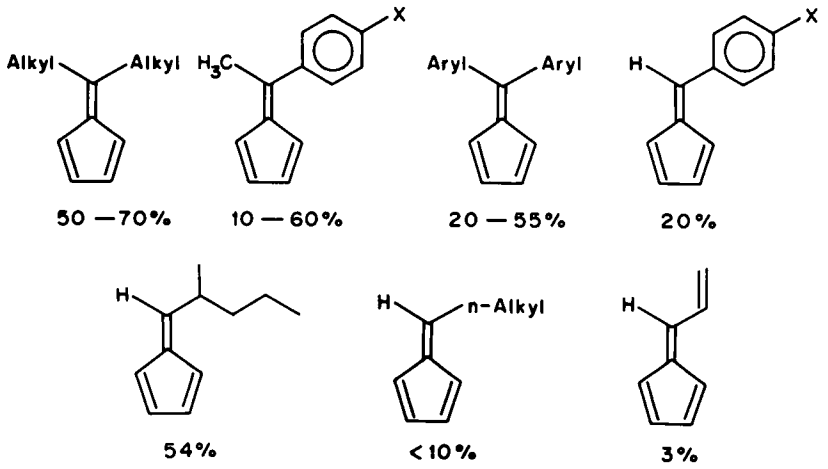
*Note the typically low yields for 6-n-alkyl- and 6-vinylfulvenes of Scheme 26.

TABLE 6. Selected 6-substituted pentafulvenes prepared according to Thiele[a] from sterically shielded or electronically stabilized aldehydes: best results



R^1	R^2	Yield (%)	Remarks	Ref.
	H	54		82
	H	68	with Na cyclopentadienide in THF	83
	H	70	with Li cyclopentadienide in THF	84
Ph	H	71	aldehyde added to NaOEt, fulvene precipitates	80
	H	69	aldehyde added to NaOEt, fulvene precipitates	80
	H	73		85
	H	79		85
	H	51		86
	H	30	KOH added to aldehyde + CPD	87
	H	47	KOH added to aldehyde + CPD	87
	H	54	KOH added to aldehyde + CPD	87
	H	30		88
	H	30		88

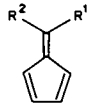
[a]Note that yields usually obtained with n-alkylaldehydes and simple acroleins are below 10%.



SCHEME 26. Approximate range of yields obtained by Thiele synthesis

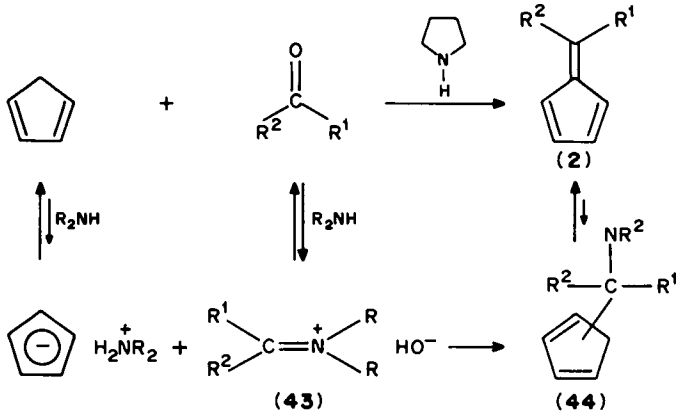
reports[101] were not easily reproducible[102], systematic investigations showed that high yields of pentafulvenes may be obtained if cyclopentadiene is reacted with aldehydes or ketones in methanol in the presence of an excess of pyrrolidine[103,104] (Table 7). According to mechanistic investigations[105], it seems that in the key step cyclopentadienide (present in low concentrations) reacts in a Mannich-type manner with the iminium ion **43** to give the aminomethylcyclopentadiene **44**[105] (Scheme 27).

TABLE 7. Selected pentafulvenes prepared from cyclopentadiene and aldehydes or ketones (base:pyrrolidine, solvent:CH_3OH)[103a]



R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
$CHMe_2$	H	98	CH_3	CH_3	81
CMe_3	H	90	$-(CH_2)_3-$		69
CH_3 | $C-(CH_2)_2C=CH_2$ | | CH_3 CH_3	H	59	$-(CH_2)_4-$		93
			$-CH_2-CH_2-CH_2-CH_2-CH-$ CH_3		
C_6H_{11}	H	96			77
Ph	H	70	$-(CH_2)_2-S-(CH_2)_2-$		95
			$-(CH_2)_2-O-(CH_2)_2-$		86

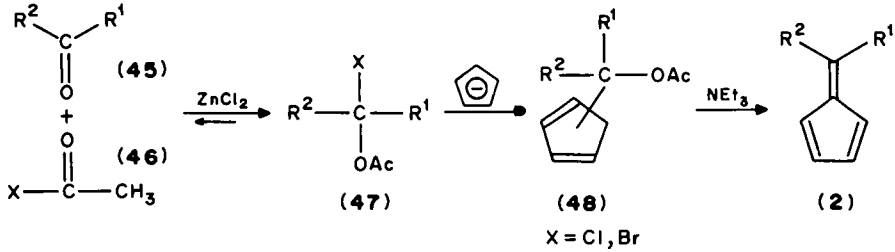
[a]For more examples see References 104–108.



SCHEME 27

2. Reaction of cyclopentadienide with bifunctional carbonyl derivatives

1-Acetoxy-1-halomethanes are easily formed by reaction of aldehydes or ketones with acetyl bromide or acetyl chloride in the presence of Lewis acids. This very old reaction[109-111] has recently been investigated in more detail[112]. The equilibrium **45** + **46** → **47** is completely on the right side for aliphatic, α,β-unsaturated and most aromatic aldehydes[113] and favoured by low reaction temperatures and unpolar solvents (Scheme 28). For alicyclic ketones the equilibrium is dependent on the ring size. By-products may be avoided[114] except with formaldehyde, so that isolation of the products **47** is not necessary in most cases. In fact, the preparative yields of acetoxychloro- or -bromomethanes **47** are very often nearly quantitative[115] (see Table 8).

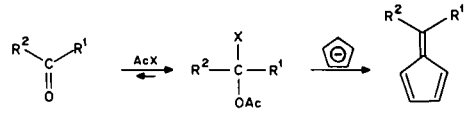


SCHEME 28

1-Acetoxy-1-halomethanes **47** react with a slight excess of cyclopentadienide at low temperature (in most cases below −20 °C) to give acetoxymethylcyclopentadienes **48** which are subsequently treated with tertiary amines to give 6-alkyl- and 6-arylfulvenes in good overall yields (Table 8)[116,117]. This sequence works well in most cases where the Thiele synthesis fails. The main reasons are that the side-reactions of Scheme 25 do not take place due to the low electrophilicity of **48** as well as the low concentration of cyclopentadienide.

The main advantages are the low reaction temperature, the use of aprotic solvents and the easy aprotic workup conditions (if needed). This is the only method giving

TABLE 8. Synthesis of 1-acetoxy-1-halo-methanes (47) and of pentafulvenes (2) from aldehydes[a]



(47) (2)

R^1	R^2	X	47 (%)[b]	2 (%)[b]	Ref.
H	H	Cl	74	20[c]	117,118
H	H	Br	75	38[c]	117
H	Me	Cl	92	55	116
H	Et	Cl	91	56	116
H	Pr	Cl	95	57	116
H	*i*-Pr	Cl	96	49	117
H	*t*-Bu	Cl	95	42	117
H	$C(CH_3)_2—CH=CH=CHC_3H_7$	Cl	90	36	117
H	CH=CHCl	Cl	80	32	117
H	CH=CHOAc	Cl	80	20	117
H	C≡CH	Cl	94	58	116
H	2-furyl	Cl	75	49	117
H	Ph	Cl	97	66	117
H	*p*-Tol	Br	99	63	119
H	*p*-FC_6H_4	Cl	96	54	119
H	*p*-ClC_6H_4	Cl	96	68	119
H	*p*-Br—C_6H_4	Cl	97	70	119
H	*p*-CNC_6H_4	Cl	99	35	119
H	*p*-$NO_2C_6H_4$	Cl	99	26	119

[a]For more examples see References 116, 117, 119.
[b]Yield based on aldehyde.
[c]For the preparation of pure **2a**, acetoxymethylcyclopentadiene has to be isolated.

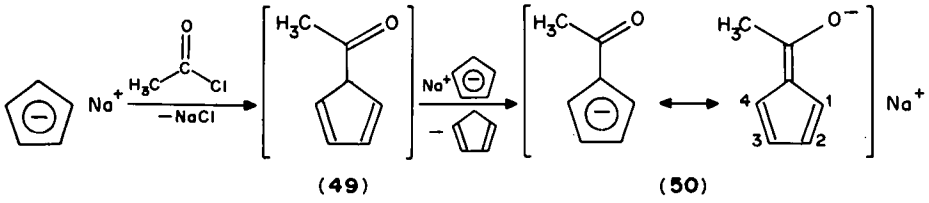
spectroscopically pure parent pentafulvene **2a** at a gram scale[118,116], and the method may be applied to 1,2-benzofulvenes[120] and 1,2–3,4-dibenzofulvenes[121] if triethylamine is replaced by stronger bases in the last step. It has to be noted, however, that for 6,6-disubstituted pentafulvenes the Thiele sequence or its modifications have to be favoured.

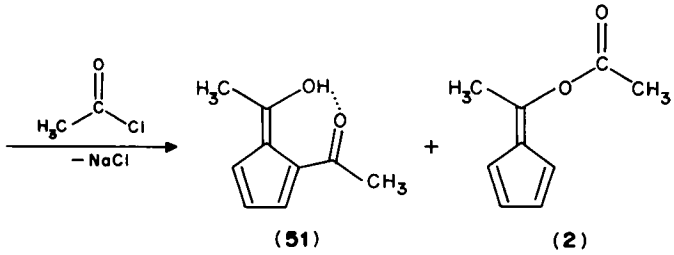
3. *Acylation of cyclopentadienide*

Due to the remarkable nucleophilicity of cyclopentadienide, acylation takes place easily and may be realized by several reagents; however, this method is limited by double acylations leading to different products.

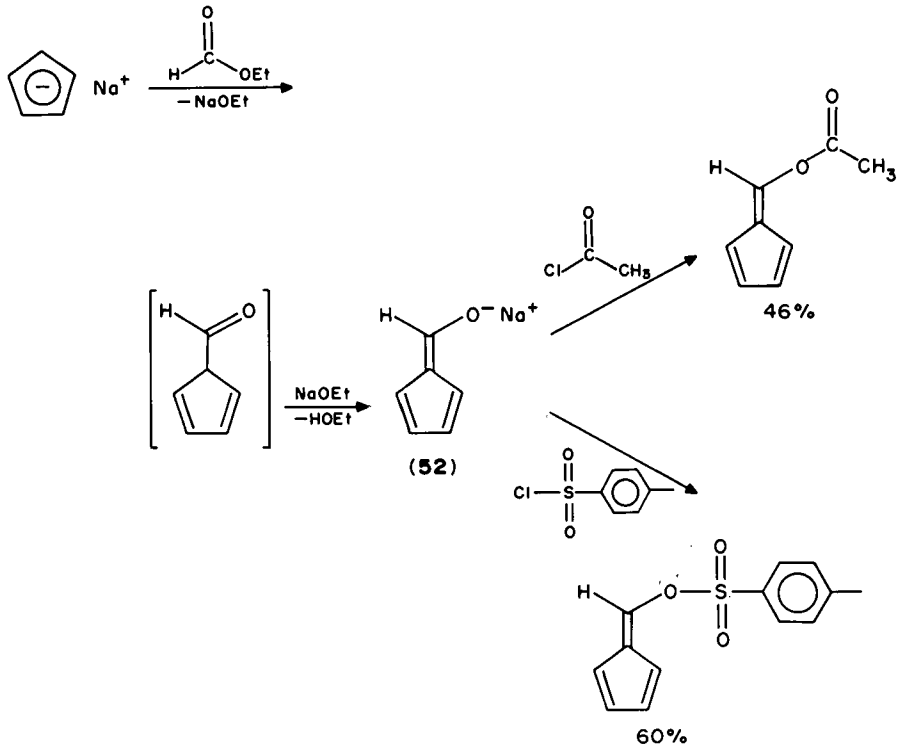
For instance, cyclopentadienide reacts easily with acetyl chloride[122–124]. Due to the fact that the primarily formed acetylcyclopentadiene **49** is more acidic than cyclopentadiene, it is easily depdrotonated to give acetylcyclopentadienide **50**, which is still nucleophilic enough to be once more acetylated (see Scheme 29); the result is a mixture of C-acylated (**51**) and O-acylated product (**2**). The factors governing regioselectivity have not yet been thoroughly studied.

Only single formylation is observed with ethyl formate giving sodium-6-hydroxy-fulvenolate **52**[123], which is a versatile reagent for the preparation of 6-acyloxy- and 6-tosyloxypentafulvenes[123] (Scheme 30). Both fulvenes are themselves synthetically useful in view of nucleophilic displacement reactions at C-6 to give new pentafulvenes[125] (see later).



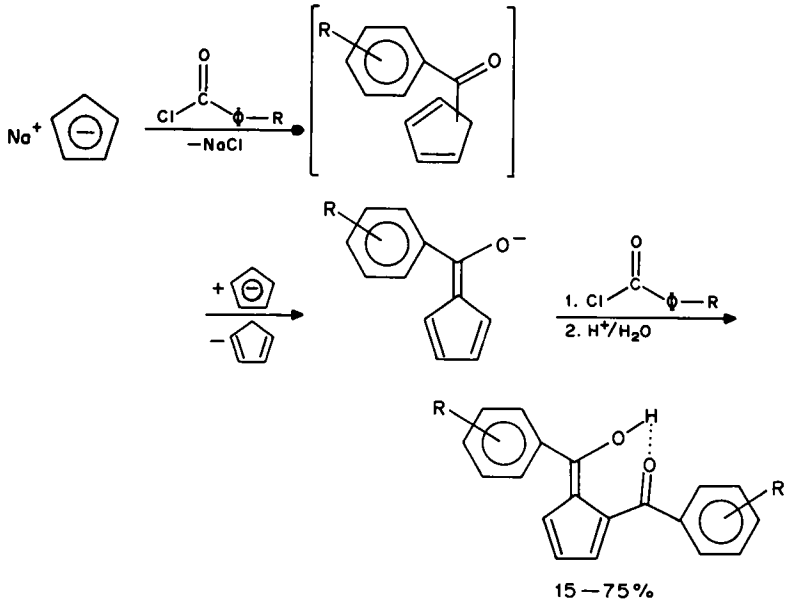


SCHEME 29

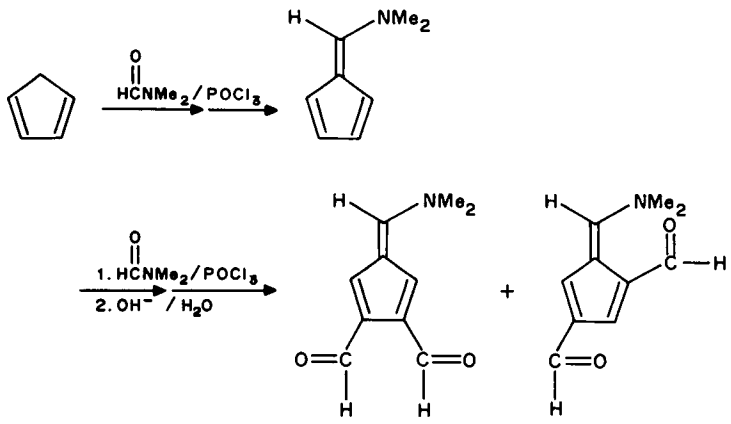


SCHEME 30

Benzoylation of cyclopentadienide has been realized with various benzoyl chlorides. After acidic hydrolysis of the reaction mixture 1-benzoyl-6-hydroxy-6-phenylfulvenes are isolated in medium yields[126] (Scheme 31). Due to the highly electrophilic character of Vilsmeier complexes, double and triple formylation of cyclopentadiene by DMF/$POCl_3$ is observed: At room temperature 2, 3-diformyl-6-dimethylaminopentafulvene is predominant, while 6-dimethylaminopentafulvene is only identified at low temperature[14,127,128] (Scheme 32).



SCHEME 31

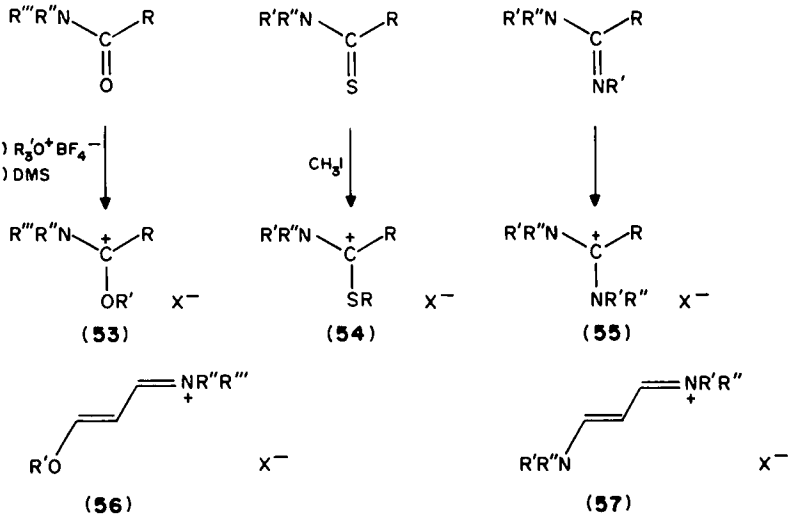


SCHEME 32

4. Reaction of cyclopentadienide with dihetero carbenium ions

Due to the basic work of Meerwein and coworkers[129] and others[130], heterosubstituted carbenium ions are easily available by alkylation of appropriate carbonyl compounds (Scheme 33). With respect to fulvene synthesis, alkylation is indispensable for amides which are not electrophilic enough to attack cyclopentadienide. Alkylation of amides, thioamides and amidines may be realized by strong electrophiles like trialkyloxonium fluoroborate, dimethyl sulfate or methyl iodide to give diheterosubstituted carbenium ions **53**, **54** and **55**. Delocalized vinylogous carbenium ions of type **56** and **57** are available too.

Some typical examples are shown in Scheme 34, and a number of fulvenes prepared by this method are listed in Table 9.

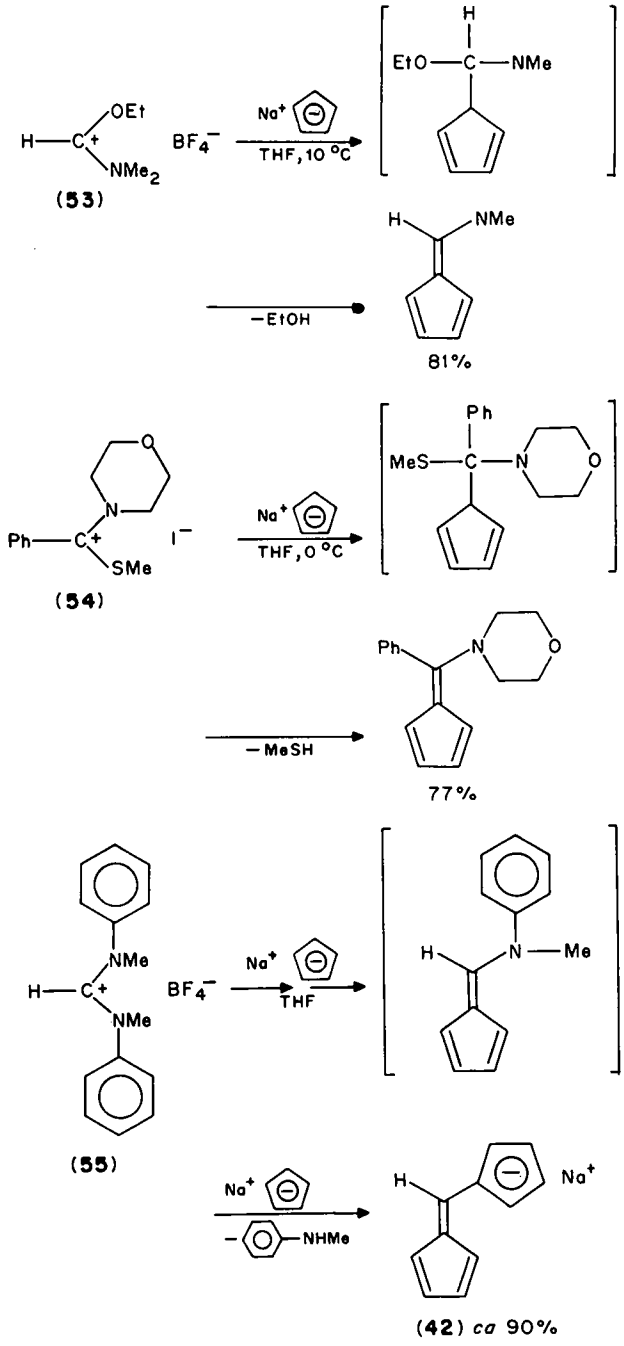


SCHEME 33

Diheterosubstituted carbenium ions react easily with cyclopentadienide at low temperature. If the carbenium ion is slowly added to cyclopentadienide, then twofold alkylation may be avoided. After elimination of the better leaving group from the intermediates, 6-aminofulvenes are formed in good yields.

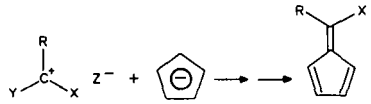
So cyclopentadienide may be reacted with *O*-alkylated *N*,*N*-dimethylformamide **53** to give 6-dimethylaminopentafulvene in a high yield[127,131]. Furthermore, S-methylated thioamides **54** are good reagents for the synthesis of various 6-alkyl- and 6-aryl-6-dialkylaminopentafulvenes[132]. It is interesting to note that 6-*N*-methylanilinopentafulvene is easily prepared by this method (Scheme 34, line 3) but reacts with an excess of cyclopentadienide in a nucleophilic displacement to give the delocalized 6-fulvenylcyclopentadienide **42**[133].

Vinylogous carbenium ions like **57** react similarly to give 8-dimethylaminovinylpentafulvenes[130]. With substituted cyclopentadienides there is the problem of regioselectivity. It is important to note that bulky anions like *t*-butylcyclopentadienide in most cases react regioselectively to form 3-*t*-butyl (or 2-*t*-butyl) pentafulvenes (see Scheme 35)[134].

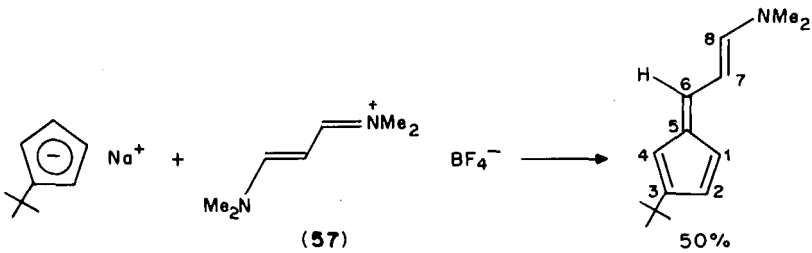


SCHEME 34[127,132,133]

TABLE 9. Selected pentafulvenes prepared from diheterosubstituted carbenium ions



R	X	Y	Z	Yield (%)	Ref.
H	NMe_2	OEt	BF_4	81	127
CH_3	NMe_2	OEt	BF_4	60	135
Ph	NMe_2	OMe	OSO_2Me	~70	136
C≡CPh	NMe_2	OEt	BF_4	9	137
Me		SMe	I	62	131
Et		SMe	I	54	131
Ph		SMe	I	77	131
Me		SMe	I	80	131
p-An		SMe	I	66	131
H	NMe_2	NMe_2	ClO_4	78	130,133
H		NMe_2	ClO_4	61	130
H		NMe_2	BF_4	75	138
H		NMe_2	BF_4	83	138
H		NMe_2	BF_4	62	88



(57) 50%

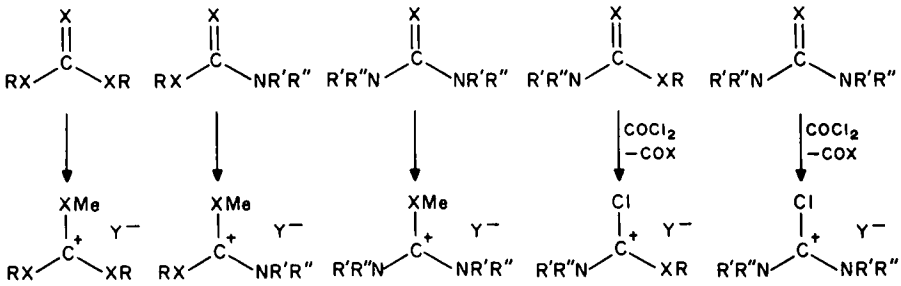
SCHEME 35*

*A considerable number of similar reactions have been realized in Hafner's group in the course of attempts to prepare substituted pentalenes. This unpublished work is cited in Reference 20.

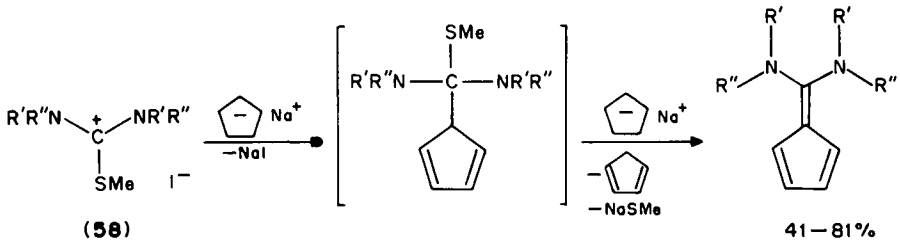
5. Reaction of cyclopentadienide with trihetero carbenium ions

Triheterosubstituted carbenium ions are easily available by alkylation of the corresponding carbonyl and thiocarbonyl compounds. Their use in pentafulvene synthesis is indispensable in cases of Scheme 36, where cyclopentadienide is no longer able to attack the electronically stabilized carbonyl or thiocarbonyl groups directly.

For instance, if methylated thiourea **58** is reacted with 2 equivalents of sodium cyclopentadienide, then 6,6-dialkylaminofulvenes are isolated in a simple one-pot procedure with good yields[139] (Scheme 37).



SCHEME 36



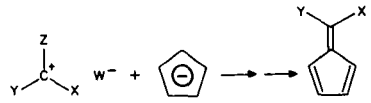
SCHEME 37

Similar to diheterocarbenium ions, some vinylogous cations are available too. As may be expected, *t*-butylcyclopentadienide attacks with the least-hindered C atom[140]. A series of typical examples is given in Table 10.

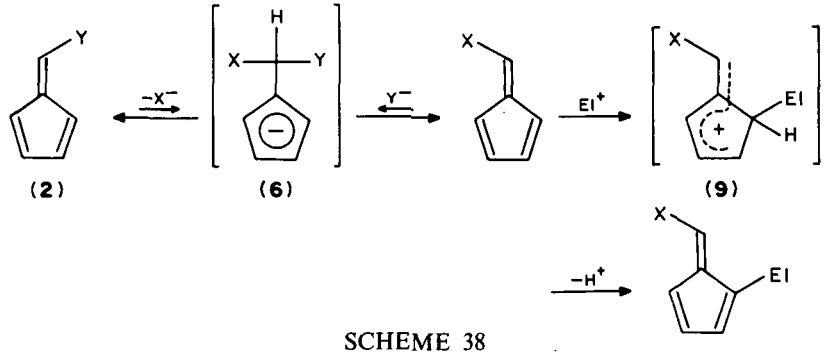
6. Pentafulvenes from pentafulvenes

The reactive behaviour of pentafulvenes **2** is characterized by nucleophilic attack at C-6 of pentafulvenes (Scheme 38), thus producing a substituted cyclopentadienide **6** and resulting in a replacement of the potential leaving group against the nucleophile Y, or by an electrophilic attack at the ring, thus producing a delocalized pentadienyl cation **9** which is stabilized by deprotonation if X is an electron-donating group (or polymerizes if X is an alkyl group). This means that in cases where the fulvene π-system may be restored, fulvenes may be used as starting materials for the synthesis of new substituted fulvenes.

TABLE 10. Selected pentafulvenes prepared from triheterosubstituted carbenium ions



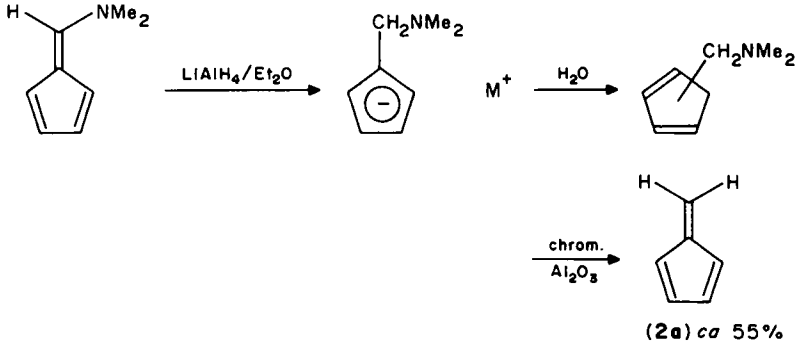
X	Y	Z	W	Yield (%)	Ref.
OEt	OEt	OEt	BF_4	25	123
NMe_2	NMe_2	OEt	$MeOSO_3$	23	123
S—CH_2—CH_2—S		SMe	$MeOSO_3$	30	141
	SMe	SMe	I	97	142
	SMe	SMe	I	85	142
	SMe	SMe	I	76	142
N(Me)Ph	NMe_2	SMe	I	62	139
$N(CHMe_2)_2$	NMe_2	SMe	I	41	139
	NMe_2	SMe	I	55	139
	NMe_2	SMe	I	62	139
N(Me)Ph	N(Me)Ph	SMe	I	78	139
NEt_2	NEt_2	SMe	I	59	139
$N[CHMe_2]_2$	NEt_2	SMe	I	42	139
		SMe	I	76	139
		SMe	I	81	139
NMe_2	NMe_2	Cl	Cl	69	139
		Cl	Cl	64	139
NMe_2	N(Me)Ph	Cl	Cl	28	139



SCHEME 38

Nucleophilic displacement at C-6

One of the first examples of this type resulted in the formation of the parent pentafulvene **2a** (Scheme 39[143]): 6-dimethylaminofulvene is attacked by hydride at C-6. The surprising point of the sequence is the last step, in which dimethylamine is eliminated by chromatography over Al_2O_3! The same method may be applied to the synthesis of 6-methylfulvene and 6-phenylfulvene[143].



SCHEME 39

Some typical examples with different leaving groups are given in Scheme 40. For more examples, see Table 11. It is not surprising that chloride is easily replaced by nucleophiles. In fact, 6-halopentafulvenes would be outstanding starting materials for synthetic purposes, and they react with nucleophiles such as amino, alkoxy and methylthio groups, Grignard reagents and alkyl as well as aryl carbanions[144–147]. The problem is, however, that simple 6-halofulvenes are not easily accessible and are thermally quite unstable[148–150].

6-Tosyloxyfulvene is a good starting material for pentafulvene syntheses as well, and has been applied to the synthesis of several 6-arylaminofulvenes[125]. Its scope is limited due to the fact that the competitive reaction to the wanted C—O clavage is a nucleophilic attack at the SO_2 group.

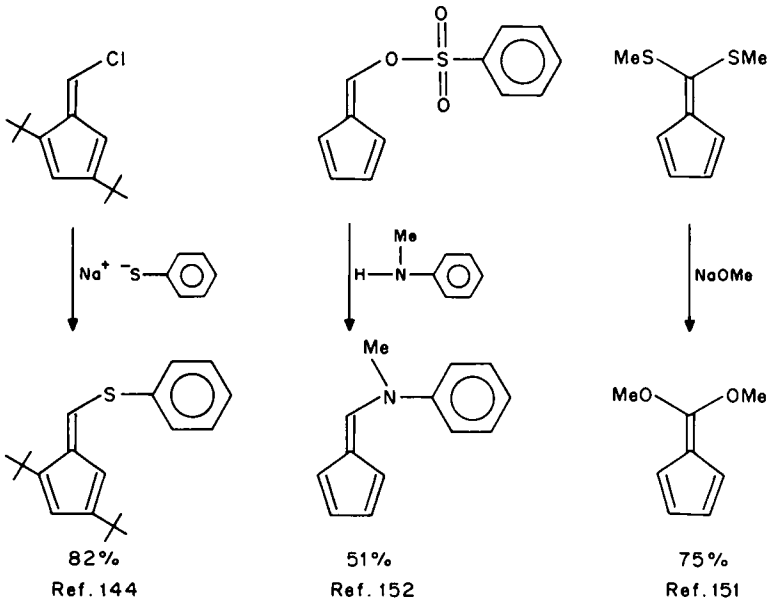
Alkylthio and cyano groups may be replaced by nucleophiles as well[151,146]. 1,2,3,4-Tetrachloro-6,6-dicyanopentafulvene reacts very easily with dialkylamines because the fulvene is electronically destabilized by the cyano groups[152].

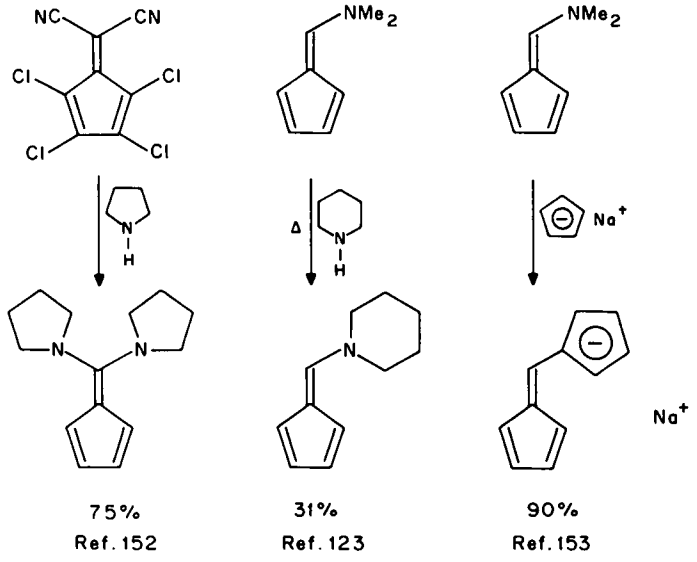
Finally, amine exchange may be realized either by using an excess of the nucleophile or by removing dimethylamine under reflux[123,140,153–156]. A similar nucleophilic replacement of 6-dialkylamino groups by hydroxy functions with sodium hydroxide gives 6-hydroxyfulvenes, which are stabilized as enols if there is an intramolecular hydrogen bridge[127,157].

A very nice last example of a nucleophilic addition–elimination sequence is given in Scheme 41. 1-Iminio-6-dimethylaminopentafulvene reacts easily with an excess of cyclopentadienide to give an intensely coloured blue solution of the delocalized polymethine anion **59**[14].

Pentafulvenes by electrophilic attack at the ring of pentafulvenes

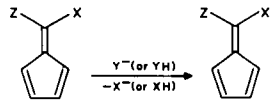
Pentafulvenes **2** are attacked by electrophiles at the ring (see Scheme 42). For electronic reasons, electrophiles should react at C-1/C-4 since the delocalized cation **9** is energetically somewhat favoured over cation **60**[158]. If the fulvene ring system may be restored, then

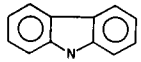
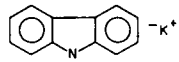

Cl
Na+ −S
S
82%
Ref. 144
O
O
S
O
Me
H—N
Me
N
51%
Ref. 152
MeS
SMe
NaOMe
MeO
OMe
75%
Ref. 151


NC
CN
Cl
Cl
Cl
Cl
N
H
N
N
75%
Ref. 152
NMe2
Δ
N
H
N
31%
Ref. 123
NMe2
Na+
Na+
90%
Ref. 153

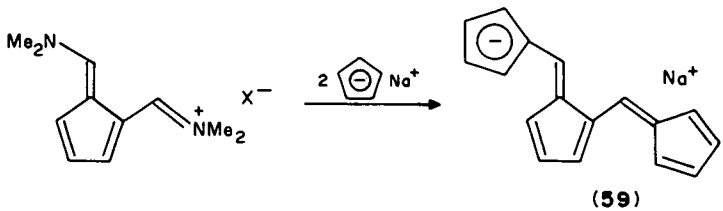
SCHEME 40

TABLE 11. Selected Pentafulvenes prepared by nucleophilic attack at C-6 of pentafulvenes[a]



Z	X	Y	Reagent	Yield (%)	Ref.
H	OTos	NMe_2	$HNMe_2$	44	125
H	OTos	N(Me)Ph	NaN(Me)Ph	51	125
H	OTos	NPh_2	$KNPh_2$	39	125
H	OTos			28	125
H	OTos	$OCMe_3$	KOBu-*t*	20	125
H	OTos	N_3	NaN_3	50	125
SMe	SMe	OMe	NaOMe	75	151[d]
SMe	SMe	OEt	NaOEt	70	151[d]
H	NMe_2	H	$LiAlH_4$	55	143[b]
H	NMe_2	Me	MeLi	86	143
H	NMe_2	Ph	PhLi	88	143
H	NMe_2	C_5H_5		~90	153
NMe_2	NMe_2	Me	CH_3Li	60	154
NMe_2	NMe_2	Ph	PhLi	41	154[c]
H	NMe_2			67	123
CH_3	NMe_2	NH_2	NH_3	51	123
NMe_2	NMe_2			62	154

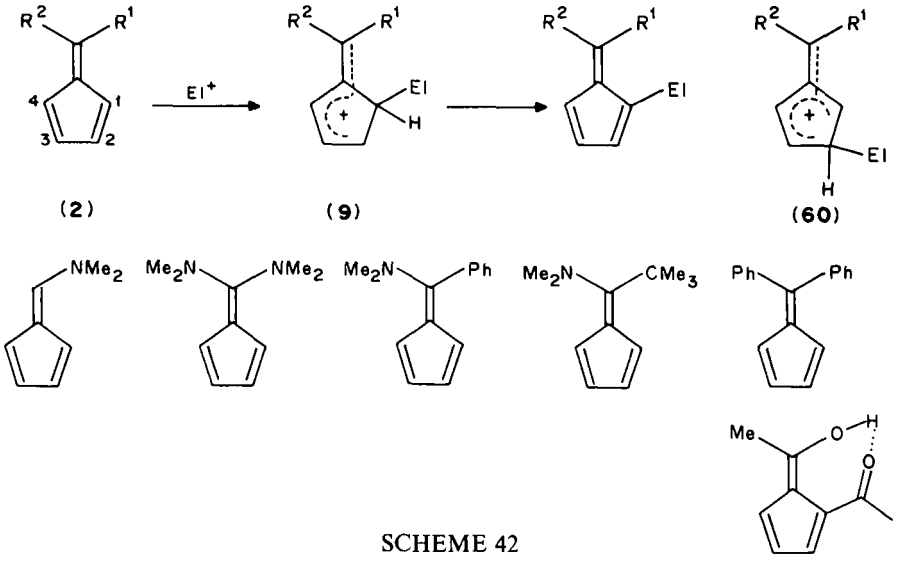
[a]For more examples with ring-substituted 6-X-pentafulvene and their vinylogues, see Reference 144.
[b]Elimination of $HNMe_2$ during chromatography over Al_2O_3.
[c]The second NMe_2 group may be replaced too.
[d]Both SMe groups are replaced.



(59)

SCHEME 41

substituted fulvenes are available by reaction of pentafulvenes with electrophiles. Numerous results show, however, that this is only the case for electronically stabilized pentafulvenes and not for simple pentafulvenes which polymerize easily under acidic or Lewis acidic conditions (see later).



SCHEME 42

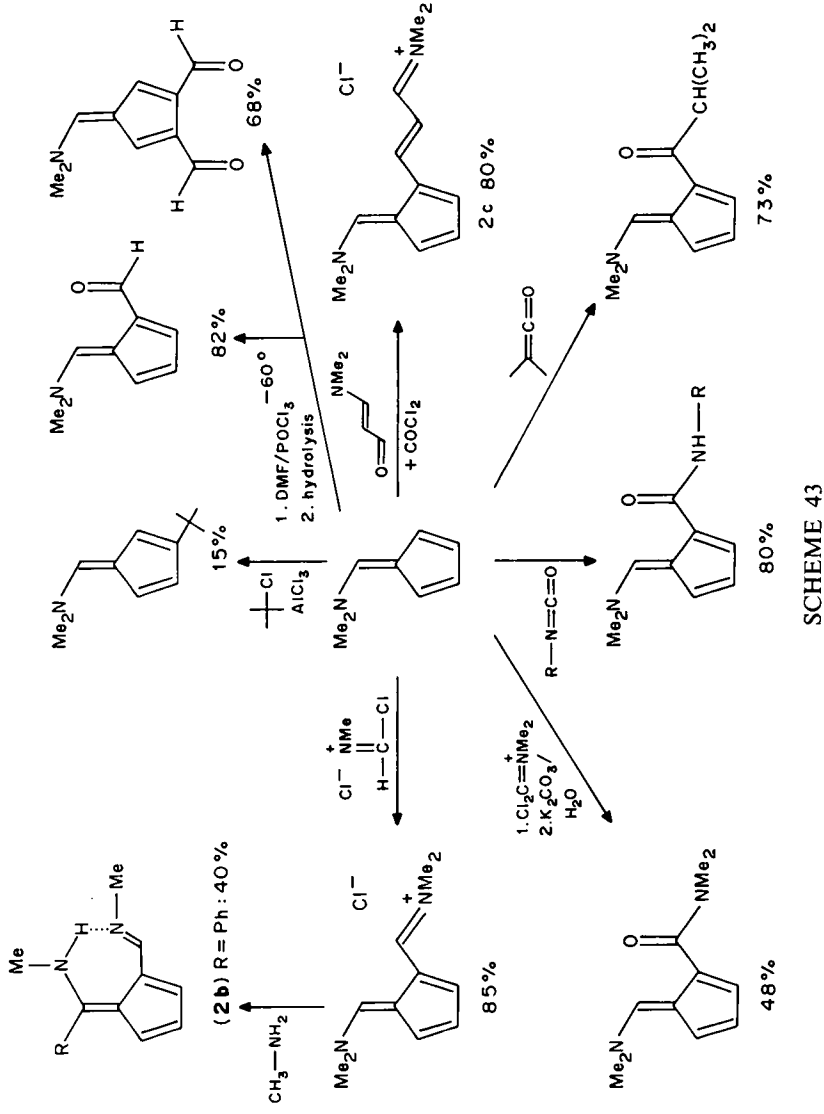
The most intensively investigated fulvene is 6-dimethylaminopentafulvene[14,127,159–164]. Much of this work has not been published so far[140]. Various examples of electrophilic substitution reactions leading to new pentafulvenes have been described for 6,6-bis(dimethylamino)pentafulvene and 6-dimethylamino-6-phenylpentafulvene, and a few examples are known for 6,6-diphenylpentafulvene[20].

The synthetic versatility of 6-dimethylaminopentafulvene is demonstrated in Scheme 43. Friedel–Crafts alkylation with bulky *t*-butyl chloride/$AlCl_3$ gives a *syn/anti* mixture of 2- and 3-*t*-butyl-6-dimethylaminofulvenes[159]. This is a case where electronic effects are overruled by the steric effect to give substitution on C-2/C-3. At $-60\,^{\circ}C$ Vilsmaier formylation takes place only at position 1, while at room temperature twofold formylation takes place[127]. Reaction with chloroformamidinium chloride gives the cyanine salts, which may be hydrolyzed or reacted with substituted amines to give N—H···N bridged derivatives of type **2b**[136]. Vinylogous Vilsmaier formylation takes place with the complex between dimethylamino-acrolein and $COCl_2$ to give the delocalized system **2c** in a high yield[160]. Aminocylation is observed with dichlorodimethylammonium chloride[161] and reaction products of the same type are obtained with isocyanates[162], while ketenes do not give [2 + 2]-cycloaddition products with 6-dimethylaminofulvene but yield 1-acyl-6-dimethylaminopentafulvene[163]. A series of ring-substituted pentafulvenes, available by electrophilic substitution of electronically stabilised pentafulvenes, is listed in Table 12.

7. *Miscellaneous*

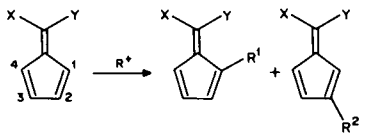
Since cyclopentadienide is strongly nucleophilic, some pentafulvenes are available by its reaction with electrophilic neutral molecules (Scheme 44).

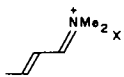
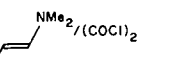
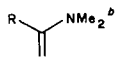
So an excess of cyclopentadienide reacts with CS_2 to give bis-thiofulvenolate **2d**, which is easily converted to 6,6-dialkylthiopentafulvenes (R = R′ = Me: 45% R,R′ = CH_2—CH_2: 91% R,R′ = CH_2—CH_2—CH_2—CH_2: 85%)[141]. Similarly, cyclopentadienide reacts with $CHCl_3$ or $CHBr_3$ to give 6-chloro- and 6-bromo-pentafulvene[148], however the yields of these instable pentafulvenes are low. A considerably improved access to the



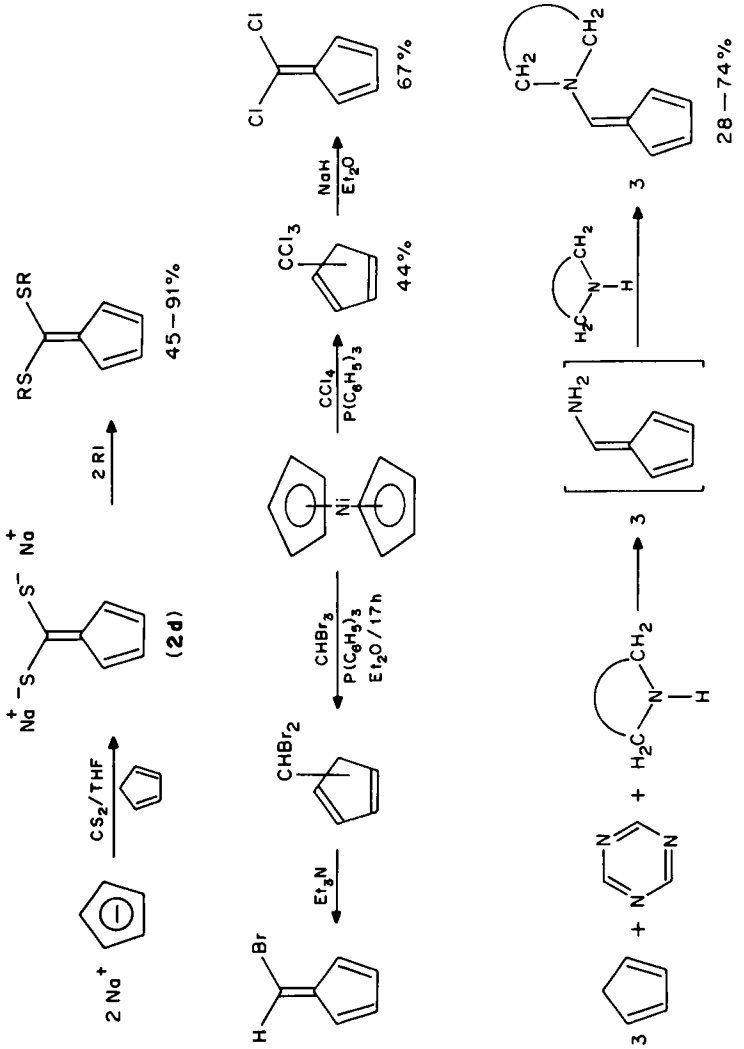
SCHEME 43

TABLE 12. Selected pentafulvenes prepared by electrophilic attack at C-1/C-4 or C-2/C-3 of electronically stabilized pentafulvenes[a]



X	Y	R^1	R^2	Reagent	Yield (%)	Ref.
NMe_2	H	CHO	—	$DMF/POCl_3$	82	127
NMe_2	H	$CH{=}\overset{+}{N}Me_2Cl^-$	—	$CHCl{=}\overset{+}{N}Me_2Cl^-$	85	136
NMe_2	H		—		80	160
NMe_2	H	$CONMe_2$	—	$Cl_2C{=}\overset{+}{N}Me_2Cl^-$	48	161
NMe_2	H	$CONHSO_2C_6H_4R$	—	$O{=}C{=}N{-}SO_2{-}C_6H_4{-}R$	59–79	162
	H	$CONMe_2$	—	$Cl_2C{=}NMe_2^+Cl^-$	52	140
	H	CONHCOOEt	—	$O{=}C{=}N{-}COOEt$	21–60	140
NMe_2	H	*t*-butyl	*t*-butyl[c]	$Me_3CCl/AlCl_3$	15	159
NMe_2	NMe_2	*d*	$CONMe_2$	$Cl_2C{=}NMe_2^+Cl^-$	60	164
NMe_2	NMe_2	CONHCOOEt	*e*	$O{=}C{=}N{-}COOEt$	22	164
NMe_2	C_6H_5	$CH{=}NMe_2^+Cl^-$	—	$CHCl{=}NMe_2^+Cl^-$	>60	136
NMe_2	C_6H_5	—	$CONMe_2$	$Cl_2C{=}NMe_2^+Cl^-$		140
C_6H_5	C_6H_5	CHO	—	$DMF/POCl_3$	62	165
Ar	Ar	COMe	—	$CH_3I + CO +$ catalyst	50	166

[a]In most cases reaction at low temperature, followed by hydrolytic workup.
[b]R = H: 60%; R = Me: 58%; R = Ph: 38%; R = NMe_2: 21%[140].
[c]Isomeric mixture of monosubstituted products.
[d]3% of C-1-substituted product.
[e]Plus 7% of C-2 substituted product.



SCHEME 44

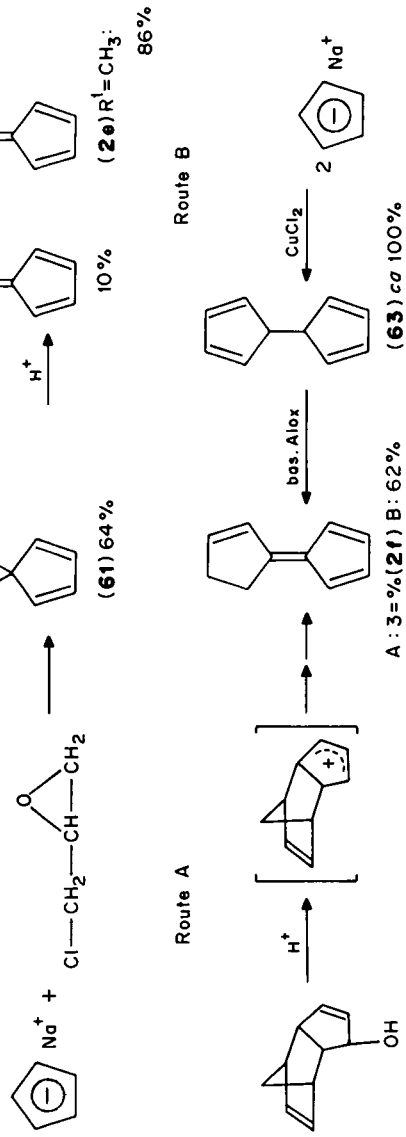
synthetically very attractive 6-halofulvenes has been published recently[149,167]: Nickelocene reacts with triphenylphosphine to give an intermediate in which σ-bound cyclopentadiene is reactive enough for a nucleophilic attack of CCl_4 or $CHBr_3$. Subsequent elimination of HX gives the reactive 6,6-dichloro- and 6-bromopentafulvenes. Furthermore, it has been shown[168] that 6,6-dialkylaminopentafulvenes may be prepared very easily by stirring a mixture of cyclopentadiene, *s*-triazine and an alicyclic secondary amine at room temperature!

Two highly reactive 6-vinylpentafulvenes have become available by acid-catalyzed rearrangements of bicyclic precursors (Scheme 45): So acid-catalyzed treatment of hydroxymethyl-spiro [2,4] hepta-4,6-diene **61** gives 6-vinylfulvene[81]. This rather special fulvene synthesis could become more important, since 6-oxiranylpentafulvenes of type **2e** are easily available now by the modified Thiele synthesis[83] and add strong nucleophiles at C-6 to give substituted 'spirodienols' **61**[83]. On the other hand, the exocyclically bridged pentafulvene **2f** (7,8-dihydropentafulvalene), which was first prepared by an acid-catalyzed treatment of 'dicyclopentadienol' **62**[169], is easily available now in 62% yield by base-catalyzed H shift of dihydropentafulvalene **63**[170].

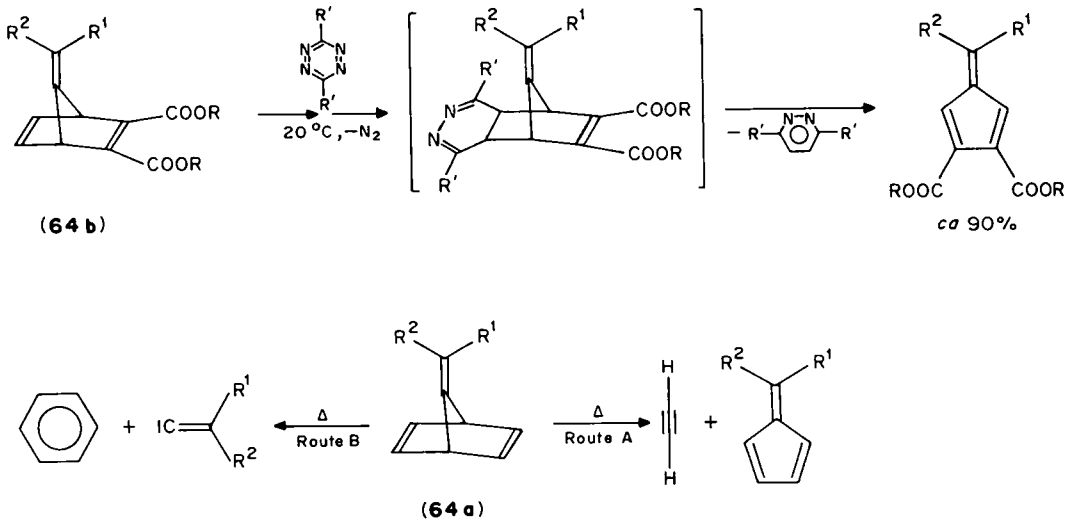
Cycloaddition–cycloreversion sequences are also an interesting route for pentafulvenes and, although some examples are known[171–177], the potential of these sequences still remains to be investigated in more detail. They are limited in many cases by the high pyrolysis temperatures which demand flash vacuum conditions if unstable pentafulvenes have to be trapped. Very mild conditions are sufficient for cycloaddition/reversion reactions of 3,6-di(2-pyridyl)1,2,4,5-tetrazines with Diels–Alder adducts of type **64b**, so that some 2,3-dimethoxycarbonylpentafulvenes have become available in very good yields[174,175]. The thermal behaviour of 7-alkylidenebicyclo [2.2.1]heptadienes **64a** has recently been investigated in more detail[177]: Thermal fragmentation proceeds mainly by two different mechanisms (Scheme 46, route A or B). In most cases route A is dominating, e.g. for R^1, R^2 = H; CH_3; F; S-$(CH_2)_3$S; Br; or R^1 = H, R^2 = OMe; Ph; and pentafulvenes are trapped and isolated in yields between 30 and 96%. The carbene mechanism (route B) may become important for bicyclic compounds **64a** bearing strong σ- or π-donor groups at C-7[177].

The parent pentafulvene **2a** as well as 6-methylenepentafulvene **2g** are available by ring contraction of benzenoid compounds[178,179]. Mechanistically rather than preparatively important is the fact that benzene, when irradiated at 254 nm, forms small amounts of pentafulvene **2a**[180]. Pure solutions of pentafulvene and benzene may be obtained by flash vacuum pyrolysis of 2-oxo-2,3-dihydrobenzofurane **65**[181] (Scheme 47): Pyrolysis of many benzenoid starting materials give reactive 6-methylenepentafulvene **2g**[181–187]. A simple recycling equipment has been described[182] which allows the preparation of gram quantities of **2g** in concentrated solution starting with phthalid (**66**). The process is induced by fragmentation of CO_2 and formation of carbene **67** which may undergo ring contraction. **2g** reacts easily with nucleophiles like methanol or dimethylamine at C-6 to give 6-methoxy-6-methylpentafulvene and 6-dimethylamino-6-methylpentafulvene, respectively.

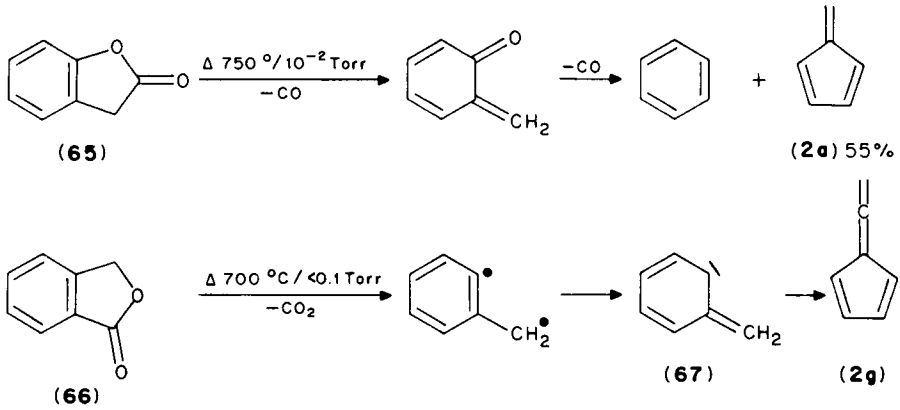
In nearly every pentafulvene synthesis where a five-membered ring is connected to a side-chain, cyclopentadienide is used as a nucleophile. This methodology is not suited for the synthesis of parent pentatriafulvalene (= 'calicene'). On the other hand, cyclopropyl-Li-carbenoids of type **30** are easily available from 1,1-dibromo-cyclopropane at low temperature[66], and cyclopentenone is a potentially electrophilic cyclopentadiene equivalent. In fact, several cyclopropyl-Li-carbenoids have been reacted with cyclopentenone according to Scheme 48. The desired CO addition of **68** is favoured over the unwanted Michael addition[188]. A crucial point so far is the acid-catalyzed H_2O elimination **69** → **70** of the sterically hindered alcohol which is often accompanied by cyclopropane ring opening.


Na+ +
Cl—CH2—CH—CH2
O
(61) 64%
CH2—OH
H+
10%
(2e) R1=CH3: 86%
R1
Route A
Route B
H+
OH
(62)
A : 3 = %(21) B: 62%
bas. Alox
(63) ca 100%
CuCl2
2
Na+

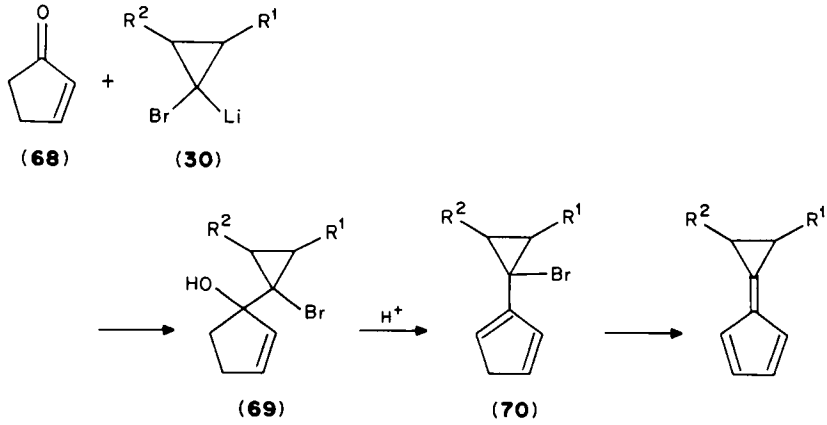
SCHEME 45


R2
R1
COOR
COOR
(64 b)
R'
20 °C, −N2
R'
ca 90%
ROOC
COOR
Δ
Route B
Δ
Route A
(64 a)

SCHEME 46



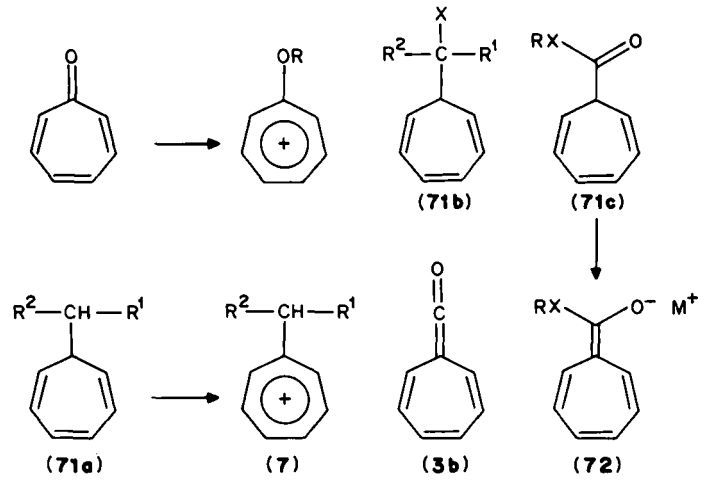
SCHEME 47



SCHEME 48

C. Synthesis of Heptafulvenes

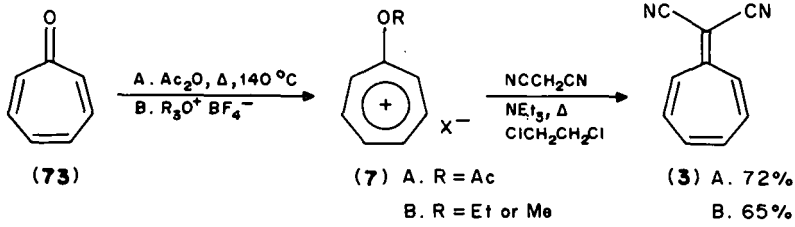
As we pointed out in the introduction, heptafulvenes (**3**) are similar to triafulvenes (**1**) concerning their ground-state properties, their polarity, substituent effects on frontier orbitals and available precursors. It is not surprising, therefore, that several synthetic methods for heptafulvenes have their analogy in the triafulvene series. Possible starting materials for heptafulvenes (Scheme 49) are tropones, which are alkylated or acylated to give tropylium salts. Substituted cycloheptatrienes may undergo hydride abstraction, **71a** → **7**, or if the exocyclic substituent has a leaving group in α-position to the seven-membered ring, then direct elimination of HX out of the cycloheptatriene **71b** is the method of choice. 1-Acyl-cycloheptatrienes **71c** may be deprotonated to give heptafulvenolates **72**, which later on are acylated or alkylated. Furthermore, several heptafulvenes have become available by transformation of sufficiently reactive heptafulvenes; a very interesting synthon in this respect is 8-oxoheptafulvene (**3b**).



SCHEME 49

1. From tropones

Electronically stabilized heptafulvenes (**3**) are formed if a mixture of tropone, an active methylene compound like malononitrile and acetic anhydride is refluxed[189]. It may be assumed that acetoxytropylium acetate (**7**) is the reactive intermediate. On the other hand, tropone may be alkylated with trialkyloxonium fluoroborate, which is then reacted with malononitrile[190]. Good yields are only obtained if the alkoxytropylium salt is refluxed together with malononitrile and triethylamine in 1,2-dichloroethane[191] (see Scheme 50).



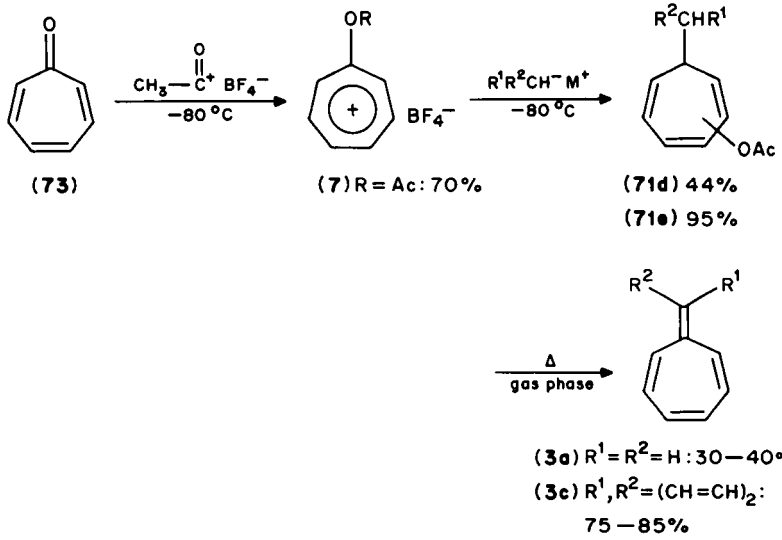
SCHEME 50

The importance of this sequence is considerably smaller for heptafulvenes than for triafulvenes, where cyclopropenones are reacted instead of tropone. First of all, condensation in the presence of acetic anhydride needs high reaction temperatures, which prevents the synthesis of thermally unstable heptafulvenes. Then acetoxy- and alkoxytropylium salts of type **7** add the methylene compound under kinetically controlled conditions, not at the sterically shielded C-1[191]. Furthermore, other activated methylene derivatives than malononitrile give very low yields[192]. It seems that the method could be improved by using reactive thiotropone[193,194] instead of tropone.

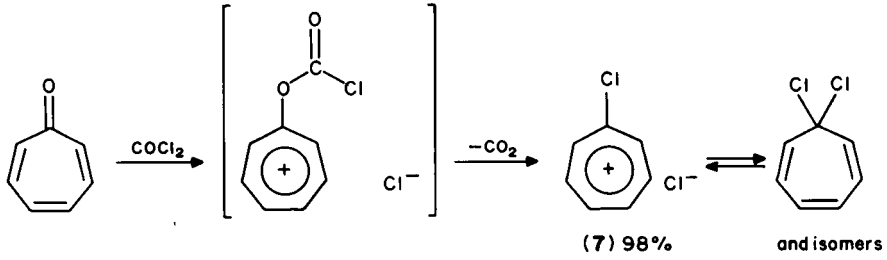
Despite of its inconveniences, the method may be applied to the synthesis of the parent heptafulvene (**3a**) and heptapentafulvalene (sesquifulvalene **3c**) if the right parameters are

chosen (Scheme 51). So acetylation **73** → **7** with acetyl fluoroborate and alkylation **7** → **71** with methyllithium or sodium cyclopentadienide may work at very low temperature, but, as mentioned before, the potential leaving group ends up in a vinylic position. It may be eliminated by gas- phase pyrolysis (because the OAc groups ends up in an allylic position after a series of 1, 5 H- shifts![195]) to give spectroscopically pure parent **3a** and **3c**[195]. This is a rare case where a convenient synthesis of pentafulvenes[116] has been applied to heptafulvenes!

It should be mentioned that tropone is easily converted to chlorotropyliumchloride **7** by reaction with phosgene or oxalyl dichloride (Scheme 52). **7** is a powerful electrophile, although its synthetic restrictions are similar to those of alkoxytropylium salts[196].

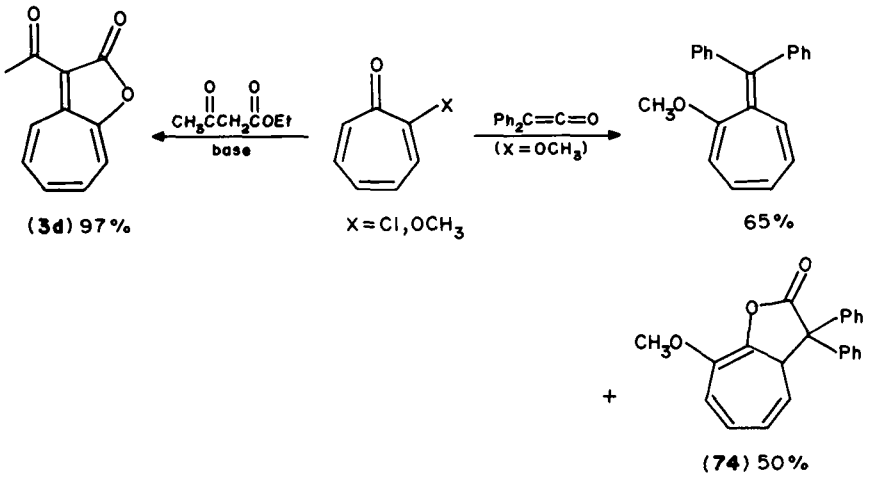


SCHEME 51



SCHEME 52

Finally, two mechanistically different sequences starting with tropone should be mentioned (Scheme 53). Cycloadditions of diphenylketene to tropones may either give [2 + 2] addition (at the C—O bond of tropone) or the [8 + 2] cycloaddition product **74**. While for tropone itself only [8 + 2] cycloaddition takes place[197] (although tropone to some extent undergoes [2 + 2] cycloaddition with dicyanoketene to give 8, 8-



SCHEME 53

dicyanoheptafulvene with 20% yield[198]), 2-methoxytropone gives minor amounts of [2 + 2] cycloaddition products from which, after elimination of CO_2, 2-methoxy-8,8-diphenylheptafulvene is generated[199]. On the other hand, acidic methylene compounds like diethyl maleate react with 2-chloro- or 2-methoxytropone to give electronically stabilized heptafulvenes **3d**[200]. It is reasonable to assume that the initial step is a nucleophilic attack of the deprotonated methylene group at C-2 of the tropone.

Some selected heptafulvenes prepared from tropone are presented in Table 13.

So far, Witting reaction[201] and Peterson olefination[202] have only been used in rare cases and are not of major importance for the synthesis of heptafulvenes.

2. *From cycloheptatrienes through tropylium salts*

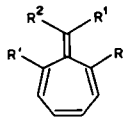
The most versatile method for the synthesis of heptafulvenes makes use of the fact that substituted tropylium salts **7** may be generated from substituted cycloheptatrienes **71** by hydride abstraction **71** → **7**. Final deprotonation **7** → **3** is in most cases easy, especially if the proton is acidified by exocyclic substituents.

The main advantages are the easy availability of cycloheptatrienes **71** (in most cases from tropylium cations) as well as the smooth reaction conditions of the last step, which makes even reactive heptafulvenes such as **3e**[203] and **3f**[204] available. Problems arise if hydride abstraction of sterically shielded cycloheptatrienes **7** is too slow. This may be overcome by thermal isomerization **71** → **71'** (Scheme 54). By this method an impressive series of heptafulvenes have been prepared, some prominent examples[204–217] being listed in Table 14.

3. *From exocyclically substituted cycloheptatrienes*

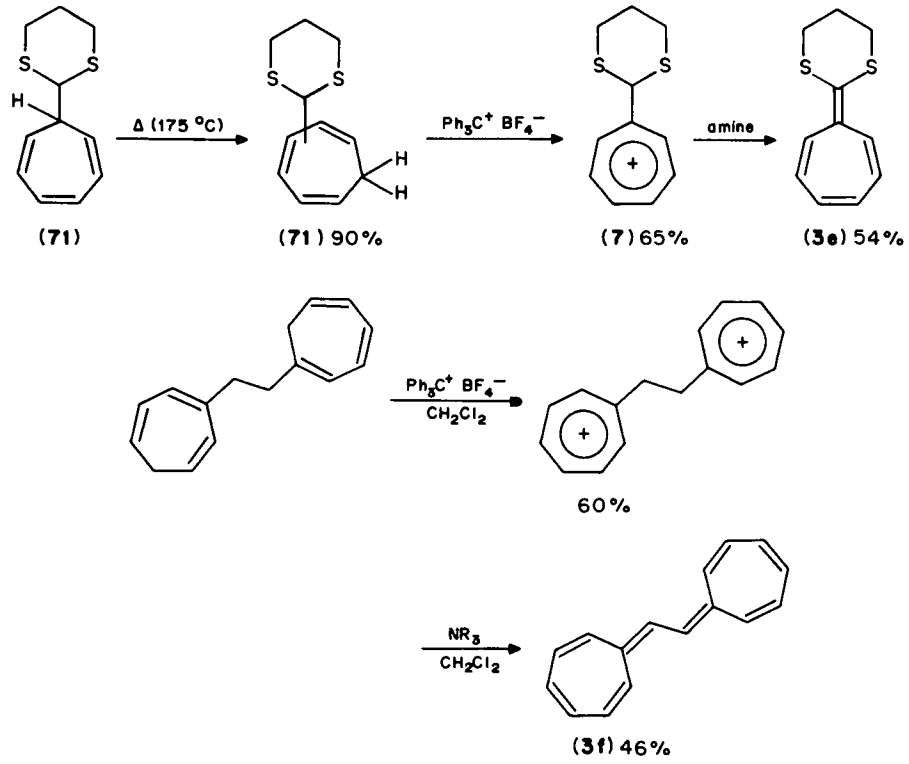
Substituted cycloheptatrienes bearing a leaving group in α-position to the seven-membered ring seem to be ideal precursors for heptafulvenes. Although the acidity of cyclohepatrienes is comparatively low (due to the antiaromatic character of the planar cycloheptatrienyl anion), direct elimination of HX from cycloheptatrienes is quite often possible.

TABLE 13. Selected heptafulvenes prepared from tropone



R^2	R^1	R	R'	Yield (%)	Remarks	Ref.
CN	CN	H	H	72	Ac_2O, Δ	189
CN	CN	H	H	65	alkylation with $Et_3O^+BF_4^-$	190, 191
H	H	H	H	9–12[a]	acetylation with $CH_3\overset{\overset{O}{\|}}{C}{}^+BF_4^-$	195
CH=CH—CH=CH		H	H	50–55[a]	acetylation with $CH_3\overset{\overset{O}{\|}}{C}{}^+BF_4^-$	195
CN	CN	CH_3	CH_3	17	Ac_2O, Δ	189
Ph	Ph	OCH_3	H	6, 5	2-methoxytropone + diphenylketene	199
COOEt	$\overset{\overset{O}{\|}}{C}—O$		H	49	2-chlorotropone + R_2CH_2	200
COMe	$\overset{\overset{O}{\|}}{C}—O$		H	97	2-chlorotropone + R_2CH_2	200

[a]Overall yield starting with tropone.



SCHEME 54

A classical example is Doering's heptafulvene synthesis consisting in a Hofmann elimination of (trimethylammonio)methylcycloheptatriene **71b**[2] (Scheme 55). Mechanistically different is the thermal or photolytic fragmentation of cycloheptatrienyldiazomethane, giving solutions of the parent heptafulvene as well[218]. Two more examples are given in Scheme 56. Especially attractive for preparative purposes is 7-oxoheptafulvene **3b**, which is easily available in solution by HX elimination from cycloheptatriene **71c**[219].

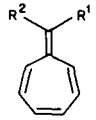
Compared with alkylcycloheptatrienes the acidity of acylcycloheptatrienes is considerably increased. If the acyl group does not bear a potential leaving group like Cl in **71C**, then deprotonation of acylcycloheptatrienes gives deeply coloured blue or green solutions of heptafulvenolates **72**[223] which may be easily O-acylated or O-alkylated[222–226] (Scheme 57). see Table 15.

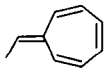
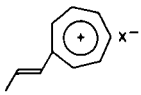
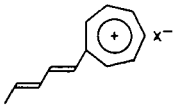
4. From other heptafulvenes

There are two important sequences by which heptafulvenes may be prepared from other heptafulvenes in synthetically useful yields. From this point of view, 8-oxoheptafulvene is the most attractive compound, although it is thermally very unstable.

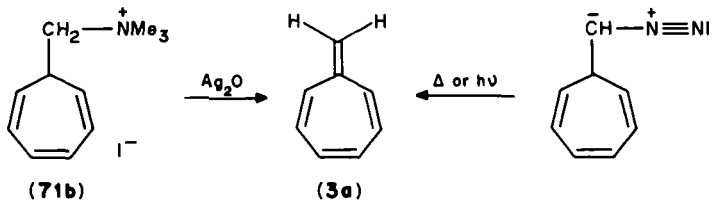
Two nice examples are outlined in Scheme 58: 8-oxoheptafulvene has the structure elements of a ketene and of a heptafulvene as well. Its ketene qualities enable it to undergo (2 + 2) cycloadditions with ketones or thioketones; as heptafulvene it may react in a (8 + 2)

TABLE 14. Selected heptafulvenes from substituted cycloheptatrienes over tropylium salts



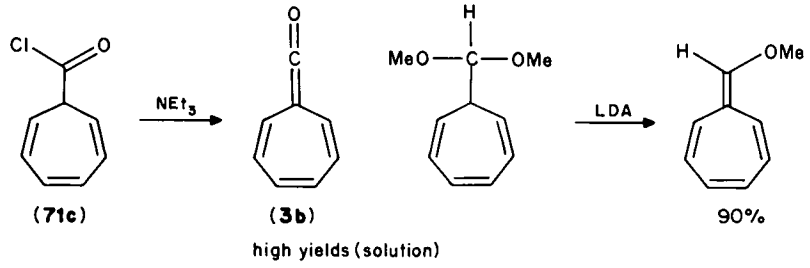
R^1	R^2	Remarks[a]	Yield[b] (%)	Ref.
$CH{=}CH_2$	H	unstable, not isolated	—	207
Ph	H	red solution	—	205
	H		28	204
	H		28	206
	H	olive green solution	—	206
CHO	H	fairly stable in solution		211
$COCH_3$	H		64	209
COOEt	H	fairly stable in solution	—	211
CN	H		68	210
$CO(CH_2)_2CH{=}CHCOOEt$	H	unstable red oil	—	216
$CH_2CH_2CH_2CH_2$		red crystal with some aromatic impurity	—	208
$S{-}CH_2CH_2CH_2{-}S$		red crystals	32	203
Ph	Ph		75	205
CHO	CHO		45	212,213
$CO{-}CH_2{-}CH_2{-}CO$		hydride abstraction with PCl_5	58	208
$(CH_2)_3COMe$	CN		31	214
$COOCH_2CH{=}CHCOOEt$	CN		20[c]	215
$(CH_2)_3CH{=}CHCOOEt$	CN		—	217

[a]If nothing is indicated, hydride abstraction has been realized by means of triphenylmethyl fluoroborate, perchlorate or hexachloroantimonate.
[b]From substituted cycloheptatrienes;—means that no yield has been reported.
[c]Yield from unsubstituted tropylium cation.

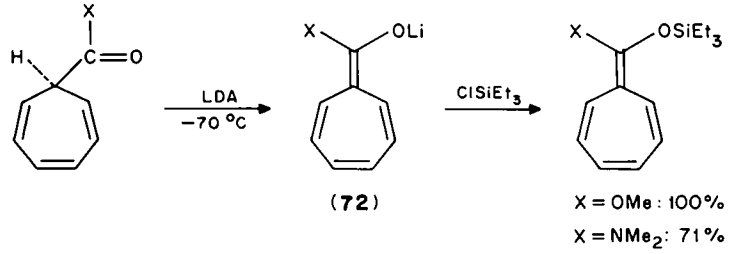


(71b) (3a)

SCHEME 55

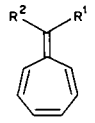


SCHEME 56[219-221]



SCHEME 57

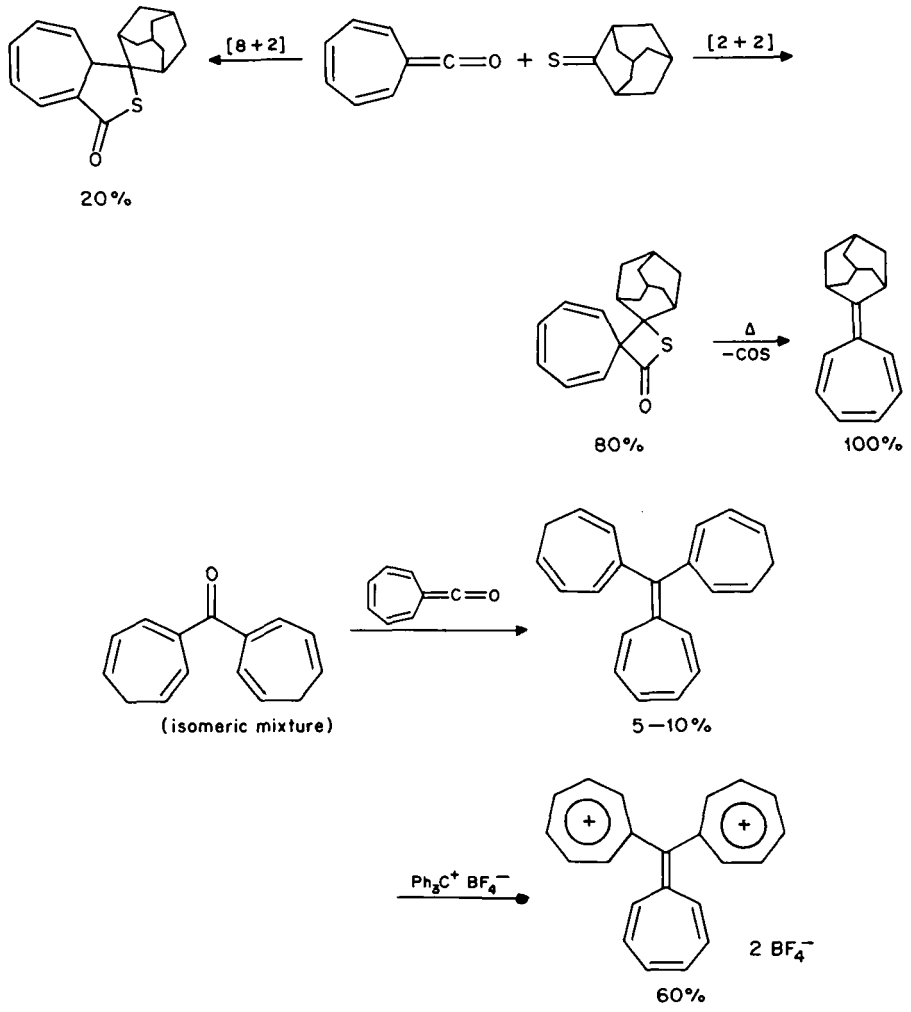
TABLE 15. Selected heptafulvenes from exocyclically substituted cycloheptatrienes



R^1	R^2	R of cyclo-heptatriene	Yield[a] (%)	Reagent, Remarks	Ref.
H	H	$CH_2\overset{+}{N}Me_3X^-$	—	Ag_2O (dil. solution)	2
H	H	CHN_2	37 18	Δ hν } (solution)	218
H	H	CH_2Br[b]	—	KOBu-*t* (solution)	208
O		COCl	very good	NEt_3 (dil. solution)	219
H	OMe	$CH(OMe)_2$	90	LDA	220, 221
Cl	Cl	CCl_3[b]	78	LDA	208
$OSiEt_3$	OMe	COOMe	~100	1. LDA, 2. $ClSiEt_3$	221, 224
$OSiMe_3$	OMe	COOMe	47	1. LDA, 2. $ClSiMe_3$	208
$OSiEt_3$	NMe_2	$CONMe_2$	71	1. LDA, 2. $ClSiEt_3$	221, 224
$OSiMe_3$	NMe_2	$CONMe_2$	53	1. LDA, 2. $ClSiMe_3$	208
OTos	Ph	COPh	—	1. KH, 2. TosF	226
OTos	An	COAn	—	1. KH, 2. TosF	226
NMe_2	NMe_2	$CONMe_2$	—	$Ti(NMe_2)_4$	222, 225
$S—CH_2CH_2—S$		COOMe	51	$R_2Al—S—CH_2CH_2—S—AlR_2$	221

[a]From substituted cycloheptatrienes;—means that no yield has been reported.
[b]The substituted cycloheptatrienes are prepared in a low yield by reaction of tropylium fluoroborate with $LiCCl_3$ at −105 °C (20%) and with $BrCH_2MgBr$ at −78 °C (10%)[208].

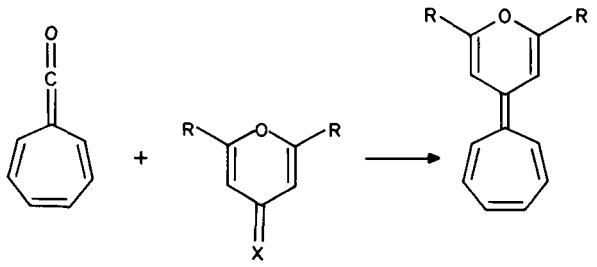
mode too. Obviously with adamantyl thione both modes are operating and both cycloaddition products are observed (Scheme 58, upper row). The synthetically useful [2 + 2] adduct is predominant; it splits off COS to give the corresponding heptafulvene after careful heating[227].



SCHEME 58

Both cycloaddition modes are observed with bis(cycloheptatrienyl) ketone as well; however [8 + 2] cycloaddition dominates, while the [2 + 2] intermediate cleaves CO_2 to give 8, 8-dicycloheptatrienylheptafulvene in a 5–10% yield[228]. The same method has been applied to the synthesis of heptafulvalenes[229].

Systematic investigations in the heterofulvalene area (Scheme 59[230]) suggest that thioketones in most cases give higher yields than ketones.

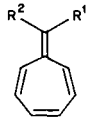


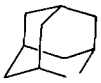
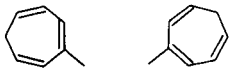
R	yield (%) X=O	X=S
H	0	51
Me	0.2	25
Ph	25	73
CO_2Me	75	100

SCHEME 59

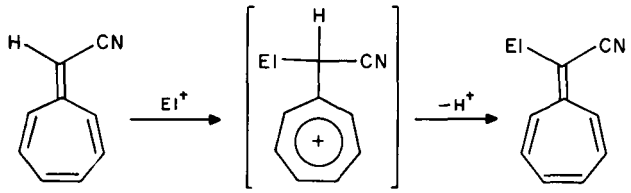
According to the reactivity pattern of heptafulvenes, they should be attacked by electrophiles at the exocyclic C-8 (Scheme 60). If the substituent is a cyano group, then the conjugative system is easily restored by deprotonation, giving new heptafulvenes in sometimes very good yields (Table 16[231,232]). Similarly, radical attack takes place at C-8

TABLE 16. Selected heptafulvenes prepared from heptafulvenes



R^1	R^2	Yield (%)	Method	Ref.
		80	oxoheptafulvene + thione	227
		5–10	oxoheptafulvene + ketone	228
CH=CHOCH=CH		51	oxoheptafulvene + thione	230
Ph	Ph			
CH=CH—O—CH=CH		73	oxoheptafulvene + thione	230
CH=CH—S—CH=CH		25	oxoheptafulvene + ketone	230
S—CH=CH—S		47	oxoheptafulvene + ketone	230
CHO	CN	47	8-cyanoheptafulvene + (Vilsmeier)	199
NO_2	CN	16	8-cyanoheptafulvene + $C(NO_2)_4$	231
$COCF_3$	CN	20	8-cyanoheptafulvene + $(CF_3CO)_2O$	231
tropyl	CN	84	8-cyanoheptafulvene + tropylium cation	232
Br	CN	87	8-cyanoheptafulvene + Br_2/NEt_3	231
Br	CN	93	8-cyanoheptafulvene + NBS	233
Cl	CN	54	8-cyanoheptafulvene + NCS	233
Br		48	10-cyanovinylheptafulvene + NBS	233
Cl		84	10-cyanovinylheptafulvene + NCS	233

of electronically stabilized heptafulvenes which may be brominated or chlorinated with bromo- or chloro-*N*-succinimide[233] (Table 16).

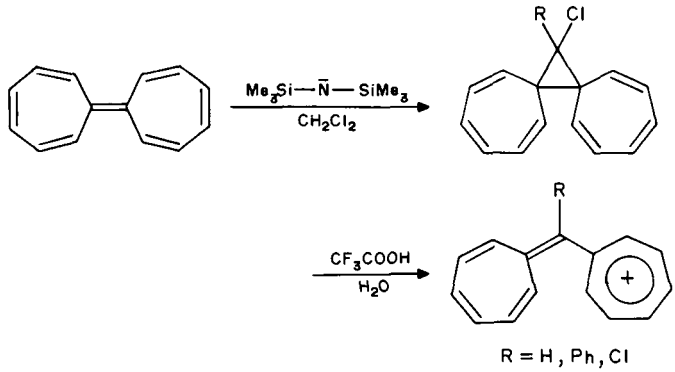


16 − 87%

El = Br, CHO, NO_2, $COCF_3$, tropyl

SCHEME 60

Parent heptafulvalene adds chlorocarbenes at the central double bond (Scheme 61). After acid-induced cyclopropane ring opening, dark blue solutions of delocalized heptafulvenyltropylium cations are generated[234].



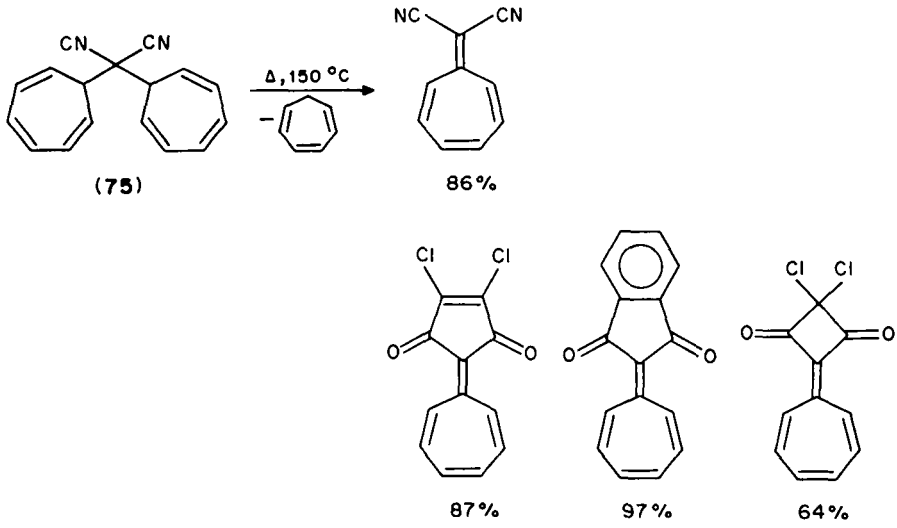
R = H, Ph, Cl

SCHEME 61

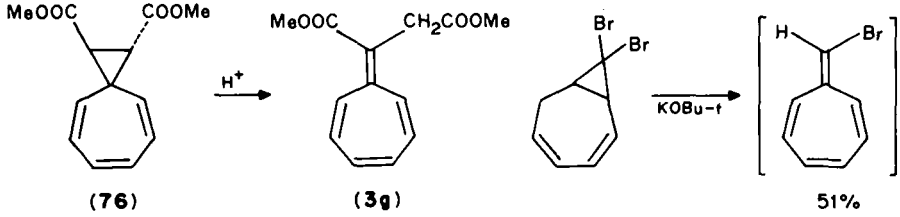
5. By fragmentation and rearrangement of precursors

A series of electronically stabilized heptafulvenes has been prepared by thermal fragmentation of dicycloheptatrienylmalononitrile and related compounds[235-237]. Although the sequence outlined in Scheme 62 is formally similar to the base-induced elimination of exocyclic leaving groups of cycloheptatrienes (see Scheme 56), it is more probably initiated by extrusion of either a tropylium cation or a cycloheptatrienyl radical of **75**.

Two rearrangements of bicyclic precursors have been reported[239,240] (see Scheme 63): acid-catalyzed rearrangement of spiro [2.6] nona-2,4,6-triene **76** gives stabilized heptafulvene **3g** in a high yield[238] (see Reference 239 too). It may be assumed that the sequence is initiated by exocyclic protonation and cyclopropane ring opening to give a substituted tropylium cation. The base-induced HBr elimination of 8,8-dibromobicyclo [5.1.0]-octa-2,4-diene is mechanistically more complicated[240]. Unstable 8-bromoheptafulvene has been trapped as an [8 + 2]-cycloaddition product.



SCHEME 62

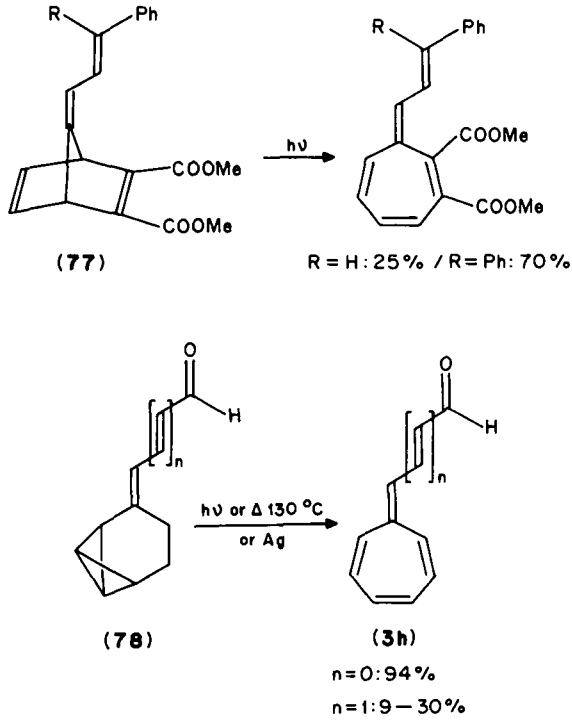


SCHEME 63

Finally, light-induced rearrangements of 7-(1-alkenylidene) 2,3-dimethoxycarbonyl-bicyclo [2.2.1] hepta-2,5-dienes **77** have been investigated (Scheme 64)[241,242]. Compounds of this type are available by Diels–Alder reactions of 6-vinylpentafulvenes (**2**)[241]. Taking into consideration that substituted quadricyclanes could have been formed by intramolecular [2 + 2] cycloaddition, it is surprising to see that 1,2-bis(methoxycarbonyl)-heptafulvene is the main product. Furthermore, rearrangement of the rather exotic starting materials **78** gives vinylogous acylheptafulvenes of type **3h**[85].

D. Synthesis of Nonafulvenes

Nonafulvenes would not have been available without the spectacular synthesis of cyclononatetraenide (**8**)[243,244]. Later on, careful investigations showed[245] that alkali metals react with 9-*anti*-chloro- or 9-*anti*-methoxy [6.1.0] nona-2,4-6-triene (cf. **82**) predominantly or exclusively to give *cis,cis,cis,trans*-cyclononatetraenide (*ccct*-**8**), which may isomerize to all-*cis*-**8**[246]. This means that two cyclic 10π-anions may be used for nonafulvene syntheses, both being available in solutions of reasonable purity.

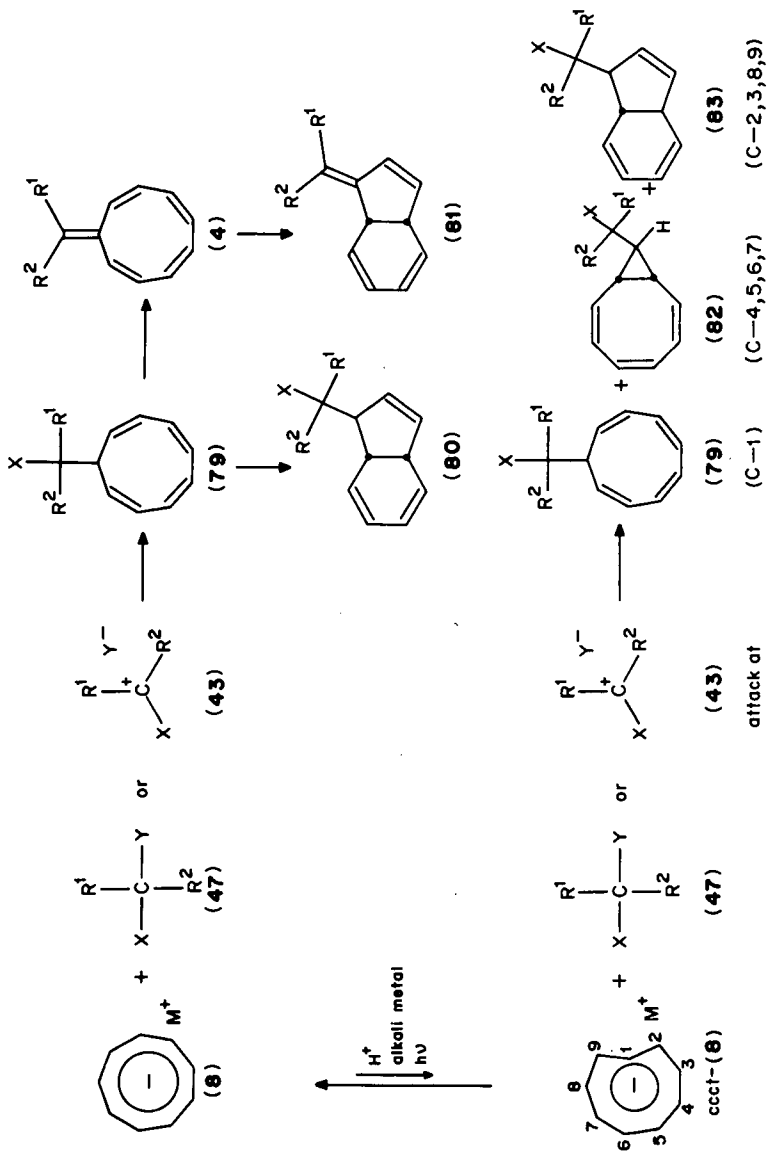


SCHEME 64

The general synthetic plan for nonafulvenes (**4**) is outlined in Scheme 65; it is analogous to most syntheses of pentafulvenes (**2**) where the 6π-anion cyclopentadienide (**6**) is applied as nucleophile: Cyclononatetraenide (**8**) (or *ccct*-**8**) reacts with electrophiles of type **47** or **43**, bearing two potential leaving groups, to give cyclononatetraenes **79**. Subsequent elimination of HX would give nonafulvenes **4**.

However, although Scheme 65 looks simple and straightforward, it is much more tricky than it seems to be[247]. One serious problem arises from the easy valence isomerization of both cyclononatetraenes (**79** → **80**) and nonafulvenes (**4** → **81**) even at reaction temperatures below – 20 °C. Furthermore, the cyclononatetraenide (**8**) is less nucleophilic than the cyclopentadienide (**6**), probably due to delocalization of the negative charge over nine carbon atoms.

Fortunately, with anions **8** and *ccct*-**8** two nucleophiles are available, of which *ccct*-**8** turns out to be more nucleophilic than **8**. However, several reaction products **79**, **82**, **83** have to be expected depending on the site of attack of the electrophile[248] (Scheme 65, bottom), and only attack at C-1 of *ccct*-**8** gives the synthetically useful cyclononatetraenes **79**. According to the experimental evidence available so far, cyclononatetraenes **79** are preferentially formed when *ccct*-**8** reacts with small electrophiles of type **47** or with most delocalized cations **43**[245,249]. When bulky electrophiles **47** react with *ccct*-**8**, then the anion preferentially reacts with C-atoms 4–7, so that bicyclo[6.1.0]nonatrienes **82** seem to be favoured[250]. These products are obtained by rearrangement of the primarily formed *cis, trans, cis, cis*-cyclononatetraenes[248].



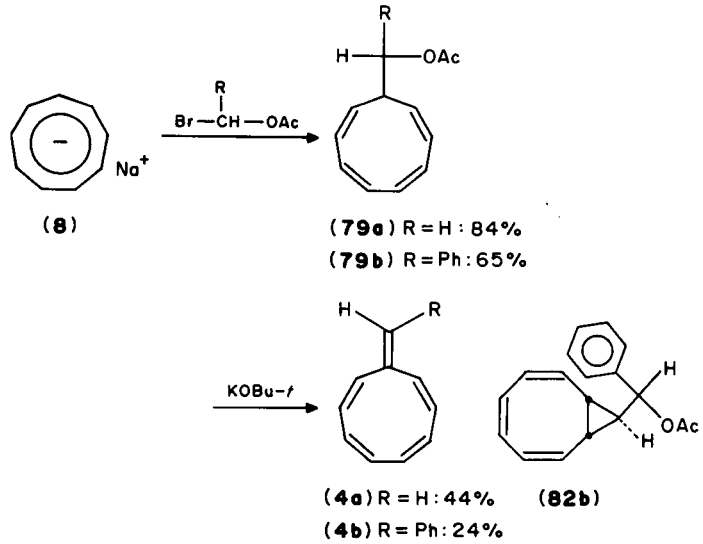
SCHEME 65

Unfortunately, preparative problems are still increased by the low acidity of cyclononatetraenes **79**: The pK_a value of cyclononatetraene has been estimated to be between that of cyclopentadiene (pK_a *ca* 15) and indene (pK_a *ca* 20)[243]. Combined with steric shielding of C-1, deprotonation of substituted cyclononatetraenes **79** is very troublesome. Finally, 1,5-proton shifts do not help as they are too slow at −20 °C.

1. Reaction of cyclononatetraenide with acetoxybromoalkanes

Acetoxychloro- as well as acetoxybromo-alkanes **47** are versatile bifunctional carbonyl derivatives[115], bearing at C-1 two leaving groups of different leaving qualities. They have been widely applied for the synthesis of a variety of 6-alkyl- and 6-aryl-pentafulvenes[116]. In fact, both sodium cyclononatetraenides **8** and *ccct*-**8** react with acetoxybromomethane at −30 °C to give acetoxymethylcyclononatetraene in a good yield, while nucleophilic substitution of acetoxychloromethane is too slow. The subsequent elimination of acetic acid out of **79a** only takes place with strong bases.

This sequence has been successfully applied to the parent nonafulvene (**4a**)[251,252] and to 10-phenylnonafulvene **4b** (Scheme 66). It is, however, very sensitive to changes in starting materials and reaction conditions. For instance, while bromobenzyl acetate reacts similarly with sodium cyclononatetraenide (**8**), reaction with sodium *cis,cis,cis,trans*-cyclononatetraenide (*ccct*-**8**) gives substituted bicyclo[6.1.0]nona-2,4,6-triene **82b**! Furthermore, elimination of HOAc from substituted cyclononatetraenes is not easy and fails to give major amounts of 10-alkylnonafulvenes.

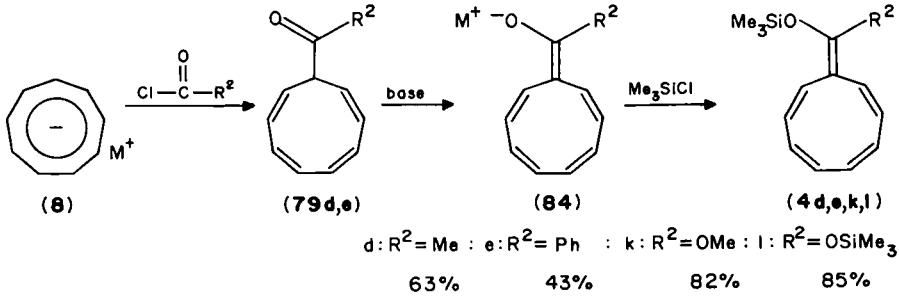


SCHEME 66

2. Acylation of cyclononatetraenide

Acylation of cyclononatetraenides **8** and *ccct*-**8** is an easy and straightforward synthetic procedure for 10-heterosubstituted nonafulvenes[253]. Both anions **8** and *ccct*-**8** react. Deprotonation **79** → **84** is facilitated because the acyl group is increasing the acidity of the

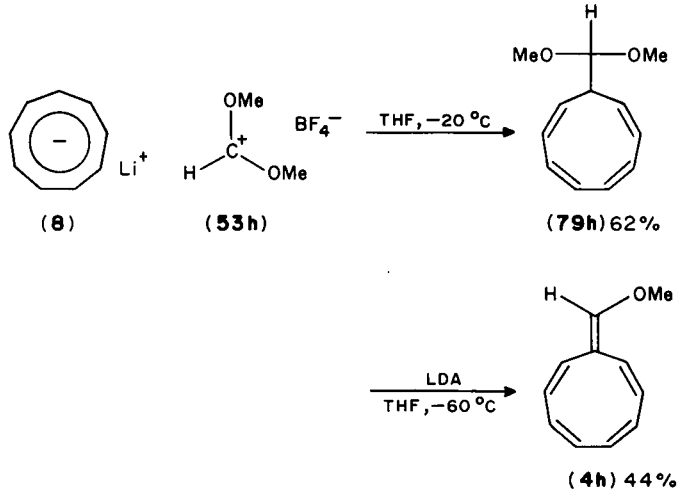
cyclononatetraene (Scheme 67). The hereby formed nonafulvenolate **84** equilibrates with the corresponding acylcyclononatetraenide[254], and final O-alkylation or O-acylation is strongly favoured over C-alkylation and C-acylation to give nonafulvenes in relatively good yields. A similar sequence using alkylated CS_2 as an electrophile gives 10,10-bis(methylthio)nonafulvene **4f**[255].



SCHEME 67

3. Reaction of cyclononatetraenides with dihetero carbenium ions

Cyclononatetraenides react easily with diheterosubstituted carbenium ions of type **53h**. So far, the sequence has been applied to the synthesis of 10-dimethylaminononafulvene (**4i**)[253] and 10-methoxynonafulvene (**4h**[256], Scheme 68). If there is a choice, all-*cis*-cyclononatetraenide **8** is the preferred nucleophile, because *ccct*-**8** may not only react with C-1 to give cyclononatetraenes **79** but also with (C-4)–(C-7) to give bicyclo[6.1.0]nonatrienes of type **82** as by-products[249]. Finally, deprotonation of cyclononatetraene **79h** needs strong bases like LDA. There is no doubt that this method is the preferred sequence for 10-heterosubstituted nonafulvenes.

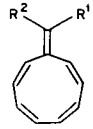


SCHEME 68

4. Reaction of cyclononatetraenides with trihetero carbenium ions

The sequence outlined in Scheme 69 is expected to give 10, 10-dihetero substituted nonafulvenes, and according to Table 17 this method has been widely used for that purpose. 10, 10-bis(dimethylamino)nonafulvene (**4r**) was the first simple nonafulvene to be prepared[7]. Although the sequence seems to be simple, it has to be mentioned that sterically hindered as well as electronically stabilized carbenium ions like **58r** need *ccct*-**8** which, with carbenium ions of type **58r**, predominantly reacts with C-1. Furthermore, if good leaving groups like Cl have to be eliminated from the intermediate cyclononatetraenes **79**,

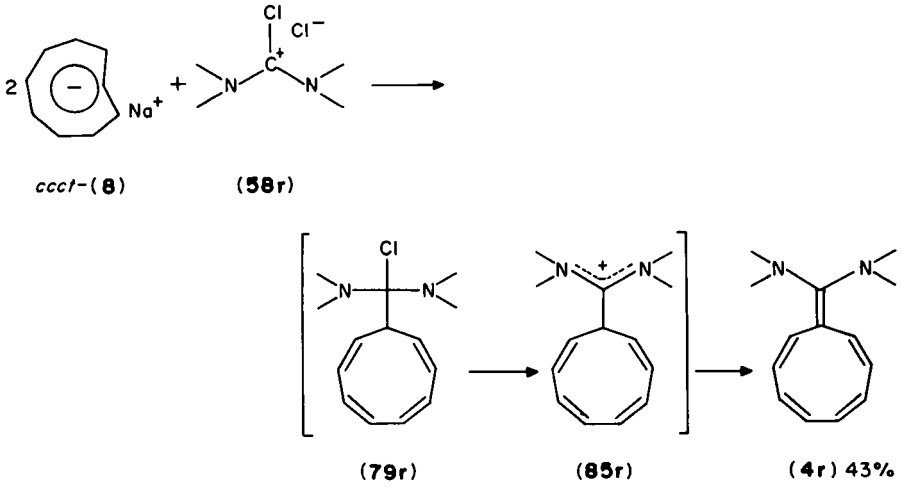
TABLE 17. Synthesis of non-annelated nonafulvenes (**4**)



No.	R^1	R^2	Reagent, conditions	Method	Yield (%)	Ref.
4a	H	H	1. $BrCH_2OAc$, 2. KO-*t*-Bu	1	37[a]	251, 252
4b	Ph	H	1. $BrCHPhOAc$, 2. KO-*t*-Bu	1	15[a]	256
4c	OAc	Me	1. AcCl, 2. K, 3. AcCl	2	80[b]	253
4d	$OSiMe_3$	Me	1. AcCl, 2. Base, 3. Me_3SiCl	2	63[b]	253
4e	$OSiMe_3$	Ph	1. $PhCOCl_2$, 2. Base, 3. Me_3SiCl	2	43[b]	253
4f	SMe	SMe	1. $CH_3S—CS^+X^-$, 2. CNT^-, 3. MeI	2(5)	70[a] (25–40)[a]	255, 256
4g	S—CH_2CH_2—S		1. CS_2, 2. CNT^-, 3.	5	51[a]	256
4h	OMe	H	1. $(MeO)_2CH^+BF_4^-$, 2. LDA	3	27[a]	256
4i	NMe_2	H	1. $Me_2N—CH^+—OMeX^-$ [2. Base]	3	80[b]	253
4k	OMe	$OSiMe_3$	*c*	2	crude	253
4l	$OSiMe_3$	$OSiMe_3$	*c*	2	crude	253
4m	OMe	OMe	1. $(MeO)_3C^+X^-$, 2. HBF_4, 3. NEt_3	4	14[a]	256
4n	O—CH_2CH_2—O		1. MeO—  X^- 2. HBF_4 3. MEt_3	4	18[a]	256
4o	OEt	OEt	1. $Me_2N—\overset{+}{C}(OEt)_2X^-$ [2. Base]	4	crude	253
4p	NMe_2	OEt	1. $Me_2N—\overset{+}{C}(OEt)_2X^-$ [2. Base]	4	mixture	253
4q	NMe_2	SMe	1. $Me_2N—\overset{+}{C}(Cl)—SMe$ [2. CNT^-]	4	41[a]	256
4r	NMe_2	NMe_2	1. $Me_2N—\overset{+}{C}(Cl)—NMe_2Cl^-$ [2. CNT^-]	4	7 43	7 256
4s	NEt_2	NMe_2	1. $Me_2N—\overset{+}{C}(Cl)—NEt_2Cl^-$ [2. CNT^-]	4	33	256
4t	NEt_2	NEt_2	1. $Et_2N—\overset{+}{C}(Cl)—NEt_2Cl^-$ [2. CNT^-]	4	crude	256

[a]Overall yield starting with cyclononatetraenide.
[b]Yield starting with acyl-cyclononatetraenide.
[c]Synthesis of appropriate acylcyclononatetraenide over several steps.

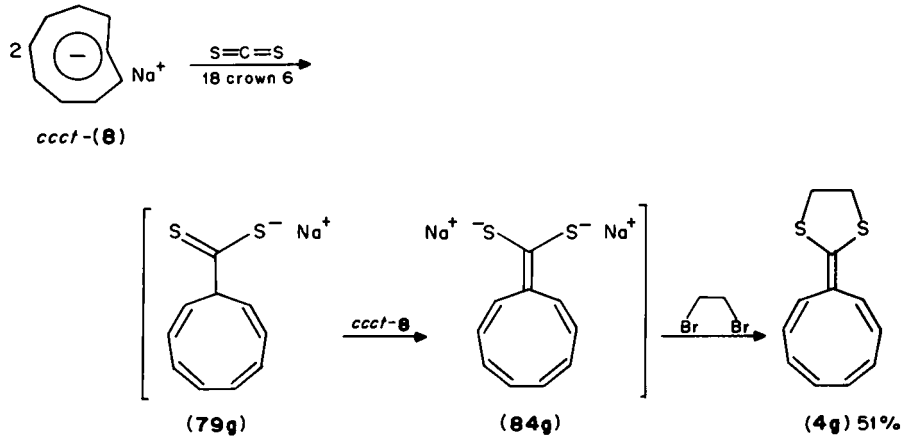
nonafulvenes are formed in a simple one-pot procedure, since *ccct*-CNT^- is acting as a base as well. Mechanistically, the sequence **79r** → **85r** → **4r** is the most reasonable pathway[256]; it is supported by an isolated intermediate of type **85r**.



SCHEME 69

5. Reaction of cyclononatetraenide with CS_2

Similarly to pentafulvenes[141], exocyclically thioalkylated nonafulvenes are available by reacting CS_2 with *ccct*-cyclononatetraenide, while lithium cyclononatetraenide is not nucleophilic enough to allow a smooth reaction (Scheme 70). Since deprotonation **79g** → **84g** takes place in the presence of *ccct*-**8**, 10,10-(ethylenedithio)-nonafulvene **4g** is available by a simple one-pot procedure[256].

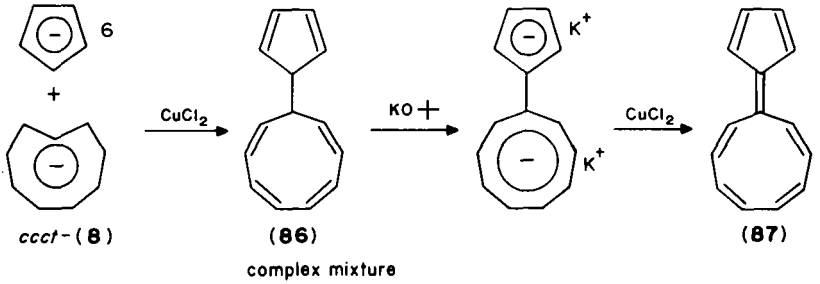


SCHEME 70

The key step of all the methods 1–5 applied for the synthesis of non-annelated nonafulvenes (Table 17) was the nucleophilic attack of cyclononatetraenides **8** and *ccct*-**8** at appropriate electrophiles of type **47** and **43**. It should be pointed out that anions **8** and *cct*-**8** may be oxidized to give delocalized radicals which may recombine.

6. *Oxidative coupling of Hückel anions 6 and 8*

Very recently, nona-penta-fulvalene (**87**) has been prepared by the coupling–deprotonation–coupling sequence shown in Scheme 71[257]. The main problem is the separation of **86** from the complex reaction mixture containing dihydropentafulvalene[170] and dihydrononafulvalene[258] as well. A similar sequence starting with *ccct*-**8** alone gives unstable nonafulvalene[259]. Both nonafulvalenes behave like very reactive nonafulvenes.



SCHEME 71

7. *Synthesis of some annelated nonafulvenes*

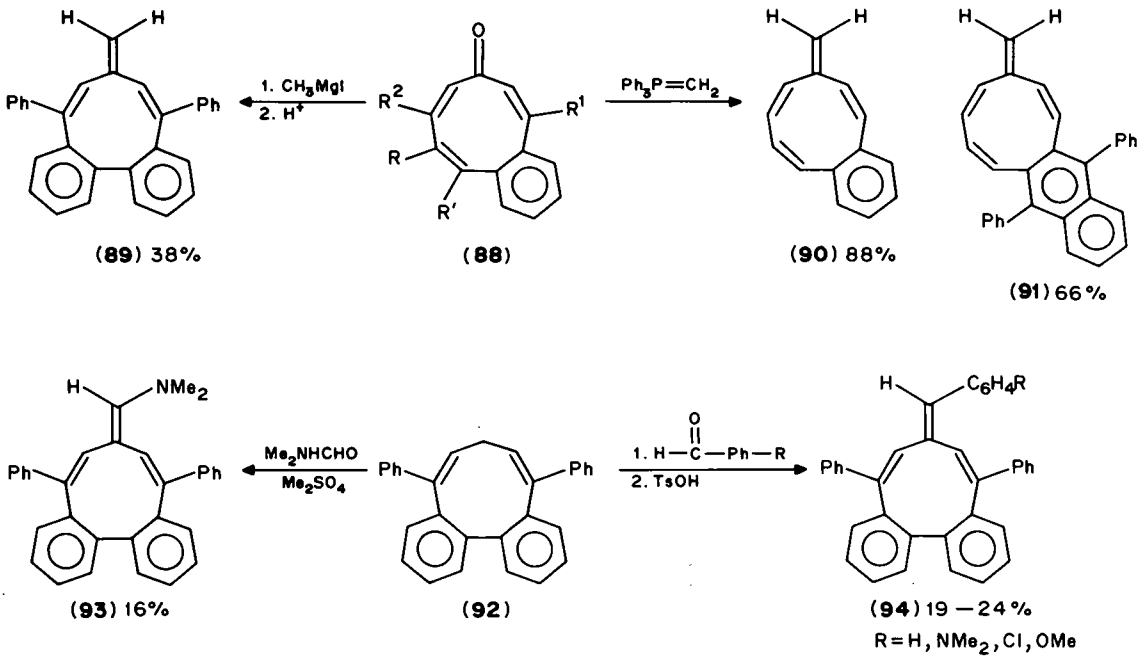
Various examples in the pentafulvene series clearly demonstrate that, with increasing annelation, the typically fulvenic character gets lost. Besides limited space, this is one major reason why annelated fulvenes are not discussed in detail in the framework of this chapter. Due to the fact that nonafulvenes are not planar (see Section V), the electronic influence of aromatic rings is expected to be quite small, although conformational equilibria may be strongly influenced by aromatic substituents or annelated rings. So there is some legitimization for a brief survey of annelated nonafulvenes.

First of all, due to the higher thermal stability of annelated starting materials **88** and **92** as well as of products (Scheme 72), considerably higher reaction temperatures (e.g. 20 °C) are allowed so that cyclononatetraenide **92** undergoes Vilsmeier reactions (**92** → **93**) as well as modified Thiele synthesis[260] (**92** → **94**). Such conditions would immediately induce polymerization of simple nonafulvenes. Furthermore, annelated cyclononatetraenones of type **88** are stable enough, so that Grignard additions (**88** → **89**) and Wittig reactions (**88** → **90**, **91**) are easily possible[260,261].

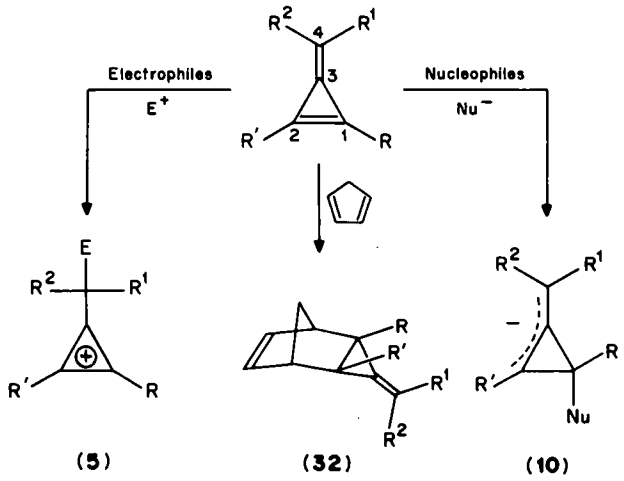
III. REACTIONS OF FULVENES

A. Reactions of Triafulvenes

Not much is known about reactions of electronically not stabilized triafulvenes, since so far the research interests were mainly focused on the synthesis and spectroscopic properties of these unstable cross-conjugated ring systems. Generally, reactivity follows the predictions based on frontier-orbital considerations as well as on the relative energy of reactive intermediates (Scheme 73; see Introduction).



SCHEME 72. Synthesis of annelated nonafulvenes



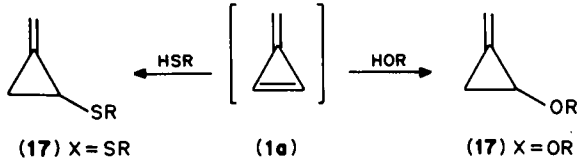
SCHEME 73

Reactions with *electrophiles* have so far been mainly limited to protonation, taking place at the exocyclic C atom to give substituted cyclopropenylium salts **5** (see, for instance, References 5, 36, 47, 48, 68, 70).

The parent triafulvene (**1a**)[64,67] as well as alkyl-substituted triafulvenes[63,68] easily undergo the expected *[4 + 2] cycloaddition* **1** → **32** with cyclopentadiene; the *endo* configuration of **32** follows from spectroscopic data[67].

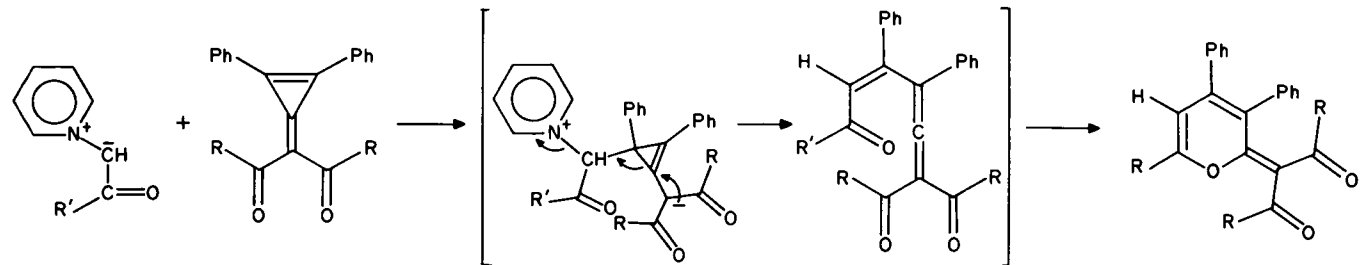
Triafulvenes add *nucleophiles* at C-1/C-2 to give delocalized allyl anions of type **10**; subsequent protonation will give substituted methylenecyclopropanes. This is so facile with **1a**, that base-catalyzed elimination of triafulvene precursors normally gives addition products **17**, instead of triafulvene itself[59–61,63–65].

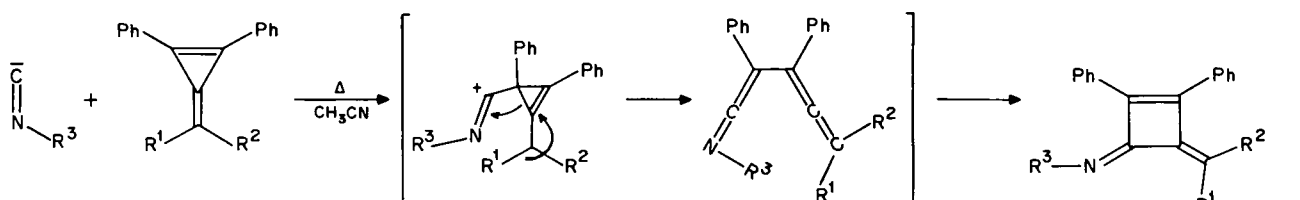
The parent triafulvene **1a** is thermally very unstable and polymerizes quickly in solution above −40 °C[64]. Stability is dramatically increased by −M substituents like CN groups at the exocyclic C atom and by bulky substituents at the ring. Therefore, much more is known about the reactive behaviour of electronically and sterically stabilized triafulvenes, especially as far as reactions with nucleophilic reagents are concerned. Some of these reactions will be summarized in the following; they are generally initiated by a nucleophilic attack at C-1/C-2 of **1** (see Scheme 73).



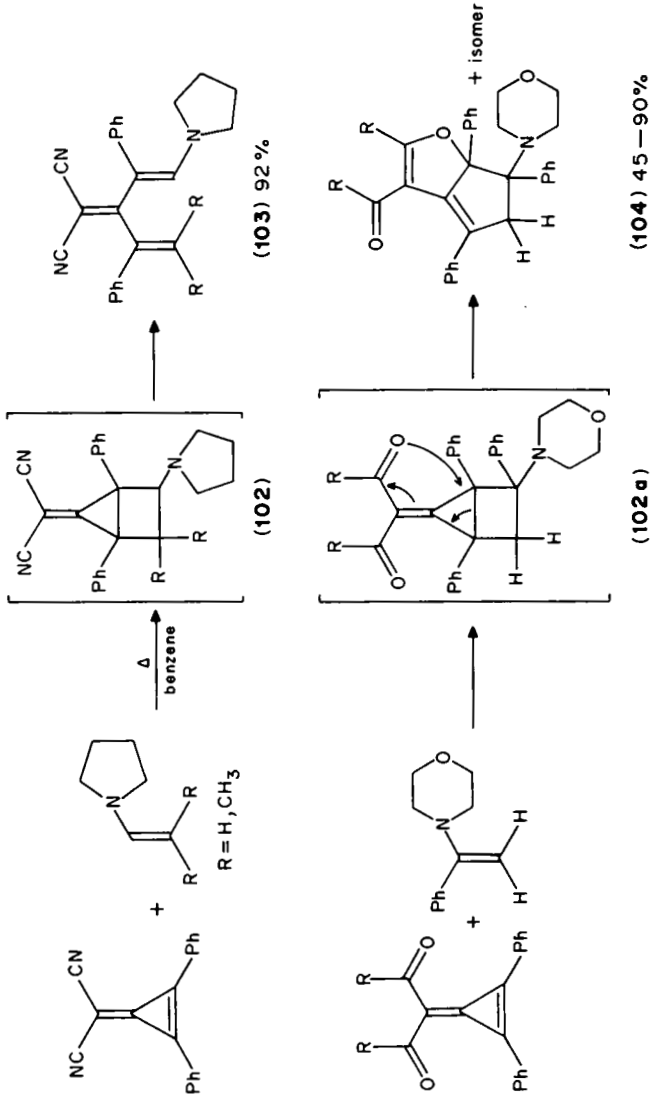
SCHEME 74

4,4-Diacyltriafulvenes react with pyridinium enolbetaines **95** to yield 2-(diacylmethylene)pyranes of type **98**. The reaction may be understood by assuming a C-nucleophilic attack at C-1 of the triafulvene followed by the rearrangement **96** → **97** → **98**[44]. Furthermore, isonitriles react with stabilized triafulvenes **1** in aprotic media to give 2-methylenecyclobutene-1-one imines **101**[262]. Once again it is reasonable to assume a





SCHEME 75

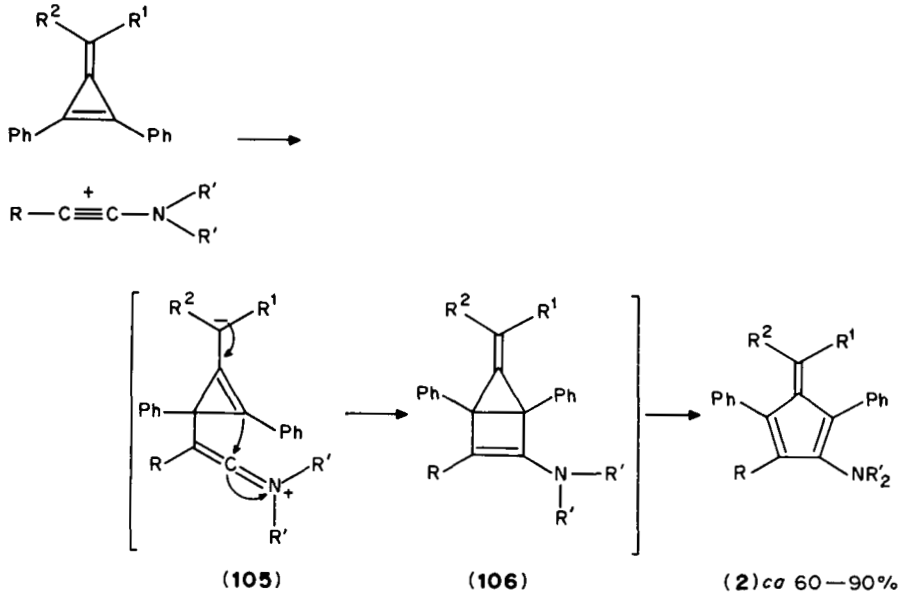


SCHEME 76

nucleophilic attack by the isonitrile at C-1 of **1** followed by ring opening **99** → **100** and electrocyclic reaction **100** → **101** (Scheme 75).

Substituted 4,4-dicyanotriafulvenes and enamines give substituted 3-dicyanomethyl-enepenta-1,4-dienes **103** with very good yields, which strongly suggests 5-methyl-enebicyclo[2.1.0]pentanes **102** as intermediates[263]. 4,4-Diacyltriafulvenes and enamines seem to form a similar intermediate, but according to the isolated products of type **104**, one of the acyl groups is involved in the rearrangement **102a** → **104** (Scheme 76[264]).

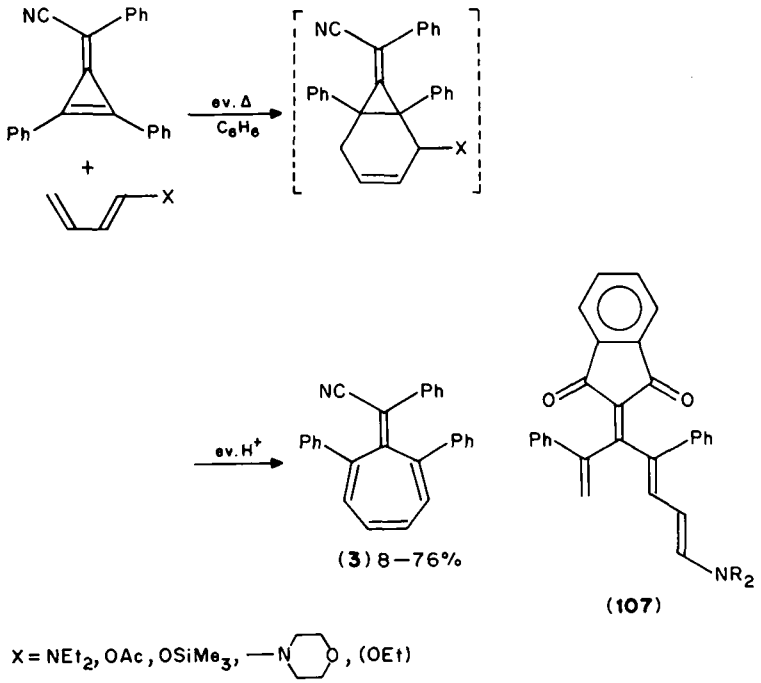
Nucleophilic ynamines react with a variety of electrophilic triafulvenes (R^1, R^2 = CN, COOR) in a similar way to enamines (Scheme 77[265,266]). The first step is again a nucleophilic attack of the ynamine to give the dipolar intermediate **105**, which in turn, by an electrocyclic reaction of **106**, gives pentafulvenes **2**. The sequence is of interest for the preparation of pentafulvenes with inverse electron demand.



SCHEME 77

It is not surprising that triafulvenes with electron-accepting substituents at C-4, such as cyano and acyl groups, may react with electron-rich dienes. This sequence has very recently been investigated in detail[267]. For X = NR_2 and OEt the bicyclic intermediates may be isolated. They are transformed to heptafulvenes **3** thermally or by acid catalysis (X = OAc, $OSiMe_3$, Scheme 78). The reason why 1-aminobutadienes in some cases add as 2π systems to give products of type **107** after ring-opening of the bicyclic intermediates (Scheme 76) is not yet known[267]. These results shown that triafulvenes are attractive precursors of heptafulvenes.

1,3-Dipolar cycloadditions of electrophilic triafulvenes[268,269] have been reported (Scheme 79) which show that triafulvenes may be used as C_3-building blocks for the synthesis of 6-membered heterocycles. In both cases shown in Scheme 79, triafulvenes bearing various electron-accepting groups have been reacted[268,269]. In one example,



SCHEME 78

diazomethane adds in the same way, but thermal treatment of the primary product gives substituted pyrazoles[270].

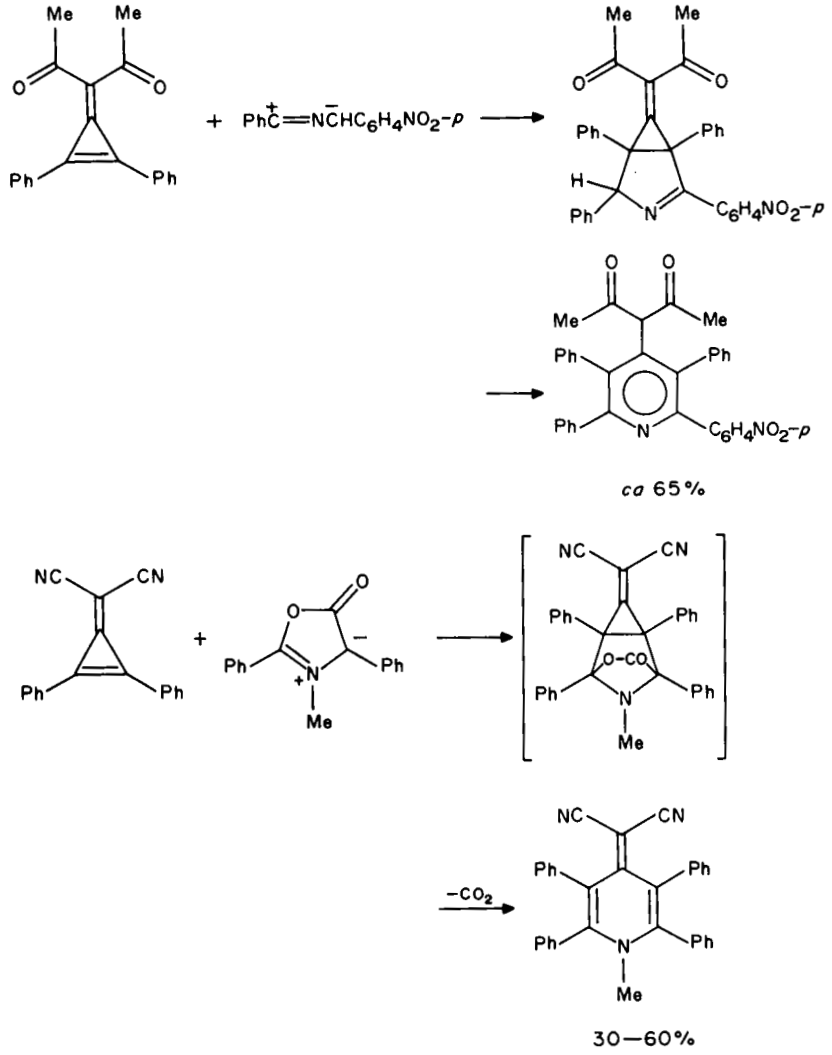
Finally, irradiation of 10^{-3} M solutions of stabilized triafulvenes initiates [2 + 2] dimerizations in which, predominantly, the C-1/C-2 double bonds are involved. The primary photodimers **108** easily rearrange to give substituted *p*-quinodimethanes **109**, which themselves are sensitive to further irradiation[271,272] (Scheme 80).

B. Reactions of Pentafulvenes

1. General remarks

Simple 6-alkyl- and 6,6-dialkylfulvenes are thermally unstable, sensitive towards oxygen and prone to acid-catalyzed polymerizations. These typical features reflect only one part of the reactivity of fulvenes, namely their trend to [4 + 2] cycloadditions (dimerizations) and their sensitivity towards electrophiles. A more detailed summary of pentafulvene reactivity is given in Scheme 81.

In fact, most pentafulvenes react easily with various electrophiles to give delocalized pentadienyl cations **9** which undergo polymerization (in the case of simple pentafulvenes) or may be stabilized by deprotonation to give substituted pentafulvenes (**9** → **2i**). On the other hand, pentafulvenes add nucleophiles at C-6. Depending on the nature of the exocyclic substituents, the cyclopentadienide intermediate **6** may undergo elimination of a leaving group X to give a new fulvene **2h**, or it may be protonated to cyclopentadienes of type **110**.

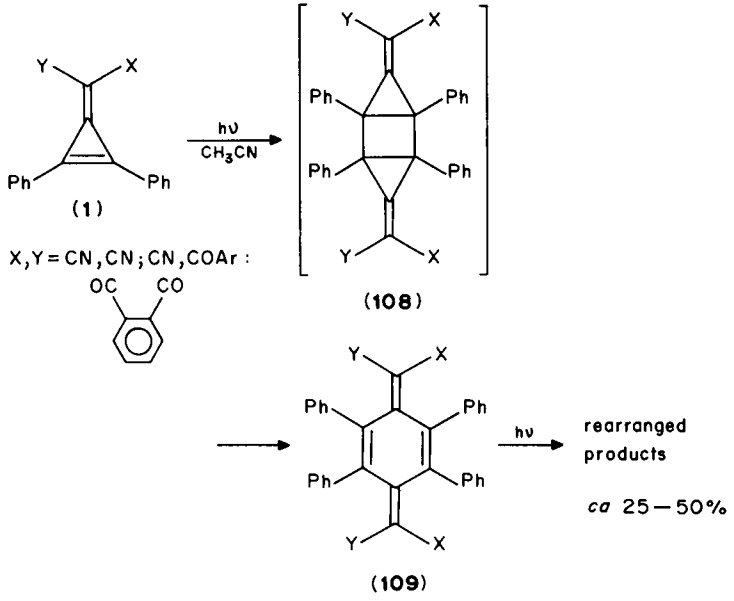


SCHEME 79

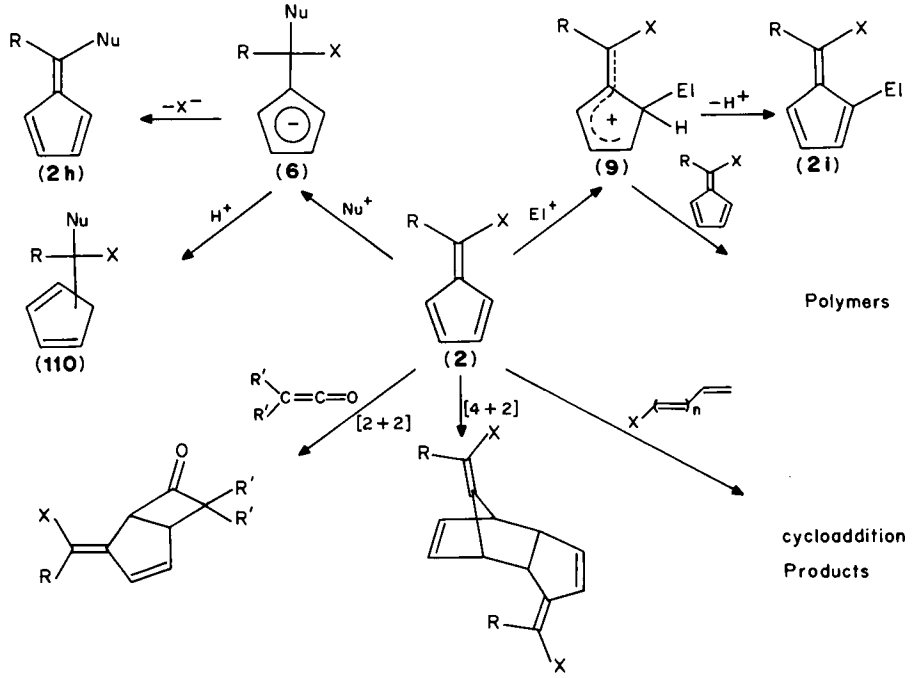
Electronically not stabilized pentafulvenes are reactive substrates for cycloaddition reactions. They may in principle react as 2π, 4π or 6π systems. In most cases, they react as 4π (or 2π) systems; e.g. in [4 + 2] dimerisation or in [4 + 2] cycloadditions with dienophiles, and in [2 + 2] cycloadditions with ketenes. So far, only some rare examples of [6 + 4]-cycloaddition reactions are known.

2. Reactions with nucleophiles and strong bases

According to expectations nucleophiles are attacking pentafulvenes at C(6) to form substituted cyclopentadienides as intermediates. When R^1 or R^2 is a good leaving group,

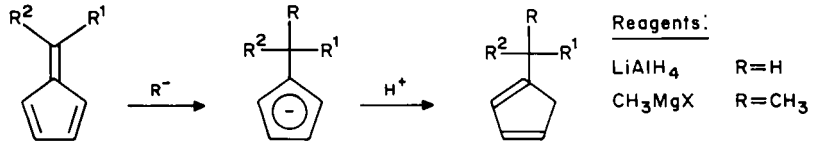


SCHEME 80



SCHEME 81

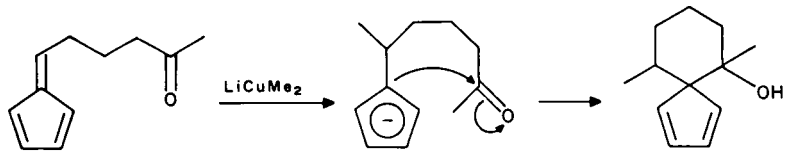
nucleophilic addition is followed by elimination; this sequence is quite frequently applied in fulvene synthesis (see Section II.B and Table 11). For alkyl- or aryl-substituted pentafulvenes, nucleophilic attack takes place as well so that substituted cyclopentadienides **6** are easily formed. Since there is no leaving group available, they are stable unless electrophiles are added. For instance, protonation gives substituted cyclopentadienes **110** with good yields[90,273,274]. Possible strong nucleophiles are $LiAlH_4$[90,273,274] or Grignard reagents without a β-hydrogen[275]; otherwise, not the C nucleophile attacks C-6 but a hydride anion is transferred[276] (Scheme 82).



(2) (6) (110)

SCHEME 82

A nice application of facile nucleophilic addition has been described in context with the synthesis of β-vetivone[108]. Nucleophilic attack of lithium dimethylcopper at C-6 of the pentafulvene derivative **2k** gives cyclopentadienide **6** which undergoes intramolecular ring closure to give the β-vetivone precursor **111** in excellent yields[108] (Scheme 83). Many other examples demonstrate that in alkyl-substituted cyclopentadienides of type **6**, C-1 is the most nucleophilic ring-C atom (Scheme 84).



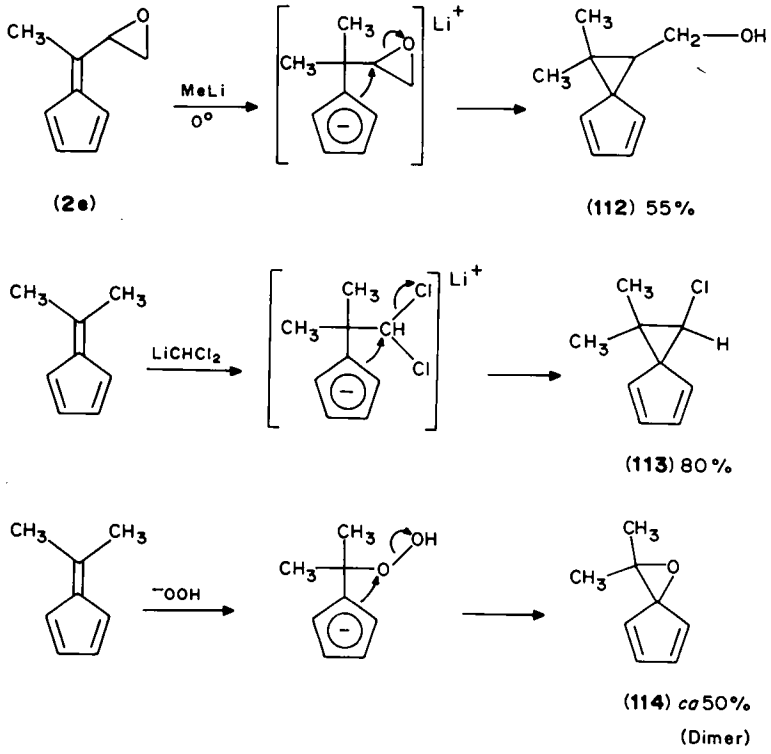
(2k) (6) (111)

SCHEME 83

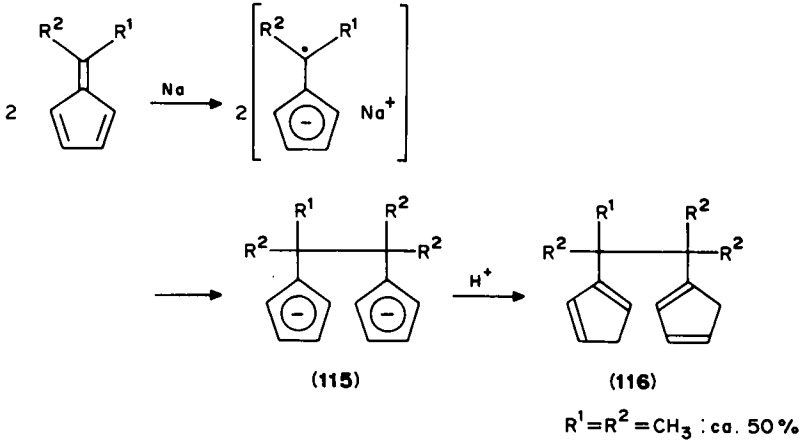
6-Methyl-6-oxiranyl-pentafulvene (**2e**) reacts with methyllithium to give substituted 1-hydroxmethyl-spiro[2.4]-hepta-4,6-diene **112**[107]; 6,6-dimethylfulvene adds a dichloromethyl carbanion at C-6, and the anionic intermediate is stabilized by intramolecular nucleophilic substitution to give **113**[277,278]. The same type of addition and nucleophilic substitution sequence is observed when 6,6-dimethylfulvene is reacted with hydroperoxide anion to give the spiro-oxirane **114**[279,280], which undergoes an easy Diels–Alder dimerization[279].

It was pointed out long ago that pentafulvenes react with sodium metal to give dimeric products of type **116**[201]. The reaction is easily understood in terms of a nucleophilic attack of an electron at C-6 followed by dimerization of the radical anion intermediate (Scheme 85). Bis-anions **115** are attractive precursors of exocyclically bridged ferrocenes[281,282] (for a review see Reference 283).

Finally, it should be mentioned that the α-protons of 6-alkyl- and 6,6-dialkylfulvenes are acidic. For 6,6-dimethylpentafulvene and 6-methyl-6-phenylfulvene pK_a values of 22.7 and 22.1 have been measured very recently in DMSO[284], while the pK_a of cyclopentadiene

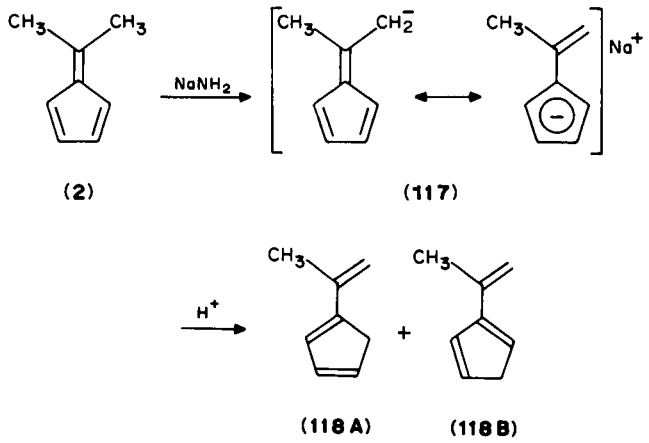


SCHEME 84



SCHEME 85

is 18.0 in the same solvent. Kinetically controlled protonation of the delocalized anion **117** gives a mixture of 4-isopropenylcyclopentadienes **118A** and **118B** together with traces of **2**[285] (Scheme 86). Under thermodynamic control, 6,6-dimethyl-pentafulvene (98%) strongly dominates over the cyclopentadiene tautomers **118A** and **118B** (totally 2%)[286]. Anions of type **117** are very reactive: they may be converted into ferrocenes[286], but they are prone to polymerizations as well[287].



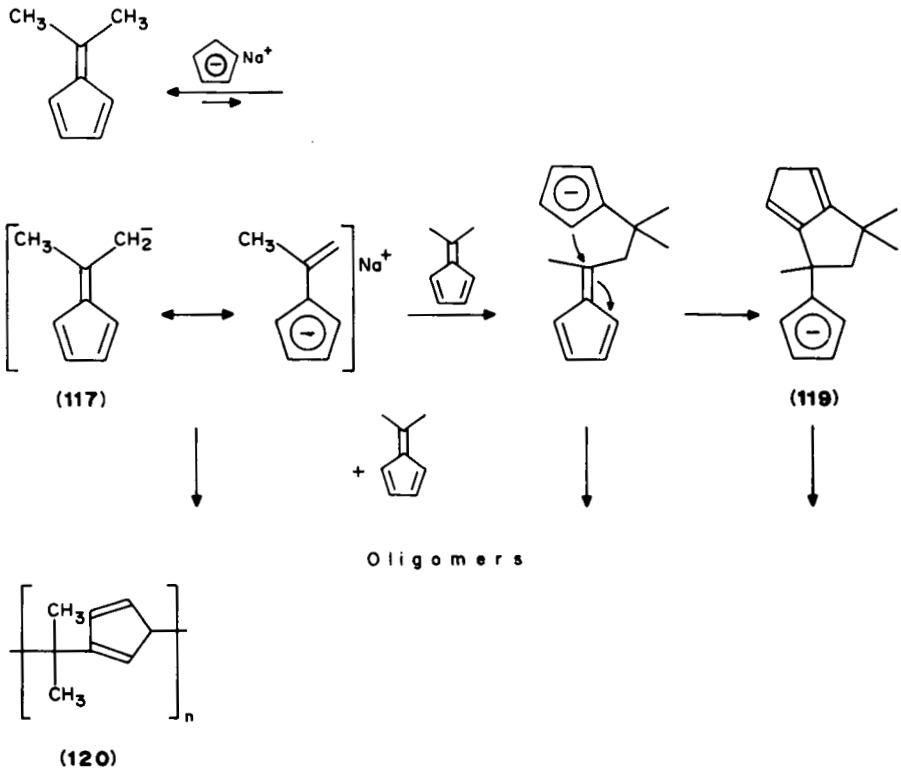
SCHEME 86

Anionic polymerization of 6,6-dimethylfulvene, originally expected to give regularly built polyfulvenes **120** with one cyclopentadiene ring per structural unit, actually gives a complex mixture of oligomers with a high amount of 1-cyclopentadienyl-1,3,3-trimethyl-1,2,3,5 tetrahydropentalene (= protonated anion **119** as a tautomeric mixture, 67% yield!) (Scheme 87)[287,288].

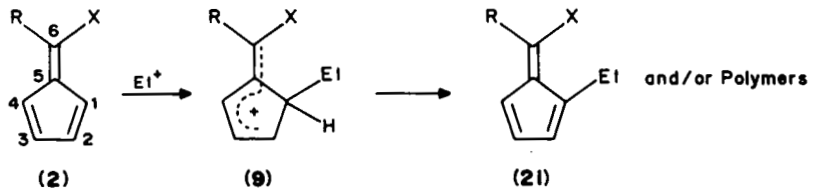
3. *Reactions with electrophiles*

Pentafulvenes have long been known to react easily with electrophiles[289]. According to charge distribution, the size of Hückel coefficients in the HOMO[290] and the relative energy of delocalized cations being formed by electrophilic attack at different positions[291], electrophiles are expected to add at C-1/C-4 (**2** → **9**). [MNDO calculations[291] show that cation **9**, obtained by electrophilic attack at C-1 of pentafulvene (**2a**) (R = X = H), is lower in energy by 8 kcal mol^{-1} than the cation which is obtained by electrophilic attack at C-2 of **2a**. Electrophilic attack at C-5 interrupts delocalization and raises the energy of the corresponding cation by 25 kcal mol^{-1} with respect to **9**.] In fact, the expected regioselectivity is often observed but sometimes overruled by steric effects. If X is an electron-donating group like NR_2, then cations **9** are normally stabilized by deprotonation **9** → **2i** to give substituted pentafulvenes (Scheme 88). On the other hand, simple 6-alkyl- and 6,6-dialkyl-pentafulvenes polymerize in the presence of strong acids or Lewis acids[288,292–295]. (A survey of former results up to 1968 can be found elsewhere[283].)

High molecular weight polymers are formed by reaction of 6,6-dimethyl-pentafulvene[292,293], other 6-alkyl- and 6,6-dialkylfulvenes, 6-phenyl- and 6,6-diphenylfulvenes with traces of strong acids (e.g. HCl) and Lewis acids (e.g. $ZnCl_2$ and $SnCl_4$)[293]. With 6,6-dimethylpentafulvene, molecular weights up to 350.000 have been measured. ^{13}C-NMR investigations show that the polymer chain of poly-6,6-



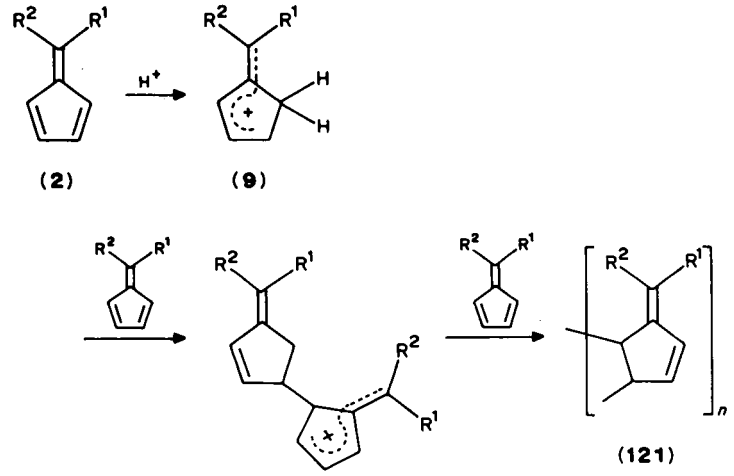
SCHEME 87



SCHEME 88

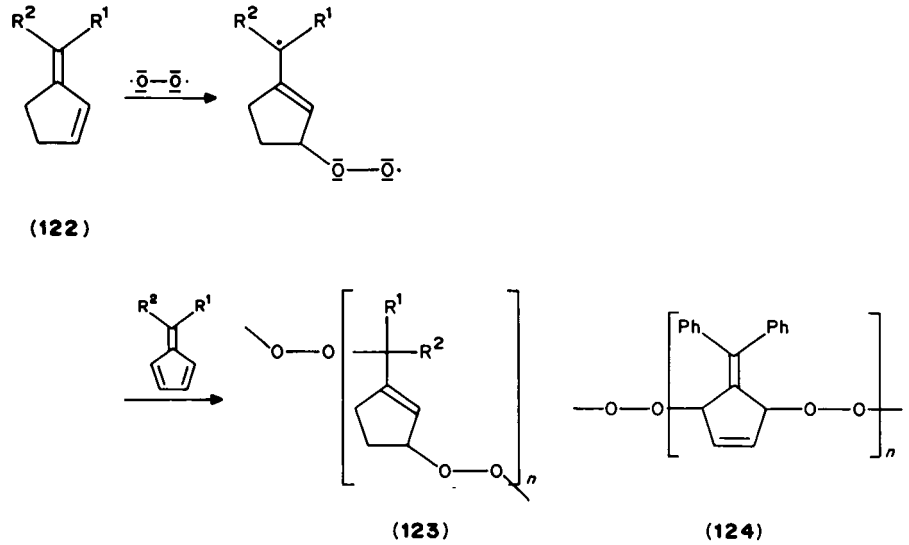
dimethylpentafulvene (**121**, $R^1 = R^2 = CH_3$) is regularly built up by structural units of type **121**[294,295] (Scheme 89). Cationic polyfulvenes are soluble in non-polar solvents like CH_2Cl_2, but they are extremely sensitive towards traces of molecular oxygen. The powdered polymer **121** ($R^1 = R^2 = CH_3$) incorporates somewhat more than 1 mol equivalent of oxygen per structural unit even in the dark; oxygen treatment induces crosslinking of the polymer chains so that insoluble products are obtained.

Simple pentafulvenes are also sensitive towards molecular oxygen. If solutions of 6-alkyl- or 6,6-dialkylfulvenes are stirred in the presence of oxygen, then crosslinked polymers slowly precipitate. Although this fact has been known since 1900[1], nothing was known about the structure of these polymers until recently.



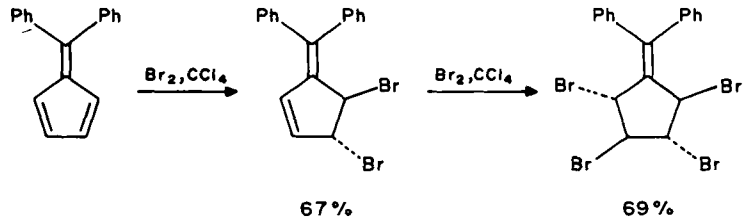
SCHEME 89

Recent investigations show that the diene system of 6,6-dialkyl-1,2-dihydropentafulvenes **122** reacts with molecular oxygen to give low-molecular-weight oligomers and polymers of type **123**[296,297], while cyclopentadiene gives oligomeric products of structure **124** (Scheme 90). These results explain perfectly the O_2 sensitivity of cationic polyfulvenes which are crosslinked by oxygen incorporation up to 1 mol O_2 per structural unit. They furthermore explain that 6,6-dialkylfulvenes are crosslinked by an oxygen uptake of up to 2 moles per structural unit[296,297]. It is not excluded, however, that 1:1 copolymers of oxygen with electronically stabilized fulvenes like 6,6-diphenyl- and 6-phenyl-6-methylpentafulvene[99,298] might have structures like **124**.



SCHEME 90

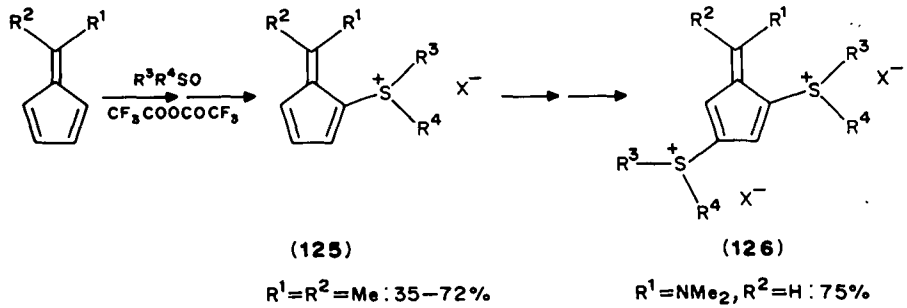
As far as halogenation of pentafulvenes is concerned, early results[283] are sometimes contradictory due to concurrent polymerizations and also the lack of spectroscopic structure determination. These results seemed to indicate that simple pentafulvenes might undergo addition and substitution as well[15,299], while the isolation of a crystalline tetrabromo compound has been reported after bromination of 6-methylfulvene in CCl_4 at 0 °C[300,301]. A reconfirmed example is given in Scheme 91[302]. On the other hand, 6,6-diphenylfulvene as well as 6-dimethylaminopentafulvene react with NBS or NCS by subsitution of ring protons to give ring-halogenated pentafulvenes[155] (see Section II.B.6).



SCHEME 91

Summarizing, we can conclude that electronically strongly stabilized fulvenes like 6-dialkylaminopentafulvenes react with electrophiles by an addition/deprotonation sequence to form substituted pentafulvenes **2i**, while simple pentafulvenes in most cases polymerize.

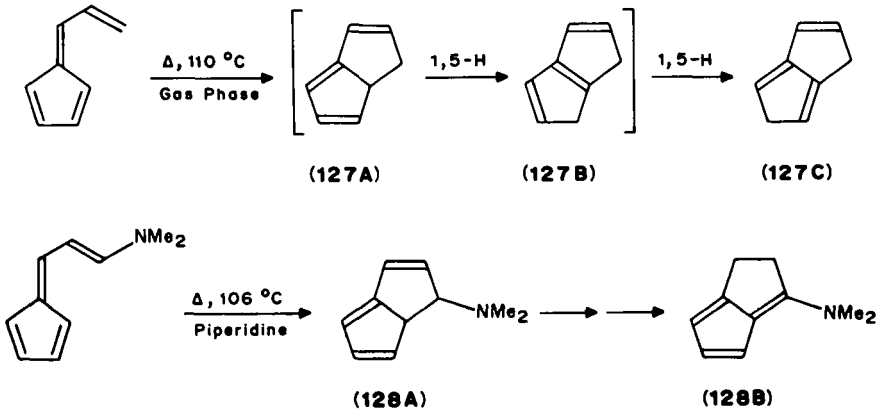
The only general method which allows an electrophilic substitution of stabilized and unstabilized pentafulvenes as well, consists in the reaction of pentafulvenes with DMSO or diarylsulfoxides to give fulvenesulfonium salts **125** ($R^1 = R^2 = Me$, Ph) and 1,3-bis- (**126**) or 2,3-*bis*-sulfonium salts for $R^1 = R^2 = NMe_2$, EtO and $R^1 = NMe_2 R^2 = H$ (Scheme 92[303]). Obviously in this case deprotonation of intermediates of type **9** is catalyzed by trifluoroacetate and is fast enough to prevent major polymerizations even of 6,6-dimethylfulvene.



SCHEME 92

4. Electrocyclic reactions of 6-vinylpentafulvenes

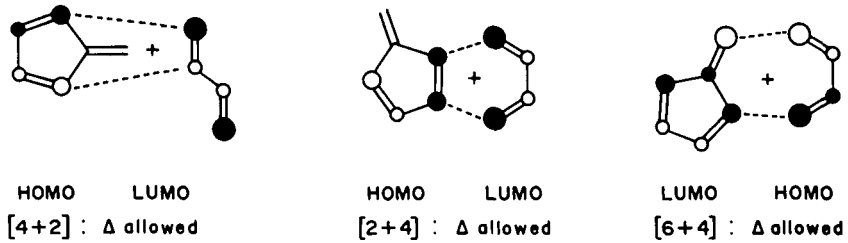
According to Scheme 93, electrocyclic ring closure to dihydropentalenes is possible for 6-vinylpentafulvene[304] (proceeding in the gas phase to give **127C**) and for 6-(2-dialkylaminovinyl) pentafulvenes[305] (proceeding in solution to give **128B**). Bicyclic aminofulvenes of type **128A** have been widely used as starting materials for pentalenes[306].



SCHEME 93

*5. Cycloaddition reactions**

Pentafulvenes may react in cycloadditions as 2π, 4π or 6π components. When a diene is approaching the pentafulvene, repulsive forces of the electron clouds are operating at a certain distance. Thus both molecules have to surpass a certain activation energy in order to form two single bonds in a cycloaddition, even if the reaction is known to be exothermic. This is true for every mode of cycloaddition, namely [2 + 2], [4 + 2], [6 + 2], [4 + 4] and [6 + 4] cycloadditions. [In the following, the first numeral in the bracket corresponds to the number of π electrons (= number of C atoms) with which the fulvene is reacting, while the second corresponds to the number of involved π electrons of the diene.] If, during the approach of the two neutral molecules, some binding interactions are increasingly felt, then it may be assumed that for that mode of addition the activation energy will be relatively low. If the process (let us say the [4 + 2] cycloaddition) is the only mode with strong binding interactions, then it may be predicted that [4 + 2] cycloaddition between the fulvene as 4π and the diene as 2π unit is the favoured reaction, because activation energy will be low.



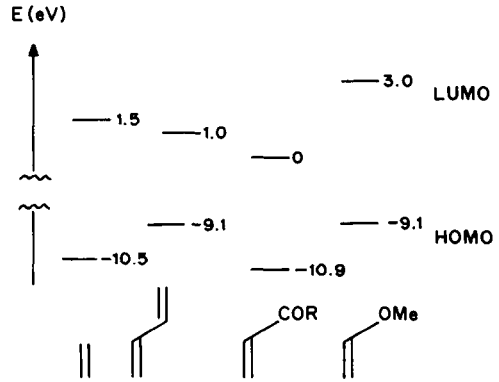
SCHEME 94. Thermally allowed supra-suprafacial cycloadditions

Such binding interactions or energy-lowering effects stem from interactions of the filled orbitals of one molecule with the empty ones of the other molecule. Frontier orbital theory

*Reactivity of fulvenes has been intensively discussed in terms of Frontier Orbital Theory[12]. A brilliant textbook concerning applications of Frontier Orbital Theory has been published[11].

says that the most important contribution stems from the interaction of the frontier orbitals, namely of the HOMO of one molecule with the LUMO of the other. If we want to see which cycloaddition modes between a pentafulvene and a diene are possible, we first draw all the different HOMO–LUMO combinations and ensure orbitals with the same sign (black–black, white–white) are approaching. Scheme 94 says that if both molecules are reacting with the same face ('suprafacial'), then [4 + 2], [2 + 4] and [6 + 4] cycloadditions are thermally allowed*. These selection rules dramatically limit the number of cycloaddition modes to two, one mode having two possible combinations (Scheme 94).

In order to decide which of the thermally allowed processes is operative, one has to look at the energy difference ($E_{HOMO} - E_{LUMO}$) of each cycloaddition, as well as at the sum of products of Hückel coefficients between the approaching carbon atoms†. If the energy difference ($E_{HOMO} - E_{LUMO}$) is comparatively small for a process of Scheme 94, then it may be assumed that this process is the favoured one, provided that the Hückel coefficients of the terminal carbon atoms are reasonably large.

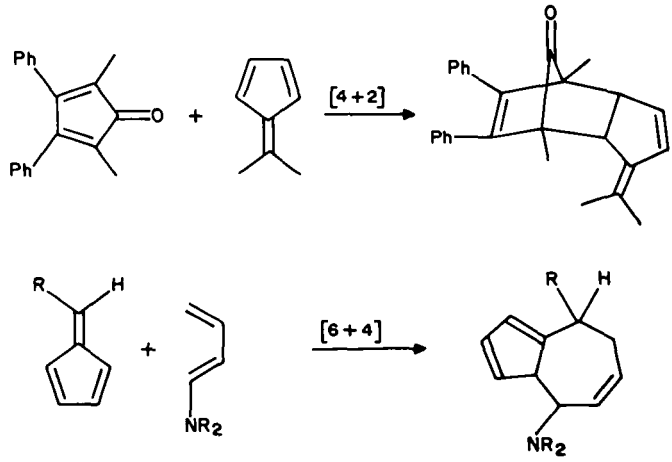


SCHEME 95. Influence of substituents on the energy of the frontier orbitals according to Reference 11

The energy of the HOMOs and LUMOs of enes, dienes, etc. is influenced by subsituents. Scheme 95 qualitatively shows substituent effects on ethylene; similar effects of terminal substituents are operative for dienes and trienes as well[11]. Generally, the energy of HOMO and LUMO of a linear olefin is lowered by −M groups like carbonyl and raised by +M groups like alkoxy (alkyl groups being considered as weak + M groups). Vinyl and aryl substituents are lowering the energy of the LUMO and raising the energy of the HOMO. As outlined in the Introduction, the same effects are induced by exocyclic substituents of pentafulvenes, with the only difference that the HOMO is practically uninfluenced because there are no Hückel coefficients at C-5 and C-6.

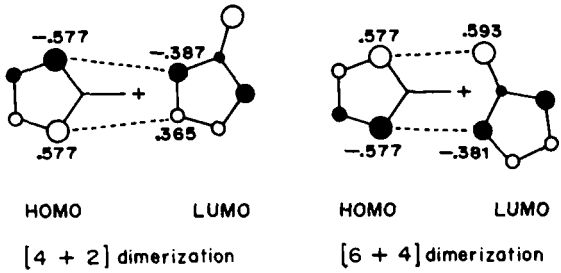
*These are the Woodward–Hoffmann Rules[307]. Note that if a molecule is photochemically activated, then an electron is promoted to a formarly empty orbital, so that another orbital now becomes the HOMO.

†According to perturbation theory[308,309], binding interactions between two approaching molecules are approximately given by $\sum[2c_a c_b \beta_{a,b}/(E_{HOMO} - E_{LUMO})]$ where c_a and c_b are the Hückel coefficients of the two approaching carbon atoms (and one has to consider both sets of terminal carbon atoms which are approaching in cycloaddition reactions), β is the resonance integral, and E_{HOMO} and E_{LUMO} are the energies of the HOMO and LUMO, respectively.



SCHEME 96

This fact is important for cycloadditions of pentafulvenes. So if pentafulvene is reacting with its HOMO (e.g. in cycloaddition with an electron-deficient diene like a cyclopentadienone, which is reacting with its low-energy LUMO), then it cannot undergo [6 + 4] cycloadditions because the Hückel coefficient at C-6 is zero; in fact a [2 + 4] cycloaddition is observed[310–312]. [6 + 4] cycloadditions of pentafulvenes are possible if the LUMO of pentafulvenes becomes the important frontier orbital. This is the case in reactions with dialkylaminobutadienes having a high-energy HOMO, where 6,6-dimethylpentafulvene reacts as a 6π system (Scheme 96[313]).



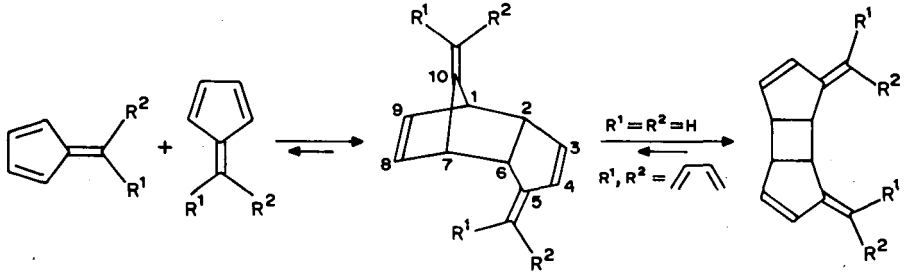
SCHEME 97. Frontie orbitals and Hückel coefficients for [4 + 2] and [6 + 4] dimerizations reactions of pentafulvenes

In dimerization reactions of pentafulvenes (Scheme 97), the most important binding contribution stems from the HOMO(fulvene)–LUMO(fulvene) interaction. Since the ($E_{HOMO} - E_{HOMO}$) difference is naturally the same for [4 + 2] and [6 + 4] dimerization, one has to look at the Hückel coefficients. Because the sum of products of coefficients is larger for the [6 + 4] mode, one would expect this mode to operate. Numerous results show, however, that the normal dimerization reaction is a [4 + 2] cycloaddition of two fulvene units, possible because steric interactions for 6-substituted pentafulvenes are much larger in [6 + 4] cycloadditions[283,314].

*6. Dimerization of pentafulvenes**

In the absence of traces of acid, 6-alkyl- and 6,6-dialkylfulvenes undergo Diels–Alder dimerization reactions to give—according to high-field NMR investigations—the *endo* stereoisomer **129**[314]. (Earlier reports assuming a polymerization of **2a** and **2b**[13,300] were erroneous.) In pure solutions stored at 20 °C the half-life of the conversion strongly increases from the parent pentafulvene (**2a**) (*ca* 3.3 h) to 6-methylpentafulvene (*ca* 1 week) and 6,6-dimethylfulvene (8–10 months!). A very fast Diels–Alder reaction has been reported for pentafulvalene **2** (R^1, R^2 = CH=CH—CH=CH)[170].

Diels–Alder dimers **129** of simple pentafulvenes are thermally quite unstable, in some cases ($R^1 = R^2 = CH_3$; R^1 = H, $R^2 = CH_3$) dissociating to the monomeric yellow pentafulvenes. For the dimers of the parent pentafulvene **2a** ($R^1 = R^2$ = H)[314] as well as of pentafulvalene (R^1, R^2 = CH=CH—CH=CH)[170], the thermal rearrangement **129** → **130** has been reported. It is easily explained by the rupture of the allylic (C-1)—(C-2) bond of the dimer followed by a switch of one fulvene unit and the formation of a new bond between (C-2) and (C-8) of **129** (Scheme 98).



(2) **(129)** *ca* 60 % **(130)**

SCHEME 98

If pure 6,6-dimethylpentafulvene is heated at 60 °C in order to accelerate the slow Diels–Alder reaction, then a trimer **132** is isolated from the reaction mixture containing other stereoisomers and oligomers[315]. The most reasonable pathway is given in Scheme 99. It shows that, although Diels–Alder dimerization dominates under kinetic control at low temperature, [6 + 4] dimers **131** could be favoured thermodynamically.

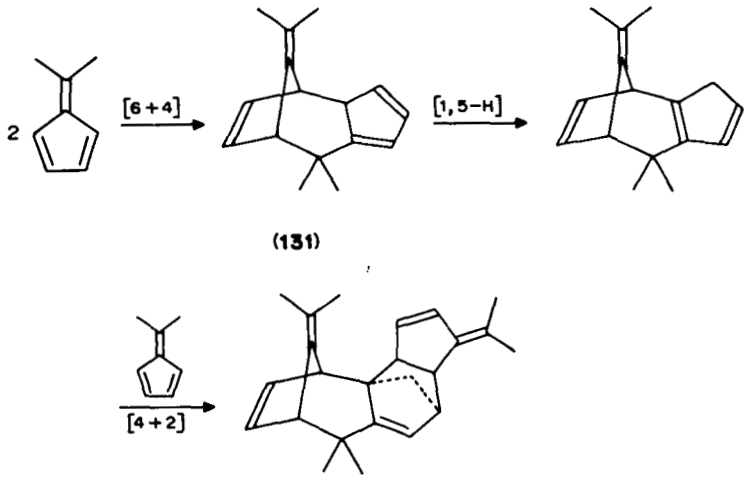
A similar example has recently been reported[316]. The highly strained bicyclic pentafulvene **133** is at low temperature in equilibrium with its stereoselectively and periselectively formed Diels–Alder dimer **134**. At 0 °C only the NMR signals of the monomer **133** are seen. Above +20 °C, **133** is irreversibly transformed into **135**, possibly by [6 + 4] cycloaddition followed by fragmentation of CO (Scheme 100).

7. Cycloadditions†

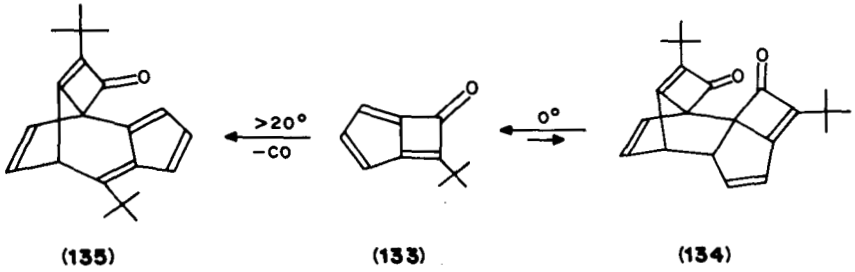
Most pentafulvenes undergo an easy [4 + 2]-cycloaddition reaction with electron-deficient *olefins* like maleic anhydride, acetylenedicarboxylate, tetracyanoethylene, *N*-phenylmaleimide, nitro- and cyano-ethylene, methyl vinyl ketone, etc. Of the two possible

*For early results see References 15, 283.

†For earlier examples see Reference 283. Numerous recent examples have been listed in Reference 313.



SCHEME 99

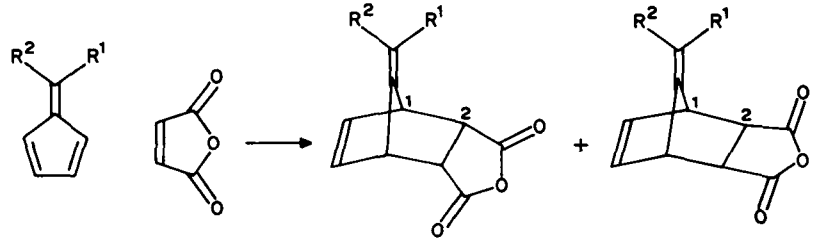


SCHEME 100

stereoisomers, *endo*-**136** is usually favoured over *exo*-**136** at low temperature, although stereoselectivity is not as high as in dimerizations. [4 + 2] cycloadditions are not easy and products of type **136** are missing in most cases of electronically stabilized pentafulvenes like 6,6-bis(dimethylamino)pentafulvene, 6,6-bis(alkoxy)pentafulvenes and 6-dimethylaminopentafulvene[123] (Scheme 101).

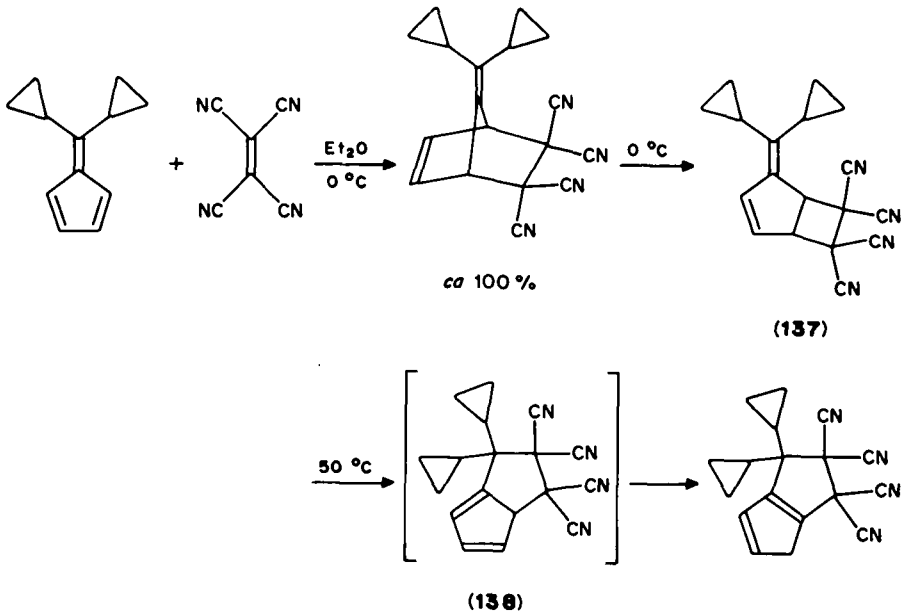
Some [4 + 2]-cycloaddition products are thermally quite unstable. A beautiful example is given in Scheme 102[317], where 6,6-dicyclopropylpentafulvene reacts with tetracyanoethylene at low temperature to give the expected [4 + 2]-cycloaddition product. It then rearranges in a clean first-order reaction, possibly through a dipolar intermediate, to give the formal [2 + 2] cycloadduct. **137** is unstable at temperatures around 50 °C and rearranges once more to the formal [6 + 2] product **138**, which finally forms the most stable tautomer by a 1,5-H shift.

If both allylic C—C bonds of the [4 + 2]-cycloaddition products are weak, then *endo*-**136** ⇄ *exo*-**136** equilibrations may take place by heating. *Exo* and *endo* stereoisomers are easily distinguished if the size of the H, H coupling constant $J_{1,2}$ may be established: $J_{1,2}$ is in the range of 4 ± 1 Hz for the *endo* isomer and below 1 Hz for the *exo* isomer[314,318].



endo-(136) *exo*-(136)

SCHEME 101



ca 100 %

(137)

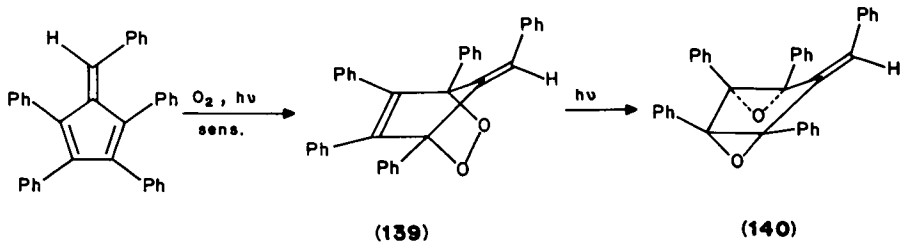
(138)

SCHEME 102

The sensitized photoreaction of oxygen with 1,2,3,4-tetra- and pentaphenylpentafulvenes[319,320] and 6,6-dimethylfulvene[321,322] may be understood as [4 + 2] cycloaddition giving 'endoperoxides' **139** as primary products, which in some cases give bis-epoxides **140** after subsequent (not sensitized) irradiation[319] and in other cases react under ring opening[320–322] (Scheme 103).

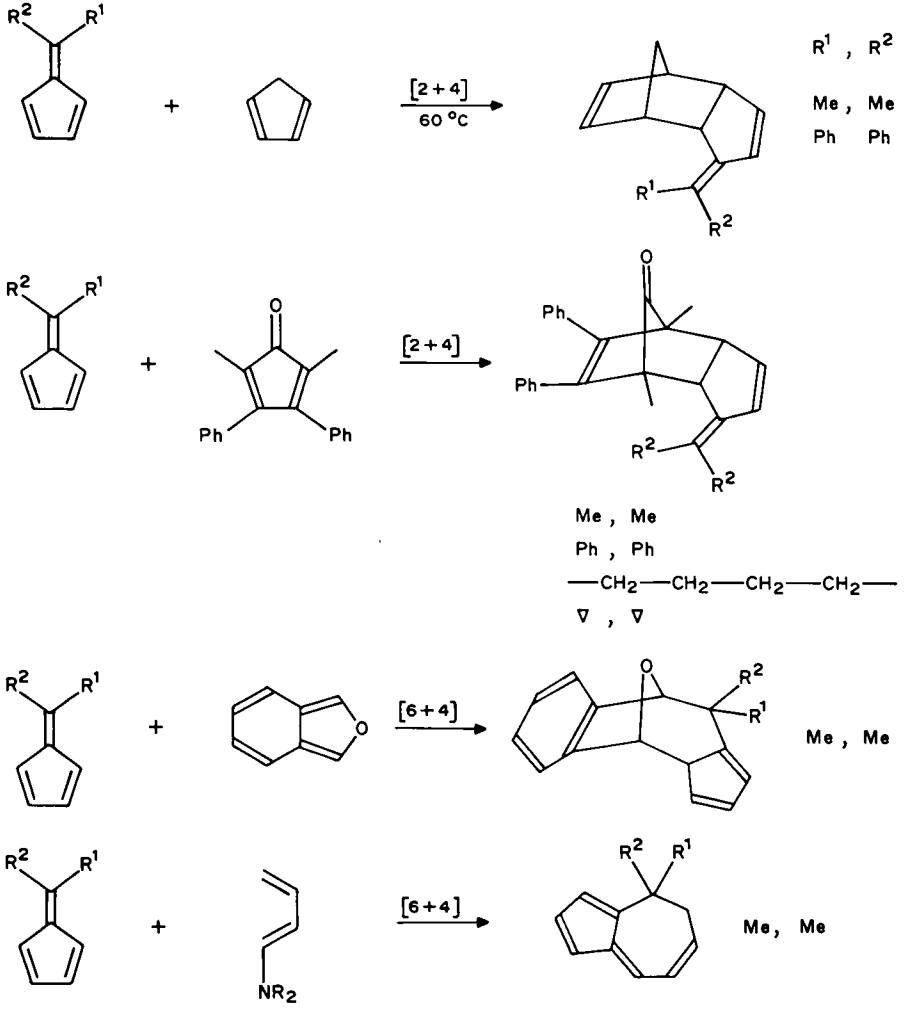
In cycloadditions of pentafulvenes with *dienes*, periselectivity depends on the nature of the diene (see Scheme 104). With simple dienes or electron-deficient dienes (with a low-energy LUMO), pentafulvenes normally react as 2π component in a [2 + 4] cycloaddition. On the other hand, with electron-rich dienes (with a high-energy HOMO), [6 + 4] cycloadditions may occur[310,322–325].

The same happens in reactions of pentafulvenes with electron-rich 1,3-dipoles, where [6 + 4] cycloaddition is the predominant process[12,326–328] (Scheme 105).

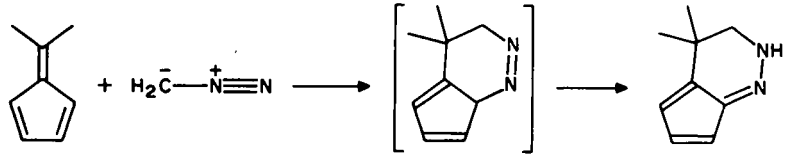


(139) (140)

SCHEME 103

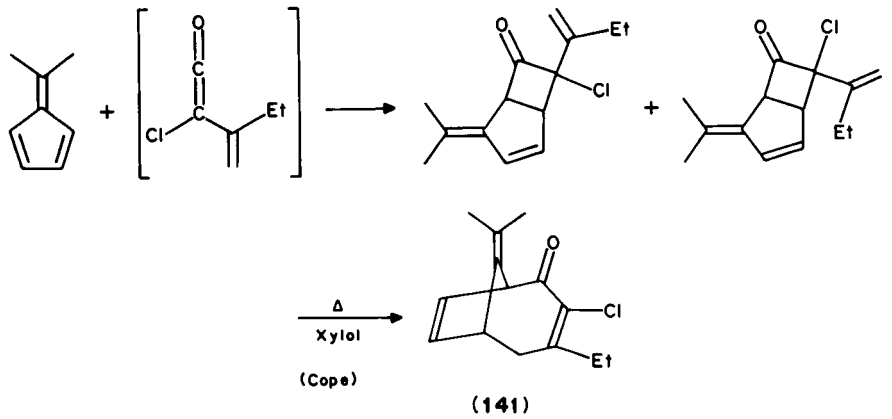


SCHEME 104[310,323–325]

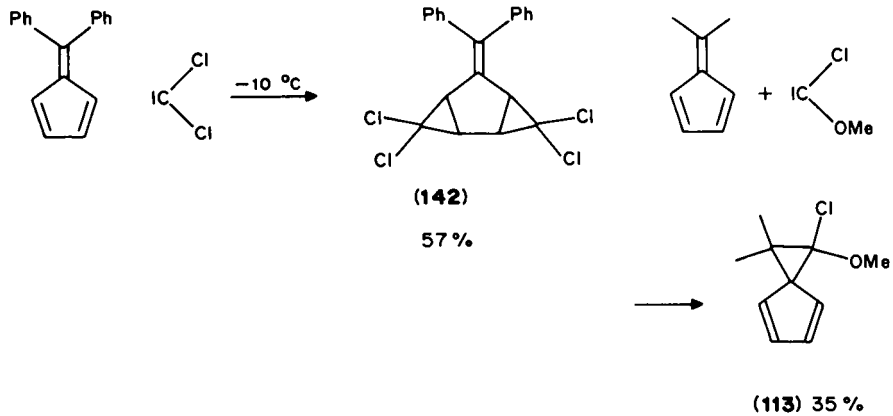


SCHEME 105[326,327]

Reactions of ketenes with pentafulvenes have recently been investigated. As long as the fulvene is not too nucleophilic (e.g. 6-dimethylaminopentafulvene reacts with ketenes by electrophilic substitution), [2 + 2]-cycloaddition reactions are observed[71,329–334]. An interesting example is shown in Scheme 106. 9-Isopropylidene-2-oxobicyclo[4.2.1]nona-3,7-dienes **141** are quite easily available by vinylketene addition to simple pentafulvenes followed by thermal Cope rearrangement[163,330].



SCHEME 106

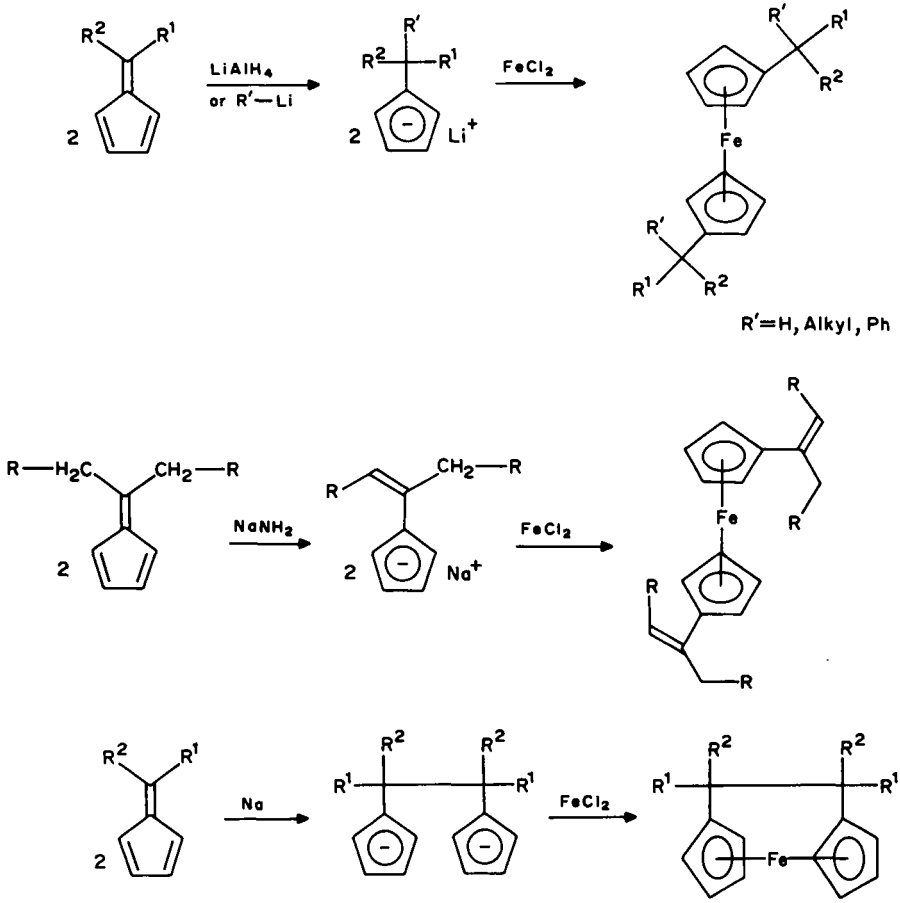


SCHEME 107

The cycloaddition mode of carbenes depends on their relative nucleophilicity and electrophilicity respectively[335]. As expected, electrophilic carbenes like dichlorocarbene add at one of the double bonds of the fulvene ring. In some cases, primary cycloaddition products of type **142** have been isolated[336,337]. Quite often, however, rearrangement to benzenoid compounds occurs[277,336–338]. On the other hand, nucleophilic carbenes like chloromethoxycarbene or dimethoxycarbene attack at the exocyclic double bond to form substituted spiro[2.4]hepta-4,6-dienes **113**[335] (Scheme 107).

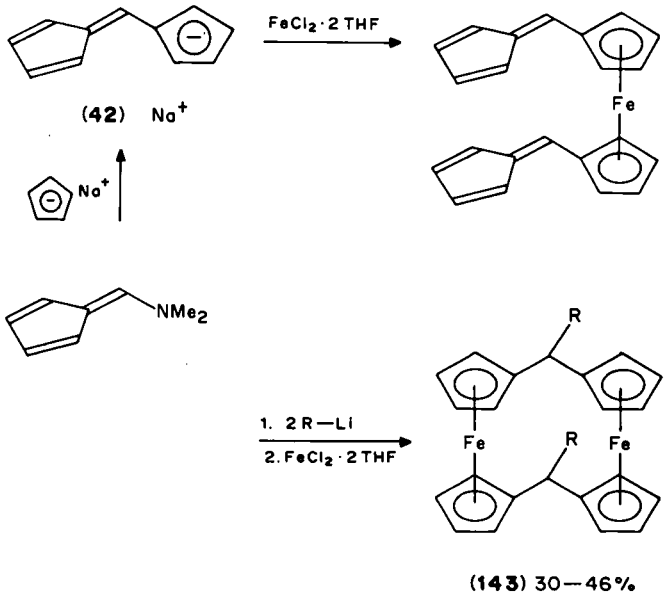
8. Ferrocenes from pentafulvenes

As mentioned in the Introduction, transformations of pentafulvenes into ferrocenes will not be discussed in detail here. A review of these conversions has already been published[283]. It is evident, however, that every reaction of pentafulvenes giving cyclopentadienides in a high yield is in principle suitable for preparing ferrocenes. The most important reactions are listed in Scheme 108.



SCHEME 108

While the first sequence makes use of the fact that pentafulvenes are attacked by nucleophiles like $LiAlH_4$, butyllithium or phenyllithium at C-6, the second generates vinylcyclopentadienides by deprotonation of α-methyl- or methylene groups. Exocyclically bridged ferrocenes may be generated by sodium-initiated coupling of pentafulvenes.



SCHEME 109

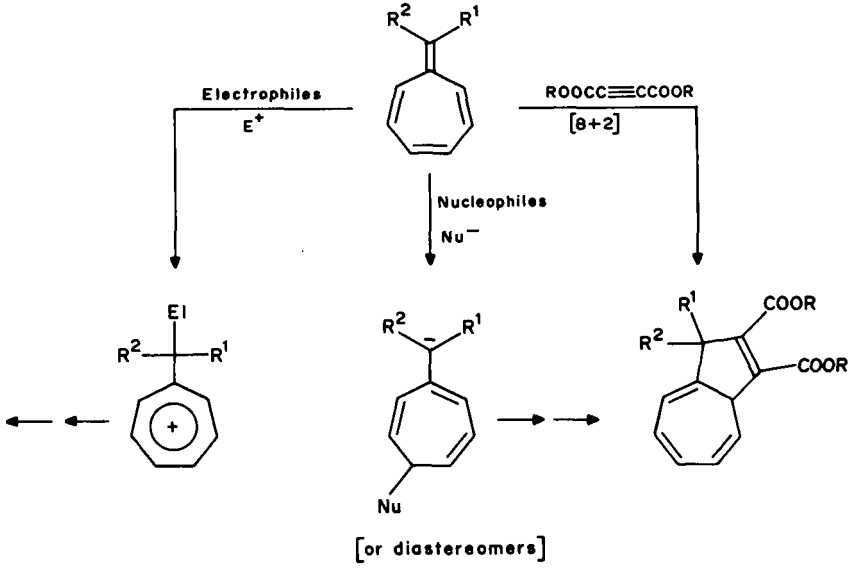
A nice application of these methods is given in Scheme 109[153] (6-pentafulvenyl)-cyclopentadienide **42** is available from 6-dimethylaminopentafulvene by nucleophilic addition of cyclopentadienide[339]; it reacts with the $FeCl_2$–THF complex to give 1, 1′-bis-(fulvenyl) ferrocene. Nucleophilic addition of $LiAlH_4$ or methyllithium give the two-fold bridged ferrocenophanes **143**[340].

C. Reactions of Heptafulvenes

1. General remarks

Reactivity of heptafulvenes has so far not been studied very intensively and certainly deserves further attention. A systematic investigation of the reactivity pattern exists only for the electronically stabilized 8-cyanoheptafulvene[341] as well as for the comparatively small class of electron-rich heptafulvenes bearing + M substituents at the exocyclic C atom. These results have been reviewed very recently[342].

Generally, the reactivity of simple heptafulvenes matches the predictions of frontier orbital consideration (see the Introduction). So it may be expected that electrophiles are attacking the exocyclic C atom (Scheme 110). The hereby formed delocalized tropylium cation may either add a nucleophile or lose an exocyclic proton to give another heptafulvene. This last sequence is the usual behaviour of electronically stabilized heptafulvenes (e.g. 8-cyanoheptafulvene). Not much is known about nucleophilic additions to heptafulvenes which are expected to take place at the ring carbon atoms.



SCHEME 110

Due to the fact that simple heptafulvenes have large Hückel coefficients at C-1/C-6 and C-8 of the HOMO, orbital symmetry allowed [8 + 2] cycloadditions are expected to take place with electron-deficient olefins. This is the most commonly tested and widely applied reactive behaviour of heptafulvenes.

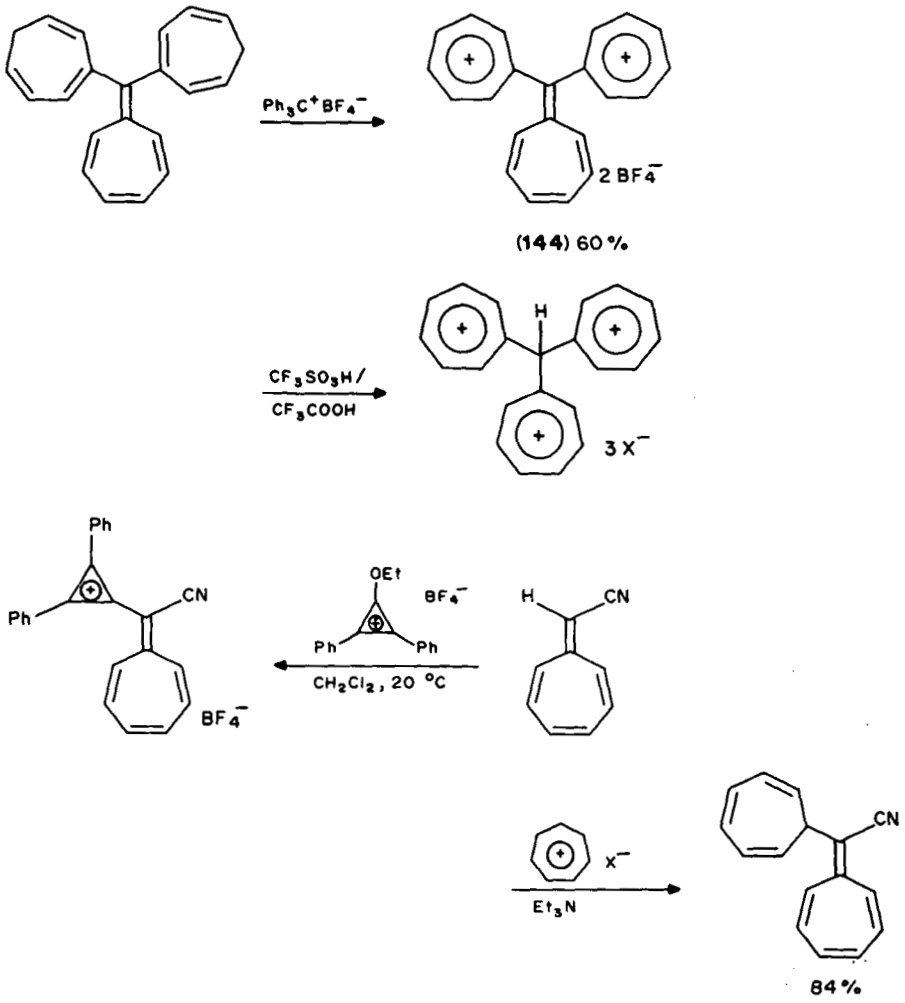
The parent heptafulvene[2,218] has been isolated at low temperatures as red crystals[343]. It may be handled in solution at low temperatures but readily polymerizes at ambient temperature. − M substituents like CN groups are electronically stabilizing the parent system, so that heptafulvenes with two − M substituents at C-8 are thermally very stable. So 8, 8-dicyanoheptafulvene survives heating at 200 °C without decomposition. Contrary to frontier orbital expectations, heptafulvenes with + M substituents at C-8[342] are thermally more stable than the parent system[343]. The increased stability might stem from steric shielding of the heptafulvene ring by the substituents R^1, R^2 as well as from an increased deviation of the seven-membered ring from planarity.

2. *Reactions with electrophiles and nucleophiles*

Heptafulvenes are expected to react with electrophiles at the exocyclic C atom. The most commonly used reaction of this type is protonation to give substituted tropylium salts. Obviously, even bis(tropylium)heptafulvene **144** may be protonated by strong acids despite Coulomb repulsion[228] (Scheme 111).

Electronically stabilized heptafulvenes like 8-cyanoheptafulvene react with various electrophiles at C-8 to give new heptafulvenes. According to Scheme 111 even delocalized cyclic cations are sufficiently electrophilic to perform the desired addition–elimination sequence[232,344] (see Section II.C.4, Scheme 60 and Table 16). It should be mentioned that radical attack takes place at C-8 of 8-cyanoheptafulvene as well, so that 8-halo-8-cyanoheptafulvenes are available by bromination with NBS or NCS[233].

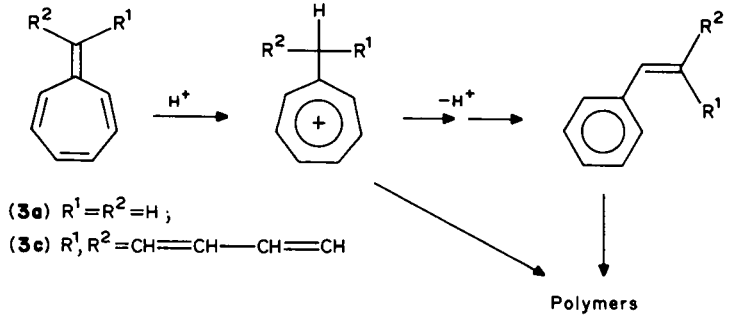
The parent heptafulvene (**3a**) is extremely sensitive to traces of acid (Scheme 112). If its



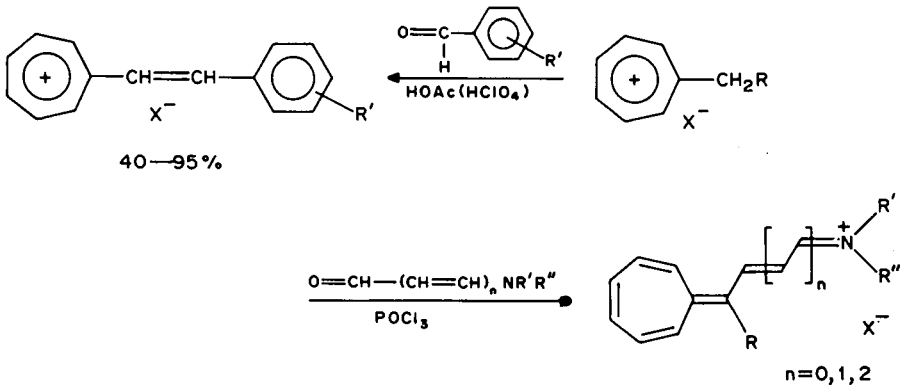
SCHEME 111

solutions are not stabilized by addition of tertiary amines, then it polymerizes easily[2,343] even in dilute solutions. It is reasonable to assume that the first step consists in an exocyclic protonation to give a methyltropylium cation[2]. However, if polymerization starts during chromatography over silica gel, then some amounts (10% yield) of styrene are isolated. The same happens with hepta-pentafulvalene **3c** where 6-phenylpentafulvene may be isolated (14%), which is sensitive to traces of acid as well! This shows that polymerizations of **3a** and **3c** are complicated processes[345]. There are some reports[346,347] which suggest that simple heptafulvenes including **3a** may be generated as intermediates from alkyltropylium salts and may react with various electrophiles (Scheme 113).

Electron-donating groups at C-8 of heptafulvenes may change the usual regioselectivity pattern of electrophilic attack (see Schemes 110 and 111). In heptafulvenolates, nucleophi-



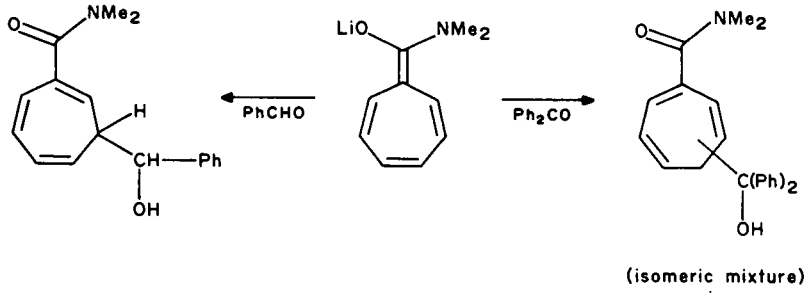
SCHEME 112



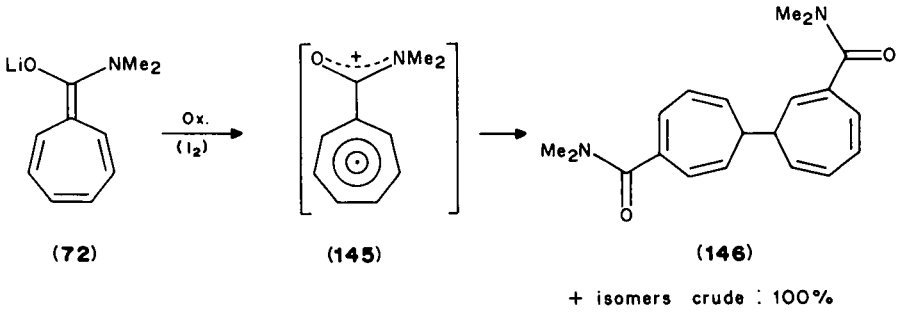
SCHEME 113

licity of the ring C atoms is largely enhanced, and in fact electrophiles like benzaldehyde and benzophenone are added at the ring[348,349] (Scheme 114).

The oxidation of electron-rich heptafulvenes has been investigated[342]. While 8-methoxyheptafulvene polymerizes in the presence of iodine, reaction of heptafulvenolate



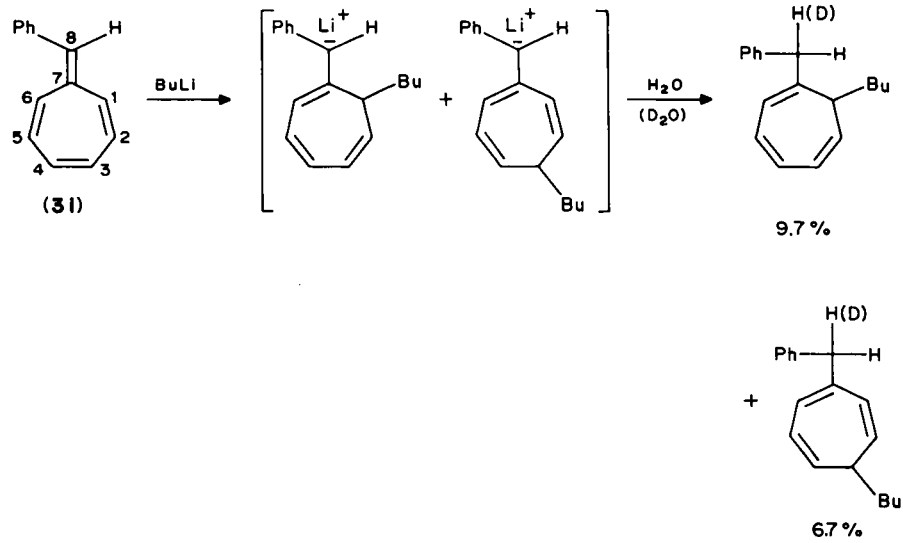
SCHEME 114



SCHEME 115

72 with iodine gives a very complex mixture of bicycloheptatrienes **146** in a high yield. This has been rationalized by assuming radical cations of type **145** as intermediates[342] (Scheme 115). A similar reactive behaviour is observed for 8,8-bis(dimethylamino)-heptafulvene[222,350].

One of the rare reports concerning reactions of heptafulvenes with nucleophiles is summarized in Scheme 116. As expected from frontier-orbital considerations (showing

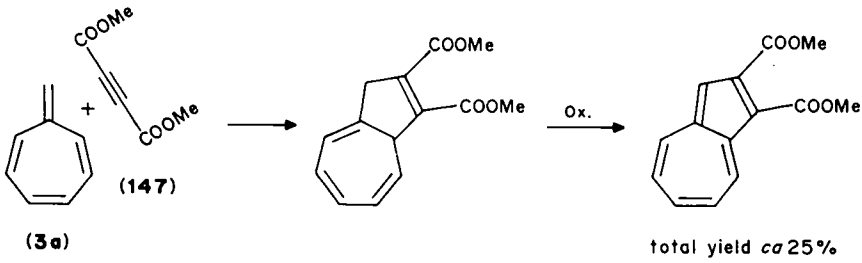


SCHEME 116

that the largest Hückel coefficients of the LUMO of **3a** are at C-1 and C-3), 6-phenylheptafulvene **3i** is attacked by butyllithium at C-1 and C-3[205]. According to quenching experiments with D_2O, the proton is mainly incorporated at the exocyclic C atom.

3. Cycloaddition reactions

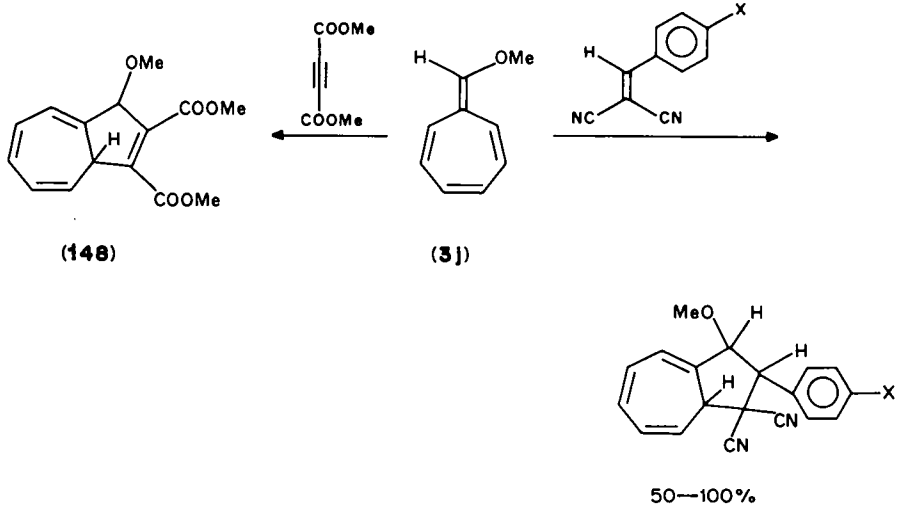
The synthetic potential of heptafulvenes as an 8π synthon was discovered long ago, but it has been hampered by the thermal instability of most heptafulvenes suited for facile cycloaddition reactions. As early as 1954 Doering and Wiley[2,351] realized that heptafulvene (**3a**) reacts with dimethyl acetylenedicarboxylate to give dihydroazulene, although in a poor yield (Scheme 117). Since that time, [8 + 2]-cycloaddition reactions



SCHEME 117

have been applied, in most cases just for characterization of unstable heptafulvenes. Excellent [8 + 2]-cycloaddition partners are 8-alkylheptafulvenes or electron-rich heptafulvenes[342] as 8π components on the one side and electron-deficient acetylenes (like **147**) or olefins (like maleic anhydride, *p*-quinones, phenyltriazolindione, cyanoethylenes etc.) on the other. The following summary will be limited to some recent examples.

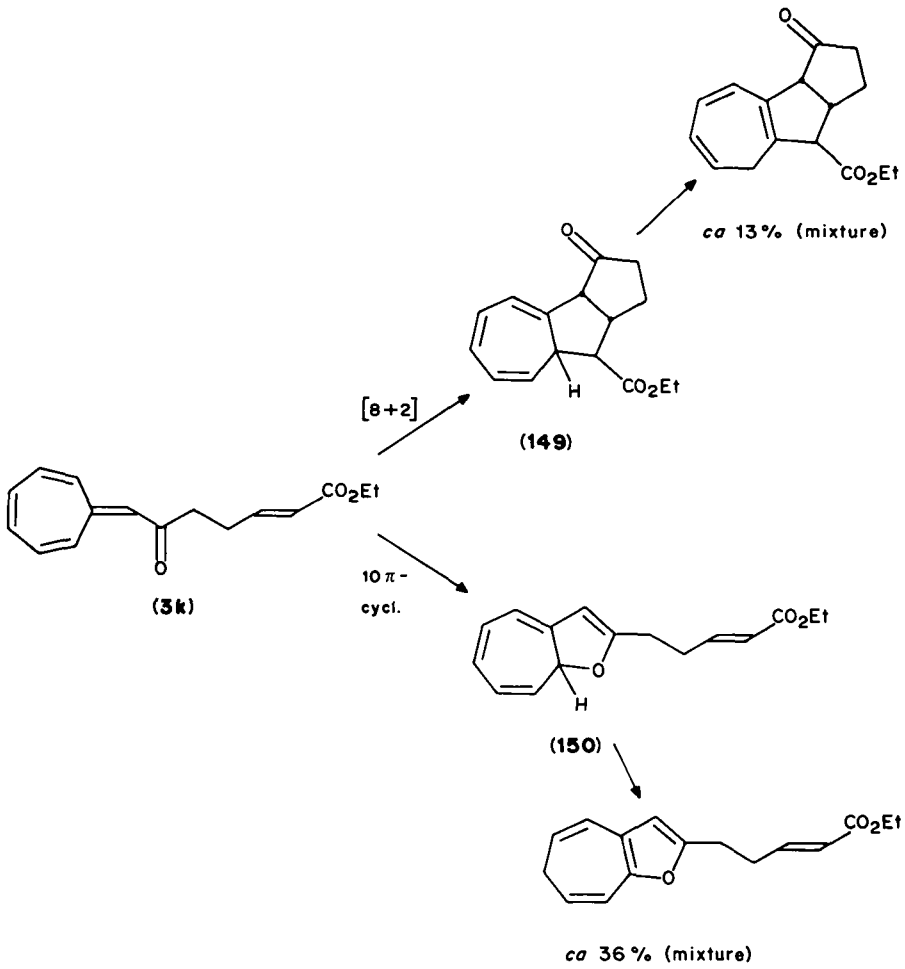
8-Methoxyheptafulvene **3j** reacts easily and stereoselectively with an excess of dimethyl acetylenedicarboxylate to give the dihydroazulene **148**, which may be oxidized to the corresponding azulene[220,352]. [8 + 2] cycloaddition of 1,1-dicyano-2-arylethylenes reveals the remarkable regioselectivity of the sequence, the terminal olefinic C atom (bearing the phenyl group) adding exclusively at C-8 of the heptafulvene[353,354] (Scheme 118).



SCHEME 118

Furthermore, electron-accepting aromatic substituents X are accelerating. This is in agreement with frontier-orbital predictions and reflects the large Hückel coefficient of C-8 of the olefin. However, stereoselectivity is poor, resulting in a complex mixture of stereoisomers[353]. [8 + 2] cycloadditions of quinones[355] and *N*-phenyltriazolindione with **3j** have been described too.

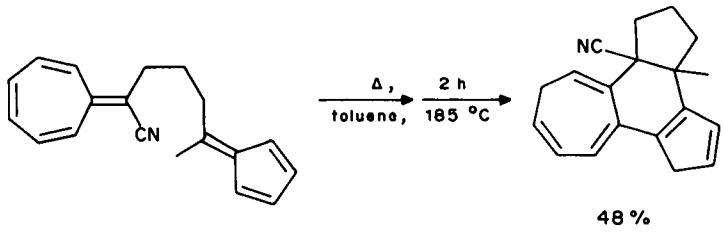
Intramolecular [8 + 2] cycloadditions are not only mechanistically interesting, but attractive as well as a one-step synthesis of tricyclic compounds. Reactions of this type have been studied intensively during the last few years[215–217]. Heptafulvenes containing an electron-deficient olefin unit in the side-chain are normally prepared via hydride abstraction from substituted cycloheptatrienes in moderate yields. [8 + 2] cycloadditions are realized by thermolysis in closed tubes at 150–200 °C, yielding tricyclic compounds in total yields from 20 up to 85%. For discussions of the stereochemical requirements see References 215–217.



SCHEME 119

The example of Scheme 119[216] shows that 8-acylheptafulvenes not only undergo the desired [8 + 2] cycloaddition **3k** → **149** with the terminal electron-deficient olefin of the side-chain, but that in this case an undesired 10π electrocyclization **3k** → **150** occurs too.

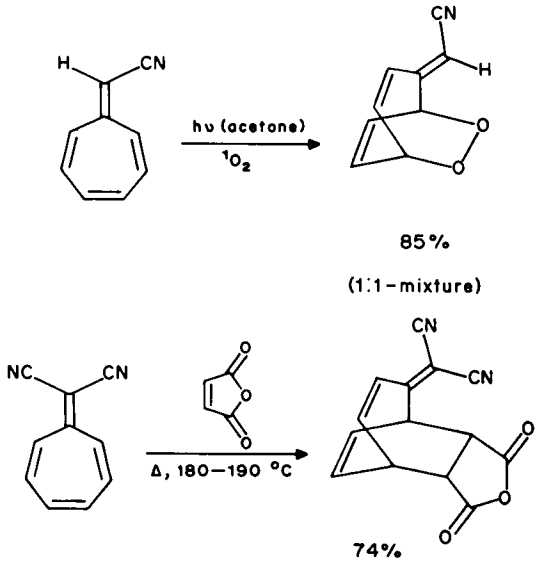
Very recently, the first intramolecular [8 + 6] cycloaddition between a heptafulvene and a pentafulvene unit was reported[214] (Scheme 120), while intermolecular [8 + 6] cycloadditions between heptafulvenes and pentafulvenes are not known.



48%

SCHEME 120

The most important result of numerous investigations is the strong tendency of heptafulvenes to act as a 8π unit in cycloaddition reactions. This is even true for electron-deficient 8-cyanoheptafulvene in reactions with electron-deficient olefins such as dimethyl acetylenedicarboxylate or maleic anhydride[341]. Furthermore, 8-cyano- as well as 8,8-dicyano-heptafulvene react with enamines in an [8 + 2] manner[356,357], presumably over dipolar intermediates. Exceptions are known for 8-oxoheptafulvene (**3b**), which has a strong tendency to undergo [2 + 2] cycloadditions besides [8 + 2] cycloadditions due to its 'ketene qualities'. As discussed earlier, this behaviour may be exploited for synthesizing new heptafulvenes (see Section II.C.4[230]).

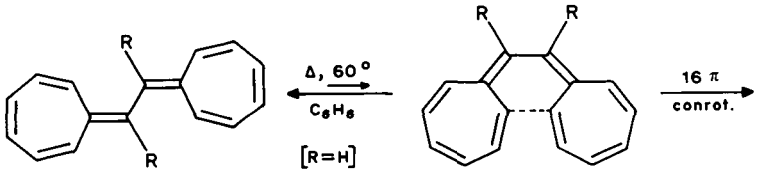


SCHEME 121

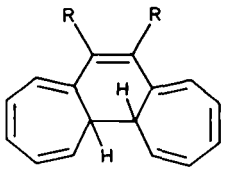
Exceptions are observed with special dienophiles too. Thus, singlet oxygen seems to react with electron-deficient heptafulvenes in a [4 + 2] manner (Scheme 121[227,358]). Furthermore, strongly electron-deficient and sterically shielded 8,8-dicyanoheptafulvene reacts with maleic anhydride and some other olefins in a [4 + 2] way[341]. With cyclopentadiene, a [6 + 4]-cycloaddition product seems to be formed at room temperature which undergoes an intramolecular rearrangement to the [8 + 2]-cycloaddition product at 70 °C[341].

4. Miscellaneous

For 8-vinylheptafulvenes[359,360] and especially for vinylogous heptafulvalenes like 8,8'-bis(heptafulvenyl) (**3f**, R = H), thermally allowed electrocyclic reactions have been observed. For instance 8,8'-bis(heptafulvenyl)[361] as well as its 8,8'-dicyanoderivative **3f** (R = CN)[233] undergo an easy conrotative 16π-electrocyclization reaction to give the tricyclic compound **151** in good yields (Scheme 122). Since reactions of this type only apply to a very small class of heptafulvenes, they are not discussed in detail here. For a recent survey see Reference 362.



(**3f**)



(**151**)

R=H : 94%

R=CN : *a*

[a]Yield 40% starting with 8-bromo-8-cyano-heptafulvene, including coupling to **3f** (R = CN).

SCHEME 122

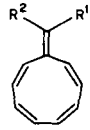
D. Reactions of Nonafulvenes

So far, the interest of chemists has been focused on the synthesis and the spectroscopic investigation of nonafulvenes (**4**).

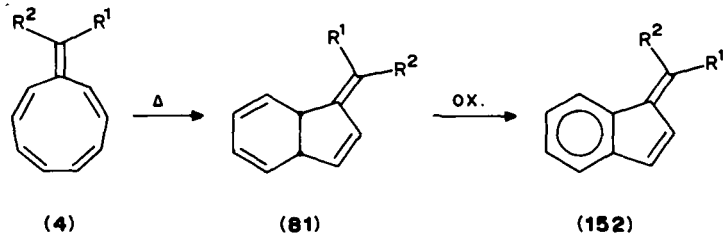
The reactivity pattern of simple nonafulvenes, bearing substituents only at the exocyclic C atom, is dominated by the facile *valence isomerization* to give diastereomeric mixtures of 3a,7a-dihydrobenzofulvenes **81** (Scheme 123).

The parent nonafulvene (**4a**) cyclizes very easily and almost quantitatively at − 10 °C in

TABLE 18. Ease of valence isomerization of nonafulvenes (4)



Compound	R^1	R^2	$\tau_{1/2}$	Temp. (°C)	Solvent	Ref.
4a	H	H	12′	10	$CDCl_3$	251
4f	SMe	SMe	24′	10	d_6-acetone	255
4d	$OSiMe_3$	Me	8′	40	$CDCl_3$	253
4e	$OSiMe_3$	Ph	9′	40	$CDCl_3$	253
4k	$OSiMe_3$	OMe	12′	40	$CDCl_3$	253
4l	$OSiMe_3$	$OSiMe_3$	13′	40	$CDCl_3$	253
4i	NMe_2	H	36′	40	$CDCl_3$	253
4p	NMe_2	OEt	54′	40	$CDCl_3$	253
4r	NMe_2	NMe_2	very slow	20	$CDCl_3$	7



(4) **(81)** **(152)**

SCHEME 123

$CDCl_3$[251], while 10,10-bis(dimethylamino)nonafulvene **4r** is stable for hours at room temperature[7]. Systematic investigations show that valence isomerization **4**→**81** slows down with increasing electron-donating capacity of the exocyclic substituents R^1 and R^2 (Table 18)[253]). In some cases, dihydrobenzopentafulvenes **81** have been oxidized to the corresponding benzopentafulvenes **152**[7,363].

IV. SYNTHETIC APPLICATIONS OF FULVENES

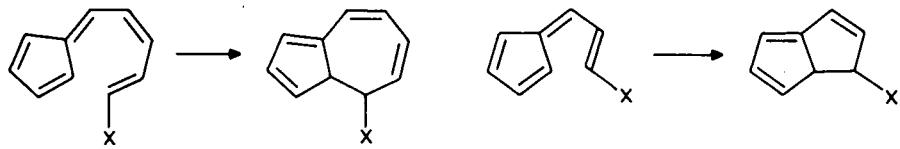
Of all the classes of fulvenes discussed in this survey, *pentafulvenes* are by far the best known and most thoroughly investigated compounds and a broad variety of them with various functional groups are available. Most of these are quite stable, and even unsubstituted pentafulvene itself may be easily handled in solution. They react with nucleophiles and electrophiles at low temperatures and in most cases regioselectively. Vinylogous pentafulvenes are prone to electrocyclic reactions, and the 6π system of these cross-conjugated molecules undergoes cycloadditions as a 2π, 4π or 6π unit, while periselectivity may be controlled by the choice of appropriate substituents of the fulvene and the reactant as well. Therefore there is no doubt that various synthetic applications of pentafulvenes are feasible, some having been investigated and others still remaining open for further investigations. Due to the fact that so far only a few applications have been

reported for triafulvenes and heptafulvenes and none for thermally unstable nonafulvenes, in this section some typical synthetic applications of pentafulvenes will be discussed.

During the last 30 years, research activities were mainly focused on synthetic applications of pentafulvenes for the synthesis of new bicyclic and polycyclic nonbenzenoid molecules.

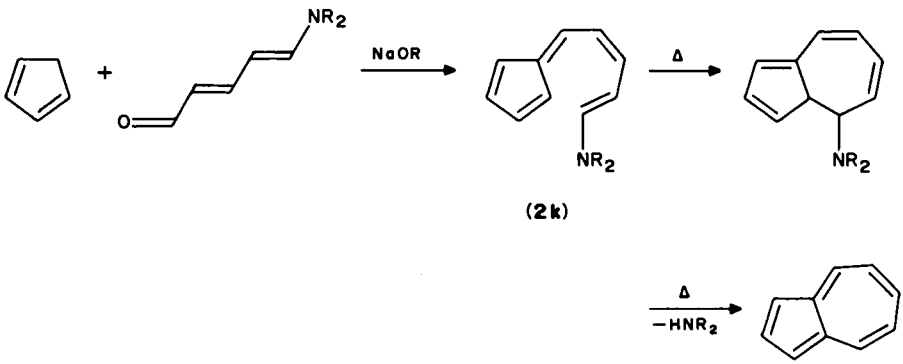
A. Synthesis of Other Cyclic Conjugated Nonbenzenoid Systems

A very important reactivity pattern of vinylogous pentafulvenes of type **2k** and **2l** are electrocyclic reactions. So 6-(1, 3-butadienyl)pentafulvenes or 6-vinylpentafulvenes may in principle give dihydroazulenes **153** or dihydropentalenes **127**. If the side-chain of the fulvene bears a potential leaving group X, then the bicyclic products **153** and **127** are attractive precursors of azulenes and pentalenes, respectively (Scheme 124).



(2k) (153) (2l) (127)

SCHEME 124



(2k)

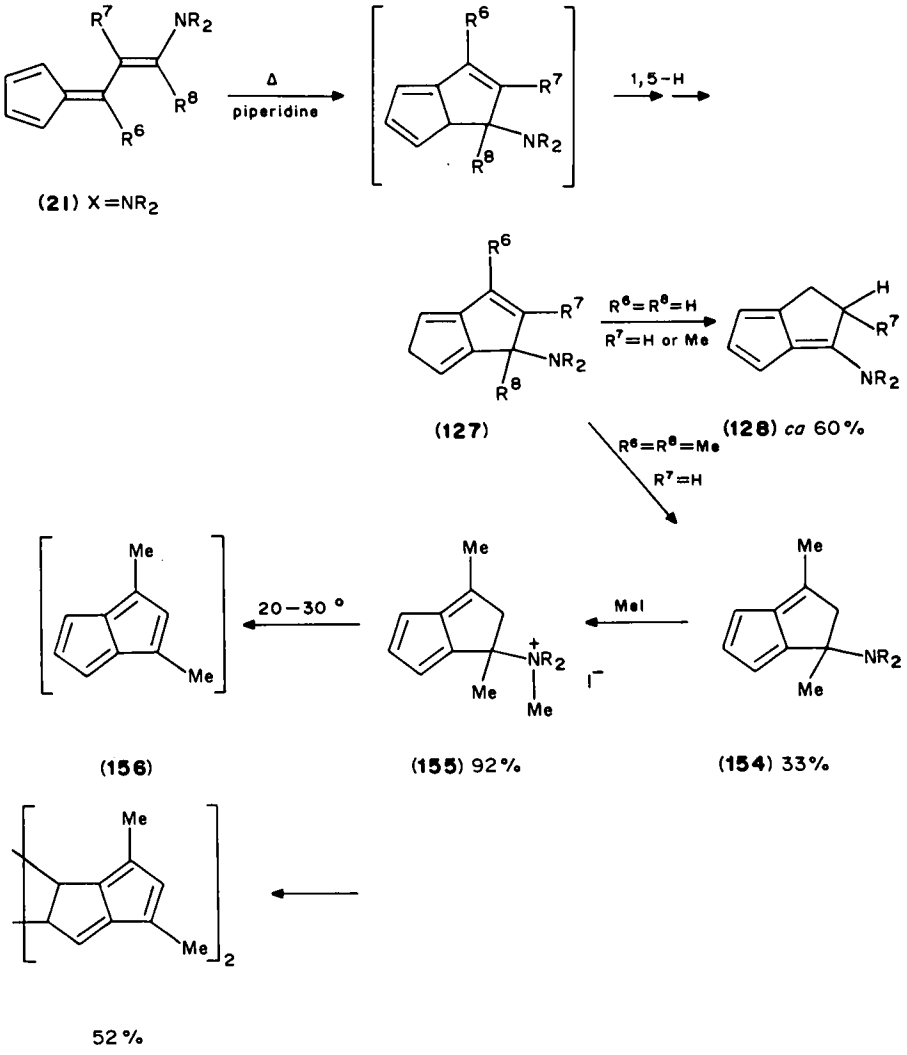
SCHEME 125

Scheme 125 represents the famous Ziegler–Hafner azulene synthesis, which was realized as long ago as 1955[364,365] and has since been applied to a series of substituted azulenes as well[80,366,367]. Due to the fact that the required aldehyde is easily available by amine-induced ring opening of pyridinium salts[368], this was the first synthesis to produce large quantities of azulenes. If pellets of a fulvene/amine mixture are slowly added to a high- boiling aromatic amine and if the azulene is continuously removed from the reaction vessel by steam distillation, then azulenes are available in a total yield up to 60% (for recent reviews see References 369 and 370).

Around 1970 it was shown that 6-vinylpentafulvenes undergo electrocyclic reactions as well, in most cases around 100 °C, to give dihydropentalenes. This is not only true for the

thermally very unstable 6-vinylfulvene and 6(1-propenylfulvene)[304], but also for electronically stabilized 6-(2-dialkylaminovinyl)pentafulvenes **21**[138,305,306].

Thermally induced cyclizations of 6-(2-dialkylaminovinyl)pentafulvenes **21** have been widely applied to the synthesis of reactive pentalenes[306]. While 8-dimethylaminovinylpentafulvene **21** cyclizes only after being refluxed in pyridine or piperidine to give electronically stabilized bicyclic pentafulvene **128** (Scheme 126), substituents at C(6) and

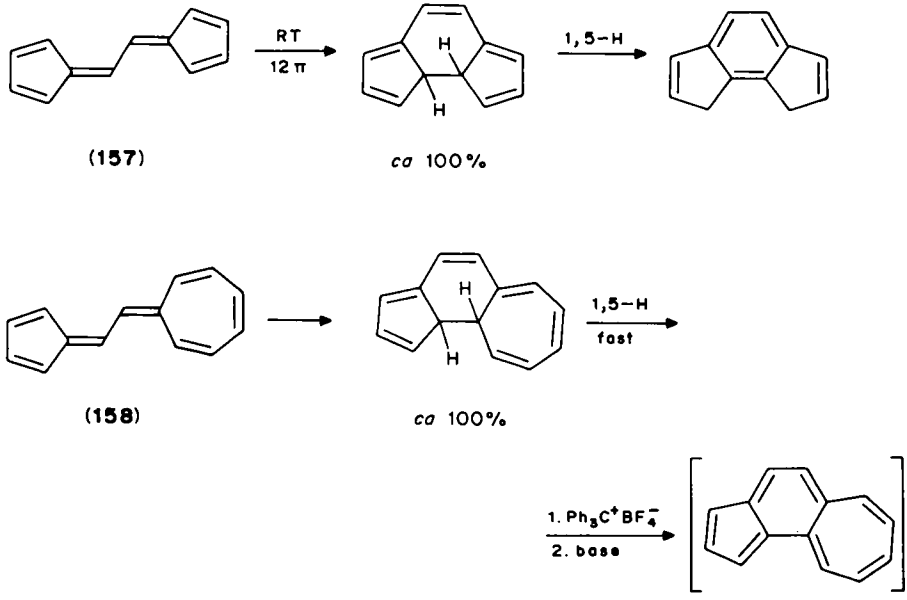


SCHEME 126

C(8) sterically favour the important cisoid conformation so that cyclization already proceeds at room temperature. Alkyl substituents at C-8 prevent the isomerization **127**

→ **128** and allow N-alkylation **154** → **155** and Hofmann elimination **155** → **156** to give thermally unstable pentalenes **156** which readily dimerize at room temperature. This attractive sequence has been thoroughly investigated[138,305,306]; for a recent review see Reference 371.

New polycyclic conjugated systems are also formed by electrocyclic reactions of the vinylogous pentafulvalene **157**[372] and sesquifulvalene **158**[373] (Scheme 127). Very natur-

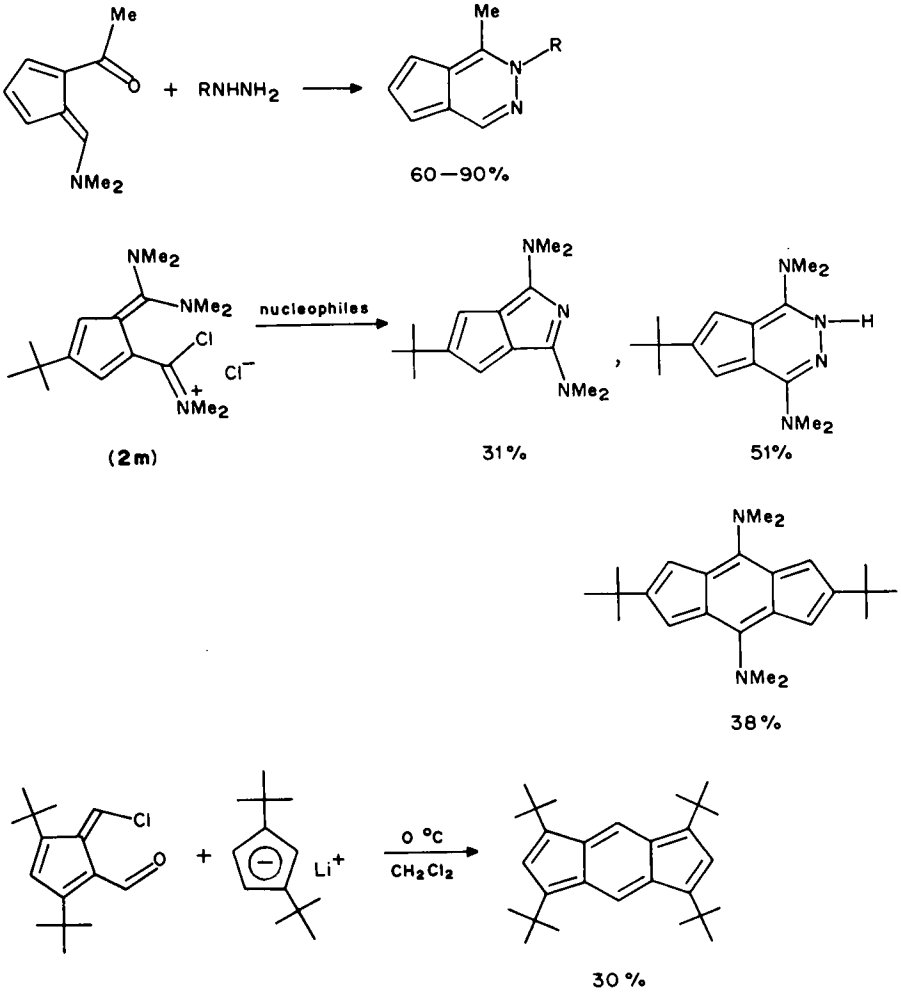


SCHEME 127

ally, in both cases ring closure proceeds from the cisoid conformations. Despite the 14π perimeter of **158**, the conrotatory process seems to be favoured due to steric reasons[362,373].

Novel nonbenzenoid bicyclic and polycyclic conjugated systems may be formed by nucleophilic displacement followed by condensation of 6-dialkylamino-2-acylpentafulvenes and their derivatives, which are available by acylation of electronically stabilized 6-dialkylaminofulvenes[14,156].

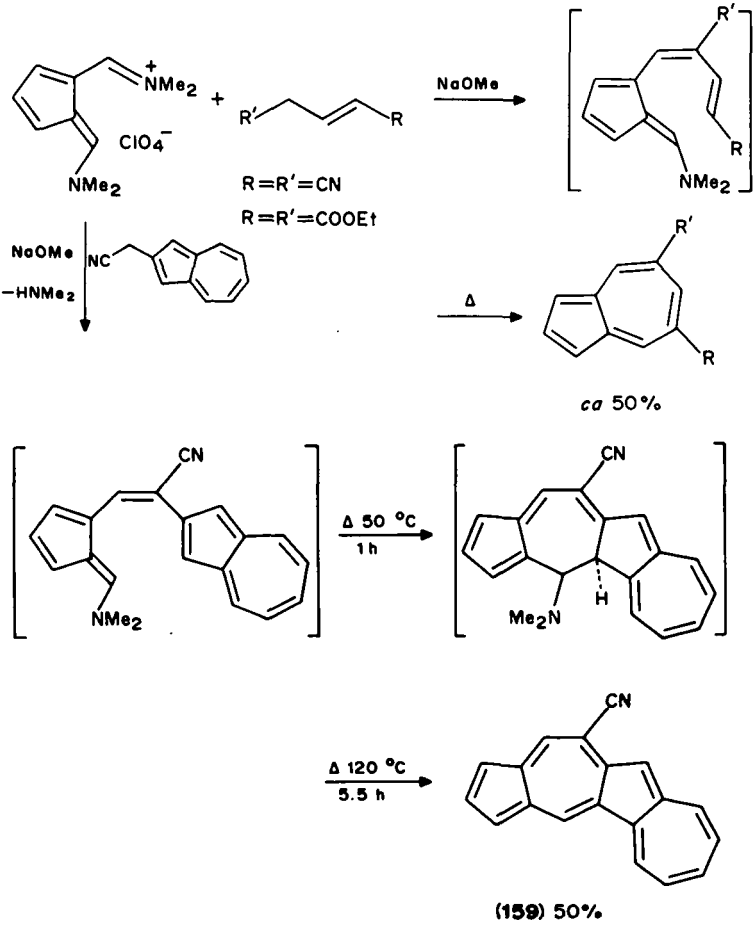
Scheme 128 shows some realized variations of the potential leaving groups at C-6 of the pentafulvene unit as well as of the carbonyl function at C-1. So 1-acetyl-6-dimethylaminopentafulvene reacts easily with hydrazines[374]. The substitution pattern of the product reveals that the first step is a nucleophilic displacement of the amino group at C-6 of the pentafulvene. Similarly, pentafulvene **2m** reacts with several nucleophiles under cyclization[161]. If the nucleophile is a cyclopentadienide, then substituted *s*-indacenes are available[375,376], which are electronically and/or sterically stabilized compared with the parent compound[377]. Especially easy are nucleophilic displacements of 6-halopentafulvenes. 1,3,5,7-(*t*-Bu)$_4$-*s*-indacene is available by an acid-catalyzed dimerization of 1,3-(*t*-Bu)$_2$-6-chloropentafulvene as well[378].



SCHEME 128

The same bifunctional pentafulvenes react with allylic anions to form substituted 1-butadienyl-6-dimethylaminopentafulvenes as intermediates (Scheme 129). Electrocyclic ring closure and thermal elimination of dimethylamine gives substituted azulenes[379]. This attractive sequence is limited so far by the fact that the alcoholates used for the generation of allylic anions react with the electrophilic pentafulvene as well. It allows the isolation of so far unavailable azulenes like azuleno[1,2-*f*]azulenes of type **159**[380] (Scheme 129) and other polycyclic azulenes, if the applied allylic anion is part of a ring system[381,382].

Finally, a nice recent example making use of a nucleophilic displacement/addition, two oxidative couplings and a deprotonation to give the di-*tert*-butylcyclopenta[*a*]-pentalenide ion **160** is shown in Scheme 130[383].

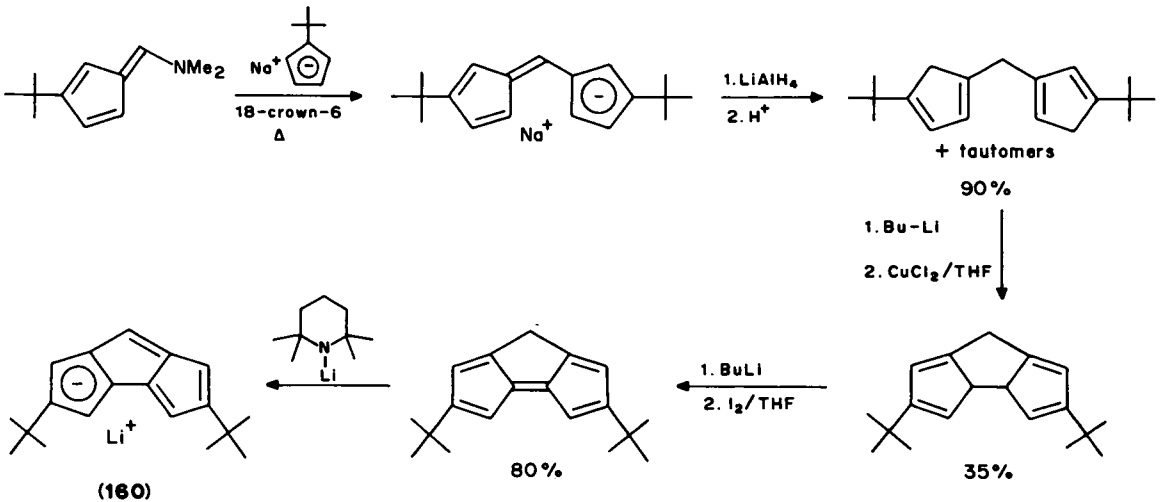


SCHEME 129

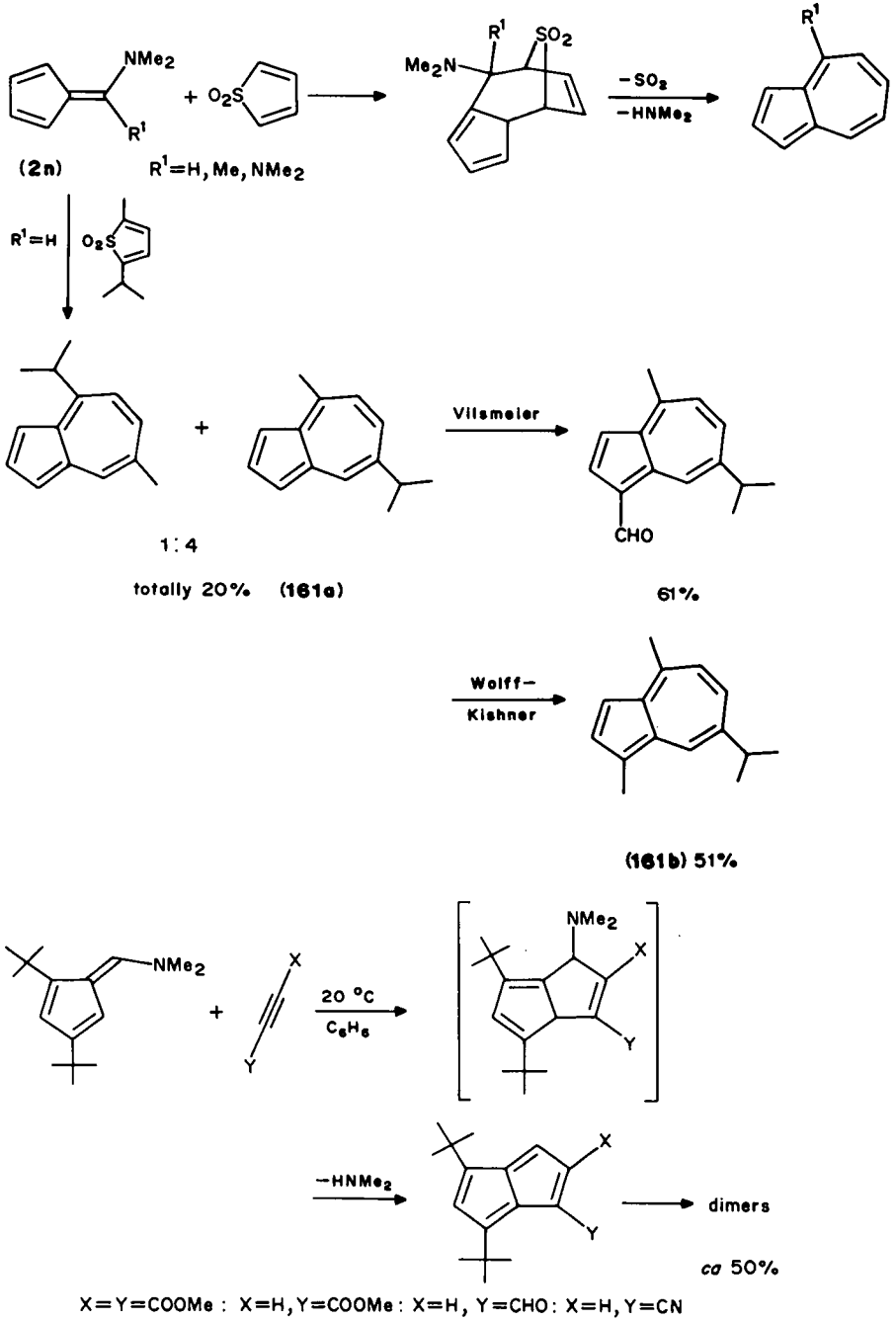
During the last 15 years it has been shown that cycloaddition reactions of pentafulvenes used as a 6π system are not only mechanistically interesting, but may be applied to the synthesis of bicyclic nonbenzenoid compounds. Pentafulvenes may react as 6π units either if their LUMO is the important frontier orbital (as in cycloadditions with dienamines) or if their NHOMO (next highest occupied molecular orbital) becomes important (as in cycloaddition of 6-dimethylaminopentafulvene)[12].

Frontier orbital calculations show that strong electron donors like NMe_2 at C-6 dramatically raise the energy of the NHOMO orbital which may even become the occupied orbital of highest energy[329]. Because the NHOMO orbital has a very large Hückel coefficient at C-6 (and a smaller one of inverse sign at C-1/C-4), 6-dimethylaminopentafulvene (**2n**) and related fulvenes may act as 6π units in cycloadditions, e.g. with electron-deficient dienes with a low-energy LUMO.

So 6-dimethylaminopentafulvenes **2n** ($R^1 = H$, CH_3, NMe_2) react with thiophene dioxides, in most cases within 1–3 days at room temperature. Cycloaddition is followed by


NMe2
Na+
18-crown-6
Δ
Na+
1. LiAlH4
2. H+
+ tautomers
90%
1. Bu-Li
2. CuCl2/THF
35%
1. BuLi
2. I2/THF
80%
N
Li
Li+
(160)

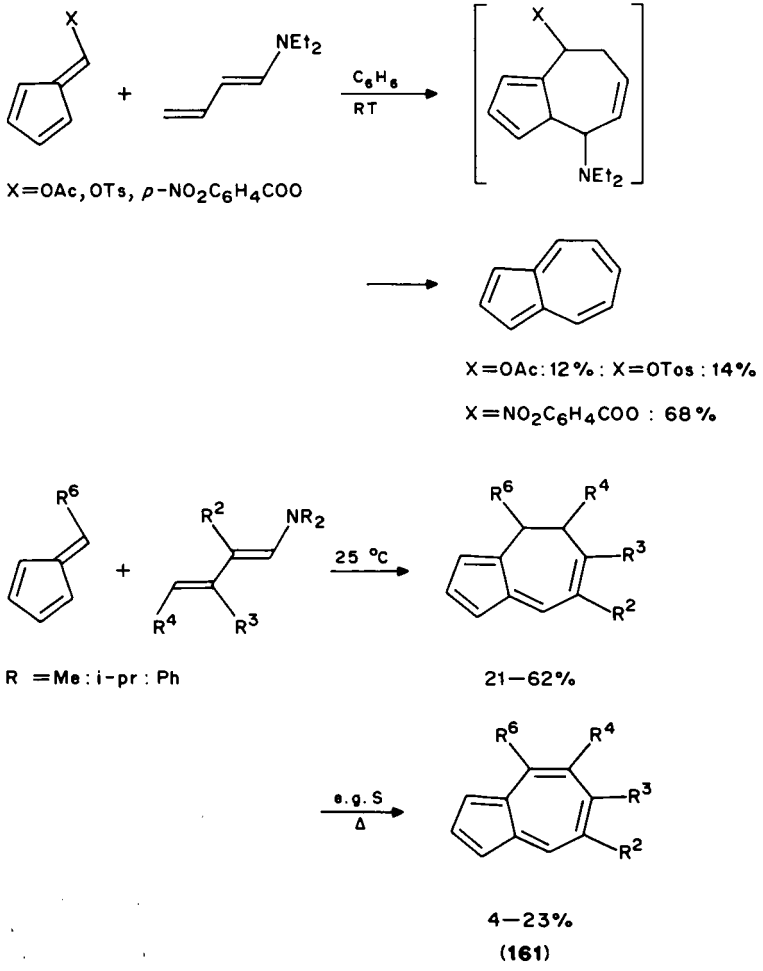
SCHEME 130


NMe2
R1
+ O2S
(2n)
R1=H, Me, NMe2
Me2N
R1
SO2
-SO2
-HNMe2
R1
R1=H
O2S
+
1 : 4
totally 20% (161a)
Vilsmeier
CHO
61%
Wolff-
Kishner
(161b) 51%
NMe2
+
X
Y
20 °C
C6H6
NMe2
X
Y
-HNMe2
X
Y
dimers
ca 50%
X=Y=COOMe : X=H,Y=COOMe : X=H, Y=CHO : X=H, Y=CN

SCHEME 131

an elimination of SO_2 and $HNMe_2$ so that azulenes are formed (Scheme 131). This synthesis is characterized by easily available starting materials and a simple procedure, however the yields in most cases range only between 5 and 30%[384,385]. As shown in Scheme 131, cycloaddition of 2-isopropyl-5-methylthiophene dioxide to **2n** proceeds with a remarkable regioselectivity (the most nucleophilic C-4 of **2n** attacks the sterically least-hindered C-5 of the thiophene dioxide) to give mainly the desired azulene **161a** in a view of the envisaged synthesis of the naturally occurring guaiazulene **161b**[386]. Similarly, [6 + 4] cycloaddition of 6-dimethylaminopentafulvene with 5-alkoxycarbonyl-2-pyrones gives azulenes in low yields[387].

6-Dimethylaminopentafulvenes not only react with electron-deficient dienes as 6π units, but with electron-deficient acetylenes as well. If 6-dimethylamino-1,3-di-*tert*-butyl-pentafulvene is reacted during 2 h in C_6H_6 at room temperature in the presence of electron-deficient acetylenes, then pentalene dimers are isolated[388] (Scheme 131).

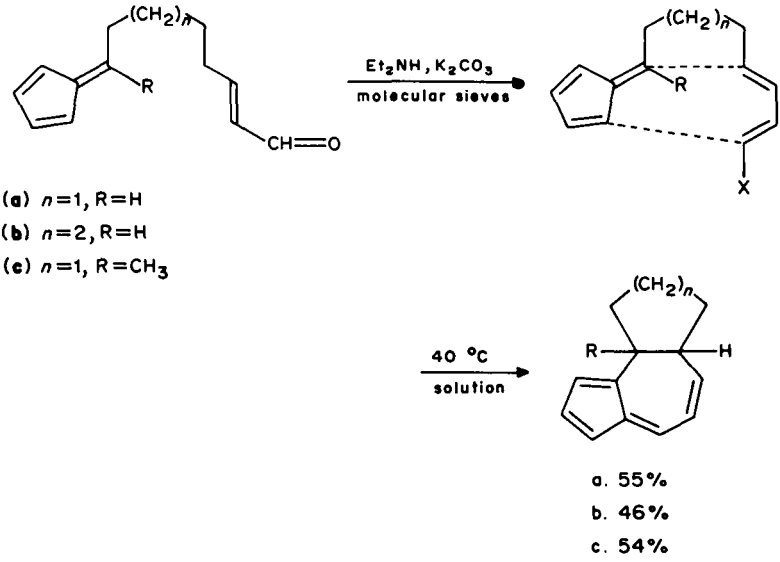


SCHEME 132

1-Dialkylaminobutadienes are characterized by a high-energy HOMO, thus favouring [6 + 4] cycloadditions with pentafulvenes with a low-energy LUMO[11,329], and that means with a relatively broad range of simple pentafulvenes, with the exception of fulvenes with electron-donating substituent[329] (Scheme 132). If X is a potential leaving group, then the synthesis of azulenes is easy and straightforward, although the yields are often moderate[389]. If R^6 is no leaving group, then the dihydro-azulenes need an oxidative treatment, which considerably hampers the yields of the isolated azulenes **161**[325,390].

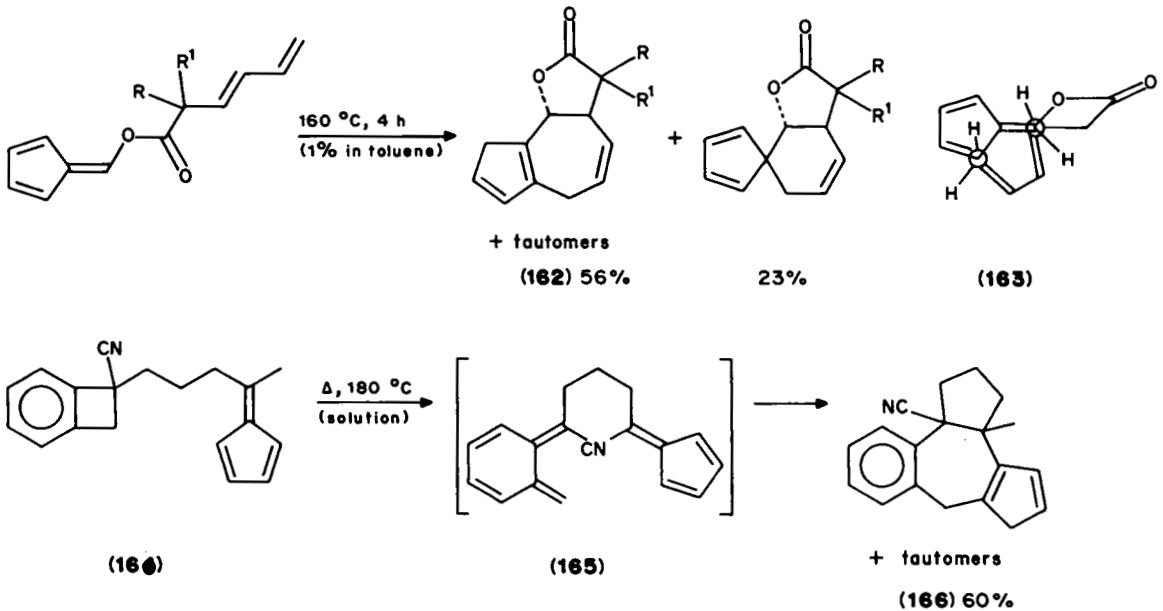
B. Synthesis of Polycyclic Ring Systems

If dienamines are increasing the tendency of pentafulvenes to undergo intermolecular [6 + 4] cycloadditions (see Scheme 132), they should favour intramolecular [6 + 4] cycloadditions even more, because the transition states for the [6 + 4] modes are sterically much better than those for the ring [2 + 4] modes[391]. Intramolecular [6 + 4] cycloadditions between a fulvene and a dienamine linked together by an appropriate spacer would give tricyclic molecules and could be synthetically very useful. In fact, intramolecular [6 + 4] cycloaddition takes place easily and gives *cis*-fused tricyclic compounds with remarkable yields[95], whose structure has been additionally supported by oxidation to the appropriate azulenes (Scheme 133).

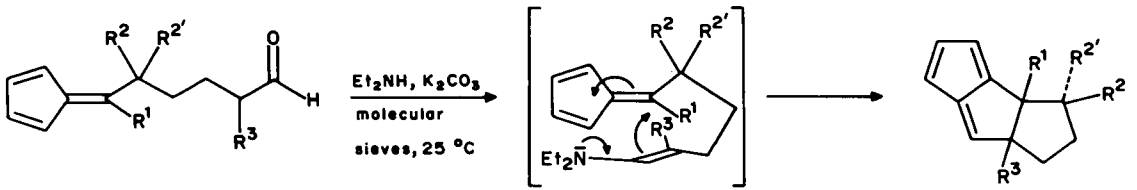


SCHEME 133

Due to conformational effects of the small side-chain, the transition state for [6 + 4] cycloadditions is much better than that for ring [2 + 4] cycloaddition. Because of that, intramolecular [6 + 4] cycloadditions are not limited to the electronically favoured cases (Schemes 131 and 132), although in both examples given in Scheme 134 much higher temperatures have to be applied. In the first case of Scheme 134[392], the favoured formation of the *trans*-fused product **162** has been explained by a favoured *exo* transition state **163**. Product analysis shows that [2 + 4] cycloaddition to the exocyclic fulvene double bond is in some cases possible too[392]. In the second example, the 4π (or 8π) unit of **165** is generated


R
R1
O
O
160 °C, 4 h
(1% in toluene)
R
R1
O
O
+
R
R1
O
O
H
H
H
O
O
+ tautomers
(162) 56%
23%
(163)
CN
Δ, 180 °C
(solution)
CN
NC
(164)
(165)
+ tautomers
(166) 60%

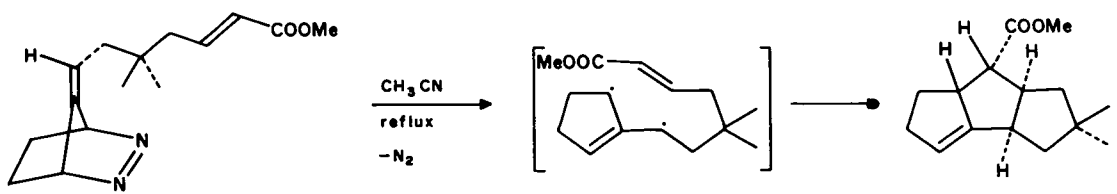
SCHEME 134



(2e)

(167) *ca* 70%

(5 examples)



(168)

(169)

(170) 50%

(not optimised)

SCHEME 135

thermally from precursor **164** and immediately reacted to give the tricyclic product **166** as a tautomeric mixture[391].

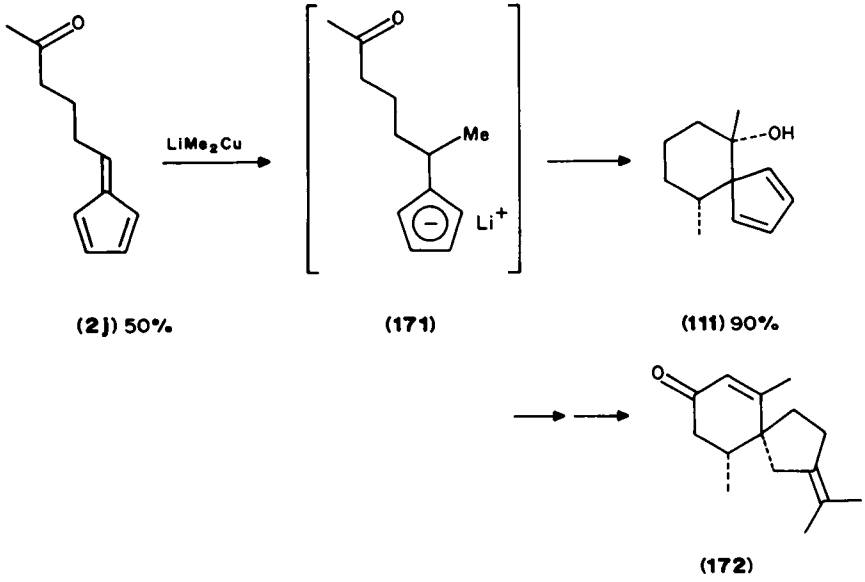
Two very interesting syntheses of linearly fused tricyclopentanoid skeletons have been reported recently (Scheme 135). Intramolecular formal [6 + 2] cycloaddition of 6-(5-dialkylamino-4-pentenyl)pentafulvenes (**2o**) gives *cis*-fused tricyclopentanoid products **167** in good yields. If the alkyl spacer has four instead of three carbon atoms, then a 2:1 mixture of *cis*- and *trans*-fused hydrocarbons is obtained[393].

Precursor **168** is prepared by [4 + 2] cycloaddition of the appropriate pentafulvene (available in a 91% yield)[394] and diazo-bis(trichloroethyl)dicarboxylate followed by catalytic hydrogenation and reductive cleavage of the carboxyls. The idea was to trap the thermally generated diradical **169** by intramolecular cycloaddition. In fact, if the precursor **168** is refluxed in acetonitrile then the tricyclopentanoid system **170** is isolated in a 50% yield. The sequence proceeds regiospecifically and is highly stereoselective[394] (Scheme 135).

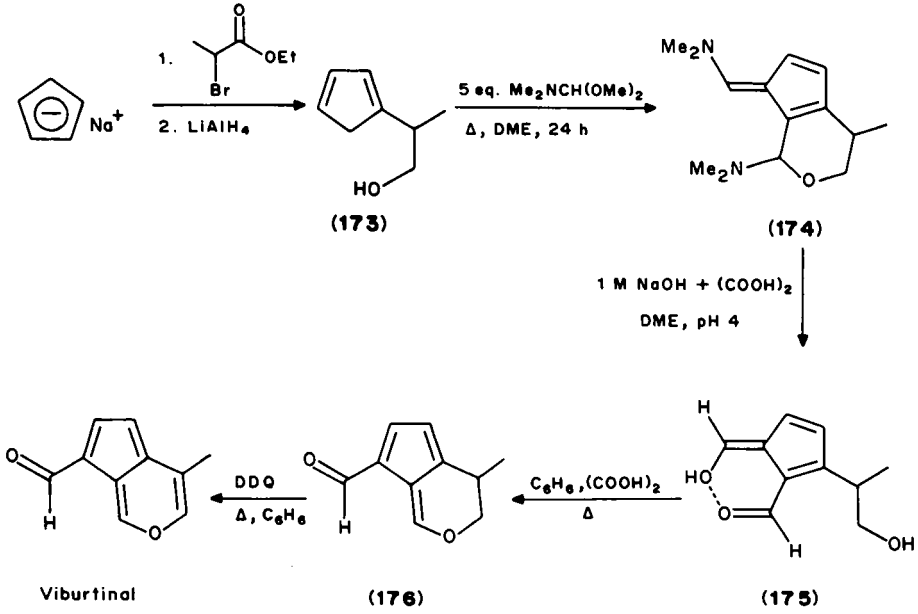
C. Synthesis of Natural Products

If one takes into account that many pentafulvenes bearing potential leaving groups are easily available and react regioselectively with nucleophiles and electrophiles as well as periselectively in cycloaddition reactions, it is rather surprising that pentafulvenes so far have only rarely been applied for the synthesis of cyclopentanoid natural products.

One of the first natural product syntheses starting with a pentafulvene was developed in 1976[108,395]. Pentafulvene **2j** is prepared according to Freiesleben[101] from cyclopentadiene and 5-oxohexanal. Reaction with lithium dimethylcopper results in a nucleophilic methylation of C-6 of the fulvene to give cyclopentadienide **171**, which undergoes intramolecular cyclization; surprisingly enough one single carbinol **111** is formed stereoselectively. Spiro-compound **111** is the key intermediate for the subsequent synthesis of β-vetivone **172**[108] (Scheme 136).

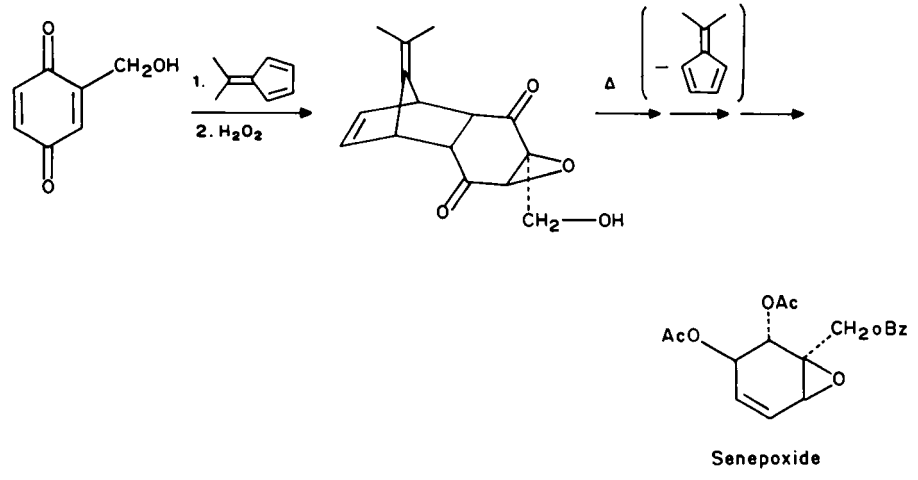


SCHEME 136



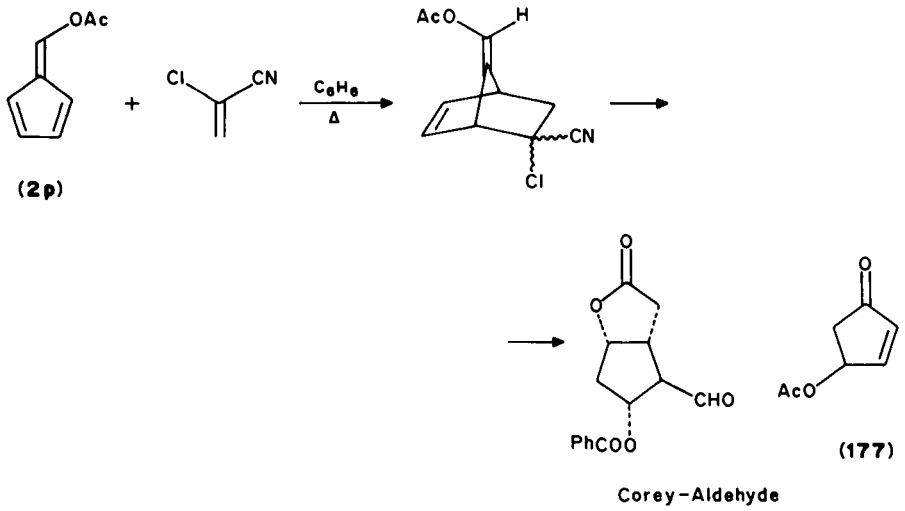
SCHEME 137

The total synthesis of viburtinal, a fulvenoid monoterpene which might play a role in the biosynthesis of indole- and ipeka-alkaloids, is given in Scheme 137[396]. The key step is the twofold formylation of cyclopentadiene **173**. It seems that the α-formylation of the primarily formed β-substituted 6-dimethylaminopentafulvene is directed by the side-chain. Subsequent hydrolysis **174** → **175** and dehydration gives the viburtinal precursor **176**.



SCHEME 138

In several cases, pentafulvenes have been used as devices for enhancing regioselectivity and stereoselectivity of epoxidations of quinones[397–399] (Scheme 138).



SCHEME 139

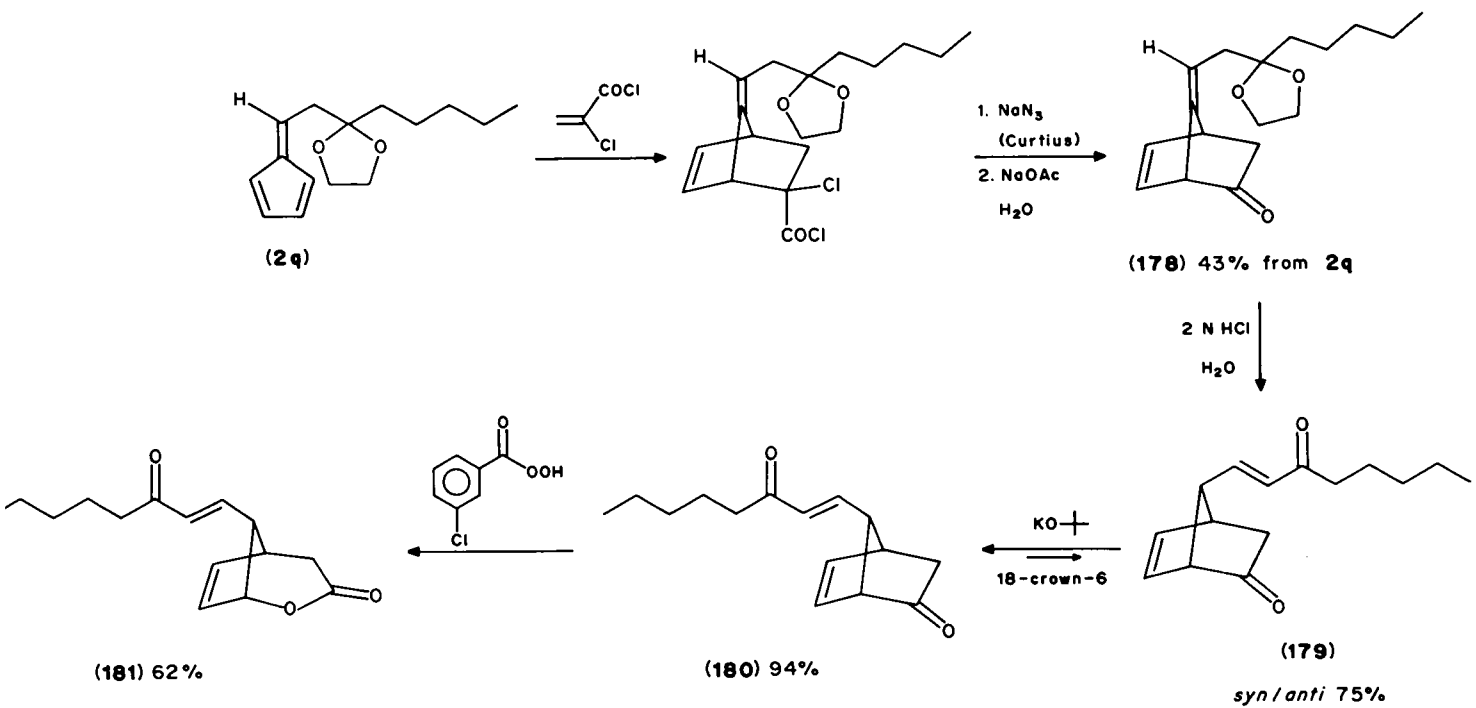
6-Acetoxypentafulvene (**2p**) may be a versatile reagent in natural products synthesis, similarly to 4-oxo-2-cyclopentenyl acetate **177**[400]. Its [4 + 2]-cycloaddition product with α-chloroacrylonitrile has been transformed into Corey's aldehyde with good yields[401] (Scheme 139).

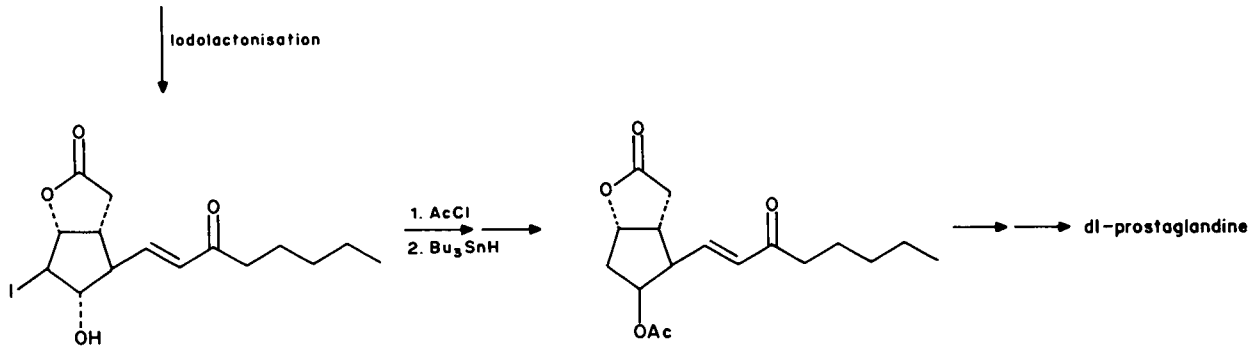
A similar, more recent sequence is presented in Scheme 140. It shows that, starting with appropriately substituted pentafulvenes **2q**, prostaglandines or their precursors are available[402]. The sequence is shorter than the classical prostaglandine syntheses and is highly stereoselective. Deketalization and double-bond isomerization **178** → **179** are realized in one step, followed by base-induced *anti–syn* isomerization **179** → **180**. Finally, the key step **181** → **182** proceeds in a high yield.

D. Synthesis of Fulvene Polymers with Special Properties

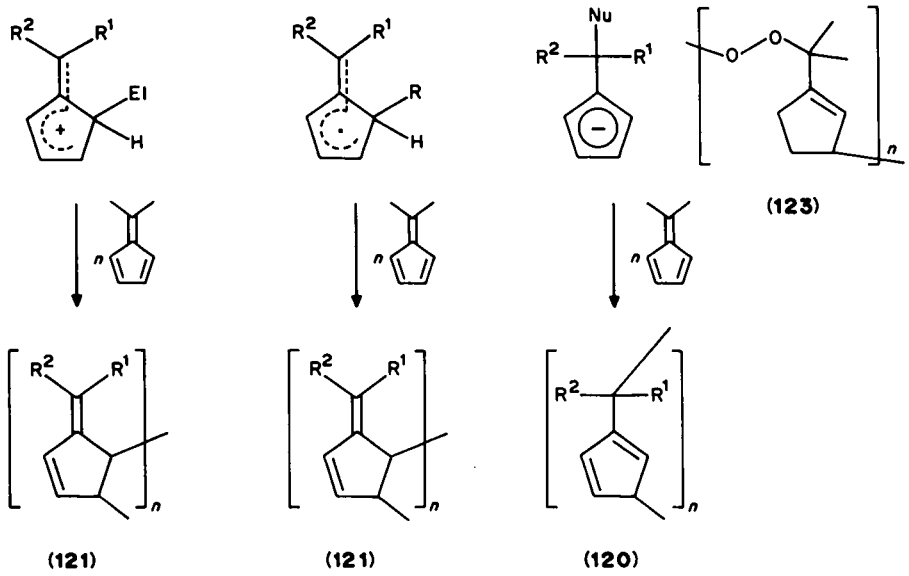
The marked tendency of simple pentafulvenes to undergo polymerizations (and especially cationic polymerizations) is well known. Although several investigations have been reported in the literature (for a review of the older literature see Reference 403) many early speculations concerning the structure of the products were erroneous.

According to ^{13}C-NMR investigations[294,295], 6,6-dimethylpentafulvene and other simple 6,6-dialkylpentafulvenes react in the presence of traces of acids or Lewis acids to give high-molecular-weight polymers of structure **121**[293]. In agreement with earlier reports[99,298], polymers of the same type but of lower molecular weight are obtained by radical polymerization of 6,6-diphenyl- and 6,6-dimethyl-pentafulvene[404]. These polymers are extremely oxygen-sensitive; they incorporate somewhat more than 1 mole-equivalent of oxygen per structural unit within hours under cross-linking. The oxygen sensitivity is related to the substituted diene unit, since treatment of 3,4-dihydropentafulvene with oxygen gives low-molecular-weight oligomers **123**[296] (Scheme 141).


H
O
O
(2q)
COCl
Cl
H
O
O
Cl
COCl
1. NaN3
(Curtius)
2. NaOAc
H2O
H
O
O
O
(178) 43% from 2q
2 N HCl
H2O
O
O
KO
18-crown-6
(179)
syn/anti 75%
O
OOH
Cl
O
(180) 94%
O
O
O
(181) 62%

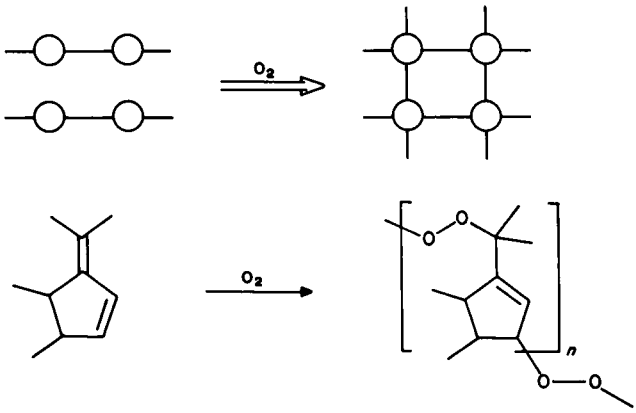

Iodolactonisation
1. AcCl
2. Bu3SnH
dl-prostaglandine
OH
OAc
(182) 86%
38%
Corey's intermediate

SCHEME 140



SCHEME 141

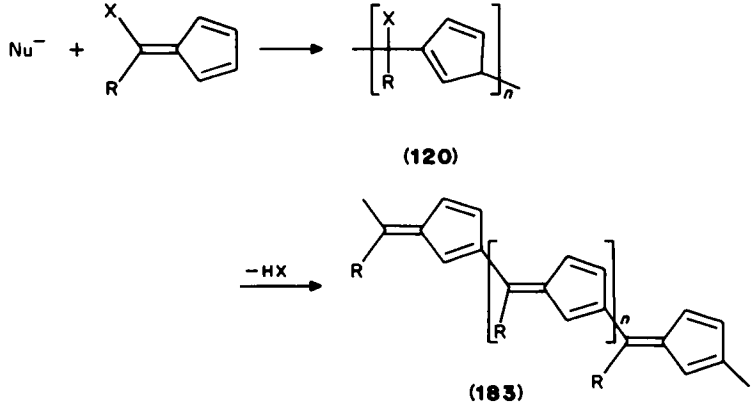
The oxygen sensitivity of the dihydropentafulvene units of polyfulvenes may be applied practically in view of crosslinking of radical[298,404,82] or cationic pentafulvene copolymers through the oxygen contact. Hence cationic copolymers of 6, 6-dimethylpentafulvene with various olefinic monomers are available[405]. If they are exposed to air, then unsoluble crosslinked products are formed according to the crosslinking reaction of Scheme 142[405].



SCHEME 142

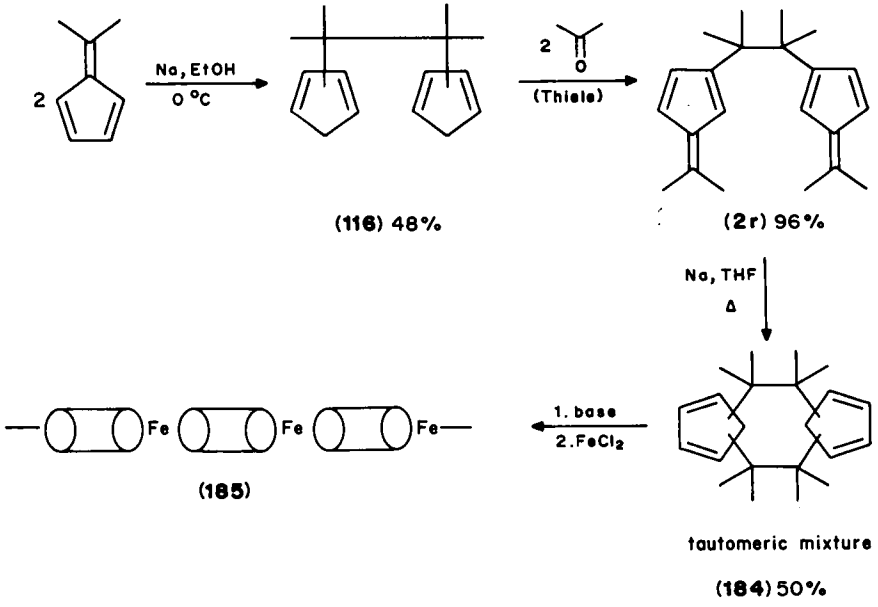
Another attractive (and not yet realized) application of pentafulvenes bearing a potential leaving group at C-6 would result from anionic polymerization, because the primarily formed polymers **120** could in principle be transformed into fully conjugated

polymer chains of type **183**. Although structural elements **120** have been claimed[406], more recent investigations show that the main reaction of 6, 6-dimethylfulvene with organolithium compounds or with cyclopentadienide is proton abstraction from a CH_3 group rather than nucleophilic attack at C-6[287,407]. So pentafulvenes suitable for the sequence of Scheme 143 should have a non-acidic substituent R besides the potential leaving group X.



SCHEME 143

Polyferrocenophanes of type **185** are interesting molecules which could have special electrical properties. Very recently, a ligand **184** for such polymers has been prepared by application of typical pentafulvene sequences (Scheme 144)[408,409].



SCHEME 144

Reductive coupling of 6,6-dimethylpentafulvene according to Rinehart[281] followed by protonation gives 1,2-dimethyl-1,2-dicyclopentadienylbutane **116**, which is transformed into the bis(fulvene) **2r** according to Thiele. Another reductive coupling with sodium metal gives the desired ligand as a tautomeric mixture. First preliminary results[409] indicate that the last step **184** → **185** to give the polyferrocenophane **185** is indeed possible.

V. π-BOND DELOCALIZATION AND AROMATICITY OF FULVENES

A. Introduction

Soon after the discovery of the first pentafulvenes by Thiele in 1900[1], these molecules started to intrigue chemists. Although pentafulvenes are isomers of benzene, they show a surprisingly high reactivity towards a variety of reagents; furthermore, they are coloured and have a dipole moment. With the synthesis of the first heptafulvenes[2], triafulvenes[3–5] and nonafulvenes[7] in the late 1950s and 1960s, the interest of chemists in cyclic cross-conjugated molecules was still increasing. As soon as the importance of Hückel's MO treatment[410] for conjugated π systems was recognized, numerous theoretical investigations concerning fulvenes were published. During a long period they were hampered by the fact that precise information about the parent fulvenes was missing. Furthermore, early calculations seemed to indicate that in fulvenes bond lengths were less strongly alternating than in open-chain olefinic molecules, while a simple HMO treatment predicted a dipole moment of 4.7 D for the parent pentafulvene[411] giving some importance to dipolar structures in the ground state.

This result was easily accepted by the experimental chemists, since the reactive behaviour of many fulvenes was compatible with an intermediate position of fulvenes between open-chain olefinic and delocalized aromatic molecules[14]. However, with increasing refinement of HMO methods, theoretical predictions for parent fulvenes more and more supported molecules with strongly alternating bond lengths and a small dipole moment. So, for the parent pentafulvene the calculated dipole moment dropped from 4.7[411] to 0.45 D[76]! (For an illustrative discussion of older theoretical predictions see Reference 17, pp. 168–184).

Before being in a position to decide whether fulvenes are aromatic or not, or even to determine their extent of aromaticity, we must first agree about *good criteria of aromaticity*[412–415]. The notion 'aromatic' was at first attributed to certain benzenoid derivatives being characterized by a typical smell. Later on it was realized that the basic parent system of all these compounds was a benzene ring. So the main interest of chemists was focused on the surprising inertness of benzene to undergo reactions typical for olefinic molecules and on the strong tendency of benzene and its derivatives to undergo substitution reactions.

Since reactivity is connected to the energy difference between the ground state of the starting material and that of the transition state, and since substitutents may stabilize both levels or mainly only one, it is dangerous to conclude from a sluggish reaction of a compound as to its aromatic character. In the following, we will look for typical ground-state properties as possible criteria for aromaticity. Due to extensive π delocalization, benzene is characterized by a low ground-state energy compared with appropriate open-chain molecules, such as hexatriene. This energy difference* ('*Dewar resonance energy*')[416] has turned out to be a good criterion for aromaticity of non-benzenoid cyclic conjugative systems as well; however, it represents the difference between two theoretically calculated values and is dependent on the suitability of the applied model. The same applies to the

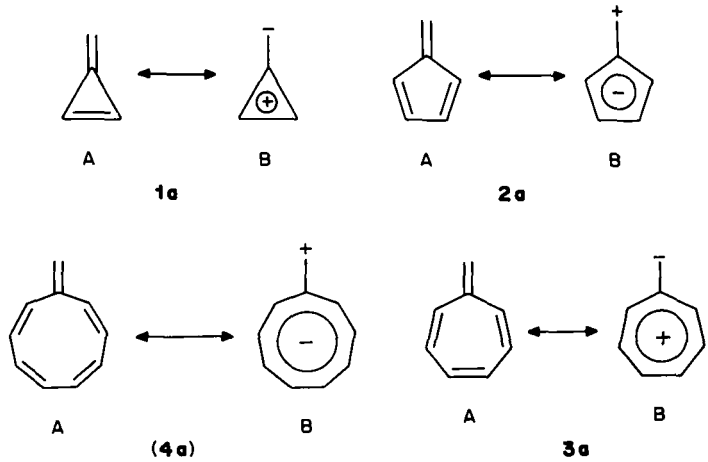
*If π systems of different ring size are compared, then resonance energies per π electron (REPE) are normally calculated.

resonance energy or *delocalization energy*, which is the energy difference between the energy calculated for the delocalized molecule minus the energy calculated for the same but localized molecule.

The results of extensive π delocalization of benzene are equal C—C bond lengths of 1.398 Å, in contrast to cyclohexene where the double bond is 1.337 Å long while the adjacent single bonds are 1.543 Å long. So *bond-length alternation* is a good qualitative criterion for deciding whether a cyclic conjugated molecule is olefinic or aromatic, provided that the data have been made available, e.g. from X-ray or microwave spectroscopy. There are pitfalls, however, especially if X-ray simulates a totally delocalized structure while in fact two or more partially localized structures are rapidly interconverting[417].

While only a few structures of fulvenes have been determined so far by X-ray or MW spectroscopy (see later), information about bond-length alternation is provided by NMR spectroscopy as well. The size of *vicinal proton–proton coupling constants* $^3J_{H,H}$ is strongly dependent on bond lengths, but unfortunately influenced by other factors as well[418], so that carefully chosen molecules have to be compared (see later). Furthermore *carbon–carbon coupling constants* $^1J_{C,C}$ are influenced by bond lengths as well, but not so easily available[419].

Highly delocalized aromatic molecules are characterized by high mobility as well as easy polarizability of the cloud of π electrons. In fact, *diamagnetic susceptibility*[420] may be taken as an indicator for aromaticity. However, the most famous effect induced by delocalized aromatic π systems is the *ring current effect*[421], by which the NMR signals of protons placed in the plane and outside of the aromatic ring are strongly shifted to higher frequencies (to the left), while protons within or slightly above the ring are strongly shifted to lower frequencies (to the right). Unfortunately, the ring current effect is not well suited for the investigation of aromaticity of fulvenes, because increasing π delocalization or aromaticity is associated with increasing importance of dipolar structures of Scheme 145, while changes in the charge density of C atoms not only influence ^{13}C-NMR shifts but ^{1}H-NMR shifts as well.



SCHEME 145

Finally, it should be mentioned that *^{13}C-NMR shifts* are very suitable for indicating changes in charge density. Since ^{13}C-NMR shifts are not influenced by ring-current effects,

they may be very indicative for deciding whether dipolar structures B (Scheme 145) are important or not.

B. Aromaticity of Parent Fulvenes

Most of the basic questions concerning parent fulvenes have been answered during the last 15 years. All the parent systems are available now (see Section II) and their spectral data have been analyzed recently. The results are listed in Table 19, and they clearly show that *parent fulvenes* **1a**, **2a**, **3a** and **4a** *are basically non-aromatic compounds.*

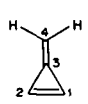
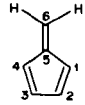
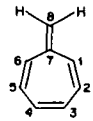
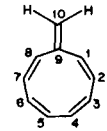
The *microwave data* show that triafulvene[8], pentafulvene[9] and heptafulvene[10] are characterized by strongly alternating bond lengths and only a small dipole moment. In the *UV spectrum*, the bathochromic shift of the longest wavelength absorption from **1a** (309 nm[65]) to **2a** (362 nm[423]) and **3a** (423 nm[343]) corresponds to the extension of the conjugative system. The dramatic hypsochromic shift of the UV absorption of nonafulvene (255 nm) is indicative of a non-planar structure[424]. In agreement with the relatively high energy of the HOMO of fulvenes, the first *ionization potential* $I_{v,1}$ is comparably small; it decreases from pentafulvene[425] to heptafulvene[425]. While the *IR spectra*[426–429] do not provide decisive information concerning the aromaticity of fulvenes, valuable conclusions may be drawn from *proton and carbon NMR spectra.*

First of all, the *proton chemical shifts* of planar pentafulvene (**2a**) and heptafulvene (**3a**) are in the olefinic region. The same is true for nonafulvene (**4a**), which deviates strongly from planarity according to UV[424] and NMR data of 10-substituted compounds[432,433]. On the other hand, the proton chemical shifts of triafulvene (**1a**) are indicative of some contribution of the dipolar form **1B** to the ground state: H-1/H-2 absorb at higher frequencies by about 1 ppm compared with cyclopropenes, while H-4/H-4′ absorb at lower frequency by 1.4 ppm compared with its cycloaddition product with cyclopentadiene[67]. *Vicinal H, H coupling constants* of the ring protons are strongly alternating for pentafulvene (**2a**)[430], heptafulvene (**3a**)[208] and nonafulvene (**4a**)[422]. This evidently shows for planar **2** and **3** that C—C bond lengths are strongly alternating too, while for the non-planar nonafulvene $^3J_{H,H}$ couplings over formal single bonds are influenced by the dihedral angle as well[432,433]. Finally, *^{13}C-chemical shifts* of **2a**, **3a** and **4a** do not show considerable contributions of dipolar forms **2B**, **3B** and **4B** to the ground state. Once again the pronounced high-field position of C-4 of triafulvene[64] compared with its [4 + 2]-cycloaddition product with cyclopentadiene (102.2 ppm[67]) is at least partially due to some negative charge density at the exocyclic C atom.

Thus, all spectroscopic results are in agreement with the basically non-aromatic character of parent fulvenes **1a**–**4a** which show strongly alternating bond lengths and only a small dipole moment, and which are best represented by the canonical structure **A**. A significant contribution of the dipolar structure **1B** is only felt in the ^{1}H- and especially in the ^{13}C-NMR spectra of triafulvene (**1a**). NMR data are completely compatible with the microwave data. This means that in all cases where MW and X-ray data are not available (and there are only a few structural data known, see later) $^3J_{H,H}$ NMR coupling constants and ^{13}C-NMR chemical shifts give a first estimate of the extent of bond-length alternation and charge distribution in these cyclic cross-conjugated molecules.

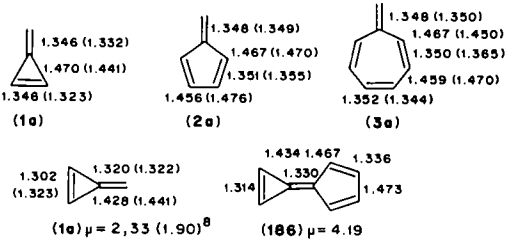
Now that structural data of the parent systems are known, it should be pointed out that more refined theoretical techniques than the simple HMO model[290,434] give a much closer fit with the experimental data. So MNDO/2 calculations give a relatively good fit with the experimental bond lengths of **1a** and **2a**[435]. The results of PPP–CI calculations (Table 20[436]) are very close to the experimental values of **2a** and **3a** and deviate only for triafulvene **1a**. A good fit for **1a** is obtained by refined *ab initio* calculations[426,437], so that the predicted bond lengths and dipole moments of as yet unknown penta-tria-fulvalene seem to be reliable (Table 20, structure **186**).

TABLE 19. Spectroscopic data of parent fulvenes

	 1a	 2a	 3a	 4a
C—C bond lengths (MW spectrum)	1,2:1.323 2,3:1.441 3,4:1.332[8]	1,2:1.355 2,3:1.476 4,5:1.470 5,6:1.348[9]	1,2:1.365 2,3:1.470 3,4:1.344 6,7:1.450 7,8:1.350[10]	unknown non-planar molecule with alternating bond lengths (NMR)[422]
Dipole moment (D) (MW spectrum)	1.90[8]	0.424[9]	0.477[10]	unknown
UV: λ_{max}(log ε)	206 (s) 309 (w)[65]	243 (4.15)[a] 362 (2.40) C_6H_{12}[423]	209 (4.52) 244 (4.16)[a] 249 (4.15)[a] 423 (2.68)[a] C_6H_{12}[343]	255 (4.14) C_6H_{14}[424]
PE (eV)	unknown	$I_{v,1}$: 8.55 $I_{v,2}$: 9.54 $I_{v,3}$: 12.80[425]	$I_{v,1}$: 7.69 $I_{v,2}$: 10.22 $I_{v,3}$: 11.24[425]	unknown[b]
IR (cm^{-1}) $\nu_{C=C}$	1770 1519[64,426]	1629 (w)[423,427]	1655 w 1591 s[343,428]	1630 (w) 1564 (w)[429]
^{1}H-NMR δ(ppm)	H1/H2: 8.18 H4 : 3.60 CD_2Cl_2[64,65]	H1/H4: 6.22 H2/H3: 6.53 H6 : 5.85 $CDCl_3$[430]	H1/H6: 5.97 H2/H5: 5.48 H3/H4: 5.65 H8 : 4.45 CD_3COCD_3[208]	H1/H8: 6.12[c] H2/H7: 5.63 H3/H6: 5.99 H4/H5: 5.82 H10 : 5.11 CD_3COCD_3[422]
^3J (Hz)		$J_{1,2} = 5.10$ $J_{2,3} = 1.95$ $CDCl_3$[430]	$J_{1,2} = 12.05$ $J_{2,3} = 7.51$ $J_{3,4} = 11.53$ CD_3COCD_3[208]	$J_{1,2} = 12.88$[c] $J_{2,3} = 3.80$ $J_{3,4} = 12.16$ $J_{4,5} = 2.94$ CD_3COCD_3[422]
^{13}C-NMR δ (ppm)	C1/C2: 132.9 C4 : 59.6 d_8-THF[64]	C1/C4: 124.9 C2/C3: 134.3 C5 : 152.6 C6 : 123.4 $CDCl_3$[430]	C1/C6: 138.3 C2/C5: 126.9 C3/C4: 130.8 C7 : 146.6 C8 : 111.9 $CDCl_3$[431]	C1/C8: 130.4[c] C2/C7: 127.2 C3/C6: 128.7 C4/C5: 126.7 C9 : 143.5 C10 : 122.0 CD_3COCD_3[422]

[a] Center of the fine-structured absorption band.
[b] PE spectrum of **4a** unknown due to easy valence isomerization of **4a**.
[c] Pairs of protons, C atoms and of coupling constants of non-planar nonafulvenes are averaged due to a fast switch of the exocyclic double bond.

TABLE 20. Predicted bond lengths (in Å) of parent fulvenes **1a–3a** according to PPP–CI calculations[436] and of triafulvene (**1a**) and penta-tria-fulvalene (**186**) (= calicene) by *ab initio* calculations[437,438] (experimental values in parentheses)



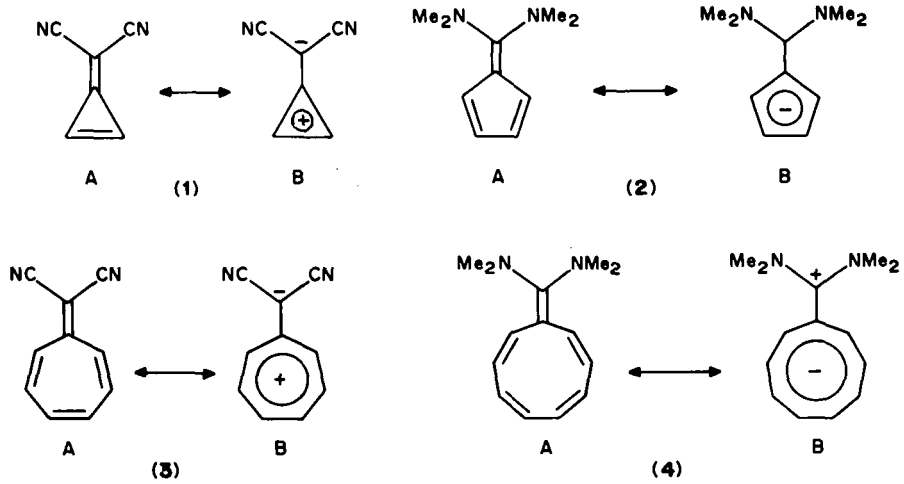
It has to be acknowledged that the 'molecules in molecules' method (MIM) describes a good picture of the electronic energy levels of fulvenes[439,440], while the calculated π-ionization potentials of **2a** and **3a** using perturbation graph theory[441] agree surprisingly well with the experimental data obtained by PE spectroscopy[425]. *Ab initio* methods have recently been applied for predicting IR absorptions of triafulvene (**1a**)[426]; discussions are somewhat hampered by the fact that the frequencies of the calculated absorptions are too high. Problems still exist with calculated resonance energies. While theoreticians generally agree now that pentafulvene (**2a**), heptafulvene (**3a**) and (planar) nonafulvene (**4a**) are non-aromatic* [436,442,443], there is much more uncertainty concerning triafulvene **1**, and quite a lot of confusion concerning fulvalenes.

C. Substituent Effects on π-Delocalization of Fulvenes

Now that parent fulvenes have been shown to be non-aromatic according to their spectroscopic behaviour, it is interesting to look at the influence of substituents on π delocalization of fulvenes. Early experimental work and measured dipole moments of substituted fulvenes indicate that substituents might considerably increase π delocalization, so that these derivatives in fact might occupy an intermediate position between non-aromatic and aromatic molecules[14,17]. Taking into account that most of the experimental evidence concerning bond-length alternation and charge distribution stems from MW and X-ray results as well as from ^{1}H- and ^{13}C-NMR investigations, the results of such investigations will be reviewed. Since fulvenes have an exocyclic double bond, they allow a systematic change of substituents of the exocyclic C atom. By varying the substituents, π delocalization and charge distribution of the ring may change while steric effects are relatively small. Furthermore, if the ring C atoms are not substituted, $^3J_{H,H}$ coupling constants of the ring protons may be observed. So if there is a choice, then fulvenes with varying exocyclic substituents and an unsubstituted ring will be studied preferentially.

According to the descriptive VB notation of Scheme 146, two classes of fulvenes must be distinguished with respect to substitutent effects. For triafulvenes **1** and heptafulvenes **3**, electron-accepting groups at the exocyclic C atom should increase π delocalization in the ring as well as charge separation. On the other hand, for pentafulvenes **2** and nonafulvenes **4**, π delocalization and charge separation should be enhanced by electron-donating substituents. In the following, we will examine the influence of exocyclic substituents on bond lengths, which is directly available from X-ray and MW data and indirectly derived from NMR data.

*Fulvenes are classified to be non-aromatic if their *Dewar resonance energy* is at about zero. This means that the cyclic system has nearly the same π-energy as the corresponding open-chain olefin.



SCHEME 146

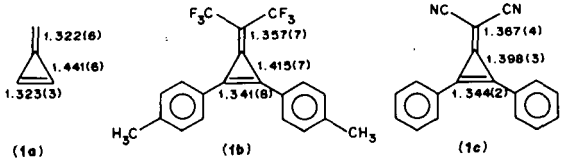
1. Triafulvenes

Due to thermal instability, only a few di- and trisubstituted triafulvenes have been prepared[5,6,48,62,63], so that no systematic NMR investigation has been possible. Most isolated triafulvenes bear phenyl groups at C-1 and C-2 as well as electron-accepting groups at C-4.

According to Table 21, electron-accepting groups at C-4 in fact reduce alternation of bond lengths and increase π delocalization in the ring. While bond lengths of the parent system vary considerably[8], all the bond lengths of 1,2-diphenyl-4,4-dicyanotriafulvene **1c**[445] are already of the same magnitude, and the dipole moment rises up to 7.9 D[3]. The 4,4-bis(trifluoromethyl) derivative **1b**[444], one of the rare examples with strong $-I$ substituents at C-4, obviously takes an intermediate position between **1a** and **1c**. It is interesting to note that the nivellation of bond lengths in the ring is mostly due to a strong decrease of the formal single bonds, while the increase of the double bond C-1/C-2 is surprisingly small.

These few structural results show that electron-accepting groups placed at the exocyclic C atom are increasing π delocalization and—according to the dipole moments—charge separation as well. Dynamic NMR experiments with unsymmetrically substituted 1,2-diaryl-4,4-diacyltriafulvenes and 1-aryl-2-methyl-4,4-diacyltriafulvenes point in the same

TABLE 21. Some microwave and X-ray results of triafulvene **1a** and of substituted triafulvenes[8,444,445]



direction[40]. With increasing electron-accepting capacity of substituents at C-4 (or with increasing electron-donating capacity of substituents at C-1/C-2) the activation energy for rotation around C-3/C-4 decreases.

2. *Pentafulvenes*

Pentafulvenes show polarization opposite to triafulvenes. According to Scheme 146, π delocalization as well as charge separation should be enhanced by electron-donating substituents at C-6.

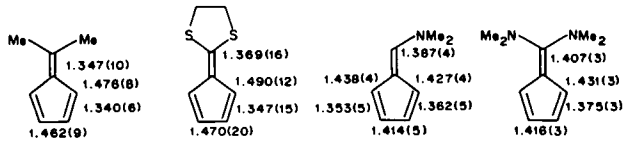
Although only a few structural analyses of simple (C-6)-substituted pentafulvenes are available, the expected trend is clearly confirmed according to Table 22. With increasing electron-donating capacity of substituents at C-6 from 6,6-dimethylpentafulvene to 6,6-bis(dimethylamino)pentafulvene, the formal double bonds are lengthened while the formal single bonds are shortened. [It is surprising to see that double-bond alternation does not significantly change from 6-dimethylamino-[449] to 6,6-bis(dimethylamino)pentafulvene[448]. This may be due to the fact that, in the first case, the substituents are in the plane of the five-membered ring while in the second case the two planes of N–C(6)–N and of the ring are twisted by 29° in the crystalline state.] In the same series, the dipole moment (which is directed towards the ring) increases from 1.44[450] to 5.4 D[123,142].

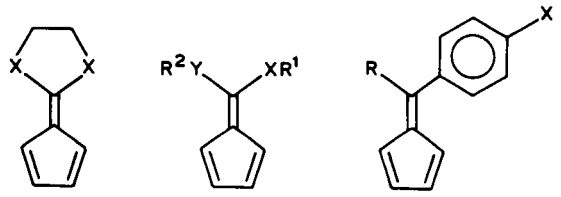
During the last 25 years, NMR spectra of pentafulvenes have been investigated intensively. (For discussion of older results up to 1968 see Reference 17.) It was pointed out quite early that ^{1}H chemical shifts are influenced by a variety of effects and do not allow conclusions concerning aromaticity[430,451], while the size of vicinal H, H coupling constants reflects qualitatively the extent of bond delocalization. From ^{13}C chemical shifts it was estimated that dipolar structures to some extent contribute to the electronic ground state[430,431]. Similar conclusions were drawn from a ^{13}C-NMR analysis of a series of pentafulvenes and pentafulvalenes[452]. While several reports dealt with dynamic effects[453–456], ^1J, ^2J and ^3J CH coupling constants of four pentafulvenes have been determined[457]. In the following, the results of a recent systematic investigation of substituent effects on ^{1}H-NMR coupling constants and ^{13}C chemical shifts[458–461] will be summarized.

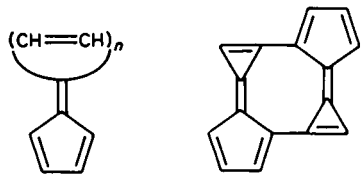
The planar π system of pentafulvenes is an attractive probe for measuring substituent effects in cross-conjugated molecules. In the following summary, mainly pentafulvenes of type **2C** will be discussed[460], although many examples of type **2D**[460] and **2E** have been investigated as well[458,459]. These results will be compared with the NMR data of pentafulvalenes **187**[461], **188**[431] and **87**[257] (Scheme 147).

Proton chemical shifts. In series of pentafulvenes **2C**, **2D** and **2E**, no linear correlations between proton chemical shifts and substituent quantities like Hammett substituent constants σ^+ or calculated bond lengths are observed, although some trends may be noticed. Generally, the overall effects induced by substituents on ring protons are small[247,458,460]. This is probably due to the fact that in dipolar pentafulvenes like 6,6-bis(dialkylamino)pentafulvenes the charge-density effect (inducing a high-field shift) and

TABLE 22. Some structural results of pentafulvenes[446–449]

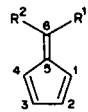






SCHEME 147

TABLE 23. $^3J_{H,H}$ coupling constants and ^{13}C-NMR shifts of exocyclically bridged pentafulvenes and parent pentafulvalenes



R^1, R^2	$J_{1,2}$	$J_{2,3}$	C-1/C-4	C-2/C-3	C-5
$(CH{=}CH)_2$	5.41	1.99[a]	122.0	136.0	147.9[b]
$(CH{=}CH)_4$	5.32	2.12[c]	121.1	132.1	143.0[c]
$(CH_2)_4$	5.2	2.05[c]	121.1	129.3	138.0[b]
$(CH{=}CH)_3$	5.2	2.2[d]	118.6	129.6	138.6[b]
$S(CH_2)_2S$	4.95	2.16[c]	119.8	128.5	132.3[b]
$O(CH_2)_2O$	4.75	2.3[c]	118.0	123.5	98.3[b]
$(CH_3)N(CH_2)_2N(CH_3)$	4.21	2.82[c]	113.4	114.0	98.6[b]

[a] CD_2Cl_2.
[b] $CDCl_3$.
[c] (D_6)acetone.
[d] (D_6)benzene.

the ring-current effect (inducing a low-field shift of ring protons) are nearly counterbalancing each other.

^{13}C chemical shifts. ^{13}C chemical shifts are an ideal tool for the investigation of charge-density effects in benzenoid aromatic molecules of similar steric environments. For

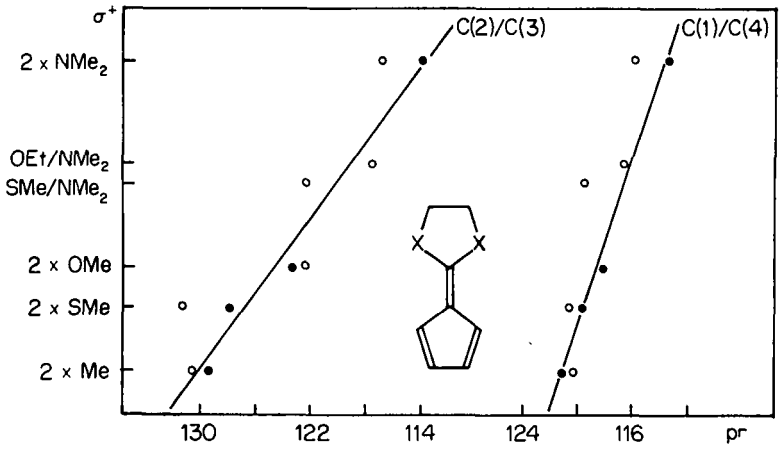


FIGURE 1. Substituent effects on ^{13}C chemical shifts of pentafulvenes **2C** (● = exocyclic bridge) and **2D** (○ = no exocyclic bridge). Reproduced by permission of Blackwell Sci. Publishers, Oxford and IUPAC

instance, good linear correlations between *p*- and *m*-carbons and Hammett σ_p^+-constants have been obtained[463,464]. In fact, as Table 23 shows, chemical shifts of pentafulvenes of type **2C** are systematically influenced by substituents X, and plots of σ_p^+ versus ^{13}C chemical shifts of ring C atoms give linear correlations for C-1/C-4 and C-2/C-3 (Figure 1). As expected, electron-releasing substituents X at the exocyclic C-6 of the fulvene induce a high-field shift of the ring C atoms which strongly decreases in the series C-5 > C-2/C-3 > C-1/C-4[460]. Pentafulvenes **2D** show the same trends with more scattering[460], and the sterically very similar pentafulvenes **2E** give linear correlations for all C atoms of the fulvene ring[458,459]. (see Scheme 147 and also ref. 460).

These results show that systematic electronic substituent effects influence ^{13}C chemical shifts. Since plots of σ^+ versus ^{13}C shifts give linear correlations for both type **2C** and **2E** pentafulvenes, the observed effects may be attributed to changes in charge density.

Vicinal proton coupling constants. It is well known that vicinal H, H coupling constants are strongly influenced by (a) the dihedral angle, (b) the ring size, (c) the electronegativity of substituents and (d) changes in bond lengths[418]. As factor (a)–(c) are small or constant for the ring protons of planar pentafulvenes with exocyclic substituents, the magnitude of the vicinal proton coupling constant $J_{1,2}$, $J_{2,3}$, $J_{3,4}$ should reflect the electronic influence of substituents on bond lengths of the fulvene ring. Figure 2 shows that this is in fact the case. With increasing electron-donating capacity of the substituent X, $J_{1,2}$ and $J_{3,4}$ decrease while $J_{2,3}$ increases. This is exactly the behaviour expected for an increasing π delocalization in the five-membered ring. For pentafulvenes **2C** (Figure 2[460]) and **2E**[458] linear correlations between Hammett constants σ^+ are obtained, while pentafulvenes **2D** show the same trend with more scattering, probably due to steric effects.

These results show that exocyclic substituents in fact influence bond lengths of pentafulvenes, so that the extent of π delocalization is accessible via vicinal proton coupling constants. Extrapolation of the two slopes in Figure 2 gives $J_{1,2} = J_{2,3} = 3.67$ Hz for a complete π delocalization[247]. It is interesting to note that coupling constants $J_{1,2} = J_{2,3} = 3.66$ Hz have been reported for dicalicene **189**[462], which seems to be fully delocalized according to X-ray data.

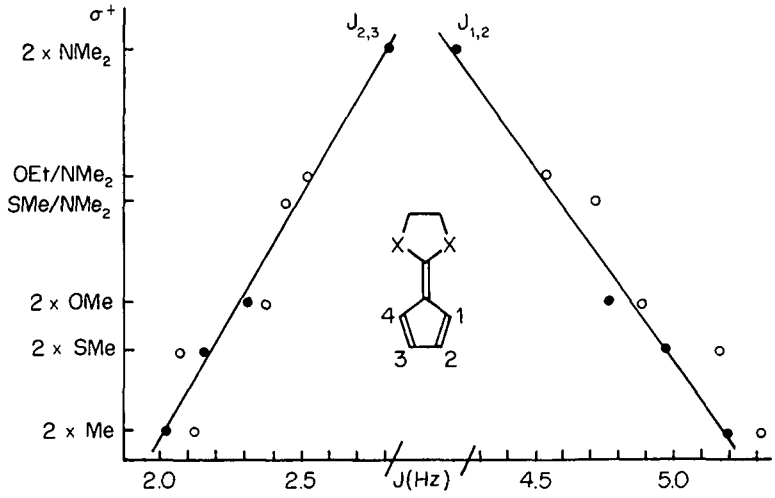


FIGURE 2. Substituent effects on vicinal H, H coupling constants of pentafulvenes. Reproduced by permission of Blackwell Sci. Publishers, Oxford and IUPAC

Data of this type may be used for estimating the extent of π delocalization and charge separation in the parent pentafulvalene **187**[461], heptapentafulvalene (**188**)[431] and nona-penta-fulvalene (**87**)[257]. According to Table 23, pentafulvalene (**187**) shows the most pronounced alternation of bond lengths and no charge separation (between the two identical rings). So π delocalization is very small for pentafulvalene (**187**) and slightly increases from **187** to **87** and to **188**, but all parent pentafulvalenes of Table 23 have strongly alternating bond lengths.

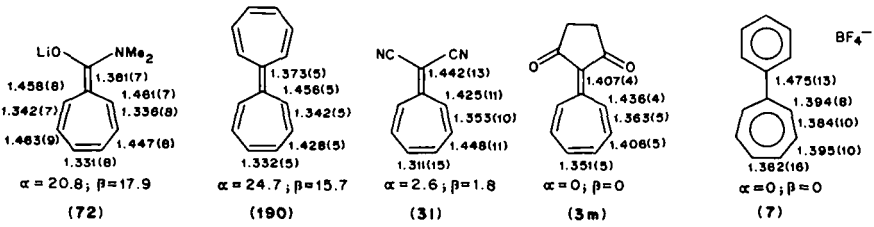
^{13}C–^{13}C coupling constants. Information about bond-length alternation could in principle be available from $^{1}J_{C,C}$ coupling constants as well[419], but the main problem is the very low concentration of isotopomers with two adjacent ^{13}C atoms at natural abundance. Very recently, a series of 6-monosubstituted pentafulvenes ranging from 6-alkylfulvenes to 6-hydroxyfulvenolate was investigated[465]. It turns out that with increasing electron-releasing effect of the substituent X, $J_{1,2}$ and $J_{3,4}$ are decreasing from about 65.8 to 60.5 Hz, while $J_{2,3}$, $J_{1,5}$ and $J_{4,5}$ are increasing from *ca* 49 to 54 Hz, and good linear correlations with σ^+ values are obtained for $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$. So bond-length alternation of the carbon skeleton may be derived from $^{1}J_{C,C}$ coupling as well!

3. Heptafulvenes

Heptafulvenes show the same polarization as triafulvenes. According to Scheme 146, π delocalization as well as charge separation should be enhanced by electron-accepting substituents at C-8. Structural problems are complicated by the fact that—in contrary to planar heptafulvene[10]—many 8,8-disubstituted heptafulvenes are predicted[466] and found experimentally to assume boat conformations with varying structural angles α and β.

On going from non-polar heptafulvalence **190** to heptafulvenes **3l** and **3m** with strongly electron-accepting groups, the structural angles α and β are nearly reduced to zero

TABLE 24. Some structural results[467–471] of 8,8-disubstituted heptafulvenes[a]



[a]For more structural data see Reference 467 and references cited therein, as well as References 226, 472–474.
[b]Complex of two Li-heptafulvenolates·4THF. The second heptafulvenolate unit has very similar bond lengths, but $\alpha = 14.8°$ and $\beta = 12.6°$.

(Table 24). It is surprising to see that π delocalization primarily influences the exocyclic double bond as well as the single bonds of the ring. The final results of this tendency is best seen in substituted tropylium salt **7**, where all the bond lengths are not much longer than the lengths of double bonds of heptafulvenes. [The fact that cyclic π delocalization of heptafulvenes induces mainly a shortening of formal single bonds but—besides (C-7) = (C-8)—not a marked lengthening of ring double bonds, has not yet been satisfactorily explained. A reasonable argument is that, as the positive charge in the ring is increasing from **72** to **7** (Table 24), Coulomb repulsion between the nuclei becomes operative[475].]

Heptafulvenolate **72** may be considered as a heptafulvene with inverse ring polarization[342]. π delocalization of this compound would result in a contribution of 'antiaromatic' 8π-acylcycloheptatrienyl anion. So compared with the planar heptafulvene it is convincing to argue that **72** takes a boat conformation[467]. In fact, compared with heptafulvalene **190** the single bonds are slightly longer, although the structural angles α and β are surrisingly small.

Since 1970, *NMR spectra of heptafulvenes* have been quite intensively investigated, although complete assignments were rare. The first complete analysis of a ^{1}H-NMR spectrum[476] revealed a marked alternation of vicinal coupling constants of 8,8-diphenylheptafulvene. Later on, due to the complexity of ^{1}H-NMR spectra, the interest was focused on ^{13}C-NMR data, and besides the parent heptafulvene[431] a series of ^{13}C-NMR spectra of substituted heptafulvenes have been assigned[205,221–223,230,361,477]. Hence it was shown that the ^{13}C-NMR shifts of the ring C atoms of 8,8-diphenylheptafulvene[205] as well as of 8,8′-bis(heptafulvenyl)[361] are very similar to those of the parent heptafulvene[431]. On the other hand, C-7 of heptafulvenes or heptafulvenolates, such as **72** with electron-donating substituents at C-8, is strongly shifted to lower frequencies. This was taken as proof of an inverse polarization of this interesting class of heptafulvenes[221–223]. For lithium 8-dimethylaminoheptafulvenolate **72** the activation energy for the rotation around C-7/C-8 ($\Delta G^{\ddagger} = 17.5$ kcal mol^{-1}) is only 3.5 kcal higher than for the corresponding 3,4-dihydro derivative, which does not support a significant contribution of an antiaromatic 8π anion to the transition state[478].

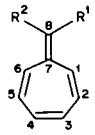
In order to look at substituent effects, we will rely on a new investigation of a series of heptafulvenes whose complex ^{1}H-NMR spectra, as well as their ^{13}C-NMR spectra, have been analyzed recently[208].

Proton chemical shifts. Contrary to pentafulvenes, proton chemical shifts of heptafulvenes are strongly affected by exocyclic substituents. While electron-donating groups induce a high-field shift, electron-accepting substituents induce a low-field shift of all the ring protons, the maximum shift differences ranging between 2.45 ppm (H-3/H-4) and 2.9 ppm (H-2/H-5)[208]. However, no linear correlations with Hammett σ^+ values are observed. It may be assumed that the charge-density effect is very important, being supported by the ring-current effect in the case of planarized heptafulvenes with electron-accepting groups. Protons H-1/H-6 are furthermore influenced by anisotropy effects of exocyclic substituents.

^{13}C chemical shifts. If exocyclic substituents influence the charge density of ring C atoms, ^{13}C chemical shifts should be strongly influenced by substituents. This is in fact the case (Table 25). With increasing electron-accepting capacity of the exocyclic substituents, the ring C atoms undergo a low-field shift which strongly decays in the series C-7 > C-2/C-5 > C-3/C-4 > C-1/C-6[208]. For C-1/C-6, the small charge-density effect is blurred by steric effects. It is interesting to see that no linear correlations with Hammet σ^+ values are obtained. This may be explained by the conformational behaviour of heptafulvenes. With an increasing planarization of the seven-membered ring, substituent effects influencing the π system should become more and more effective, which is in fact observed.

Vicinal proton–proton coupling constants. Exocyclic substituents influence ^3J coupling constants over formal single bonds differently from ^3J coupling over formal double bonds (Table 25[208]). The pronounced increase in $J_{2,3}$ and $J_{4,5}$ with increasing electron-withdrawing capacity of the substituent reflects the ring-flattening (decrease of the dihedral angles) and the reduction of bond lengths as well. This behaviour is in agreement with the X-ray data of Table 24 which additionally show that the bond lengths of formal double bonds remain almost uninfluenced by substituents. Accordingly, ^3J coupling constants over formal double bonds are only very slightly influenced by substituents.

TABLE 25. $^3J_{H,H}$ coupling constants and ^{13}C chemical shifts of 8,8-disubstituted heptafulvenes as well as of 7-methoxytropylium fluoroborate



R^1	R^2	$J_{1,2}/J_{5,6}$	$J_{2,3}/J_{4,5}$	$J_{3,4}$	C-7	C-2/C-5	C-3/C-4	C-1/C-6	C-8
NMe_2	NMe_2[a]	12.03	6.92	11.63	105.70	120.80	130.80	139.30	157.50
$(CH_2)_4$[b]		?	7.20	11.62	129.67	125.36	131.00	135.86	139.73
Ph	Ph[a]	12.13	7.21	11.28	136.61	127.48	132.00	135.71	135.62
H	H[a]	12.05	7.51	11.53	146.60[c]	126.90	130.80	138.30	111.90[c]
Cl	Cl[b]	11.91	7.24	11.93	135.54	130.15	132.35	130.62	113.15
$COCH_2CH_2CO$[a]		11.91	8.39	10.45	158.94	142.93	140.60	139.02	114.52
CN	CN[a]	11.82	8.27	10.88	163.70	138.65	137.42	135.30	70.10
OCH_3[b]		11.40	9.19	9.93	182.17	151.73	148.01	138.92	—

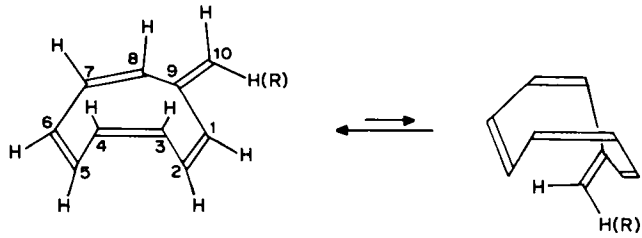
[a] ^1H-NMR spectra in d_6-acetone; ^{13}C-NMR spectra in $CDCl_3$.
[b] ^1H-NMR spectra and ^{13}C-NMR spectra in d_6-acetone.
[c] ^{13}C resonances of C-7 and C-8 of **3a** ($R^1 = R^2 = H$) are not comparable due to missing substituents at C-8.

While $J_{1,2}$ and $J_{5,6}$ remain practically constant, $J_{3,4}$ decreases slightly only for very strong electron-accepting groups. The origin of this influence is so far unknown.

Therefore despite the fact that the interpretation of NMR results is complicated by the conformational behaviour of heptafulvenes, they allow qualitative conclusions concerning substituent effects on charge distribution (^{13}C-NMR) and bond-length alternation ($^3J_{H,H}$).

4. Nonafulvenes

Planar nonafulvenes should exhibit the same π polarization as pentafulvenes. According to Scheme 146, π delocalization as well as charge separation should be enhanced by electron-donating substituents at C-10. Structural problems are complicated by the fact that non-polar nonafulvenes are found experimentally to be non-planar. This is easily derived from the longest-wavelength absorption of the parent nonafulvene (**4a**) ($\lambda_{max} = 255$ nm in hexane[424]) compared with pentafulvene (**2a**) ($\lambda_{max} = 362$ nm[423]) and heptafulvene (**3a**) ($\lambda_{max} = 423$ nm[343]). On the other hand, pairs of ring protons and of ring C atoms of the parent **4a** are equivalent, which hints at an easy switch of the exocyclic double bond, by which diastereotopic ring segments are transformed into each other (Scheme 148[424]).



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These early conclusions have very recently been supported by extensive NMR investigations[422,432,433]. So far, no X-ray analysis of a nonafulvene has been reported.

The experimental high-resolution ^{1}H-NMR spectrum of **4i** is shown in Figure 3 (upper trace). Extensive analysis of the complex nine-spin system gives the chemical shifts and 27 coupling constants different from zero. All the chemical shifts are in the olefinic range, and there is no dependence on solvent polarity or temperature; consequently, 10-dimethylaminononafulvene (**4i**) is an olefinic molecule[433].

There is an extreme alternation of vicinal H, H-coupling constants of **4i**. While ^3J couplings over formal double bonds are large, ^3J couplings over formal single bonds are surprisingly small, showing the influence of bond length *and* dihedral angle and confirming the non-planar geometry of the ring. Furthermore, $J_{6,7}$ is nearly twice as large as $J_{2,3}$ and $J_{4,5}$. This means that the dihedral angle between H—C(6) and H—C(7) is small compared with the dihedral angle of protons H—C(2) and H—C(3) or H—C(4) and H—C(5). According to Dreiding molecular models and MNDO calculations, this is the case if the fulvene contains a nearly planar *E*-configurated dienamine unit consisting of atoms N–C(10)–C(9)–C(8)–C(7). As a consequence, the C(6)–C(7) bond shows a medium deviation out of the plane of the dienamine unit while double bonds C(1)=C(2) and C(3)=C(4) are strongly out-of-plane. In the conformational equilibrium *E*-**4i** $\rightleftarrows$ *Z*-**4i**, *E*-**4i** is probably favoured because the steric interactions of the substituent with H—C(1) are smaller.

The 1:1 equilibria of type *E*-**4** $\rightleftarrows$ *Z*-**4** are expected and found for substituted nonafulvenes bearing two identical substituents at C(10). Furthermore, chemical shifts of pairs

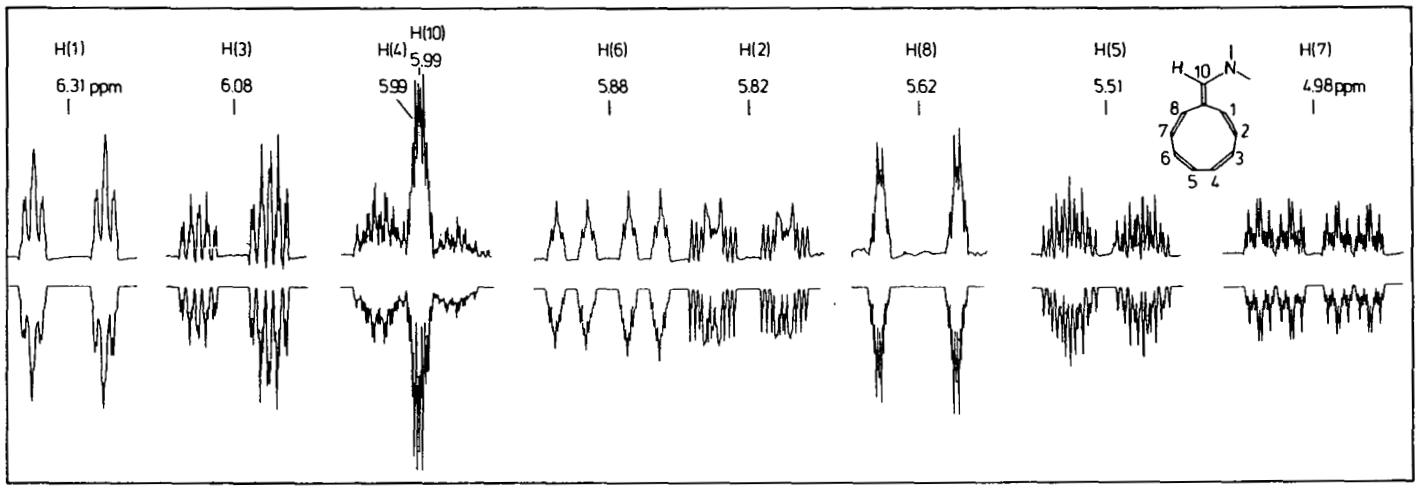
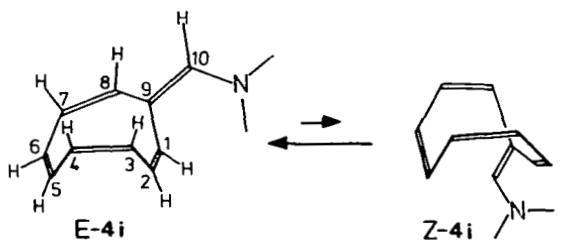


FIGURE 3. ^{1}H-NMR spectrum of 10-dimethylaminononafulvene (**4i**) (400 MHz, CD_2Cl_2, $-10°$). Upper trace: experimental spectrum; lower trace: calculated spectrum with the final set of δ and J values (see below)[433]. Reproduced by permission of Blackwell Sci. Publishers, Oxford and IUPAC



$J_{1,2} = 12.00$, $J_{5,6} = 12.28$, $J_{2,5} = 2.21$,
$J_{2,3} = 2.73$, $J_{6,7} = 5.27$, $J_{3,6} = 0.40$,
$J_{3,4} = 11.82$, $J_{7,8} = 13.05$, $J_{4,7} = 2.03$,
$J_{4,5} = 3.03$, $J_{1,4} = 0.31$, $J_{5,8} = 0.82$.

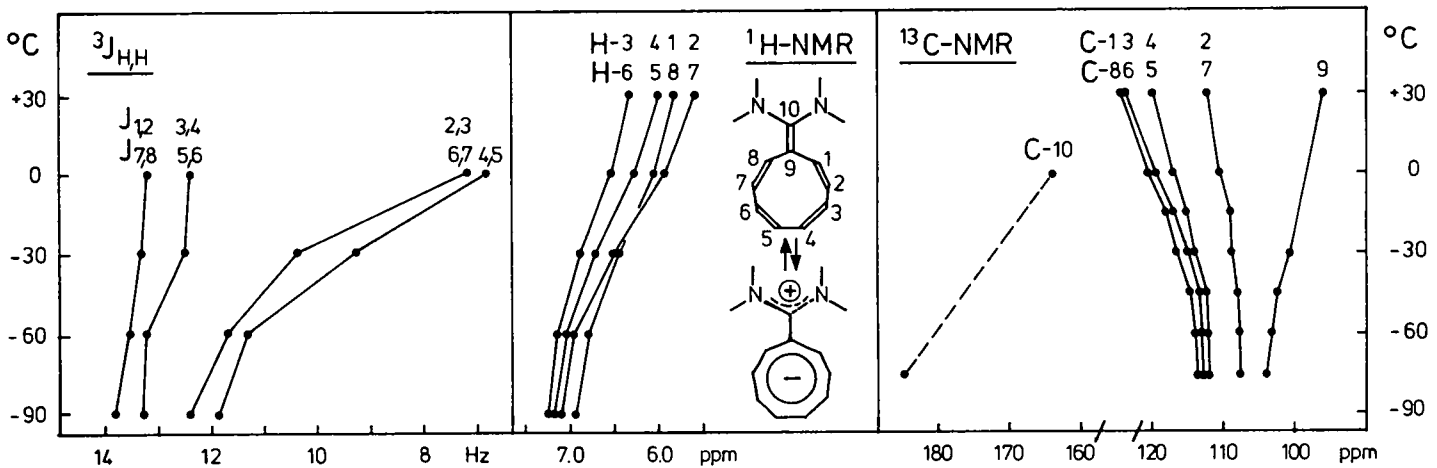


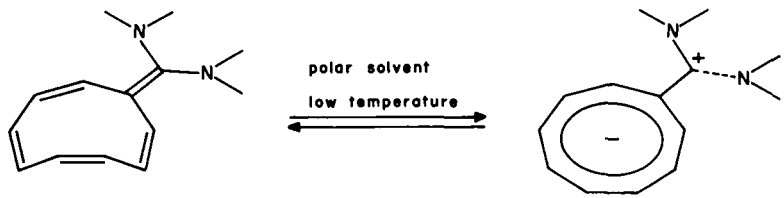
FIGURE 4. Influence of temperature on vicinal proton–proton coupling constants/^{1}H chemical shifts/^{13}C chemical shifts of 10,10-bis(dimethylamino)nonafulvene (**4r**). Reproduced by permission of Blackwell Sci. Publishers, Oxford and IUPAC

of ring protons and ring C atoms as well as of coupling constants are averaged[422]. Hence electronic substituent effects are best investigated for 10-monosubstituted nonafulvenes favouring *E*-**4** conformations. With an increasing electron-donating effect of the substituent at C(10), proton chemical shifts are not much affected with the exception of H—C(7), which experiences a high-field shift. Similarly, considerable high-field shifts are observed in the ^{13}C NMR for C(9) > C(7) > C(5). Finally $J_{6,7}$ increases. This shows that the substituent mainly influences the planarized diene segment C(7)=C(8)—C(9)=C(10).

With one exception, all the nonafulvenes prepared so far do not show any dependence of ^{1}H chemical shifts, ^{13}C chemical shifts or coupling constants on temperature or solvent polarity. The exception is 10,10-bis(dimethylamino)nonafulvene (**4r**)[7,363], whose NMR investigation has recently been completed[453,479].

Lowering temperature (or increasing solvent polarity) has a dramatic effect on NMR parameters of **4r**: vicinal H, H-coupling constants over formal single bonds drastically increase and approach coupling constants over formal double bonds (Figure 4, left). This change is in agreement with a planarization and an increase in π delocalization of the nine-membered ring. Ring protons experience a low-field shift from the olefinic range (6.32–5.59 ppm) to the aromatic range of the spectrum (7.24–6.92 ppm), which is only partially balanced by the charge-density effect. This behaviour supports an increasing π delocalization. Ring C atoms C-1 to C-8 undergo a high-field shift, which decreases in the series C-1/C-8 ≃ C-3/C-6 > C-4/C-5 > C-2/C-7 and is reversed for C-9. This behaviour is in agreement with an increasing charge density in the ring.

These data are in agreement with an equilibrium between non-planar olefinic nonafulvene **4r** being favoured in non-polar solvents or at ambient temperature and a dipolar formamidinium cyclononatetranide **4r**$^{\pm}$[254] being stabilized by polar solvents (solvatation) or at low temperature (due to a negative reaction entropy[363]). (See Scheme 149). The behaviour of **4r** is very similar to that of sodium nonafulvenolates, which exist as acylcyclononatetranides in polar solvents or at low temperatures[254].



(**4r**) (**4r**)$^{\pm}$

SCHEME 149

If all the nonafulvenes prepared so far are examined, three classes may be distinguished (Figure 5). *Type A nonafulvenes* with weakly electron-donating substituents exist in the non-planar olefinic form, and the activation energy for a rotation around the exocyclic double bond (over a dipolar intermediate) is high. With increasing electron-donating capacity of the substituents the energy of the dipolar intermediate is lowered, so that the activation energy for a rotation around the exocyclic double bond is smaller (*Type B nonafulvenes*). **4r** is the exponent of *Type C nonafulvenes*, in which the energy of the non-planar olefinic form **4** is so close to the level of the dipolar form **4**$^{\pm}$ that solvent or temperature effects may favour **4** or **4**$^{\pm}$. Finally, so far unknown *Type D nonafulvenes* may be foreseen in which the dipolar form **4**$^{\pm}$ is much lower in energy than the nonafulvene form.

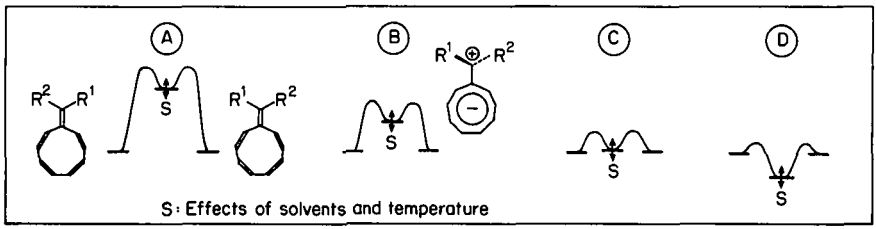


FIGURE 5. Different types of nonafulvenes dependent on the difference in free energy between the non-planar nonafulvene **4** and the dipolar carbenium cyclononatetranide $\mathbf{4}^{\pm}$. Reproduced by permission of Blackwell Sci. Publishers, Oxford and IUPAC

D. Concluding Remarks

All the spectroscopic data show conclusively that the parent fulvenes are non-aromatic compounds with strongly alternating bond lengths and a small dipole moment. However, substituents at the exocyclic C atom of fulvenes may increase π delocalization as well as charge separation, favour planarization of the ring and considerably reduce the extent of bond-length alternation. According to Scheme 146 these are substituents which favour a Hückel-type electron configuration in the ring, namely electron-accepting groups for triafulvenes and heptafulvenes and electron-donating groups for pentafulvenes and nonafulvenes. Substituted fulvenes of that type in fact take an intermediate position between olefinic and aromatic molecules. So in this case the intuitive feeling of experimental chemists (relying on reactivity) has been confirmed by spectroscopy. Finally, recent results show that in cases where X-ray or microwave results are missing, important information concerning bond-length alternation and charge distribution is available from NMR data of a representative fulvene series: while $^3J_{H,H}$ coupling constants of planar fulvenes allow conclusions concerning relative changes in bond lengths, ^{13}C chemical shifts of ring C atoms give valuable information concerning changes of charge distribution.

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The Chemistry of Double-bonded Functional Groups
Edited by S. Patai

CHAPTER **17**

The thiocarbonyl group

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I. INTRODUCTION

The transition from a carbonyl to a thiocarbonyl compound does not just imply a small step in the periodic table, but leads to another world of chemistry. The differences in chemical reactivity and stability reflect the changes in atomic radii, electronegativity and polarizability between oxygen and sulfur.

An unambigous quantitative assessment is possible for the covalent radii of the involved atoms. Obviously, when compared to oxygen (70.2 nm) as bonding partner in a 2p–2p π bond, the larger covalent radius of sulfur (104.9 nm) leads to less efficient overlap with the p_z orbital of carbon (covalent radius 77.2 nm) in a 2p–3p π bond[1,2]. Because of this difference, the dissociation energy of the C=S double bond (115 kcal mol^{-1}) is significantly lower than that of the corresponding bond with oxygen (162 kcal mol^{-1})[3].

The electronegativities give a correlation of electron affinities, ionization energies and bond energies. In Table 1, they are shown for carbon, oxygen and sulfur. The figures suggest an unambiguous polarization for the carbonyl group with a partial negative charge on oxygen and a partial positive charge on carbon. In contrast, the values for carbon and sulfur as given by various authors allow no clear-cut prediction as to the polarization of the C=S bond. The results of *ab initio* calculations will be discussed in Section II.C.

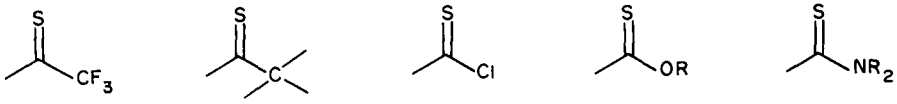
The Sanderson scale of electronegativities is based on the 'compactness' of an atom's electron cloud emphasizing the polarizability[2], which is obviously quite pronounced for sulfur. This implies that the substituents on the thiocarbonyl group will have a strong influence on the physical and chemical properties of the derivative in question. Taking

TABLE 1. Electronegativities of carbon, oxygen and sulfur on different scales[a]

Element	Pauling	Mulliken	Allred and Rochow	Sanderson
C	2.50	2.63	2.50	2.746
O	3.44	3.17	3.17	3.654
S	2.58	2.41	2.44	2.957

[a]References 2 and 4.

thioformaldehyde as a basis, substituents may lead to a decrease in the charge density on sulfur resulting in a polarization that is the inverse of the charge distribution in carbonyl compounds, or substituents may have the opposite effect. For some typical residues, the following order of increasing nucleophilicity and accordingly decreasing electrophilicity of the sulfur may be given:



Thus, hexafluorothioacetone is the prototype of a thiocarbonyl compound with electrophilic sulfur and numerous examples of a—relative to ketones—'inverse' sense of addition reactions have been reported[5]. The other extreme is found in the chemistry of thioamides and thioureas, where resonance interaction between the non-bonding electron pair on nitrogen and the carbon–sulfur π bond leads to a negatively charged sulfur atom with pronounced nucleophilicity:

A similar situation is found for heterocumulenes with a C=S unit. Here, the electronic character of the thiocarbonyl group depends on whether the atom at the other end of the heterocumulene is an electron acceptor or donor. For $X = R_2C$, there are six interacting electrons and resonance structure **1b** is of particular importance, whereas in heterocumulenes with an electron-donating terminus ($X = R_2C{=}C$, $Ph_3P{=}C$, RN, O, S) eight electrons are involved in the resonance interaction and structure **1c** gives an adequate picture of the reactivity[6].

$$X{=}C{=}S \leftrightarrow X^- — C{\equiv}S^+ \leftrightarrow X^+{\equiv}C — S^-$$

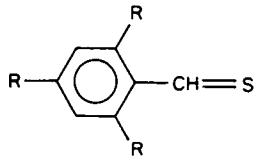
(1a) **(1b)** **(1c)**

Usually, thiocarbonyl compounds with an electron-rich sulfur atom are fairly stable and only moderately reactive. On the contrary, thiocarbonyl derivatives with no pronounced charge separation in the CS moiety or with a resonance contribution of type **1b** are often difficult to isolate and highly reactive.

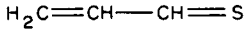
Thioaldehydes (thials) and thioketones (thiones) occupy a medium position between thiocarbonyl derivatives with electrophilic and nucleophilic sulfur, which makes them 'typical' thiocarbonyl compounds. Consequently, the present review will focus on their

chemistry as well as on that of the related thioketenes and thioquinones; the emphasis will be on common properties of the thiocarbonyl group rather than on the individual classes of compounds. The reader who prefers rapid information on specific features of thioaldehyde[7,8], thioketone[9-11] or thioketene chemistry[6,12] is referred to special reviews. The chemistry of 'atypical' thiocarbonyl compounds such as thioamides[13], thiohydrazides[14] or thioesters[15] has been covered in other parts of this series. For a timely review on isothiocyanates, see Reference 16.

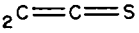
In accord with their ambiphilic nature, thioaldehydes, thioketones and thioketenes often show a high tendency to oligomerize or even polymerize. This is particularly true for simple aliphatic thioketones as well as for most thioketenes and thioaldehydes such as thiobenzaldehyde (**2a**), which polymerizes above $-150\,^{\circ}C$, or thioacrolein (**3**), which gives appreciable decomposition at the temperature of liquid air[17]. Striking exceptions are derivatives with bulky substituents such as thiopivalaldehyde *t*-BuCH=S (**4**), which is quite stable in the absence of Lewis acids or bases[18], the substituted thiobenzaldehyde **2b**[19], di-*t*-butylthioketene (**5a**)[20], or bis(trifluoromethyl)-thioketene (**5b**)[21], where electrostatic repulsion between individual molecules slows down the rate of dimerization.



(**2a**) R = H
(**2b**) R = *t*-Bu

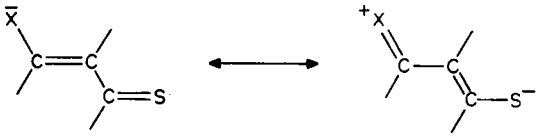


(**3**)



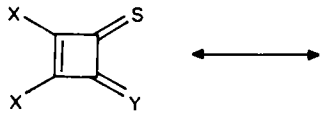
(**5a**) R = *t*-Bu
(**5b**) R = CF_3
(**5c**) R = Ph

Besides the kinetic stabilization by voluminous substituents, some thermodynamic stabilization of the thiocarbonyl group in thials, thiones and thioketenes may be achieved by resonance effects similar to those discussed above. Thus, α,β-unsaturated thioaldehydes or thioketones **6** with an electron-donating substituent on $C_{(\beta)}$(X = OR, SR, NR_2) may be looked upon as vinylogous (di)thioesters and thioamides, respectively, and are usually quite stable. Obviously their chemistry will show many similarities to that of the corresponding acid derivatives.



(**6**)

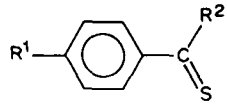
A similar bonding situation as in **6** is found in thiosquaric acid derivatives[22]:



X = OR, SR, NR_2
Y = O, S

In thioketones, some resonance stabilization can also be achieved by one or two aromatic rings as substituents, particularly for substitution of the ring by alkoxy

(7, $R^1 = OR$) or amino groups (7, $R^1 = NR_2$) giving phenylogous thioesters, thiocarbonates, thioamides and thioureas, respectively.



(7)

Even the unsubstituted benzene ring (7, $R^1 = H$, $R^2 = Ph$) leads to diminished electron density in the C=S bond making thiobenzophenone a reasonably stable compound.

In the thioketene field, the available evidence gives no clear picture as to the electronic effect of substituents on the thermodynamic stability[6]. However, stabilization of the thioketene system is observed for (hetero)alkylidene thioketenes, in which X acts as an electron donor:

$$X{=}C{=}C{=}S \leftrightarrow X^+{-}C{\equiv}C{-}S^-$$

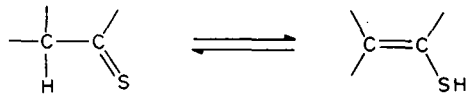
Examples include carbon subsulfide (X = S=C)[23], its recently generated monooxygen analog (X=O=C)[24], and thioketenes such as triphenylphosphoranylidenethioketene ($X = Ph_3P{=}C$)[25] and (aminoalkylidene)thioketenes [$X = R(R_2N)C{=}C$][6,26]. Here, to avoid the unfavourable C=S π bond, a high contribution of the zwitterionic resonance structure is probable leading to a special chemistry and thioketene nomenclature is used for convenience only.

The early chemistry of thiocarbonyl compounds was mainly the chemistry of aromatic thiones (7, R^2 = aryl) and has been reviewed in this series[27]. In the meantime, new methods and techniques have allowed one to synthesize and study a broad range of thioaldehydes, thioketones and thioketenes with widely varying stability calling for the present overview. The limited evidence that is available for thioquinones[28,29] will be included as well.

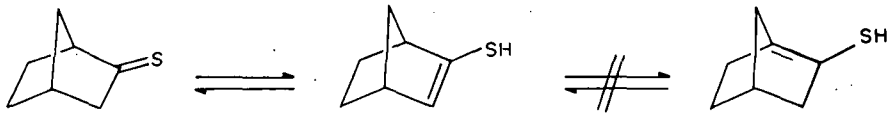
II. SPECTROSCOPIC AND STRUCTURAL CHARACTERISTICS

A. Thione–Enethiol Tautomerism

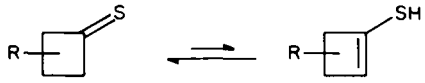
In thials and thiones with α hydrogen(s), formation of the corresponding enethiol is possible and, to avoid the inefficient p_π–p_π C=S bond, is much more favored than enolization for carbonyl compounds.



Thus, on generating a thioketone, quite often a rapid transition of the thiocarbonyl tautomer into the enethiol form occurs. This is true for 1, 3-diphenyl-2-propanethione[30] or for cyclopentanethione whereas, on rapid work-up of the reaction mixture (see Section III.C.1), cyclohexane- and cycloheptanethione can be detected in the ^{13}C NMR spectrum[31]. In accordance with the Bredt rule, norbornanethione forms the enethiol using $H_{(3)}$ rather than $H_{(1)}$[32]:

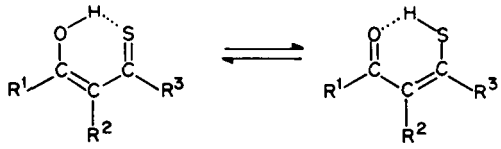


In cyclobutanethiones, formation of the enethiol is disfavored because of ring strain[33]:

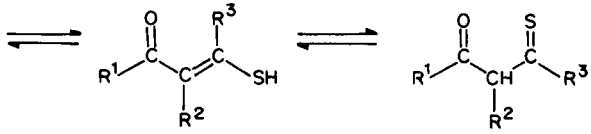


The thione/enethiol tautomers may be separated by vapor-phase chromatography[34-39].

A special situation is encountered in β-thioxo ketones, which have been studied intensively by the group of Duus[40-42]. Here, evidence has been obtained for the presence of three forms which have been identified as the (*Z*)-enol **8A**, the (*Z*)-enethiol **8B** and the (*E*)-enethiol **8C**, respectively.



(8A) **(8B)**



(8C) **(8D)**

For $R^2 = H$, only the enolic form **8A** can be detected in the solid state while, for solutions, the spectroscopic data point toward a tautomeric equilibrium between **8A** and **8B** with the first being preferred, e.g. with a ratio of 61:39 for monothioacetylacetone ($R^1 = R^3 = Me$)[43]. A rapid interconversion by intramolecular proton transfer appears to occur between the two species. The exact position of the equilibrium is governed principally by the nature of R^1 and R^3 and only secondarily by external factors such as the solvent. ESCA spectroscopy has proven helpful in establishing the position of the equilibrium[43].

β-Thioxo ketones with an α substituent ($R^2 \neq H$) appear to exist as species **8A**, though with a freely rotating C=S moiety, and also as tautomer **8C**[40]. In β-thioxo esters ($R^3 = OR^4$) and amides ($R^3 = NR_2^4$) usually tautomers **8B** and **8C** are found[44-48], but in ethyl 2-isopropyl-3-thioxo-butanoate (**8**, $R^1 = Me$, $R^2 = i\text{-}Pr$, $R^3 = OEt$) the bulky R^2 substituent leads to 96% of the otherwise undetectable tautomer **8D**[46].

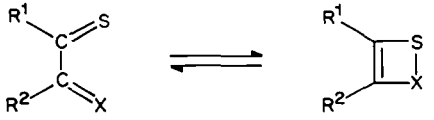
A similar equilibrium with alkynethiols may be discussed for aldothioketenes, but the structure investigations point toward only a minor contribution of the thiol form, if any[49,50]:

$$RCH{=}C{=}S \rightleftharpoons RC{\equiv}CSH$$

While the experimental evidence is quite unambiguous, SCF or SCF–CI computations predict a preference of the thiol tautomer[51-53]. However, the opposite result was deduced from *ab initio* STO-4G calculations[54,55].

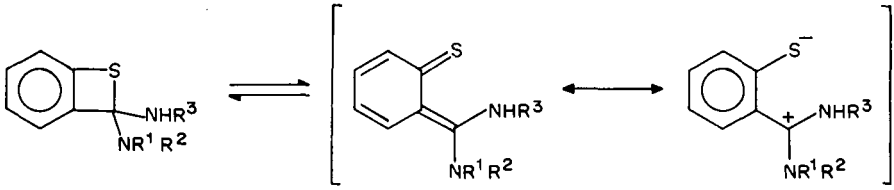
B. Valence Tautomerism

α,β- Unsaturated thiocarbonyl compounds may exist in an equilibrium with a cyclic form:



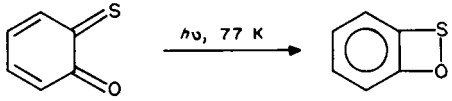
Obviously, the driving force for electrocyclic ring closure stems from the opportunity to break the unfavorable CS π bond possibly with concomitant formation of a stable C=C π bond. However, at the same time the conjugation of the acyclic form is lost and ring strain is built up. Thus, the exact position of the equilibrium is strongly dependent on the nature of X as well as on R^1 and R^2.

For simple enethiones, i.e. for a carbon moiety in the X position, only the acyclic form is detected. However, the situation changes for *o*-quinomonomethane derivatives (X = CR_2, $R^1 + R^2$ = CH=CH—CH=CH). Here the bicyclic species with the aromatic benzene moiety is found in equilibrium with the acyclic form. The distribution depends on R^1–R^3 with higher substitution favoring the zwitterionic resonance structure and consequently giving a higher percent of the quinomethane form[56]:

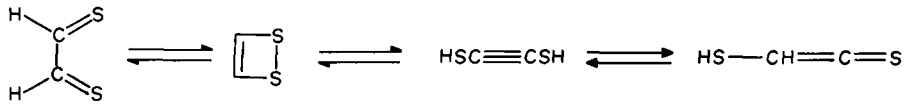


Moreover, the equilibrium is shifted toward the acyclic form by heating in toluene, allowing one to trap the *o*-quinonoid species[57,58].

Also, for simple α-thioxoketones (X = O) such as monothiobenzil (R^1, R^2 = Ph) no cyclic isomer is found. However, incorporation of the unit into an unsaturated six-membered ring allows conversion of the acyclic into the cyclic structure[59]:

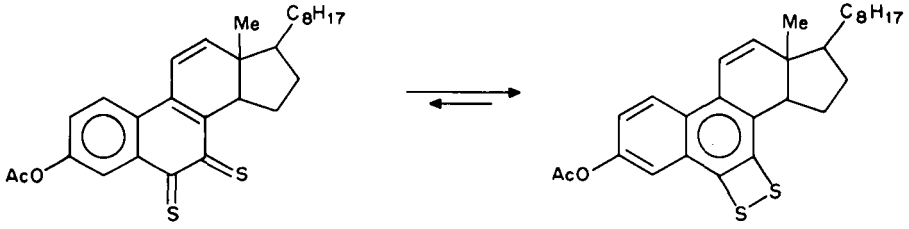


The equilibrium between α-dithiones and 1,2-dithietes (X = S) has been the object of many theoretical and experimental studies. For the simplest example, dithioglyoxal **9**, calculations using the CNDO/2 method predict the cyclic form **9B** to be the more stable isomer, whereas the EH method favors dithial **9A**[59]. The latter result was supported by an *ab initio* calculation at the STO-4G level, though only a small energy difference between the two species was found. Even ethynedithiol (**9C**) and mercaptothioketene (**9D**) have similar energies[61].



(9A) **(9B)** **(9C)** **(9D)**

With the energy difference between the individual species being small, a strong effect of the substituents on the position of the equilibrium can be expected. It has been predicted that electron-donating substituents stabilize the open form, while both conjugative and inductive electron-withdrawing substituents stabilize the cyclic structure with respect to the α-dithione isomer[62]. In fact, for $R^2C{=}S$ being a thioester ($R^2 = OR$) or thioamide ($R^2 = NR_2$) moiety[63,64], the cyclic isomer is not detected, and also the work of Kusters and de Mayo confirms these effects[65,66]. Thus dithiobenzil was found to exist as diphenyldithiete rather than as such, but the corresponding bis-*p*-dimethylamino compound in the solid state exists in the α-dithione form. In solution, the dithione and dithiete forms are in equilibrium and this is sensitive to light, temperature and solvent. In contrast, trifluoromethyl substitution gives a clear preference for the cyclic form[67]. For an *o*-dithioquinone, the possibility to form the aromatic benzodithiete strongly favors this species and the parent *o*-dithioquinone could not even be detected on generation from an appropriate precursor[59,68]. The same situation is encountered for an example in steroid chemistry[69]:

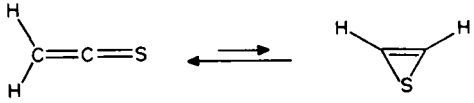


A steric effect on the position of the equilibrium between α-dithiones and 1,2-dithietes in favor of the latter is observed for bulky substituents, e.g. *t*-butyl[70] or structurally related groups[71,72].

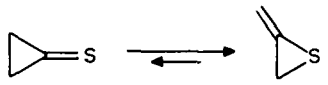
Electrocyclic ring closure of thioacyl (thio)ketenes (X, Y = O or S) would lead to thietones:

Contrary to the all-oxygen example (X = Y = O), thiobenzoyl(phenyl)ketene ($R^1 = R^2 = Ph$, X = O, Y = S) exists in the cyclic thietone form[73]. As for the equilibrium between thioformylthioketene and 2-thietone ($R^1 = R^2 = H$, X = Y = S), a preference for the cyclic form was claimed[74] and supported by experimental results[75].

Thioketene is isomeric not only with ethynethiol (see Section II.A), but also with thiirene. However, in accord with thiirene being a formally antiaromatic 4π electron system, the cyclic form was calculated to be much higher in energy[52].



Cyclopropanethione (**10**) is an elusive species because of its ready transition into methylenethiirane (**11**) in a formal 1,3-sigmatropic shift[76–78].



(10) (11)

Contrary to the analogous oxygen system, the cyclic species **11** was calculated to be 7 kcal mol^{-1} more stable than the thione[76].

C. Quantum Chemical Description of the Thione Group

Until very recently, sulfur has been a tricky element for the theoretical chemist owing to the number of electrons involved[79]. Particularly, the question of $3d_{yz}$-orbital participation in chemical bonds with sulfur has given rise to some controversy[80,81].

In the sixties and early seventies, efforts concentrated on the application of semiempirical SCF methods, such as the PPP approach, to calculate the absorption spectra of thiones[82,83]. In the meantime, excellent *ab initio* methods have become available and allowed a very exact description of the C=S bond. For verification of the theoretical values, photoelectron spectroscopy has proven very helpful (see Section II.D).

Because of its relative simplicity, thioformaldehyde is the most intensively studied example of a thiocarbonyl compound[61,84–88] and a clear picture on the bonding situation has emerged. The HOMO is localized on the sulfur atom and the description as nonbonding electron pair appears to be a good approximation[61]. In striking contrast to formaldehyde, there is a net negative charge on the thiocarbonyl carbon which results from a carbonyl-like polarization of the π bond and a superimposed stronger and inverse polarization of the σ bond[85]; with the aid of an INDO–MO calculation, the same polarization was derived for di-*t*-butyl thioketone[89].

The effect of charge separation is partially reduced by involvement of d orbitals, though their influence is small[61]. An analysis of quadrupole coupling constants in the microwave spectrum (see Section II.E.) indicates 27% of s participation and only 10% of d hybridization in the σ bond[88].

In addition to calculations to evaluate the relative stabilities of C_2H_2S isomers (see Sections II.A and II.B), geometry optimizations of the thioketene system[53,55,74] and an MNDO calculation were published[90].

D. Spectroscopic Evidence for the Thione Group

In recent years, numerous spectroscopic data have been accumulated for thiocarbonyl compounds. This was made possible by highly improved techniques in the measurement of spectra as well as progress in the generation of unstable thiocarbonyl derivatives.

1. Ultraviolet and visible spectra

The traditional spectroscopic method for the characterization of thiocarbonyl compounds is UV/VIS spectroscopy. Reasons are the relatively early availability of the method along with the fact that thioaldehydes, thioketones, thioketenes and thioquinones are invariably colored compounds. The range of colors goes from yellow for bis-

(trimethylsilyl)thioketene[91], red for aliphatic thiones[11] and the parent thioketene[92], purple for dialkylthioketenes[20,93], blue for diarylthioketones[10] and -thioketenes[49] to green for monothioanthraquinone (**12**)[28]. There is general agreement that the color is due to excitation of the $n \rightarrow \pi^*$ transition[6,83], and this assignment is supported by computations[83,86,87], the solvent effect[89] as well as by the low intensity of this symmetry-forbidden transition.

The qualitative trends are supported by measurements of the spectra in the visible range (Table 2). Absorptions at long wavelengths and with relatively high intensities are found on conjugation of the thiocarbonyl moiety with C=C π bonds as in monothioanthraquinone (**12**)[28], in aryl-substituted thiones[94] or in thiobenzaldehyde (**2a**)[17]. The bathochromic effect is particularly pronounced when coplanarity of the C=S and aryl moieties is achieved by incorporation into a bicyclic system such as **13**[94].

Cumulation of the C=S with a C=C bond gives the same effect as conjugation, as shown by $n \rightarrow \pi^*$ transitions for thioketenes in the range of 575 to 624 nm (Table 2). Again, aryl substitution leads to band positions at particularly long wavelengths. The same tendency is seen on comparison of diphenyl thioketene (**5c**) with alkyl-substituted thioketenes.

The $n \rightarrow \pi^*$ transitions for trifluoromethyl- or silyl-substituted thiocarbonyl derivatives occur at relatively short wavelengths (Table 2). Tropothione (**14**)[95] or diphenylcyclopropenethione (**15**)[96] show intense absorption maxima outside the visible range. This makes an assignment to the $n \rightarrow \pi^*$ transition questionable and rather points to a strong contribution of the zwitterionic resonance structure with an aromatic ring, e.g. for **15**:

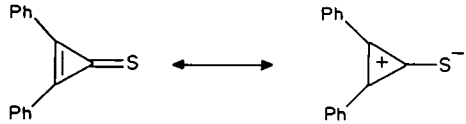


TABLE 2. Ultraviolet-visible spectra for some typical thiocarbonyl compounds

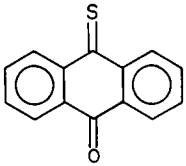
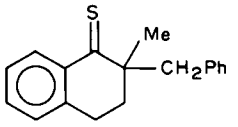
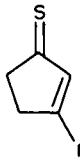
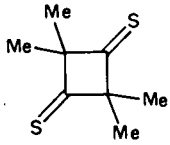
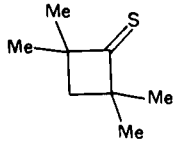
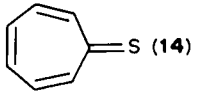
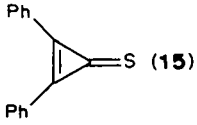
Compound	$n \rightarrow \pi^*$ band		UV transitions		Solvent	References
	λ_{max} (nm)	logε	λ_{max} (nm)	logε		
 (**12**)	697	1.67	334 270	4.16 4.41	$CHCl_3$	28
MeCSCOMe[a]	625	?	380	?	none	17
$Ph_2C{=}C{=}S$ (**5c**)	624	2.5	275	4.5	CH_2Cl_2	49,98
Me(Ph) C=C=S	613	1.9			$CFCl_3$	9,49
t-Bu(*i*-Pr) C=C=S	590	0.9	240	3.58	isooctane	99
 (**13**)	592	2.48	317 235 228	3.93 3.89 4.89	hexane	94

TABLE 2. (*continued*)

Compound	n→π* band λ_{max} (nm)	n→π* band log ε	UV transitions λ_{max} (nm)	UV transitions log ε	Solvent	References
t-BuCH=C=S	575	1.0	?		$CFCl_3$	49
$(t\text{-Bu})_2C{=}C{=}S$ (**5a**)	575	0.9	239	3.55	isooctane	99
PhCH=S	575	?	320	?	none	17
			228	?		
	569	1.31	293	4.2	cyclo-	97
	542	1.85	222	3.5	hexane	
$PhCSCMe_2CH_2Ph$	565	2.04	298	3.59	hexane	94
			250(sh)	3.77		
$(Me_3Si)_2C{=}S$	530		320			100
			230			
$t\text{-Bu}_2C{=}S$	536	0.95	237	3.90	EtOH	89
t-BuCH=S (**4**)	508	1.21			?	18, 101
$(F_3C)_2C{=}C{=}S$ (**5b**)	503	0.9	239	3.75	isooctane	21, 102
	500	1.35	298	2.61	hexane	103
			227	4.33		
	500	1.08	230	3.85	hexane	103
			215	3.70		
$(Me_3Si)_2C{=}C{=}S$	413	1.0				91
			380	4.23	EtOH	95
			250–260(sh)			
			236	4.25		
			360	3.81	cyclo-	96
			264	4.09	hexane	
			234	4.04		
			227	4.08		

[a]Partially in the enethiol form.

Similarly, a cumulated thioketene with a high contribution of resonance structure **1c** shows a UV absorption at 380 nm (in chloroform)[26], i.e. well outside the usual range of thioketenes (Table 2).

Besides the band in the visible spectra, thiocarbonyl compounds show at least one band in the UV range. The high intensities indicate symmetry-allowed transitions and the assignment to the $\pi \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ transition, respectively, is obvious[97]. However, the effects of substituents are not as clear-cut as for the band in the visible range.

MO calculations have proven useful for the interpretation of the spectra and have been discussed in Section II.C.

2. *Vibrational spectra*

IR spectra give useful qualitative information on the existence of enethiol tautomers (see Section II.A) with characteristic absorptions around 2550 cm^{-1} for the SH and 1640 cm^{-1} for the C=C group. However, the C=S stretching vibration of the thiocarbonyl group is usually only of medium intensity and the position in the fingerprint region of the spectra makes identification quite difficult. A range of 1244–1270 cm^{-1} for aliphatic thiones and a position at slightly lower wave number for aromatic thiones have been reported[104], but for t-Bu_2C=S a value of 1115 cm^{-1} was given[89]. For tropothione (**14**) a value of 1087 cm^{-1} is in line with a high contribution of the tropyliumthiolate resonance structure resulting in a low double-bond character[105]. On the other hand, the C=S absorption of cyclopropylthiones is found around 1280 cm^{-1} and this points toward very little conjugation between the CS π bond and the three-membered ring[106].

For matrix-isolated thioformaldehyde, a band at 1063 cm^{-1} was assigned to the C=S stretching vibration[80] and a similar position of 1085 cm^{-1} was found for thiopivalaldehyde (**4**)[18]. Caculation of the vibrational frequencies for thioformaldehyde gives values between 1002 and 1189 cm^{-1} depending on the method[61].

Thioketenes do not show an isolated C=S vibration, but coupling of the CCS system occurs and gives rise to a strong antisymmetric vibration around 1750 cm^{-1}. Owing to the intensity and position in an otherwise usually empty region, this band has high diagnostic value. However, the influence of substituents on the position of the band is obscured by different conditions of measurement (Table 3).

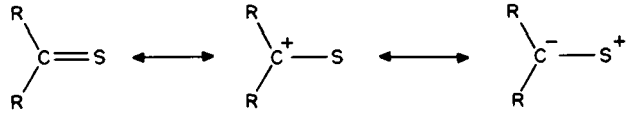
3. *Nuclear magnetic resonance spectra*

Proton NMR spectroscopy is widely used to characterize the substituents on the thiocarbonyl group and for a quantitative assessment of the thione/enethiol ratio (see Section II.A)[34–37]. However, ^{13}C NMR spectroscopy allows direct insights into the

TABLE 3. Characteristic infrared bands of thioketenes R^1R^2C=C=S

Compound R^1	R^2	ν(C=C=S)(cm^{-1})	References
Me	Me	1789	107
F_3C	F_3C	1783	21, 102
t-Bu_2P(S)	RCH_2	1760–1745	108
t-Bu	H	1758	49
Me_3Si	Me_3Si	1757	91
H	H	1755	109, 110
t-Bu	t-Bu	1737	20
Ph	Ph	1725	49

nature of the thiocarbonyl carbon. A striking feature is the extreme low-field position of this signal (Table 4). Compared to the analogous carbonyl carbon, $\delta_{C=S}$ is shifted to lower field by 35–63 ppm[31]. The straightforward interpretation of a high contribution by resonance structure **16b** resulting in reduced charge density at the thiocarbonyl carbon and, consequently, increased deshielding, cannot be correct in light of the discussion in Section II.C. In contrast, it has been assumed that the high value of $\delta_{C=S}$ is due to the paramagnetic term of the chemical shift[111], and this seems reasonable in the correlation with excitation energies of thiocarbonyl compounds[89] (cf. Section II.D.1). Thus, a plot of the wavelengths of the $n \rightarrow \pi^*$ transition vs ^{13}C chemical shifts of the central thioketene carbon gives a straight line, whereas no such correlation exists for ketenes or allenes[9].



(16a) **(16b)** **(16c)**

Attempts to establish a general formula to correlate the chemical shifts of carbonyl and thiocarbonyl carbons have met with failure[30,111,112] and this has been interpreted as confirming the importance of steric effects[89]. For aromatic thiones, the equation allows

$$\delta_{C=S} = 1.57 \cdot \delta_{C=O} - 71.45$$

reasonable predictions[112]. In any case, the influence of substituents is more pronounced for thiocarbonyl than for carbonyl compounds[113], and an inspection of Table 4 reveals at least some qualitative trends. Thus, aliphatic thiones as well as thiopivalaldehyde (**4**) show $\delta_{C=S}$ values between 252 and almost 282 ppm with increased branching leading to more deshielding. This trend has been interpreted as reflecting a higher contribution of canonical formula **16b** by α-methyl substitutents[113]. The chemical shifts of thiocarbonyl carbons in dialkyl- and diarylthioketenes fall into the same range, but aryl substitution results in notable shielding for aromatic thiones such as thiobenzophenone (**17**) or thiofluorenone (**18**). Similarly, silyl and particularly trifluoromethyl substituted derivatives (cf. **5b**) show comparatively low $\delta_{C=S}$ values.

Tropothione (**14**) or diphenylthiocyclopropenone (**15**), i.e. compounds, for which canonical structures with the thiocarbonyl unit have only minor importance, show the expected relative shielding of the thiocarbonyl carbon (Table 4). For the same reason, Viehe's thioketene (**19**) is found at the lower end of the scale of $\delta_{C=S}$ values confirming its character as an alkynylthiolate of the type **1c**, where the positive charge is stabilized by the enamine moiety, rather than of a true thioketene.

The chemical shifts of α carbons in thiones show the expected trend based on the substitution (Table 4). However, an unusual feature is seen in the δ values of the formally olefinic $C_{(2)}$ in thioketenes, which occurs at notably high field. By analogy with ketenes and allenes[120], this effect has been discussed in terms of a strong contribution by the zwitterionic canonical form **1b** with a negative charge on $C_{(2)}$. Even $C_{(3)}$ is affected by this shielding and this results in an inversion of the usual positions of quaternary ($\delta = 31.2$ ppm) and methyl carbon signals ($\delta = 32.0$ ppm) in the *t*-Bu residue of *t*-Bu_2C=C=S.

Protonation of thiones gives decreased shielding for aliphatic thiones, e.g. a change from 261.4 ppm to 282.7 ppm for cycloheptanethione, whereas the aromatic thiones **17** and **18** show the opposite trend[31]. Increased shielding is also observed on methylation of thiobenzophenone (**17**) to give Ph_2C^+SMe with $\delta = 230.5$ for the original thiocarbonyl carbon[121].

TABLE 4. Chemical shifts, δ(ppm), of thiocarbonyl and α carbons

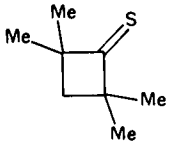
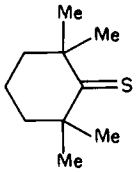
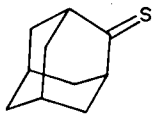
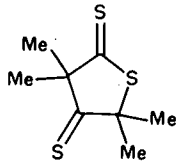
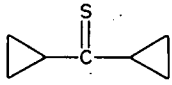
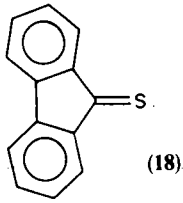
Compound	$\delta_{C=S}$ (ppm)	$\delta_{\alpha-C}$(ppm)	References
	289.1	56.48	103
	279.8	?	31
t-$Bu_2C{=}S$	278.4	53.7	113
i-$Pr_2C{=}S$	276.5	48.9	113
t-Bu(i-Pr)C=C=S	272.9	98.0	99, 114
$Ph_2C{=}C{=}S$ (**5c**)	271.2	92.3	115
	270.5	57.5	113
	267.7, 245.2	70.96, 77.89	103
$(Me_3Si)_2C{=}S$	267.0	—	100
	259.7	33.3	113
t-BuCH=S (**4**)	255.6	—[a]	101
$Me_2C{=}S$	252.7	30.9	104, 113
$Me_3Si(Ph)C{=}C{=}S$	240.3	69.0	116
$Ph_2C{=}S$ (**17**)	240.1 (239)	147.2	31, 117
 (**18**)	229.5	?	31
$(F_3C)_2C{=}C{=}S$ (**5b**)	225.8	82.7	118

TABLE 4. (*continued*)

Compound	δ_{C-S}(ppm)	$\delta_{\alpha-C}$(ppm)	References
14	215.95	153.71	105
$(Me_3Si)_2C{=}C{=}S$	214.4	52.0	91
15	178.2		96
t-Bu$(Me_2N)C{=}C{=}C{=}S$ (**19**)	165.3	86.9	26, 119

[a]Uncertain due to interfering trimer and oligomer signals.

4. Photoelectron spectra

Photoelectron spectra (PES) hold special interest to support the results of MO calculations (see Section II.C), though special applications such as identification of a dithiete **9A** vs a dithione **9B** (see Section II.B)[72] or product analysis of pyrolysis mixtures[86] have been reported. Usually, two well-separated bands are observed, corresponding to the two highest occupied orbitals. In conjunction with CNDO/S[122] or MNDO calculations[86], these are identified as n_s and π_s orbitals, respectively. A third band, which is due to the $n^a s$ orbital, is often obscured by the continuum of the carbon framework.

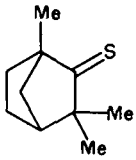
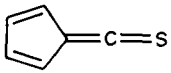
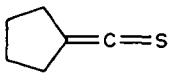
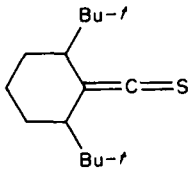
The measured ionization energies show a marked sensitivity to the nature of the substituents on the thiocarbonyl group (Table 5). Taking $H_2C{=}S$ as standard, methyl substitution appears to lead to increased importance of resonance structure **16b** as the positive charge on the thiocarbonyl carbon is stabilized by methyl hyperconjugation[86]. For isolated as well as cumulated thiocarbonyl compounds, the first ionization potential is always lower than for the corresponding carbonyl derivative due to the smaller effective nuclear charge on sulfur[86,123]. A plot of the ionization energies of thials and thiones vs those of the corresponding aldehydes and ketones even shows a linear relationship which, provided that the ionization energy of a carbonyl compound is known, allows one to identify an unknown thiocarbonyl derivative with the same substituents[86].

X-ray photoelectron spectroscopy (XPS, ESCA spectroscopy) has been used to record the O_{1s} and S_{2p} ionization spectra of β-thioxo ketones and allowed one to elucidate the position of the tautomeric equilibrium **8A–D**[43]. Also, the XPS spectrum of a thioketene has been obtained[124].

5. Electron spin resonance spectra

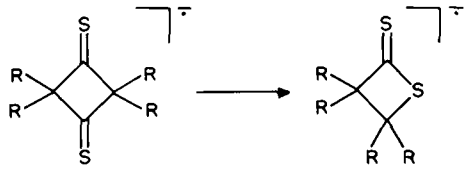
Di-*t*-alkylthioketones[128,191], 4*H*-thiopyran-4-thione[129] or sterically shielded dialkylthioketenes[130] can be electrochemically reduced in polar aprotic solvents to give radical anions which can be studied by ESR spectroscopy. In addition, frozen solutions allow one to determine the anisotropic ESR parameters[130,131]. As expected, based on the weaker CS π bond, the reduction potentials $E_{1/2}$ are generally lower for thiocarbonyl than for the corresponding carbonyl derivatives. From the ^{13}C coupling constants it can be concluded that the spin density is mainly located on the thiocarbonyl carbon and the observed temperature dependence of the coupling constants suggests that the thioketyl moiety is planar[128]. For thioketene radical anions, the ^{13}C hyperfine splittings indicate a nonplanar C_s geometry suggesting their classification as σ rather than as π radicals[130]. This is supported by the low g values (about 2.0038) as compared to those of dialkylthioketyls (g values about 2.0060[128])[130].

TABLE 5. Photoelectron spectra of thiocarbonyl compounds (IE = vertical ionization energy)

Compound	1st IE (eV)	2nd IE (eV)	3rd IE (eV)	References
$H_2C{=}S$	9.34	11.78	13.9	86
	9.33	11.90	?	122
$MeCH{=}S$	9.00	11.00	(12.7)[a]	86
$Me_2C{=}S$	8.60	10.3	(12.7)[a]	86
$PhCH{=}S$ (**2a**)	9.1	(9.5)[a]	11.7	86
$H_2C{=}CH{-}CH{=}S$ (**3**)	8.86	8.90	12.13	86
	8.1	9.6	?	122
$(F_3C)_2C{=}C{=}S$ (**5b**)	9.96	12.58	13.16	90
$(NC)_2C{=}C{=}S$	9.94	?	?	123
$H_2C{=}C{=}S$	8.89	11.32	12.14	52
	8.52	8.67	11.14	125
	7.92	10.50	?	126
	7.35	9.5	?	127

[a] Position uncertain due to overlapping bands.

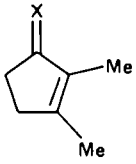
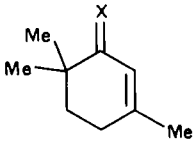
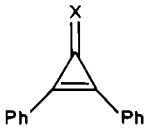
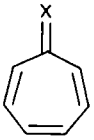
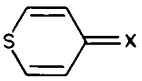
Thioketyls of 1,3-cyclobutanedithiones can only be detected if the substrates are reduced at 200 K. Otherwise, rearrangement to the radical anions of the isomeric β-dithiolactones occurs[132].



E. Molecular Characteristics of the Thione Group

Dipole moments of various types of thiocarbonyl derivatives have been obtained (Table 6). For simple examples, the dipole moment of a thiocarbonyl compound is

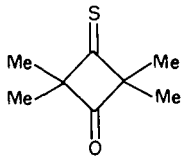
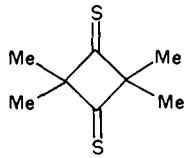
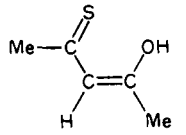
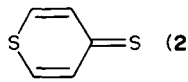
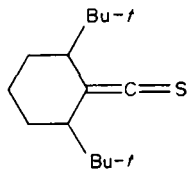
TABLE 6. Dipole moments of selected carbonyl and thiocarbonyl derivatives

Compound	μ(D) X = O	References	X = S	References
$H_2C{=}X$	2.328[a]	134	1.6483[a]	88
$D_2C{=}X$	2.344[a]	134	1.6588[a]	88
$MeCH{=}X$	2.69 [a]	135	2.33[a]	136
$t\text{-}Bu_2C{=}X$	2.37	137	2.19	137
	3.81	97	3.87	97
	3.82	97	3.30	97
	5.08	97	5.8	97
	4.30	138	3.88	138
	?		3.9	137
$H_2C{=}C{=}X$	1.41[a]	139	1.02–1.07[a]	140, 141
$MeCH{=}C{=}X$	1.79[a]	142	1.54[a]	50
$t\text{-}Bu_2C{=}C{=}X$	2.04	99	1.91	99
$(F_3C)_2C{=}C{=}X$	?		1.95	102
$Ph_3P{=}C{=}C{=}X$	6.77	133	8.50	133

[a]Gas phase measurement.

consistently lower than for the corresponding carbonyl derivative[133] confirming the reduced polarity of the thiocarbonyl group and this tendency also includes thioketenes (Table 6). However, for α,β-unsaturated derivatives, the difference may be quite small, and for examples where the thiocarbonyl group is involved in a special type of resonance interaction, the usual order is reversed. Thus, the dipole moment of tropone is considerably smaller than that of tropothione (**14**) in accord with a high contribution of the tropylium thiolate resonance structure, and the same relation holds for diphenylcyclopropenone and -thione (**15**). Similarly, triphenylphosphoranylidenethioketene (**20**)

TABLE 7. Bond lengths and angles for selected thiocarbonyl compounds

Compound	Method[a]	Bond lengths (pm) C=S	Bond lengths (pm) $C_{(\alpha)}$—CS	Angle (deg) CCS	References
$H_2C{=}S$	MW	161.08	—	127.68	146
		161.38	—		88
$D_2C{=}S$	MW	161.36	—	128.5	88
MeCH=S	MW	161.0	150.6	125.28	136
 (21a)	X-R	154.7	154.9, 155.9	133.6	147
 (21b)	X-R	159.9	153.1	113.3	148
$Ph_2C{=}S$ (17)	X-R	163.6	148.5	120.7, 121.9	149
$(4\text{-}HOC_6H_4)_2C{=}S$	X-R	164.7	152.5	119.5	150
$H_2C{=}CH{-}CH{=}S$ (3)	MW	161	145.5	125.5	151
 (22)	X-R	167.9	140.9	125.0, 118.6	152
 (23)	MW	167.1	140.6	125	137
14	X-R	167.6	143.1, 146.1	119.0	138
$H_2C{=}C{=}S$	MW	155.4	131.4	?	140
MeCH=C=S	MW	155.2–156.2	131.4–133.2	?	50
	X-R	156.6	128.7	178.1	124, 145
t-Bu(Me_2N)C=C=C=S (19)	X-R	162, 163	120,125	168, 177	26, 153
$Ph_3P{=}C{=}C{=}S$ (20)	X-R	159.5	120.9	178.3	154

[a] MW = microwave spectroscopy, X-R = single-crystal X-ray structural analysis.

shows a much higher dipole moment than the corresponding ketene, proving the importance of a type-**1c** resonance structure **20B**:

$$Ph_3P{=}C{=}C{=}S \leftrightarrow Ph_3P^+{-}C{\equiv}C{-}S^-$$

(20A) **(20B)**

Details of the molecular structure of thiocarbonyl compounds have been elucidated with the aid of *microwave spectra* and *X-ray structural analyses* (Table 7). There is no general consent as to the value of a 'typical' CS double bond, but a value of 156 pm[143] is certainly too low. Taking the CS bond length in thioformaldehyde as a basis (Table 7), it is obvious that conjugation with a CC π bond or hydrogen bonding to the thiocarbonyl sulfur will give a longer C=S bond. The first-mentioned effect operates in thiobenzophenone (**17**), tropothione (**14**) or 4*H*-thiopyran-4-thione (**23**), whereas in 4,4'-dihydroxythiobenzophenone or the thioxoenol **22** the C=S bond is further elongated by inter- and intramolecular hydrogen bonding, respectively. On the other hand, substitution of the thiocarbonyl group by electronegative fluorine atoms in $F_2C{=}S$ gives a shorter C=S bond than in thioformaldehyde[144]. However, there is no apparent reason for the particularly short C=S bond in the cyclobutanethione **21a**, particularly in light of the normal value for the related dithione **21b** (Table 7).

The transition from an sp^2 to an sp hybridized thiocarbonyl carbon leads to the expected shortening of the C=S bond and to a change of the CCS bond angle from the 120° to the 180° range (Table 7). However, conjugation between the thiocarbonyl group and the alkylidene moiety as in Viehe's thioketene **19** or in triphenylphosphoranylidenethioketene (**20**) again results in a stretching of the C=S bond.

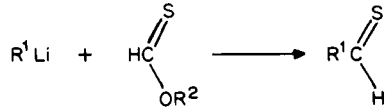
The $C_{(\alpha)}$—CS bond lengths reflect the hybridization of the thiocarbonyl carbon and of $C_{(\alpha)}$ (Table 7). Interestingly, ketenes show a tendency to a shorter C=C distance than thioketenes, though ketenes would be expected to have a higher contribution of the zwitterionic resonance structure **1b** and, consequently, a longer C=C bond[145].

III. SYNTHESES

The synthesis of thiocarbonyl compounds is rendered difficult by the high tendency of many representatives to dimerize, oligomerize or even polymerize. Diarylthioketones are usually quite stable, and so the early thiocarbonyl chemistry was mostly thiobenzophenone chemistry[27]. For the detection or at least trapping of unstable thiocarbonyl derivatives, special measures have to be taken and here particularly flash-vacuum pyrolyses or generation at low temperatures allowed considerable progress in recent years. To emphasize the scope and limitations of the individual methods, the following overview is organized by the type of bond that is formed and the reagent used.

A. Formation of the α-Carbon–Thiocarbonyl Bond

Sterically stabilized thioaldehydes may be obtained by the reaction of organolithium compounds with O-alkyl thioformate (equation 1). Usually the O-ethyl ester is em-



(1)

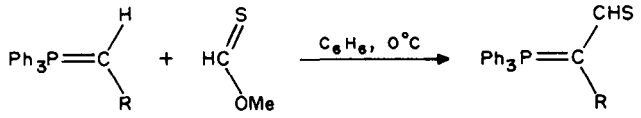
$R^1 = t\text{-Bu}$ (**4**); 30–40%[101]

$R^1 = 2,4,6\text{-}t\text{-Bu}_3C_6H_2$; 56%[19]

$R^1 = (Me_3Si)_3C$[156]

ployed[19,101], but the [1-D] O-cholesteryl derivative was used to obtain a C-deuterated thioaldehyde[155]. In the synthesis of thiopivalaldehyde (4), the primary product is an O-ethyl hemithioacetal, which is thermally cleaved to afford the thioaldehyde[101].

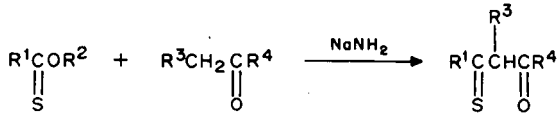
By the same type of reagent, a vinylic hydrogen in methylene or ethylidene phosphorane can be replaced by the thioformyl group[157] (equation 2).



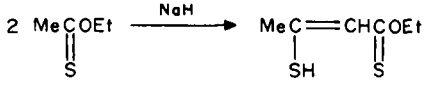
48–54%

(2)

O-Alkyl esters of higher thioalkanoates react with the enolates of ketones to give β-thioxoalkanones in a Claisen-type condensation (equation 3)[158–162]. Cyclic ketones lead to 2-thioacyl-1-cycloalkanones[162]. Besides sodium amide, *t*-BuLi has been suggested as base[163]. A Claisen condensation is also possible between two molecules of O-ethyl thioacetate to give highly enethiolized dithioacetoacetate[164] (equation 4).

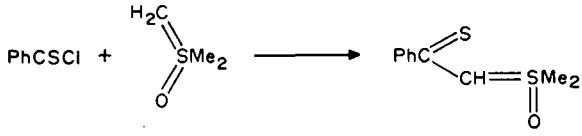


(3)



(4)

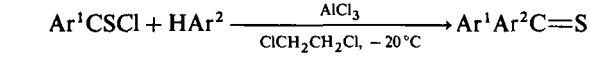
Thioacylation to give thioketones has also been observed with thioacyl chlorides. Thus, thiobenzoyl chloride reacts with a sulfur ylide to give a thione[165] (equation 5).



30 %

(5)

A more general method is the Friedel–Crafts-type reaction of thioaroyl chlorides with benzene derivatives to give symmetrically or asymmetrically substituted thiobenzophenones[166] (equation 6).



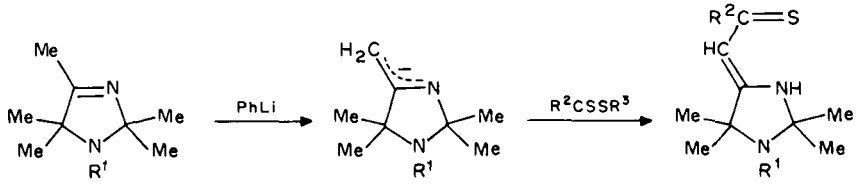
34–54%

(6)

Also, thiophosgene may be employed and provides di-2-pyrryl thioketones in the reaction with pyrroles[167].

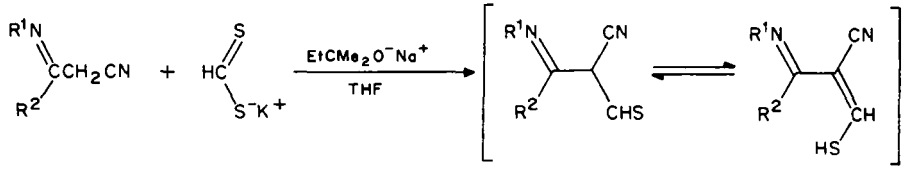
Dithioesters have been used to thioacylate Grignard reagents, but the yield of thiones are quite low[168]. The same limitation holds for the reaction of alkyl or aryl dithiochlorocarbonates ClCSSR with Grignard reagents to give α-alkylthio- or α-arylthio-substi-

tuted thiones[169]. However, C-thioacylation of the enamine moiety in imidazolines with dithioesters gives enaminothiones in 40–50% yield[170] (equation 7).



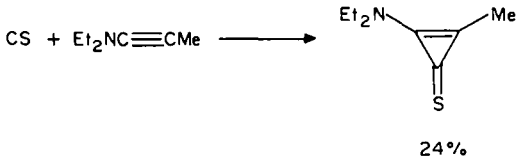
(7)

β-Imino nitriles can be thioformylated by potassium dithioformate to give β-imino thioaldehydes, which are in equilibrium with the enethiol tautomer (see Section II.A)[171] (equation 8).



(8)

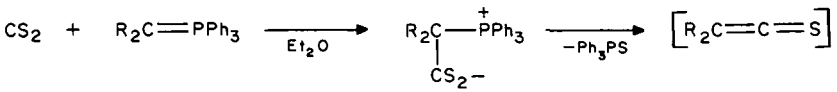
Two $C_{(\alpha)}$—CS bonds are formed simultaneously in the [2 + 1] cycloaddition of carbon monosulfide to ynamines or ynediamines[172] (see e.g. equation 9[173]).



(9)

24%

Formation of a $C_{(\alpha)}$=CS bond in a Wittig olefination between carbon disulfide and a phosphorus ylide provides seemingly simple access to thioketenes. However, depending on the nature of the alkylidene moiety of the ylide, complications have to be considered. Thus, for dialkylmethylene phosphoranes the reaction stops at the stage of zwitterionic 1:1 adducts which display a thioketenoid behavior in the reaction with nucleophiles[174–176] (equation 10).

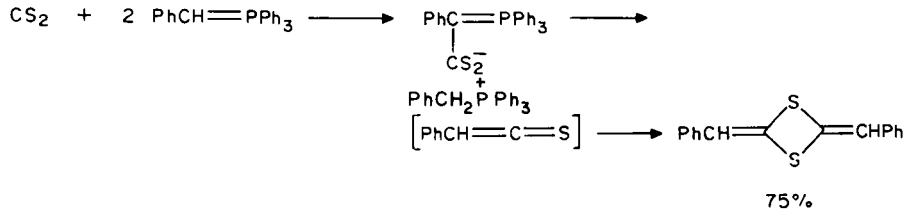


(10)

Similarly, benzylidene triphenylphosphorane reacts with carbon disulfide to yield a phosphonium salt which, when poured into water, provides dimeric phenylthioketene[177] (equation 11).

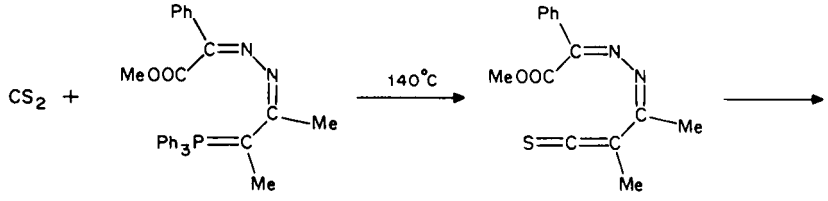
Thioketene dimer formation is also observed in the reaction of carbon disulfide with an azine-substituted phosphorane (equation 12). At the same time, the intermediate thioketene undergoes an intramolecular [4 + 2] cycloaddition to give a pyrazole derivative (see Section IV.E.4)[178]. Substitution of the phosphorus atom by bulky alkyl

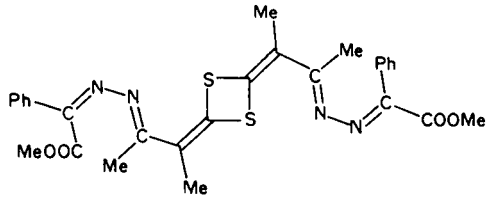
groups and fluorine allows olefination of carbon disulfide to give a thiophosphoryl thioketene[179] (equation 13).



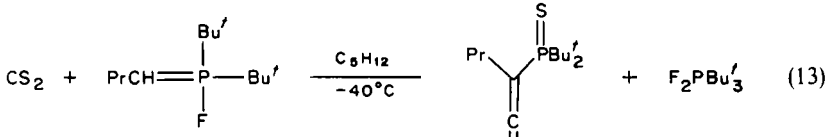
75%

(11)





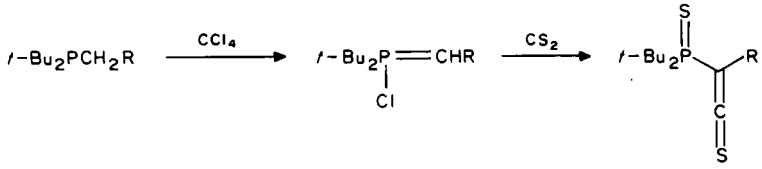
(12)



35% 38%

(13)

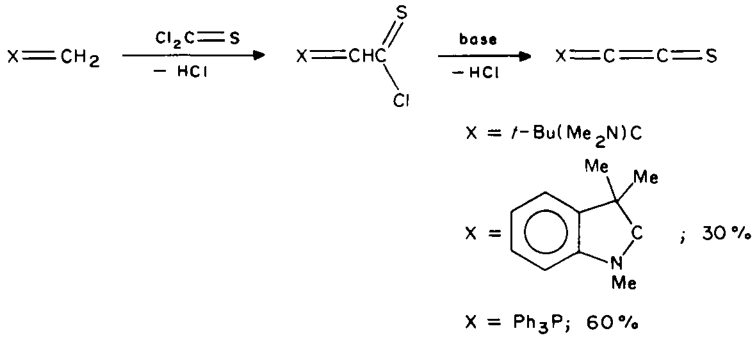
Related thioketenes are formed by the simultaneous addition of carbon disulfide and carbon tetrachloride to a sterically shielded phosphane[108] (equation 14). A chlorophosphorane is assumed to be an intermediate.



R = Me, Pr, *i*-Pr; 75–80%

(14)

The $C_{(\alpha)}$—CS bond in a thioketene may also be formed by the reaction of an appropriate alkene with thiophosgene giving a thioacyl chloride and subsequent elimination of HCl. Thus, this approach provides alkylidene thioketenes[26,119] or triphenylphosphoranylidenethioketene[180,181] (equation 15).



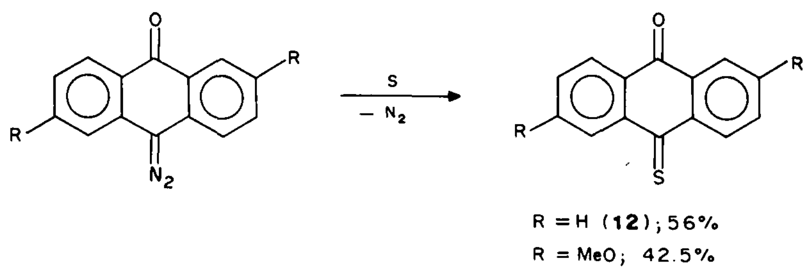
(15)

B. Addition of Sulfur to Carbenes

For many years, the only noteworthy example of thione formation from a carbene or carbenoid was the reaction of perfluorinated diisopropyl mercury and sulfur to yield hexafluorothioacetone (60%)[182] (equation 16).

$$[(F_3C)_2CF]_2Hg + S \rightarrow F_3C\underset{\underset{S}{\parallel}}{C}CF_3 \qquad (16)$$

A more recent interesting example is the reaction of 10-diazoanthrones with sulfur in DMF at 130–150 °C to give the only known examples of reasonably stable thioquinones[28] (equation 17).



(17)

In a related reaction, product **12** has been obtained by the addition of the deprotonated anthrone to *N*, *N*-bis(phthalimidyl) disulfide at 80 °C in DMF (yield 55%); the reaction is supposed to proceed through initial attack of the anthrone anion on one of the sulfur atoms of the disulfide reagent[183].

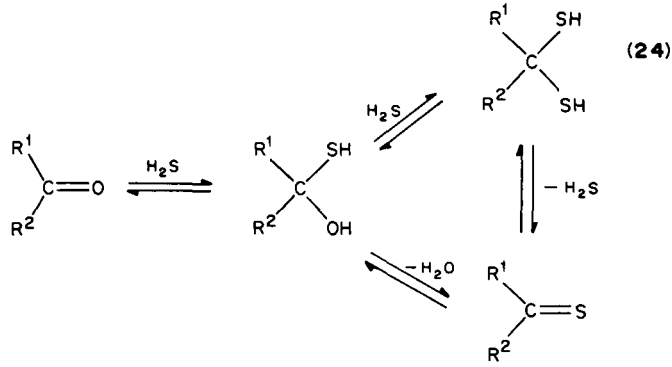
C. Thionation of Carbonyl Derivatives

1. *Carbonyl compounds*

O/S exchange in a carbonyl compound is an obvious and frequently used route to thiocarbonyl derivatives. The reaction is usually carried out with inorganic sulfides

including H_2S, but phosphorus(V) derivatives are the most popular reagents[184,185].

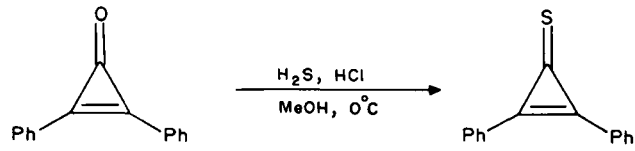
The primary product of the reaction between a ketone and H_2S in the presence of HCl is a geminal dithiol **24** (equation 18). For a convenient synthesis of the thiocarbonyl derivative, the formation of **24** has either to be avoided by working at low temperatures[186] or the dithiol **24** is isolated and thermally cleaved to the desired product in a subsequent step[187]. Thus, by working at −80 °C in ethanol, the reaction even allows synthesis of highly reactive dialkylthioketones[186].



(18)

$R^1 = R^2 = Et$, 55%[186]
$R^1 = R^2 = Pr$, 58%[186], 80%[187]
$R^1 = R^2 = (CH_2)_5$, 34%[186]
$R^1 = Me$, $R^2 = Pr$, 70%[187]

The reaction can be extended to cycloalkylthioketones[188], γ,δ-unsaturated thiones[189–191] and substituted cyclobutanethiones[33,103,192,193] (35–50%). However, the approach fails for the unsubstituted cyclobutanethione, which trimerizes under the acidic reaction conditions[193]. α,β-Unsaturated carbonyl compounds can be converted into the corresponding thiones by working at 0 °C in methanol provided that they are β,β-disubstituted (20–75%)[97] or that an electron-donating β-residue is present to give thiones of type **6**[194–197]. Also, diphenylcyclopropenethione is accessible via this route (75–85%)[103] (equation 19).



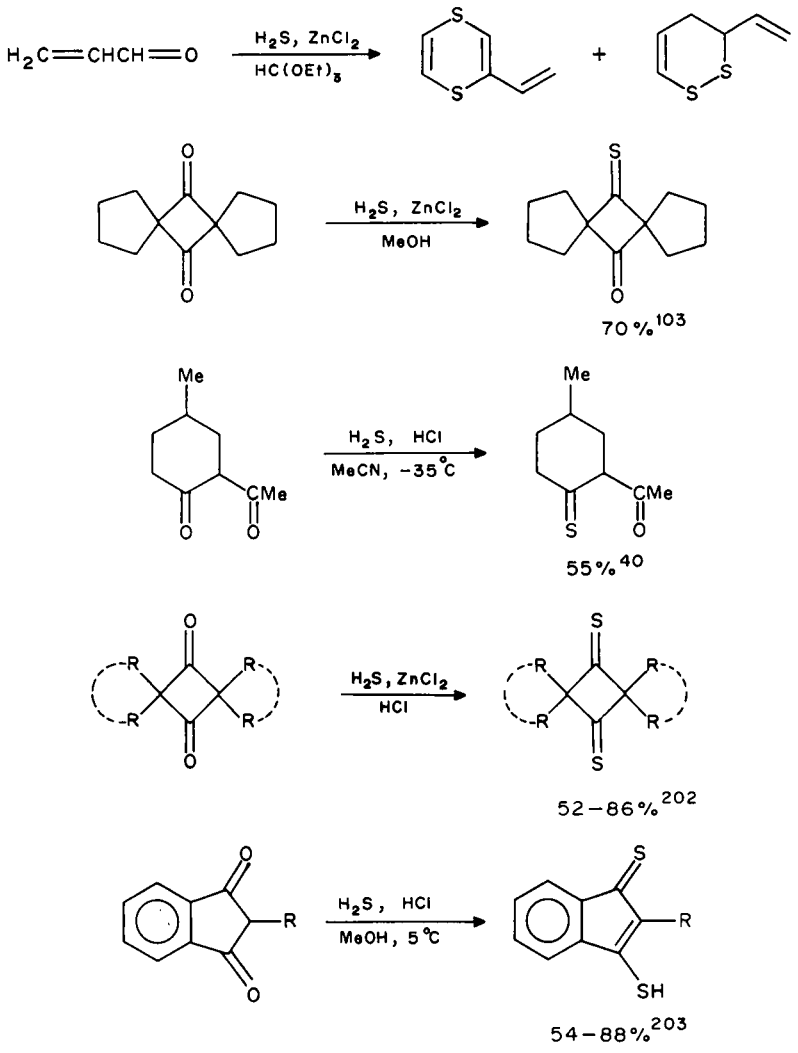
(19)

Alternatively, thioacetic acid has been used as reagent in the thionation of the cyclopropenone giving the same yield[198].

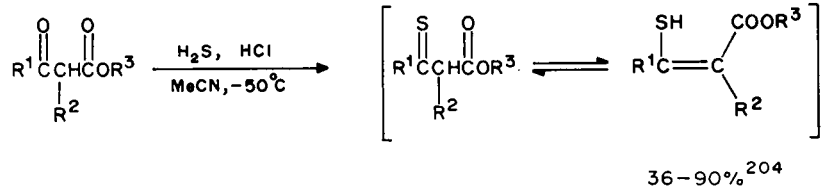
An attempt to convert acrolein into thial **3** gave only dimers which are formed in [4 + 2] cycloadditions[199] (See Section IV.E); the products are constituents of the asparagus flavor (equation 20).

The system H_2S/acid also allows one to convert diones into thioxoketones, though with certain limitations. Thus, with α-dicarbonyl compounds as substrates, the reaction fails to

provide monothiobenzil[200], but gives *t*-BuC(S)COOEt[201]. 1,3-Diketones yield mono- or bis-thionated products as shown in the examples presented in equations 21.



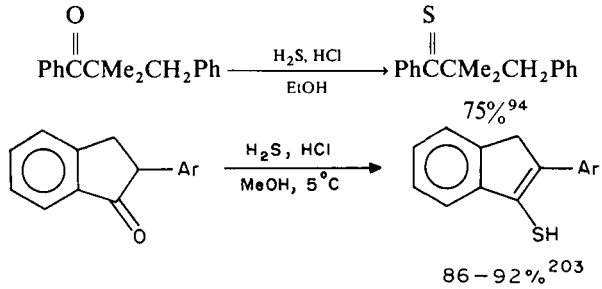
In β-oxoesters, the keto carbonyl group is much more reactive than the ester moiety giving enethiolized β-thioxo esters, usually in good yields[46,204] (equation 22).



36–90%[204]

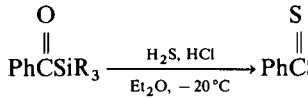
Similarly, thiolysis of β-oxo dithioesters yields enethiolized β-thioxo derivatives[205].

Aromatic thioketones are conveniently obtained by the reaction of the corresponding carbonyl derivatives with H_2S and HCl[27,206,207]. There are also numerous examples for the synthesis of aralkyl thiones using this approach (equation 23).



(23)

In a recent extension of the scope of the reaction, silyl thioketones have been obtained from the corresponding ketones[208]. Even a thione with an optically active silyl residue was synthesized[209] (equation 24).



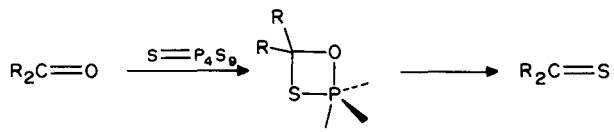
(24)

R = Me, Ph; 58–85%[208]

R_3Si = Me(Ph)Si$C_{10}H_7$-α; 95%[209]

Besides acid catalysis in the thionation of carbonyl compounds with H_2S, base catalysis may be used. In this reaction, isolation of the intermediate dithiols **24** can usually not be avoided so that, to obtain thiones, a subsequent thermolysis is required[210]. However—unless carried out as flash-vacuum pyrolysis[112]—this cleavage step may fail in the attempt to synthesize cyclobutanethione[33]. On the other hand, there are examples for the base-catalyzed conversion of 1,3-diketones into β-thioxo ketones[211].

Among the phosphorus(V) reagents for the conversion of carbonyl into thiocarbonyl compounds, till very recently P_2S_5 was most frequently used. A simple mechanism with a Wittig-type four-membered ring **25** as intermediate may be written, but the actual reaction pathway is somewhat mysterious. In particular, the mechanism of equation 25 cannot explain the striking solvent dependence of the yields. Quite often pyridine gives the best results[12,94], but in many instances aromatic hydrocarbons (toluene, xylene)[112], ethers (1,2-dimethoxyethane, diglyme, THF[212,213]), acetonitrile[213] or petroleum ether[112] are used with advantage. The rate of the reaction is enhanced by addition of basic compounds such as sodium sulfide, carbonate or hydrogen-carbonate[213] suggesting that the actually attacking species is OPS_2^- or SPS_2^-; similarly, NEt_3[105,214] or alkali metal hydroxides[215] have been employed.

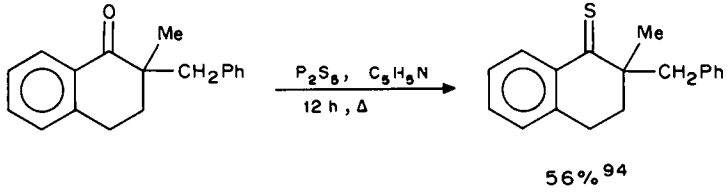


(25)

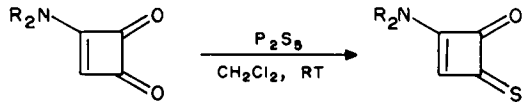
(**25**)

Besides the traditional application in the synthesis of aromatic thioketones[27], recent uses include the thionation of a 1-tetralone (equation 26)[94], a semisquaric acid amide (equation 27)[216], or of a bis-spiro annulated cyclobutanedithione, which cannot be obtained from the dione in a single step (equation 28)[103]. As an example of a highly reactive thione, thiomesoxalate can be generated in the presence of a scavenger (equation 29)[212]. In the thioaldehyde field, the reaction is limited to the thionation of vinylogous formamides (equation 30)[217].

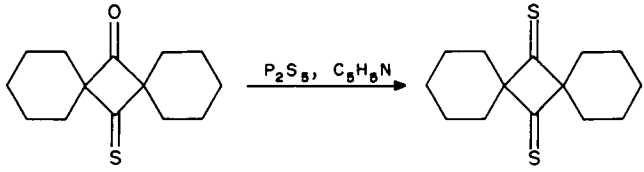
In some cases, α,β-unsaturated thiones can also be obtained from the corresponding ketones by the action of P_2S_5. However, this requires stabilization of the product by cross-



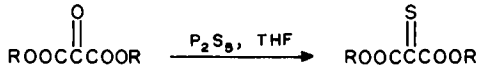
56%[94] (26)



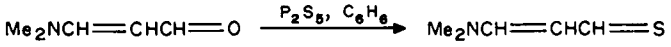
42–66%[216] (27)



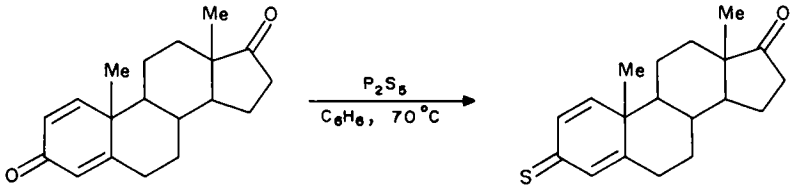
45%[103] (28)



(29)

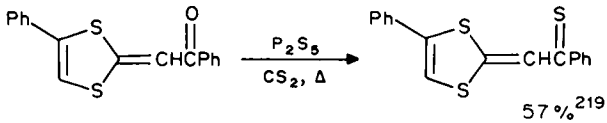


(30)

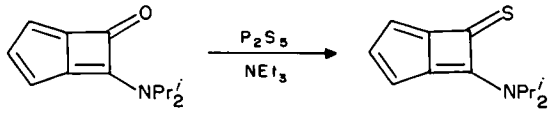


71%[218] (31)

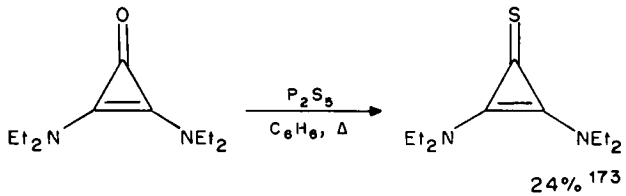
conjugation (equation 31)[218] or by an electron-donating substituent in a β-(equation 32)[219] or in a more remote position (equation 33)[214]. In addition, cyclopropenethiones[173] and tropothione (**14**)[95,105], where the thiocarbonyl group is attached to a potentially aromatic ring, are accessible using P_2S_5 (equations 34 and 35).



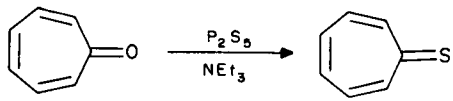
(32)



(33)

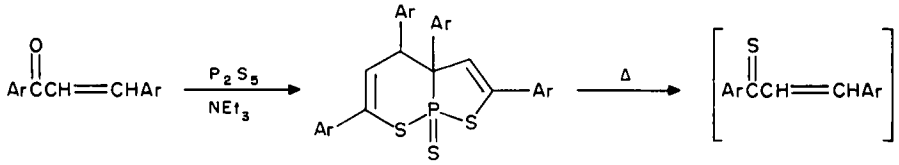


(34)



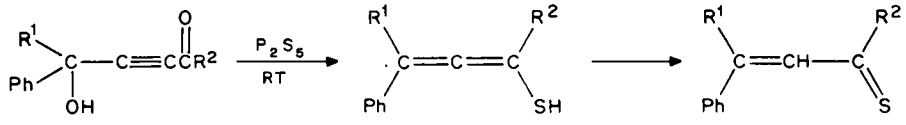
(35)

α,β-Unsaturated ketones which lack mesomeric or steric stabilization, on heating with P_2S_5, yield phosphorus-containing heterocycles (equation 36)[220,221]. However, the desired product can be liberated by heating and be intercepted.



(36)

In γ-hydroxy ynones, the oxygen/sulfur exchange is accompanied by propargyl rearrangement[222] (equation 37).

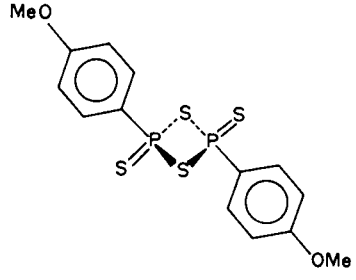


(37)

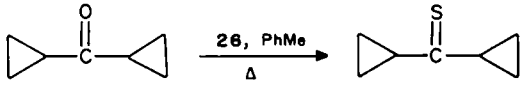
Another successful application of P_2S_5 is the conversion of sterically hindered acyl chlorides into kinetically stabilized thioketenes in pyridine solution[20,93,145] (equation 38).

$$R_2CHCOCl \xrightarrow[\Delta]{P_2S_5,\ C_5H_5N} R_2C{=}C{=}S \qquad (38)$$

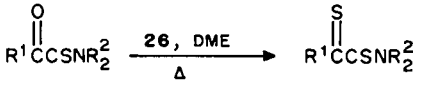
Considerable progress in the scope of the thionation reaction and in yields has been achieved by the use of the Lawesson reagent **26**[185,223]. This compound was first used in a synthesis of thiobenzophenone from benzophenone[224], but later put to broad use by Lawesson and named after himself[30,185]. The reagent, which is readily prepared by heating P_2S_5 with anisol[225], allows lower reaction temperatures than P_2S_5 and facilitates work-up. Based on a kinetic analysis, the three-coordinated phosphorus(V) species $AnPS_2$ was suggested as the reactive intermediate which is generated *in situ* by symmetrical cleavage of **26**[226]. Illustrative examples for the use of **26** are the synthesis of dicyclopropylthioketone (equation 39)[30], of α-thioxothioamides (equation 40)[227] and of enethiones (equation 41)[228].



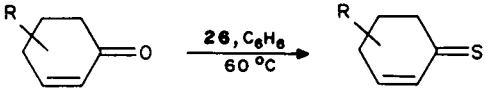
(26)



83 %[30] (39)

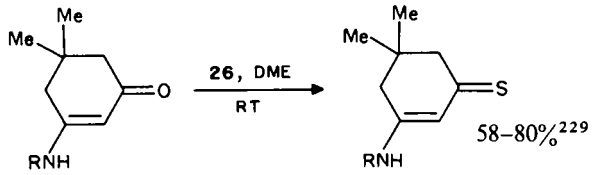


21–77%[227] (40)



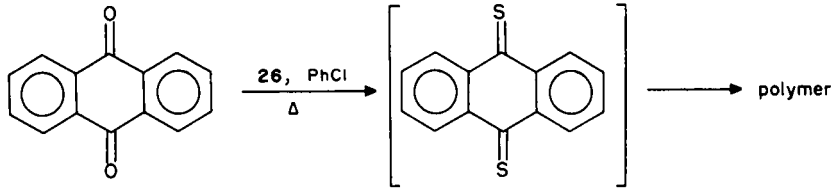
25–86% (41)

In the synthesis of enethiones **6** with an electron-donating amino group on $C_{(\beta)}$, the reagent **26** gives higher yields and cleaner products than P_2S_5[229–231]; an example is given in equation 42.



(42)

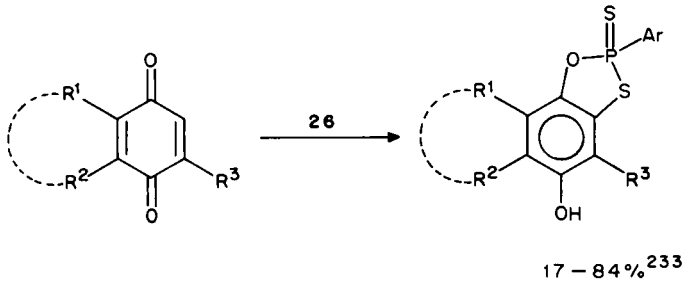
However, for an arylthio group as β-substituent, heating of the enone with **26** in carbon disulfide only gives the dimer of the desired enethione (8–24%)[232]. Similarly, the reaction conditions of the thionation reaction do not allow one to isolate a dithioquinone, but give polymerization[29] (equation 43).



(43)

In the light of this evidence, the claim of a dithioanthraquinone synthesis seems highly improbable[233]. Also, the report[234] that monothioanthraquinone (**12**) can be obtained by thionation of the oxo precursor with the aid of **26** has been refuted[29] and also the claim of an *o*-dithioquinone synthesis has turned out to be untenable[235].

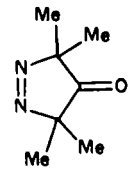
In other examples, the reagent **26** reacts with the substrate or with the thionation product[228,233,236]; see e.g. equation 44.



17 – 84%[233]

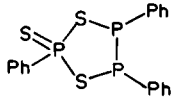
(44)

Further limitations in the use of **26** are steric hindrance of the substrate as in **27**[237] or decomposition of the reagent. This seems to occur on heating in pyridine and so **26** cannot replace P_2S_5 in the reaction of equation 38.

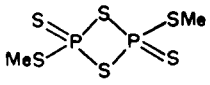


(27)

Some modifications of reagent **26** have been considered for further improved yields and scope. Compound **28** reacts more slowly than **26**, but **29**, which is obtained by heating P_2S_5 with methanol, allows lower reaction temperatures and has some promise as an improved thionating reagent[238].

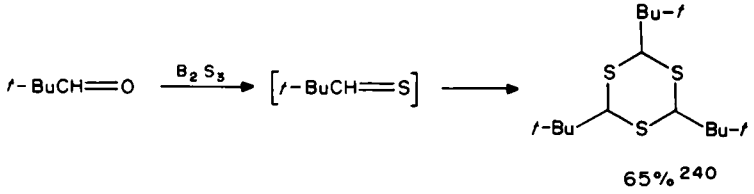


(28)



(29)

Compared to P_2S_5, sulfides of other elements have only found limited use in thionation reactions. SiS_2 and the more efficient B_2S_3 have been recommended as particularly mild reagents[239], though their low solubility in the common solvents is a serious drawback. With B_2S_3, it is advantageous to generate the reagent *in situ* by the reaction of BCl_3 with bis(tricyclohexyltin) sulfide[240]. This combination of reagents gives good yields of thiones from ketones, but, in attempts to synthesize thioaldehydes, only trimers were isolated (see e.g. equation 45).



65%[240] (45)

A promising system for the conversion of carbonyl into thiocarbonyl compounds is bis(trimethylsilyl) sulfide in the presence of a catalytic amount of BuLi. Under these conditions, aldehydes give thioaldehydes, which can be trapped with cyclopentadiene providing [4 + 2] cycloadducts in 80–97% yield (see Section IV.E.4). The reactive species which transfers the sulfur appears to be Me_3SiS^- and Me_3SiO^- then continues the catalytic cycle[241] (equation 46).

$$\mathrm{RCH{=}O \xrightarrow[(Me_3Si)_2S,\ 10\text{–}55\,^\circ C]{\text{cat. BuLi}} [RCH{=}S]} \qquad (46)$$

R = Pr, *t*-Bu, Ph, 2-Thi

Similarly, bis(diethylaluminium) sulfide was found to react with acetophenone or xanthone to give the corresponding thiocarbonyl compounds (equation 47), but more complicated results were obtained in the case of aliphatic ketones[242].

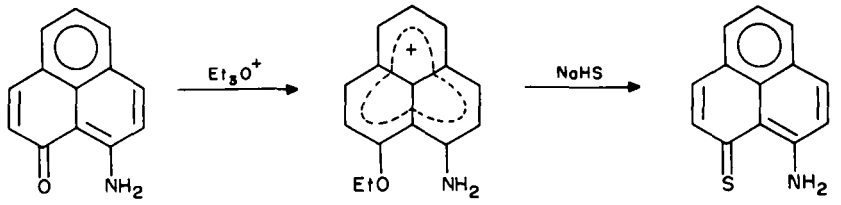
$$\mathrm{R^1R^2C{=}O \xrightarrow[50\text{–}60\,^\circ C]{(Et_2Al)_2S,\ C_6H_6} R^1R^2C{=}S} \qquad (47)$$

35–93%[242]

2. Acetals

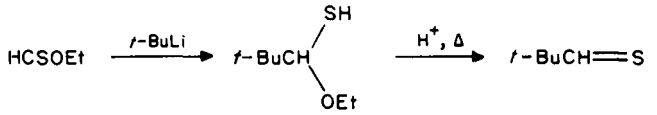
In some cases, it is advantageous to employe acetals in the thionation reaction with H_2S/sulfuric acid rather than use the carbonyl compounds[243]. Similarly, 9-amino-1-phenalenethione is obtained via an ethoxy phenalenium derivative[244] (equation 48).

Addition of *t*-BuLi to O-ethyl thioformate yields an O,S-acetal, which is cleaved on heating with acid to yield thiopivalaldehyde (50%)[18] (equation 49).



81% 50%

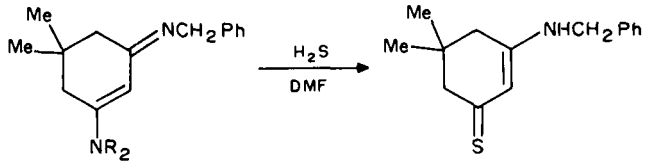
(48)



(49)

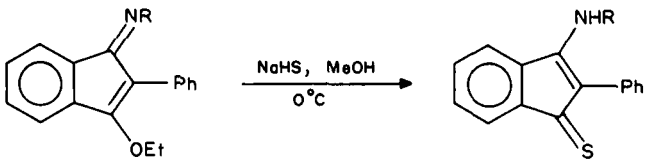
3. *Enol ethers and enamines*

Thiolysis of vinylogous imidates or amidines gives resonance-stabilized thiocarbonyl derivatives. The examples in equations 50–52 illustrate the method.



83%[245,246]

(50)



Ref. 247

(51)

$$R^1_2NCH{=}CHCOOR^2 \xrightarrow[DMF,\ RT]{H_2S,\ F_3CCOOH} HSCH{=}CHCOOR^2 \qquad (52)$$

51–100%[248]

4. *Imino derivatives*

As an intermediate in the total synthesis of chlorophyll, a pyrrole-2-thiocarbaldehyde, one of the first thioaldehydes which is actually a doubly vinylogous thioformamide, was obtained by Woodward in the reaction of an *N*-ethyl imine with H_2S in the presence of methoxide[249].

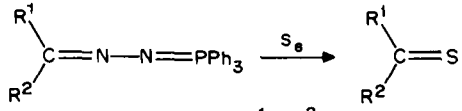
N-Phenylketimines are a source of very pure thiones in the reaction with H_2S in the presence of benzoic anhydride[250] (equation 53).

$$R_2C{=}NPh \xrightarrow[Ph_2CH_2,\ 0\,^\circ C]{H_2S,\ (PhCO)_2O} R_2C{=}S \qquad (53)$$

R = Me, 75%
R = Et, 80%
2R = $(CH_2)_5$, 75%

The thiolysis of oximes with thioacetic acid is an alternative to the reaction of equation 18 in the synthesis of diarylthiones (yields 70–80%)[251].

The reaction of triphenylphosphoranylidene hydrazones with sulfur presents a useful route to sterically hindered thioketones; however, the method cannot be used to obtain thioacetophenone or thiocamphor[252] (equation 54).



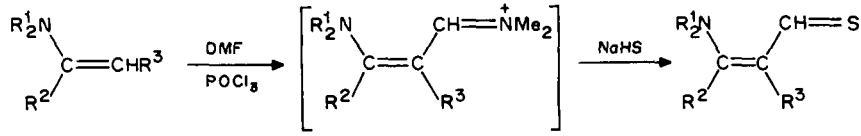
(54)

e.g. $R^1 = R^2 = t\text{-Bu}$, 83%

$R^1 + R^2 = CMe_2(CH_2)_3CMe_2$, 41%

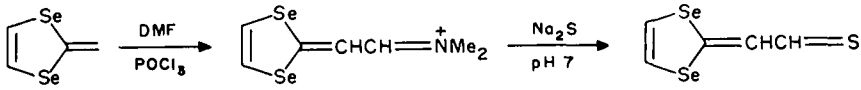
The related reaction of hydrazones with S_2Cl_2 proceeds via the [3 + 2] cycloreversion of a heterocyclic intermediate and will be discussed in Section III.F.4.

In a modification of the Vilsmeier synthesis of aromatic aldehydes, thiolysis of the iminium intermediate provides a route to thioaldehydes which are stabilized by resonance with an electron-donating β-heterosubstituent, such as an amino group (equation 55)[253] or a selenium functionality (equation 56)[254]. The heterosubstituent may also be part of a heterocyclic ring (equation 57)[255–257].



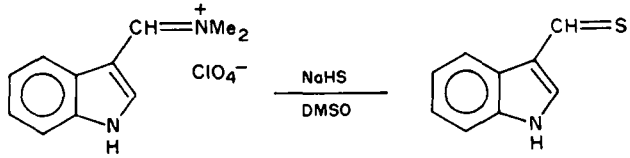
23–61%

(55)



77%[254]

(56)



(57)

90%[256]

5. Sulfur or selenium exchange

For the synthesis of ^{33}S-labeled thiocarbonyl compounds, the yields of the conventional preparative routes are usually not satisfactory and would involve a lengthy procedure to obtain the sulfur transfer reagent such as H_2S or P_2S_5 in a labeled form. However, sulfur can be introduced directly by an exchange of the common ^{32}S for ^{33}S or ^{34}S[257]. Alternatively, a sulfur/selenium exchange is possible[257] (equation 58).

$$t\text{-}Bu_2C{=}S \xrightarrow[140\,^\circ C]{S_8^*} t\text{-}Bu_2C{=}S^* \xleftarrow[\substack{140\,^\circ C,\\ \text{hexane}}]{S_8^*} t\text{-}Bu_2C{=}Se \tag{58}$$

6. Halogen exchange

A few instances have been reported where geminal dichlorides were converted into thiones. Various sulfur transfer reagents have been used to achieve this transformation. Thus, thioacetic acid gives cyclopropenethiones on heating with the corresponding dichlorides[258], and the synthesis of aromatic thiones from Ar_2CCl_2 was carried out with potassium O-ethyl dithiocarbonate[259], hexamethyldisilthiane[260] or *t*-BuSH under acid catalysis[30] (equation 59).

$$Ph_2CCl_2 \xrightarrow[F_3CCOOH]{t\text{-BuSH}} \underset{73\text{–}75\%^{30}}{Ph_2C{=}S} \tag{59}$$

Similarly, thioketene dimers have been obtained in the reaction of 2-acyl-1,1-dichloroethylenes with sodium sulfide[261].

D. Addition Reactions to Alkynes

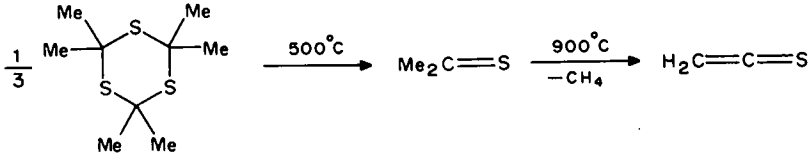
Under irradiation with light[262] or X-rays[263], alkynes add H_2S to give enethiols of thials ($R^2 = H$; 8–73%) or of thiones (R^2 = Me, CF_3; 24–60%) (equation 60).

$$R^1C{\equiv}CR^2 + H_2S \xrightarrow{h\nu} R^1CH{=}CR^2SH \tag{60}$$

E. Elimination Reactions

1. C,C cleavage

When thioacetone is generated in a pyrolysis reaction from its trimer (see Section III.E.2) and heated to 900 °C, thioketene is formed via C,C cleavage[104,264]. This reaction is analogous to the Schmidlin method of ketene generation[265] (equation 61).



(61)

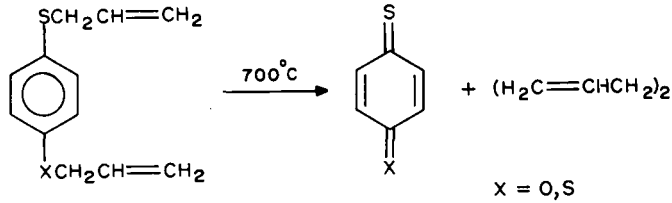
2. C,S cleavage

Cleavage of a carbon–sulfur bond to give a thiocarbonyl derivative can be induced thermally, photochemically or by appropriate reagents. Gas-phase pyrolyses are usually

carried out for physical studies rather than for synthetic purposes and require that the thiocarbonyl product be rapidly removed from the hot reactor to avoid decomposition. Thermodynamically, formation of the high-energy CS π bond is only possible if the parallel fragment of the cleavage reaction is energetically favored. This is the case in the thermal decomposition of allylic sulfides giving rise to the resonance-stabilized allyl radical and, eventually, mostly to propene. Thiocarbonyl compounds which have been generated using this approach include thioformaldehyde[86] (equation 62), thioacrolein (**3**)[17,266,267] (equation 63), monothiobiacetyl[17] (91%) as well as mono- (X = O) and the purple dithiobenzoquinone[268] (X = S; equation 64). Reaction conditions may be optimized using PE spectroscopy[86]. A synthesis of the parent thioketene[92] is based on the parallel formation of the *t*-Bu radical and eventually isobutene (equation 65). Similarly, besides thioaldehyde **4** and propargylthioaldehyde (HC≡C—CH=S), allene is formed via the propargyl radical in equation 66 and thioacetone is detected in the analogous decomposition of propargyl isopropyl sulfide[269].

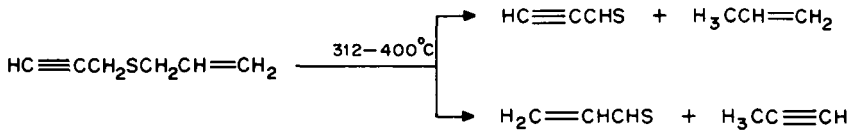
$$MeSCH_2CH{=}CH_2 \xrightarrow{430\,^\circ C} CH_2{=}S + H_3CCH{=}CH_2 \qquad (62)$$

$$S(CH_2CH{=}CH_2) \xrightarrow{550\,^\circ C} CH_2{=}CH{-}CH{=}S \qquad (63)$$



(64)

$$HC{\equiv}CSBu\text{-}t \xrightarrow{500\,^\circ C} H_2C{=}C{=}S + C_4H_8 \qquad (65)$$



(66)

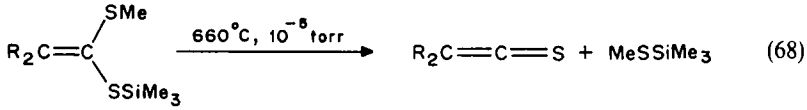
Contrary to the reaction of equation 62, thermal C,S cleavage in methyl thiocyanate MeSCN *is not a clean source of thioformaldehyde*[86].

In some cases, attempts to synthesize thioaldehydes or thioketones yield trimers rather than the monomers, but the trimers may thermally be converted into the parent thiocarbonyl compounds under thermal[32,270] or photolytic conditions[271]. For thiopivalaldehyde, cleavage of the trimer (*t*-BuCH=S)$_3$ is not an efficient process, but the monomer is conveniently obtained from the polymer. This approach allows one to generate the thioaldehyde in the absence of acids or bases which would again catalyze tri- and polymerization, making it a fairly stable compound with a half-life of several hours at room temperature[18,101].

β-Elimination reactions involving C,S cleavage have been employed to generate

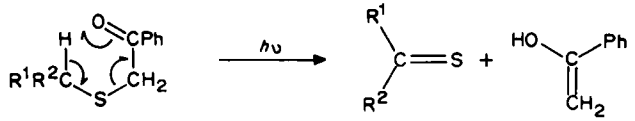
thioketenes. Thus, the parent thioketene could be detected by PE spectroscopy on thermolysis of dithioacetic acid[24,51] (equation 67) and flash-vacuum pyrolysis of ketene S-methyl-S-(trimethylsilyl)acetals has been developed into a useful thioketene synthesis including methylenethioketene[272] (equation 68).

$$MeCSSH \xrightarrow{460\,^{\circ}C} H_2C{=}C{=}S + H_2S \tag{67}$$



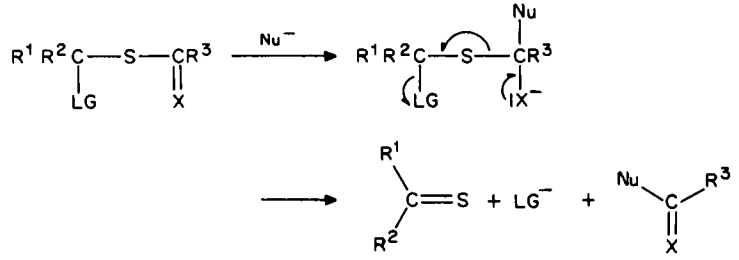
(68)

The photochemical Norrish-II-type cleavage of phenacyl sulfides **30** offers a convenient and very flexible route to highly reactive thiocarbonyl derivatives (equation 69). The approach was first suggested by Woodward[273], but shown by Vedejs to be quite general[18,101,274,275]. In particular, thioaldehydes ($R^2 = H$) containing virtually any α-substituent can be generated by photofragmentation of sulfides **30** including the parent ($R^1 = H$) and even quite exotic thioaldehydes with $R^1 = Ph_2P(O)$, $PhSO_2$, Me_3Si or CN as well as more conventional alkyl- or acyl-substituted derivatives[274]. For the unstable examples, the reaction conditions allow trapping by various reagents, especially Diels–Alder reactions with dienes (see Section IV.E.4). Thus synthetic applications, e.g. in the cytochalasane field, are possible[275]. Of course, the method works equally well for thioketones (R^2 = alkyl) as shown by the synthesis of cyclododecanethione [$R^1 + R^2 = (CH_2)_{11}$; 90%], 2-acetoxycyclohexanethione [$R^1 + R^2 = (CH_2)_4CHOAc$; 78%], 2-acetoxy-1-phenylethanethione (7, $R^1 = H$, $R^2 = CH_2OAc$; 98%) or monothiocyclohexanedione [$R^1 + R^2 = (CH_2)_3C(O)CH_2$; 39%][275].



(30) (69)

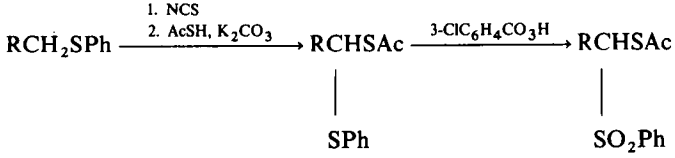
Besides pyrolysis or photolysis, S, C cleavage may be induced by nucleophiles (or bases) in substrates with an electrophilic (or acidic) center and a leaving-group LG next to the sulfur (equation 70).



(70)

Various examples follow the general scheme of equation 70. The Vedejs group supplied a reaction sequence which allows the conversion of simple sulfides into the thioaldehyde

targets[276] (equation 71). The given yields refer to the trapping products as obtained with cyclopentadiene (cf. Section IV.E.4).



$$\xrightarrow{Et_2NH} RCH{=}S + {}^{-}SO_2Ph + Et_2NAc \qquad (71)$$

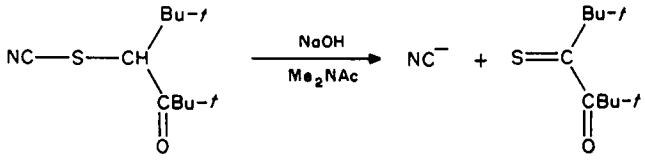
R = H; 51%

R = $PhCH_2Ch_2$; 7%

R = *i*-Pr; 29%

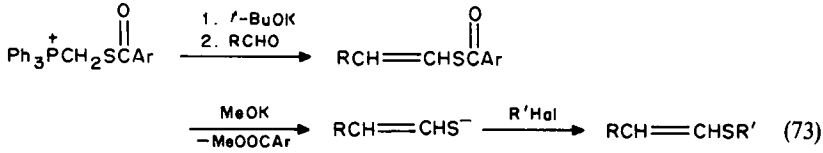
R = Ph; 15%

Similarly, the S—CN bond in thiocyanates can be cleaved by base allowing a convenient synthesis of monothiopivalil[277] (36%) (equation 72).



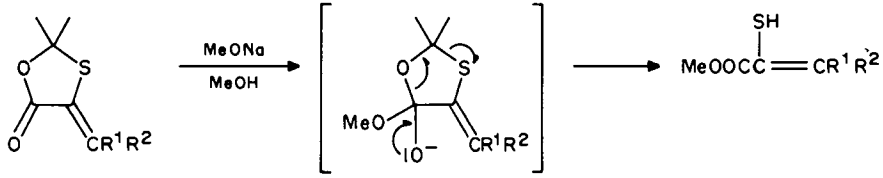
(72)

If an α-hydrogen is present in the generated thiocarbonyl compound, the basic conditions of equation 70 usually lead to the thioenolate[278,279] which may eventually be trapped by alkylation[279] (equation 73).

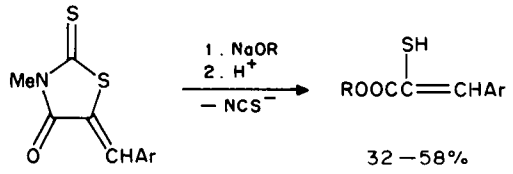


(73)

The approach of equation 70 also applies to examples where the sulfur functionality is part of a heterocyclic ring. Thus, from 3-oxathiolanes (equation 74)[280] or thiazolidines (equation 75)[281], thioenolized α-thioxo esters are accessible. Similarly, treatment of 2-dialkyliminium-1, 3-dithioles with sodium hydroxide yields alkene-1, 2-dithiolates[282].

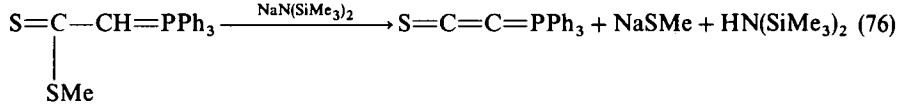


(74)



(75)

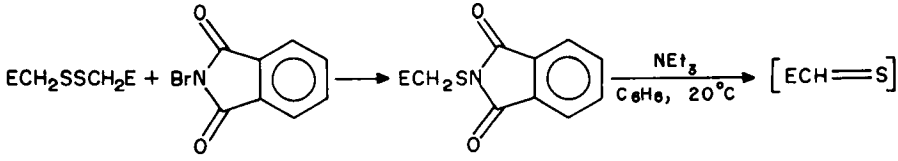
Finally, generation of triphenylphosphoranylidenethioketene by deprotonation of a triphenylphosphoranylidene dithiocarboxylate may be mentioned[283] (equation 76).



(76)

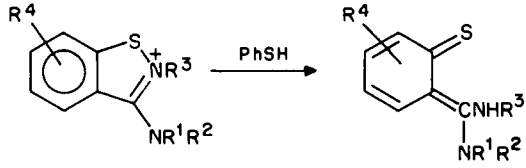
3. S, N cleavage

The S—N bond in a sulfenamide may be cleaved by base to give ester-substituted thioaldehydes, which cannot be isolated but are scavenged by dienes in Diels–Alder reactions (see Section IV.E.4)[284] (equation 77).



(77)

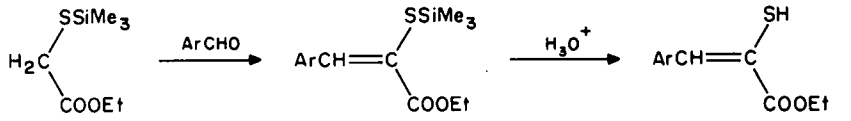
Isothiazolium salts, on treatment with nucleophiles, yield β-amino enethiones[285,286], whereas thiophenol induces a reductive cleavage of the S—N bond in 3-aminobenziso-thiazolium salts[56] (equation 78).



(78)

4. S, Si cleavage

As an alternative to the reaction of equation 74, silylated thioglycolate allows an aldol-type condensation with aldehydes and, subsequently, cleavage of the S, Si bond to give α-mercapto cinnamates[287] (equation 79).



(79)

5. S,S cleavage

Pyrolysis of MeSSMe yields thioformaldehyde[87,88], but the high temperature of 670 °C favors decomposition to H_2S or CS_2 and the approach offers no advantages over the reaction of equation 62. On the other hand, the thermal generation of $(Me_3Si)_2C{=}S$ by thermolysis of $(Me_3Si)_3CS_4C(SiMe_3)_3$ may be a synthetic alternative to the approach of equation 81[100].

A flexible route to various thiocarbonyl derivatives is outlined in equation 80.

$$R^1R^2C(H)-S-SX \xrightarrow[-HX]{} R^1R^2C{=}S \qquad (80)$$

The elimination can be induced thermally or by base (E1cB mechanism[288]). In the thermal approach, the SX moiety is S(O)R, i.e. an S-alkyl thiosulfinate is cleaved to give a thiocarbonyl compound along with phenylsulfenic acid. Thus, mono-oxidation of symmetrical disulfides giving $RCH_2SS(O)CH_2SR$ and subsequent heating in toluene furnishes thioaldehydes such as thioacetaldehyde (R = Me) and thiobenzaldehyde (**2a**)[289]. Similarly, bis(trimethylsilyl)thioketone can be generated; in spite of a tendency to rearrange to a dithioester, the thione can be trapped in Diels–Alder reactions (see Section IV.E.4)[290] (equation 81).

$$(Me_3Si)_2CHSH \xrightarrow[Et_2O]{ClSOR,\ C_5H_5N} (Me_3Si)_2CH\overset{+}{S}SR\ (O^-) \xrightarrow[-RSOH]{\Delta,\ C_6H_6} (Me_3Si)_2C{=}S \xrightarrow{RSOH} Me_3SiC(=S)SR \qquad (81)$$

53–86%

Contrary to the pyrolysis of thiosulfinates, thiosulfonates (equation 80 with $X = SO_2R$) yield thioaldehydes via deprotonation with NEt_3 or preferably Hünig base ($i\text{-}Pr_2NEt$); the initially generated thioaldehyde reacts with the liberated toluenesulfinate, but a second equivalent of base allows trapping of the thioaldehyde by dienes[291] (equation 82).

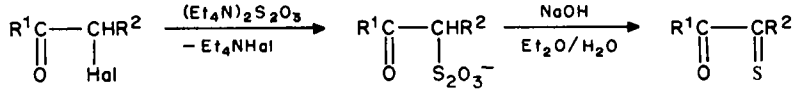
$$RCH_2SSO_2Tol \xrightarrow{NR_3} RCH_2SSCHR(SO_2Tol) \xrightarrow{NR_3} RCH{=}S + TolSO_2^- \ R_3\overset{+}{N}H \qquad (82)$$

R = Ar, EtOOC, 4-$BrC_6H_4C(O)$

Formation of thiocarbonyl compounds via Bunte salts is an example of equation 80 with $SX = SO_3^-$. The method has been exploited for the synthesis of α-thioxo carbonyl compounds[292–300]. Because of a phase-transfer effect, a particularly smooth reaction and good yields are observed when the counterion is the tetraethylammonium cation[294,300] (equation 83).

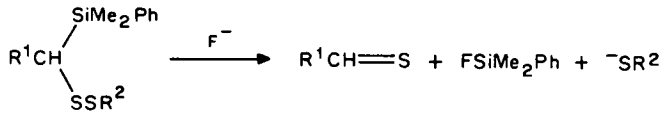
The Bunte salt method has also been successfully employed for diaryl thioketones[301] and for thioaldehydes of the type EWGCH=S (EWG = electron withdrawing group such as PhNHC(O), PhC(O), NC, 4-$O_2NC_6H_4$)[302].

Base-induced cleavage of disulfides $R_2CHSSAr$ represents another application of



$R^1, R^2 = t\text{-Bu}, Ar;\quad 52-91\%^{294}$ (83)

equation 80 with SX = SAr which has been employed in the generation of diaryl thioketones (yields 15–85%)[303]. In an interesting modification, the intermediate anion is obtained via α-desilylation by fluoride (Bu_4NF; −78 °C or KF, CsF; RT) offering a convenient route to thioaldehydes[304] (equation 84).

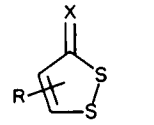


(84)

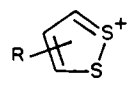
R^1 = H, alkyl, Ph; R^2 = 4-ClC_6H_4, 4-$O_2NC_6H_4$

It has been pointed out earlier that S,S cleavage is probably the crucial step in the reaction of the anthrone anion with *N*,*N*-bis(phthalimidyl) disulfide to give monothioanthraquinone (**12**; see Section III.B).

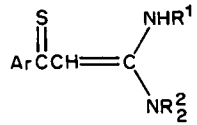
Several routes to thiocarbonyl compounds involve S,S cleavage in heterocycles such as 1,2-dithioles **31** or dithiolium salts **32**. Treatment of **31a** with Bu_3P yields thioacyl ketenes RC(S)C(R)C=C=O, which can be trapped in [4 + 2] cycloadditions[305]. The analogous reaction of **31b** in the presence of cyclohexylamine gives thioamides via thioacyl thioketenes[306]. Similarly, the reaction of imines **31c** with $Bu_3P/HNEt_2$ or piperidine yields vinylogous thioamides **33a** (66–85%)[307]. On the other hand, heating of **31b** in the presence of alkynes $R^2C{\equiv}CR^2$ gives thioaldehydes (**3b**, R^1 = H)[227,308,309] or thioketones **3b** ($R^1 \neq H$)[308,310–312]. Grignard reagents RMgX open compounds **31c** to thioacylketene S,N acetals **34b**[313].



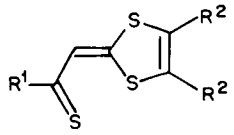
(**31a**) X = O
(**31b**) X = S
(**31c**) X = NR



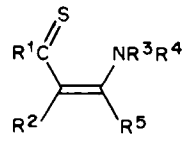
(**32**)



(**33a**)



(**33b**)



(**34a**) R^5 = alkyl, Ar
(**34b**) R^5 = SR

S, S cleavage in salts **32** is achieved by amines to give vinylogous thiourea **34a** (with $R^1 = NR_2$)[314–317]. Finally, phosphorus-induced desulfurization in isothiazol-5-thiones generates reactive iminothioketenes RC(NR)–C(R)C=C=S which can be trapped by amines to give vinylogous thiourea **34a** (with $R^1 = NR_2$)[318].

6. *S,Se cleavage*

Similar to the thermolytic elimination of sulfenic acid in equation 81, selenenic acid is easily split off from the corresponding precursor and thiobenzaldehyde can be detected by its color as well as be trapped by cyclopentadiene (see Section IV.E.4)[319] (equation 85).

$$\mathrm{PhCH_2S\overset{+}{S}eR\,(O^-)} \xrightarrow[-\,\mathrm{RSeOH}]{} \mathrm{PhCH{=}S} \tag{85}$$

7. *S, halogen cleavage*

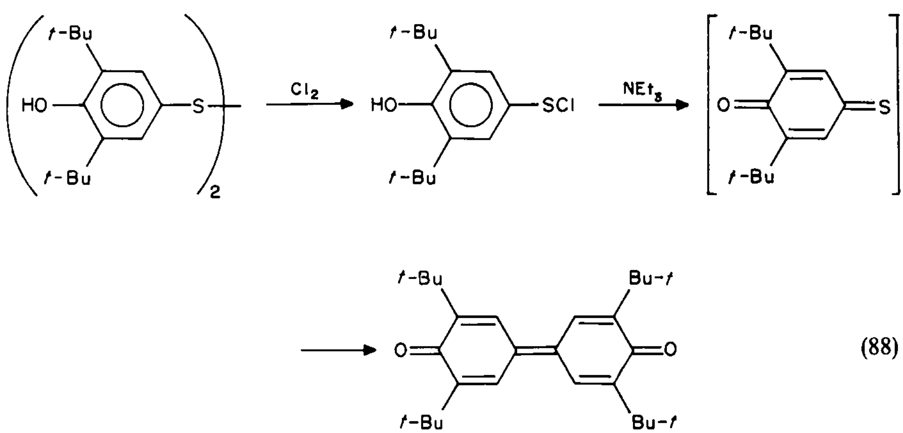
The elimination of HCl or HBr from the corresponding sulfenyl halides has been used in the synthesis of some highly reactive thiocarbonyl compounds. At 590 °C, MeSCl yields thioformaldehyde; the parallel product HCl can be removed by addition of the stoichiometric amoung of NH_3[86,87]. Equation 86[320] gives an example for base-induced S, Hal cleavage; in equation 87[100], elimination of Me_3SiBr occurs.

$$\mathrm{ROOCCH_2SCl} \xrightarrow[\mathrm{C_6H_6/MeOH}]{\mathrm{NEt_3,\ RT}} [\mathrm{ROOCCH{=}S}] \tag{86}$$

$$R = \mathrm{Me, Et}$$

$$\mathrm{(Me_3Si)_3CSH} \xrightarrow[2.\ \mathrm{Br_2}]{1.\ \mathrm{MeLi}} \mathrm{(Me_3Si)_3CSBr} \xrightarrow{\Delta} \mathrm{(Me_3Si)_2C{=}S} \tag{87}$$

A 1, 6-elimination of HCl has been tried in an attempt to generate a monothioquinone. However, formation of a C=C bond was observed and the thioquinone can only be suspected as an intermediate[321] (equation 88).



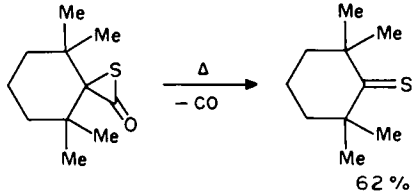
(88)

F. Cycloreversion Reactions

The term 'cycloreversion' is synonymous with 'cycloelimination', indicating the relationship of C=S generating cycloreversions with the elimination reactions of Section III.E. However, cycloreversion is the thermally or photochemically induced cleavage of two σ bonds in a carbo- or heterocyclic ring without involvement of a reagent[322]. Fragments with π bonds are formed and, under the appropriate conditions, the approach offers useful routes to thiocarbonyl compounds.

1. *[2 + 1] Cycloreversion*

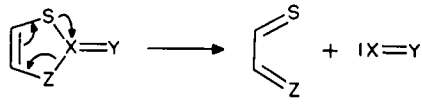
α-Thiolactones which are obtained by oxidation of sterically hindered thioketenes with nitrones (cf. Section IV.A) are thermally cleaved to carbon monoxide and a thioketone[323,324]; see e.g. equation 89.



(89)

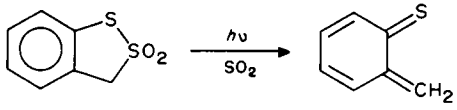
2. *[4 + 1] Cycloreversion*

[4 + 1] Cycloreversions offer a route to α,β-unsaturated thiocarbonyl compounds (equation 90).

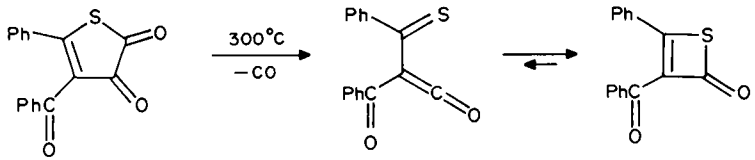


(90)

Enethione-type products are formed for $Z = CR_2$. Examples are the photochemical generation of a thio-*o*-quinomonomethane (equation 91)[325] and the cleavage of thiophenediones to give benzoyl(thiobenzoyl)ketene, which exists in the thermodynamically more stable thietone form (equation 92; cf. Section II.B)[73,326].



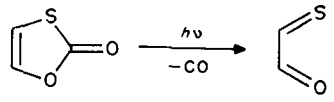
(91)



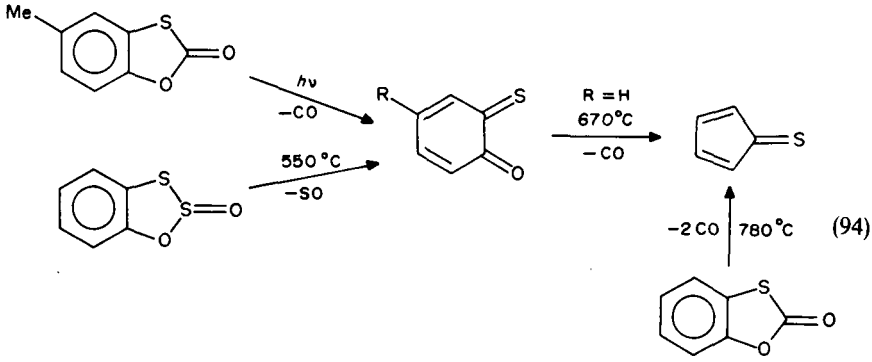
(92)

2*H*-1, 3-Oxathiole derivatives allow generation of α-thioxo carbonyl compounds. This includes as the simplest example monothioglyoxal, which could be trapped in an argon matrix and characterized by IR spectroscopy (equation 93)[327] and a photochemical[59] as

well as a thermal route[328] to monothio-*o*-quinones (equation 94). The product may again decarbonylate to give cyclopentadienethione, which is also accessible directly by a [4 + 1] cycloreversion[328].

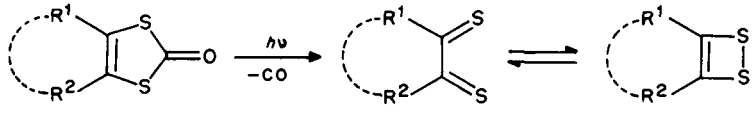


(93)



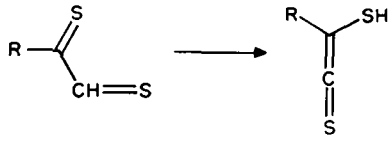
(94)

Photolytic extrusion of carbon monoxide from 1,3-dithiole-3-ones allows detection and, in some instances, even isolation of α-dithiones. The bis(4,4'-dimethylaminophenyl) derivative ($R^1 = R^2 = 4\text{-}Me_2NC_6H_4$) is particularly noteworthy as it does not immediately cyclize to a dithiete **9B** and was thus the first α-dithione to be studied (see Section II.B)[66]. Other α-dithiones which have been generated by the route of equation 95 are dithioglyoxal ($(R^1 = R^2 = H)$[277], 3,3-dimethyl-2-thionobutanethial ($(R^1 = t\text{-}Bu$, $R^2 = H)$[277], 4-methyldithiocamphorquinone[277] and dithioacenaphthenequinone ($R^1 + R^2 =$ biphenylene)[329]. In a subsequent reaction, products **9A** with $R^1 = H$ or Me, $R^2 = H$ tautomerize to a mercaptothioketene (equation 96)[330].



(95)

(9A) **(9B)**



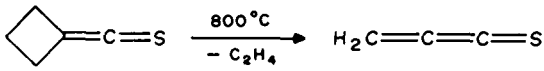
(96)

3. [2 + 2] cycloreversion

In principle, retrograde [2 + 2] cycloaddition of cyclobutanethiones offers a route to thioketenes, but only in a few cases has the approach been developed into a synthetic

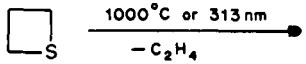
method. The examples are pyrolysis of 2, 2, 4, 4-tetramethyl-1, 3-cyclobutanedithione (**21b**) to give dimethylthioketene (equation 97)[107] and the cleavage of thiocarbonylcyclobutane yielding methylenethioketene (equation 98)[331,332].

$$\mathbf{21b} \xrightarrow[10^{-3}\,\text{torr}]{800\text{–}900\,^\circ\text{C}} 2\,Me_2C{=}C{=}S \tag{97}$$



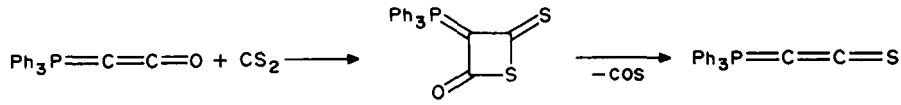
(98)

The [2 + 2] cycloreversion of the parent thietane can be achieved by gas-phase thermolysis[333] or photolysis[334] (equation 99). The product thioformaldehyde is detected spectroscopically or trapped in Diels–Alder reactions (cf. Section IV.E.4).



(99)

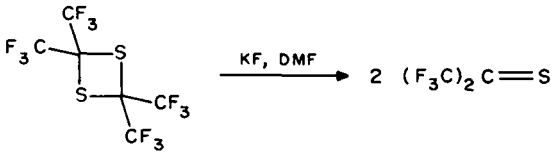
Contrary to the extreme conditions of equation 99, a thietane is only an intermediate in a sequence of cycloaddition/cycloreversion reactions, when triphenylphosphoranylideneketene reacts with CS_2 to generate the corresponding thioketene **20** (equation 100)[335].



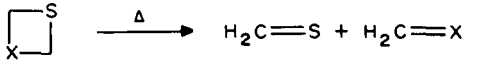
(**20**)

(100)

1, 3-Dithietanes represent the most common type of four-membered ring giving thiocarbonyl derivatives in [2 + 2] cycloreversions[336a]. Quite often, this ring system is formed in the decomposition of reactive C=S systems (cf. Section IV.E.2). Considering the possibility of a cycloreversion, dimers of the 1, 3-dithietane type represent a convenient way of storing labile thiocarbonyl derivatives. An illustrative example is the liberation of hexafluorothioacetone from its dimer thermally[182] or on treatment with KF in DMF (equation 101)[337–339]. 1, 3-Dithietane itself (**35**; X = S) is cleaved to give thioformaldehyde at fairly high temperatures of 450–600 °C; for the corresponding S-oxide (**35**, X = SO), only 350 °C are required (equation 102)[86,340].



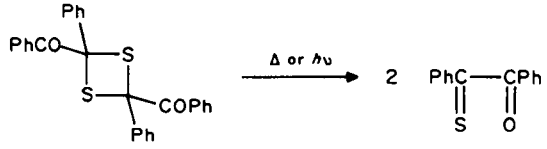
(101)



(**35**)

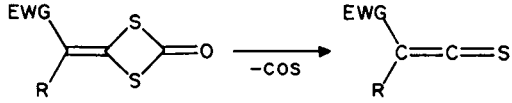
(102)

For dimeric monothiobenzil, the [2 + 2] cycloreversion to the monomer occurs at temperatures above 210 °C, but at RT on irradiation (equation 103)[341].



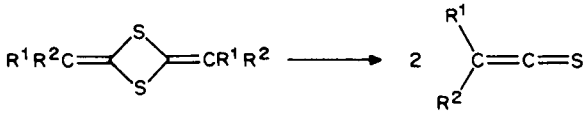
(103)

Various modifications have been reported for the [2 + 2] cycloreversion of alkylidene-substituted 1, 3-dithietanes to give thioketenes. A particularly smooth process is the cleavage of 4-alkylidene-1, 3-dithietane-2-ones liberating carbonyl sulfide along with the thioketene (equation 104); this reaction occurs on gentle heating, photochemically, by the action of Lewis acids, or on attempted chromatographic purification[342–345]. However, a prerequisite is that at least one strongly electron-withdrawing groups (EWG) is present on the exocyclic C=C bond [EWG = RC(O)[344], ROOC[346], NC[342,345] $(RO)_2P(O)$[343]].



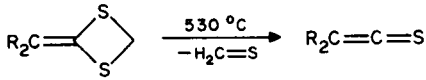
(104)

Contrary to the above facile cleavage, [2 + 2] cycloreversions of 2, 4-bis(alkylidene)-1, 3-dithietanes, i.e. of thioketene dimers, require quite high temperatures (equation 105). In synthetic applications, the reaction is best carried out as flash-vacuum pyrolysis[49], but may be hampered by the low volatility of many thioketene dimers (e.g. $R^1 + R^2$ = fluorenylidene[49]). The approach represents the standard method of generating bis(trifluoromethyl)thioketene ($R^1 = R^2 = F_3C$)[21,102,347]. On the other hand, cleavage of thioketene dimers by nucleophiles has been reported[348,349].



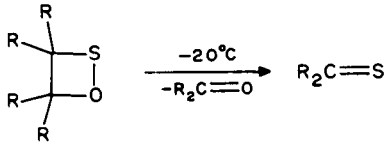
(105)

Pyrolysis of 2-alkylidene-1, 3-dithietanes yields thioketenes [$R_2C = (NC)_2C$, cyclopentadienylidene] along with thioformaldehyde (equation 106)[86].

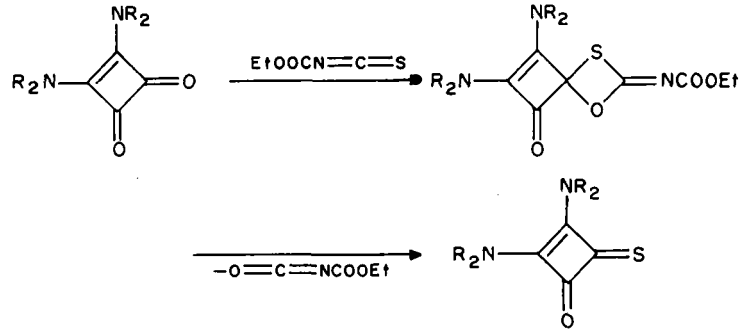


(106)

Oxathietanes represent another type of four-membered heterocycle which, on appropriate substitution, may yield thiocarbonyl compounds by way of a [2 + 2] cycloreversion. Examples for the 1, 2- (equation 107; R = H, Me)[350] and 1, 3-arrangement of the heteroatoms (equation 108)[351] have been reported. In the latter case, selective thionation of one carbonyl group in a squaric acid amide is achieved in a sequence of [2 + 2] cycloaddition/cycloreversion.

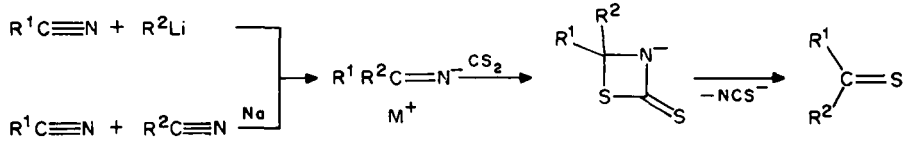


(107)



(108)

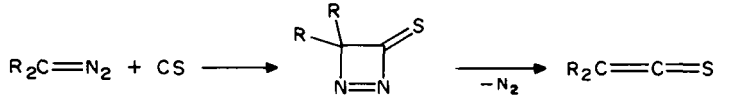
A useful thioketone synthesis employs N-metalated imines of nonenolizable ketones. Addition of carbon disulfide appears to yield 1,3-thiazetidine-2-thiones as intermediates, which give *in situ* a [2 + 2] cycloreversion (equation 109)[191,192,352-357]. The approach represents a particularly convenient synthesis of sterically hindered dialkylthiones such as $(t\text{-Bu})_2C{=}S$[89,358]. For aromatic thiones, carbon disulfide may be replaced by $HC(S)NMe_2$[352].



(109)

Cleavage of an intermediate 1,3-thiazetidine is also observed in the reaction of PhCH=NMe with $Ph_2C{=}S$, when the liberated thiobenzaldehyde is trapped by excess imine[359].

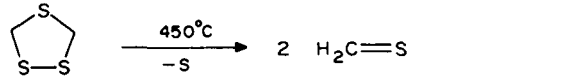
A 1,2-diazetine-3-thione is the suspected intermediate in the reaction of sterically hindered diazo compounds with carbon monosulfide; $t\text{-Bu}_2C{=}C{=}S$ (**5a**) and related thioketenes were obtained by this approach (equation 110)[360-362].



(110)

4. [2 + 3] cycloreversion

The best pyrolytic method of generating thioformaldehyde is the thermolysis of 1,2,4-trithiolane, as the precursor is readily available and only a relatively low temperature is required (equation 111)[86,363].

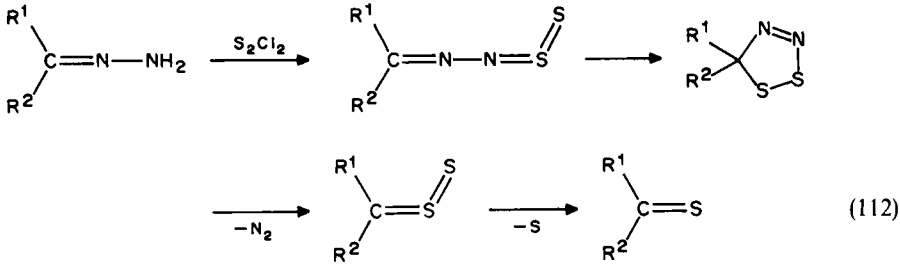


(111)

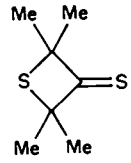
Using substituted trithiolanes, the approach of equation 111 has also proved useful for the generation of MeCH=S, PhCH=S, $Me_2C{=}S$ and cycloalkanethiones, though the latter are contaminated by the corresponding cycloalkenes[86].

In the conversion of hydrazones into thiocarbonyl compounds by the action of S_2Cl_2

(cf. Section III.C.4), 1,2,3,4-dithiadiazoles are the crucial intermediates giving a facile [3 + 2] cycloreversion. Together with the loss of nitrogen, thiosulfines are liberated which eliminate sulfur *in situ* and give thiocarbonyl products (equation 112)[364,365]. The method is apparently the best way to obtain sterically extremely hindered thiocarbonyl compounds as shown by the successful synthesis of 2,4,6-tri-*t*-butylthiobenzaldehyde (**2b**; 40%)[19] and of thione **36** (51%) which is not accessible from the corresponding ketone using P_2S_5 (equation 25) or by de Mayo's method (equation 54), whereas the Lawesson reagent **26** (cf. equations 39–44) or H_2S (equation 18) give very low yields[237].

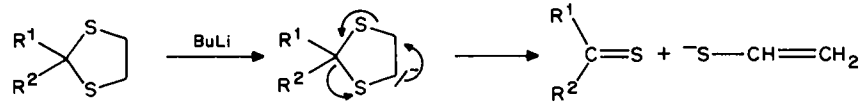


(112)



(36)

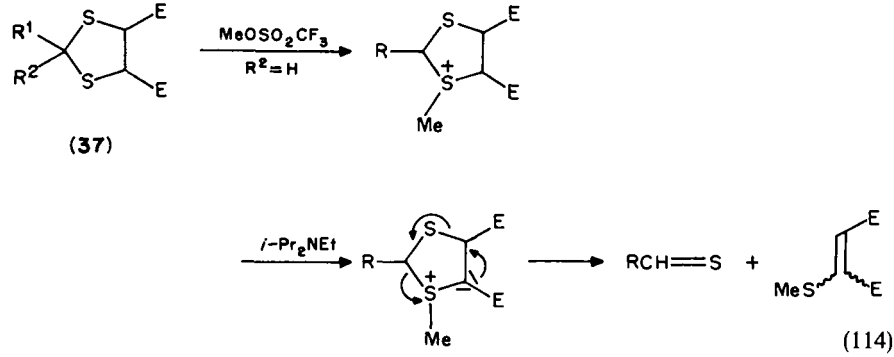
In addition to the methods of equations 111 and 112, several very useful [3 + 2] cycloreversions are based on the generation of a negative charge on a five-membered ring. Wilson noted that 1,3-dithiolanes may be deprotonated on $C_{(4)}$ even for R^1 or $R^2 = H$ and that the resulting anions give an instantaneous cleavage into a thioaldehyde or a thioketone along with an anionic fragment (equation 113)[366]. Stable thiones such as thiocamphor may be isolated by this approach (yield 62%), but BuLi, which is required as base in most cases, gives reduction[367] or thiophilic attack[368] (cf. Section IV.C.2) as secondary reactions with the thiocarbonyl product. Thus, the reaction could be developed into a useful synthesis of aliphatic thiols[367]. Use of LDA gives rise to radical cations and rather complex subsequent reactions[369]. However, the method is of synthetic interest for aralkyl thiones **7** and, in combination with a hydrolysis reaction, can be used to unmask ketones which had been protected as 1,3-dithiolanes[370].



(113)

1,3-Dithiolane derivatives with a more acidic $H_{(4)}$ than in the parent system (equation 113) should allow one to avoid side-reactions and, consequently, offer a more general entry into thiocarbonyl chemistry, in particular, when the modification gives rise to a more efficient leaving group in the [3 + 2] cycloreversion. Following these lines, precursors have

been developed which lead to thiocarbonyl compounds under mild thermal conditions (well below RT)[371,372]. To generate thioaldehydes, S-methylation together with 4,5-disubstitution by ester groups gives the required activation and allows regiospecific deprotonation (equation 114)[373].



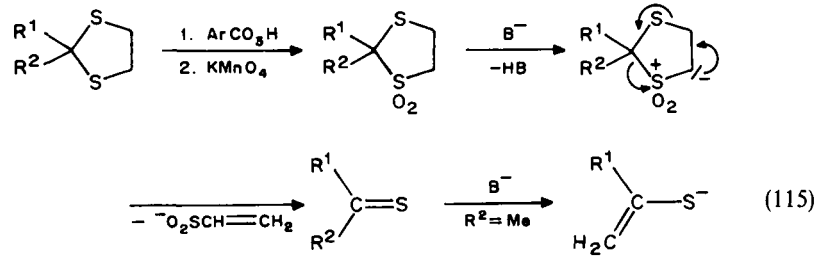
(37)

E = COOMe

(114)

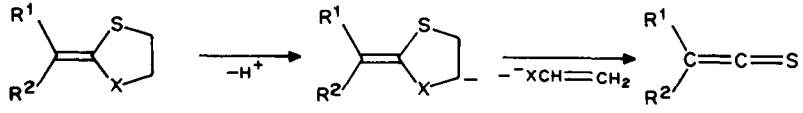
The methylation step in equation 114 fails in the attempted synthesis of thioacrolein, but this thioaldehyde can be generated directly and trapped by deprotonation of **37** ($R^1 = H_2C{=}CH$, $R^2 = H$) with LDA[373]. By the same method, thiones such as $Me_2C{=}S$, PhC(S)Me or $Ph_2C{=}S$ are obtained from the corresponding dithiolanes **37**[374]. Under these conditions, volatile thiones can be conveniently trapped *in situ* without being molested by their unpleasant smell[27].

In an alternative approach, thioketones can be generated from 1,3-dithiolane S,S-dioxides via deprotonation with LDA or *t*-BuOK but, under the required strongly basic conditions, thiones with α-hydrogen are deprotonated *in situ* to give the corresponding enethiolates (equation 115)[375,374].



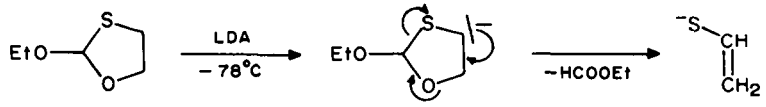
(115)

Activation of the 1,3-dithiolane system for cycloreversion by introducing an S-ylide (equation 114) or a sulfone moiety (equation 115) can also be applied to thioketene synthesis[371,372]. Thus, 2-alkylidene derivatives with $X = S^+$ Ar, S^+Et (for $R^1 = R^2 =$ Ph)[376,377] or $X = SO_2$[375,376] give thioketenes on treatment with base (equation 116).



(116)

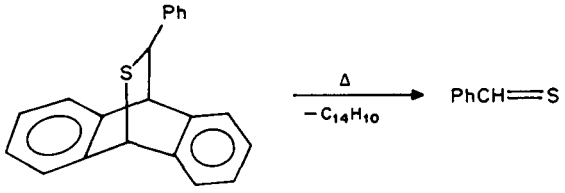
In a related example of a [3 + 2] cycloreversion, the anion of 2-ethoxy-1, 3-oxathiolane yields the enethiolate of thioacetaldehyde (equation 117), which may be trapped by alkylation (cf. Section IV.B)[378].



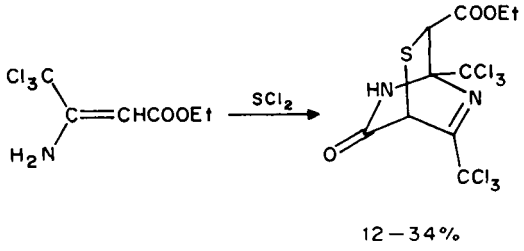
(117)

5. [2 + 4] cycloreversion

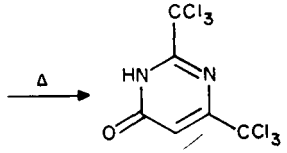
Retro-Diels–Alder reactions giving thiocarbonyl compounds are favored, when simultaneously a comparatively stable diene is formed. Thus, thioaldehydes (equation 118)[289,379] and similarly methylenethioketene $H_2C{=}C{=}C{=}S$[272] can be generated together with anthracene, and monothioglyoxalate with concomitant formation of a pyrimidine derivative (equation 119)[380], but even cyclopentadiene is a possible parallel product (equation 120)[381].



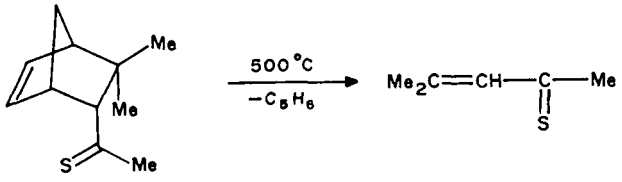
(118)



12–34%

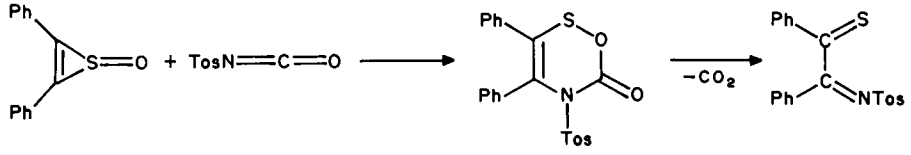


(119)



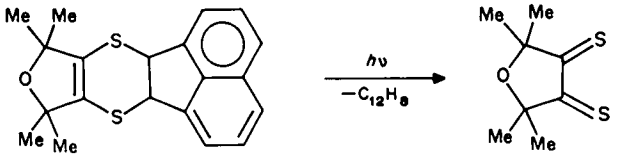
(120)

In the reaction of a thiirene S-oxide with tosylisocyanate, an oxathiazine is suspected as an intermediate and apparently cleaves quite readily to an iminothione along with carbon dioxide (equation 121)[382].



(121)

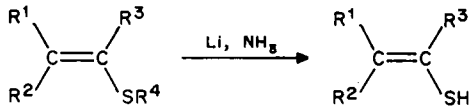
α-Dithiones are obtained from 2,3-dihydro-1,4-dithiins in a light-induced [4 + 2] cycloreversion. Equation 122 shows an example with concomitant formation of acenaphthylene[383]; a related steroid-derived dithione exists in the dithiete form and was discussed earlier (see Section II.B)[69].



(122)

G. Reductive C, S Cleavage

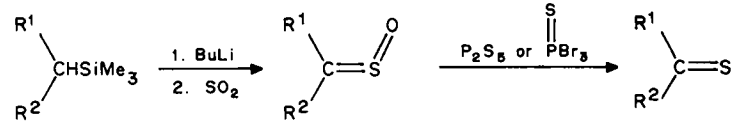
The bond between the olefinic carbon and the sulfur in 1-alkenyl sulfides can be cleaved with lithium in liquid NH_3 to give enethiols; under the reaction conditions no tautomerization to the corresponding thials or thiones is observed (equation 123)[384].



(123)

H. Reduction of Sulfines

Sulfines (thiocarbonyl S-oxides) are readily obtained by oxidation of the parent thiocarbonyl compound (see Section IV.A) and the reverse reaction was useless for a long time. However, Zwanenburg's discovery that the Peterson olefination can be applied to SO_2[385,386] offers an independent route to sulfines and so their reduction to thiocarbonyl compounds becomes of interest. Appropriate reducing agents are P_2S_5 or thiophosphoryl bromide, $P(S)Br_3$ (equation 124)[387].



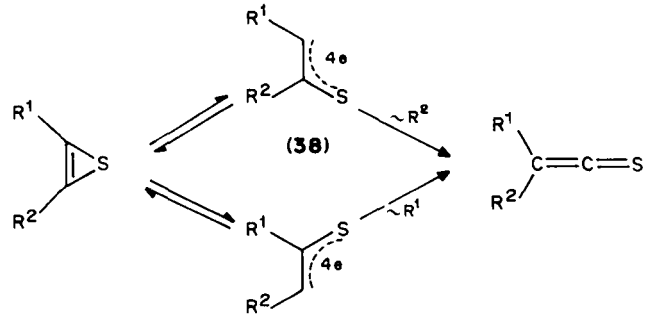
(124)

I. Sigmatropic Shifts

1. [1,2] shifts

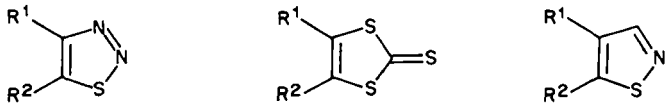
Various examples have been reported where a 1,2 shift yields thioketenes. The common intermediate in these rearrangements is the four-electron species **38**, which may be

considered either as a diradical[388], as a 1,3-dipole[389] or as a carbene[390,391]. In any case, the 1,2-shift of R^2 yields a thioketene. However, the experimental evidence suggests that **38** may cyclize to a thiirene, though this is a formally antiaromatic species, and subsequently reopen to give an isomeric four-electron species[54,109,392–395]. From here, a 1,2 shift of R^1 gives the thioketene product (equation 125). This implies that migratory aptitudes of R^1, R^2 need not be considered in the design of the precursor of a specific thioketene[396].



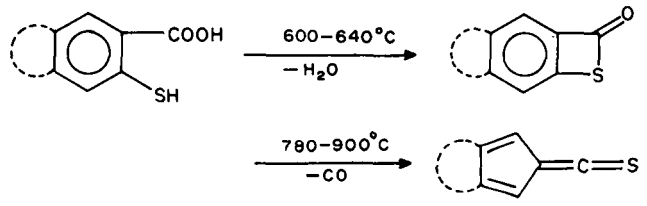
(125)

The most convenient sources of species **38** are 1,2,3-thiadiazoles **39**. These heterocycles are valence tautomers of the unknown α-diazothioketones and this suggests that the overall reaction of **39** to thioketenes may be considered to be the sulfur version of the Wolff rearrangement. Loss of nitrogen from **39** may be achieved by irradiation or by thermolysis. While photolysis in solution leads to complex product mixtures[388,390,397–400], low-temperature irradiation of precursors **39** confirms thioketene formation usually with the intermediacy of thiirenes[109,391,401–404]. For a clean reaction, thermolysis of thiadiazoles **39** should be carried out as flash-vacuum thermolysis at 520–530 °C and a pressure of 10^{-2} to 10^{-4} torr[49,396,405], though heating of **39** with a trapping reagent sometimes also allows one to isolate thioketene-derived products[406–411].



(39) **(40)** **(41)**

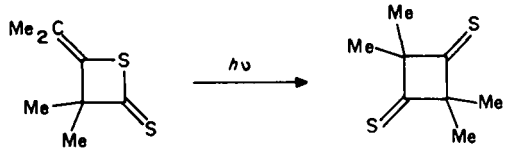
Alternative routes to the four-electron species **38** employ 1,3-dithiole-2-thiones **40** via elimination of CS_2[402] or isothiazoles **41** via loss of HCN[401], but these methods are much less important than the use of thiadiazoles **39**. The same is true for loss of CO from a β-thiolactone, which has so far only been employed for the generation of the thiocarbonylcyclopentadiene system (equation 126)[125,412,413].



(126)

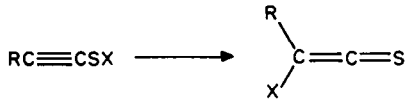
2. [1,3] shifts

Irradiation of a formal dimethylthioketene dimer of the β-dithiolactone type results in rearrangement to dithione **21b** in 60% yield (equation 127; cf. Section II.D.5)[103].



(21b) (127)

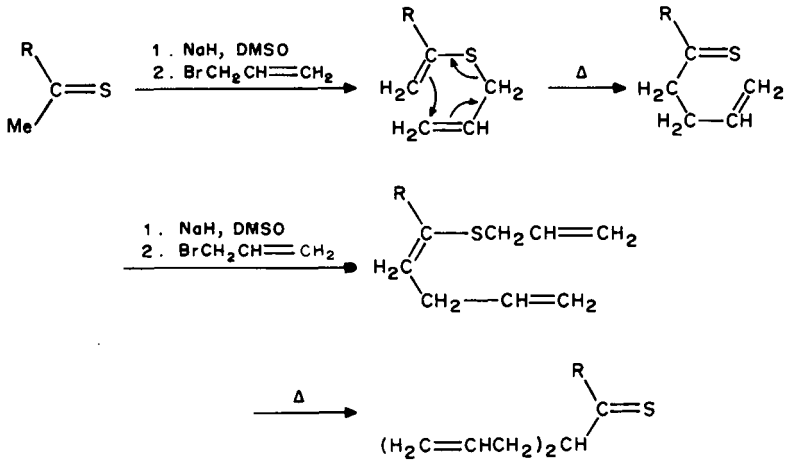
Thioketenes may be formed from alkynyl sulfides via a 1, 3 shift of the group X (equation 128). As to X = H, it was mentioned earlier (see Section II.A) that the equilibrium between aldothioketenes and alkynylthiols is entirely on the side of the thiocarbonyl species and that the latter are only transient intermediates on protonation of alkynyl thiolates[414,415]. On silylation of alkynyl thiolates, alkynyl silyl sulfides are formed which may rearrange to silylthioketenes (equation 128; X = SiR_3)[6]. For R = Me_3Si, the sulfide can be isolated, if Me_3SiBr is employed as silylating agent, whereas use of the chloride directly leads to bis(trimethylsilyl)thioketene (R = X = Me_3Si)[91]. An example for X = SMe was reported as well[416].



(128)

3. [3,3] shifts

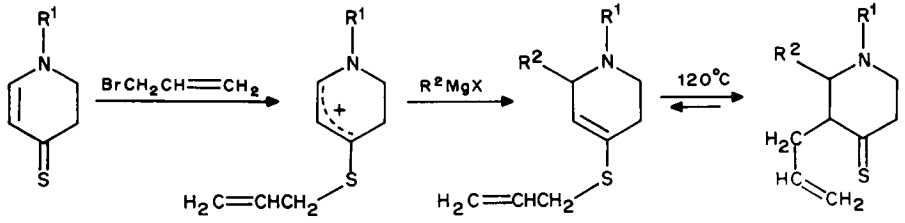
The thio-Claisen rearrangement of 1-alkenyl(allyl)sulfides yields homoallylthioketones (equation 129)[417]. The approach is usually applied for the C-elongation of methyl thioketones: via primary S-allylation (see Section IV.B), the unsaturated three-carbon unit is added in a formal [3,3] sigmatropic shift; the procedure may be repeated to give thioketones with two α-allyl residues (yields 50–80%)[418].



(129)

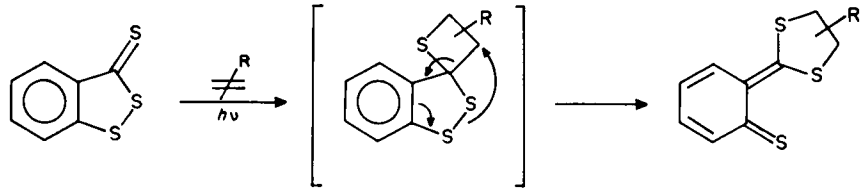
The rearrangement of 1-alkenyl sulfides with the other S-substituent being a 2-butenyl or a propargyl residue gives less satisfactory results[418]. Allyl(2, 2-dicyanovinyl) sulfides fail to give thioketones in a thermal thio-Claisen rearrangement[419].

Starting from an enethione, the rearrangement may be combined with alkylation in the β-position (equation 130)[231].



(130)

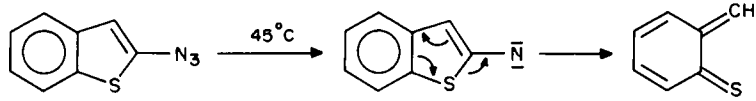
The [2 + 2] photocycloaddition of alkenes to 3H-1,2-benzodithioles ("benzotrithiones") yields thietanes, which *in situ* rearrange in what may be classified as a [3,3] shift. The resulting *o*-thioquinone methides with an exocyclic ketene S,S-acetal moiety (equation 131) readily dimerize in a formal [4 + 4] cycloaddition[420–422].



(131)

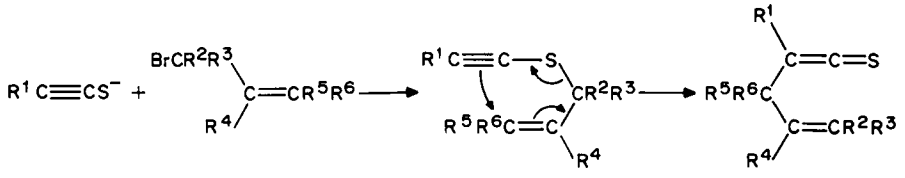
The rearrangement has also been reported for [1,2:*d*] and [2,1:*d*] annulation of naphthalene to the 1,2-dithiole-3-thione ring[423].

In a related reaction, the nitrene species resulting from azidobenzo[*b*]thiophenes by loss of nitrogen gives cyano-substituted *o*-thioquinone methides (equation 132), which dimerize *in situ* yielding [4 + 2] cycloadducts (see Section IV.E.4)[424].



(132)

When the 1-alkenyl unit in equation 129 is replaced by an 1-alkynyl residue, the thio-Claisen rearrangement yields allyl-substituted thioketenes; the starting material is readily available by S-allylation of alkynyl thiolates (equation 133). With the synthesis of allyl-



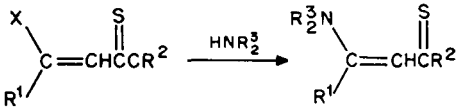
(133)

(*t*-butyl)thioketene (as in equation 133, with, $R^1 = t$-Bu, R^2–$R^6 = H$), the approach represents the most facile access to a thioketene[425,426]. Moreover, the rearrangement proceeds particularly smoothly for silylethynyl sulfides offering an elegant and convenient synthesis of allyl(silyl)thioketenes (**5**, $R^1 = R_3Si$)[427,428].

Various modifications of the approach of equation 133 were reported which do not allow isolation of the formed thioketenes, but trapping, usually by amines (see Section IV.C.1)[426,428–431].

J. From Other Thiocarbonyl Derivatives

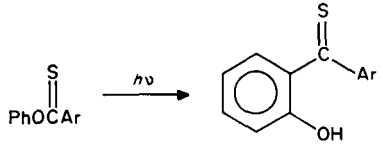
The X substituent in vinylogous thio acids ($X = OH$)[432–434], dithioacids ($X = SH$)[435–438] or thioamides ($X = NR_2$)[194,439,440] may be replaced by NH_2 or NR'_2 in nucleophilic substitution reactions with ammonia or amines (equation 134).



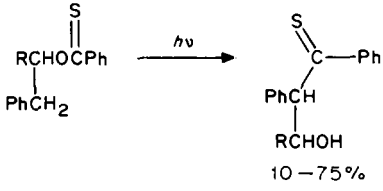
(134)

In analogous reactions, dithiosquaric acid amides yield di-, tri- or tetrathiosquarates on treatment with hydroxide or hydrogen sulfide[441,442].

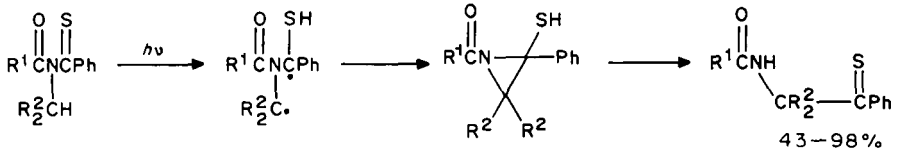
On irradiation in the visible range, O-phenyl thiobenzoates yield 2-hydroxy thiobenzophenones in a 'photo-Fries' rearrangement (equation 135)[443]. An aliphatic (equation 136)[444] and an aza version of this reaction (equation 137)[445] have also been reported. The aziridinethiol intermediate in equation 137 was detected by acylation[199].



(135)



(136)



(137)

IV. CHEMICAL PROPERTIES OF THIOCARBONYL COMPOUNDS

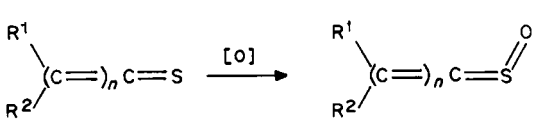
In general, thiocarbonyl compounds are more reactive than their carbonyl congeners[27,41,446]. This qualitative impression is supported by MO calculations which

indicate a higher HOMO and a lower LUMO than for the corresponding carbonyl compounds[447]. Consequently, thiocarbonyl compounds should be more nucleophilic and also more electrophilic than carbonyl compounds. However, the pronounced reactivity includes reactions between individual molecules of the thiocarbonyl compound in question resulting in di-, oligo- or polymerization and so, on addition of a given reagent, competition of the desired attack with that of another C=S group has to be considered.

In addition to the typical features of carbonyl chemistry, the presence of the sulfur atom leads to some reactions which are characteristic of thiocarbonyl compounds. Noteworthy examples are the formation of S-oxides (Section IV.A) and thiophilic attack of organometallics (Section IV.C.2). Moreover, thiocarbonyl compounds show a striking variety of cycloaddition reactions (Section IV.E). For thioketenes, these cycloadditions may occur across the C=C bond as is typical of most ketene cycloadditions, but many reactions across the C=S bond are known.

A. Oxidation

A typical reaction of thiocarbonyl compounds is oxidation to give thiocarbonyl S-oxides (sulfines)[386]. These compounds are in general less stable than their thiocarbonyl precursors, making their isolation sometimes difficult. The oxidation is most frequently carried out with peracids, in particular 3-chloroperbenzoic acid[448-450], but H_2O_2 may also be used[20,451]. Successful examples include nonenethiolizable[448] or aromatic thiones[449] (equation 138; $n = 0$), thiopivalaldehyde (**4**; $R^1 = t$-Bu, $R^2 = H$, $n = 0$)[18] and sterically hindered dialkylthioketenes ($n = 1$)[323,386,452]. However, the reaction fails to provide S-oxides of thioketones with α-H[448] or of more reactive thioketenes[6].



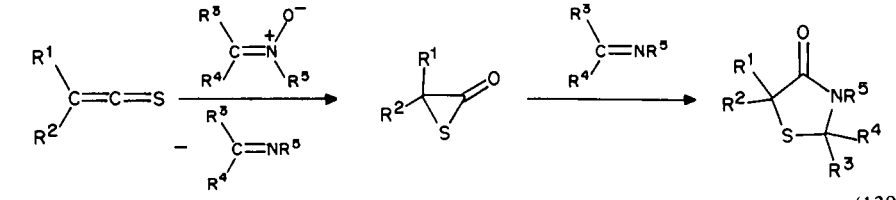
(138)

Singlet oxygen appears to give the reaction of equation 138 as well, but usually secondary reactions ensue. The S-oxide could be isolated starting from t-Bu_2C=S, whereas 2,2,4,4-tetramethylcyclobutanethione gave only minor amounts of the sulfine[453]. Under more forcing conditions or for more reactive substrates, desulfurization to ketones occurs[454,455]; this reaction may well proceed via an oxadithietane intermediate, which is then cleaved in a [2 + 2] cycloreversion[322]. Similarly, oxidation of dialkylthioketenes with singlet oxygen yields only some S-oxide along with other products, which seem to stem from attack of the reagent at the thiocarbonyl carbon[456,457].

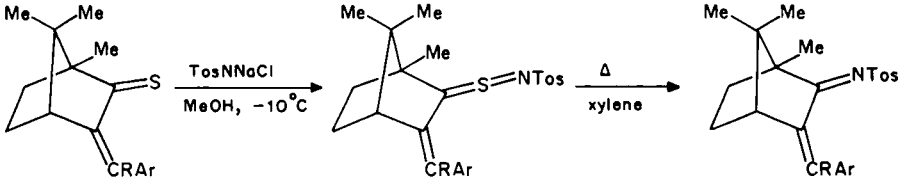
Ozone gives no S-oxide in the reaction with thiobenzophenone (**17**), but the ketone—probably via a trioxathiolane[458]. In contrast, ozone oxidizes sterically hindered dialkylthioketenes to their S-oxides[456]. Other reagents that have been used to convert thioketones into ketones by oxidative desulfurization are $Pb(OAc)_4$[105] and benzeneseleninic anhydride, $(PhSeO)_2O$[459].

A remarkable oxidation is observed on treatment of thioketenes carrying bulky alkyl substituents with nitrones: α-thiolactones are isolated (equation 139)[323,324]. These three-membered rings are apparently also intermediates in the reaction of less hindered thioketenes with nitrones to give thiazolidin-4-ones[6].

Chloramine T, $TosNNaCl \cdot 3H_2O$, was reported to react as a combined nucleophile and oxidizing agent in the reaction with aliphatic or aromatic thiones. Ph_2C=S and adamantanethione afforded 1,2,4-trithiolane derivatives ('thioozonides')[460]. However, by analogy with equation 139, thiocarbonyl S-imides have been isolated, though they tend to eliminate sulfur on heating (equation 140)[450,461]. The S-imides are formed as a mixture of E and Z isomers with respect to the C=S bond.



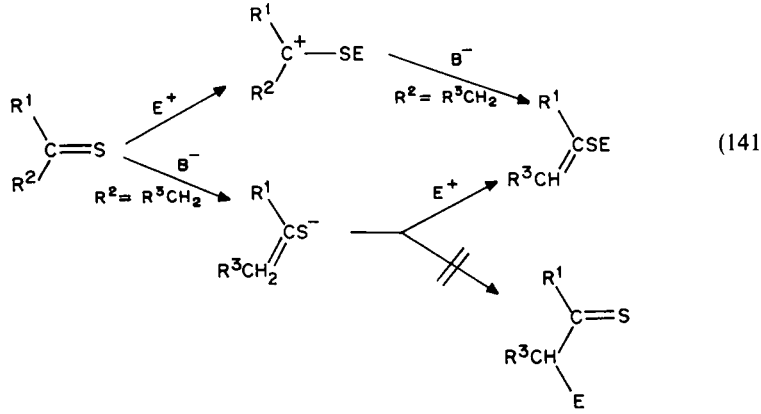
(139)



(140)

B. Electrophilic Additions

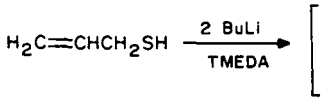
Due to the highly nucleophilic and polarizable thiocarbonyl sulfur, thioketones react with a large variety of electrophiles E^+, whereas for thioaldehydes this branch of their chemistry remains to be explored and for thioketenes this mode of addition is encountered in a few examples only. The primary product of attack by E^+ is a salt (equation 141). For enethiolizable thiones, a secondary reaction with a base B^- yields uncharged products. Alternatively, enethiolates may be employed in the reaction with E^+ and, actually, display an enhanced nucleophilicity. It is noteworthy that, also for enethiolates as starting materials, electrophilic attack is regiospecific on the thiocarbonyl sulfur and is never observed on the α-carbon.

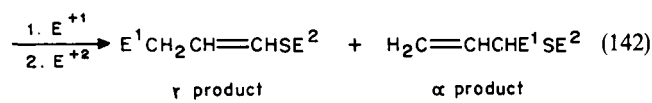


(141)

The simplest example of electrophilic attack is protonation, to give mercaptocarbenium salts (equation 141; $E^+ = H^+$). The reaction is best carried out with FSO_3H/SbF_5 in SO_2ClF[31] and has been realised for aromatic as well as aliphatic thiones[462]. In contrast, HCl adds to thioketenes to yield yellow-orange thioacyl chlorides, $R_2CHC(S)Cl$[98].

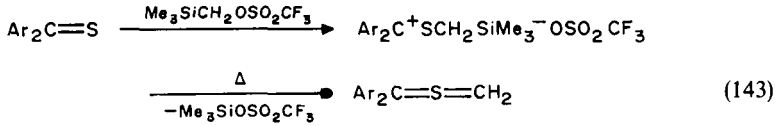
The most common electrophilic addition reaction is alkylation. Methylation (equation 141; $E^+ = Me^+$) of unactivated thiones is achieved with $Me_3O^+\ SbCl_6^-$ [121] or magic methyl, $MeOSO_2F$ [105], whereas for enethiolates [193,278,280,374] or activated thiones such as tropothione (**14**) [105] methyl iodide may be used. Dimethylsulfoxonium methylide, $Me_2S(O)\ ^+CH_2^-$, allows clean methylation of enethiolizable thiones, but gives methylene transfer with diarylthioketones [463]. In addition to simple thiones, methylation or other alkylation reactions can be applied to cyclobutanethiones [193], enethiones [464], β-aminoenethiones [465] or enethiolized α-thioxocarboxylates [280]. A special case is encountered in the electrophilic attack on doubly deprotonated 2-propenethiol, which may be looked upon as the α,β-dianion of propanethial. Here, in the first addition step, E^{+1} may either react on $C_{(\alpha)}$ or on $C_{(\gamma)}$ with the latter mode of addition being preferred by 3:1 (equation 142); the reaction is terminated by addition of a second electrophile E^{+2} [466].





(142)

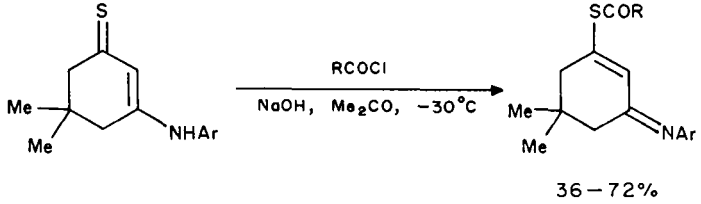
The reaction of diarylthioketones with (trimethylsilyl)methyl triflate holds special interest as, via elimination of silyl triflate, it gives an entry into thiocarbonyl ylide chemistry (equation 143) [467].



(143)

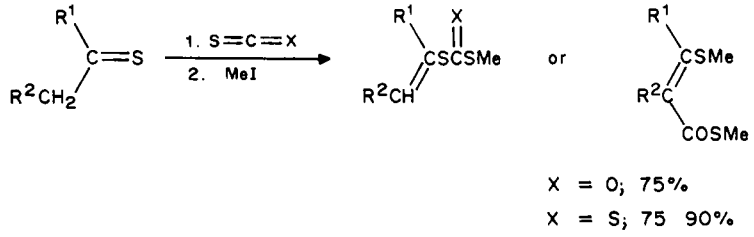
Alternatively, thiocarbonyl ylides have been obtained by addition of diarylcarbenes to the thiocarbonyl sulfur in sterically hindered dialkylthioketones [468].

Besides alkylation, a number of other electrophilic reagents allow formation of an S—C bond using thiones with α-hydrogen or enethiones with γ-hydrogen. S-Arylation is achieved with the electron-poor 1-chloro-2, 4-dinitrobenzene (yield 50–80%) [469] and S-acylation by reaction with acyl chlorides [469,470], anhydrides [231,464] or ketenes (yield 60–95%) [469]. Interestingly, the attack occurs regiospecifically on sulfur even for β-aminoenethiones with an NH group (equation 144) [470].



(144)

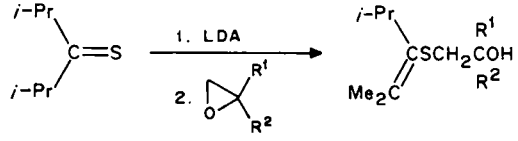
Reaction of enethiolizable thiones with carbonyl sulfide (X = O) or carbon disulfide (X = S) and subsequent addition of methyl iodide gives S-methoxy(di)thiocarbonyl derivatives (equation 145) [469].



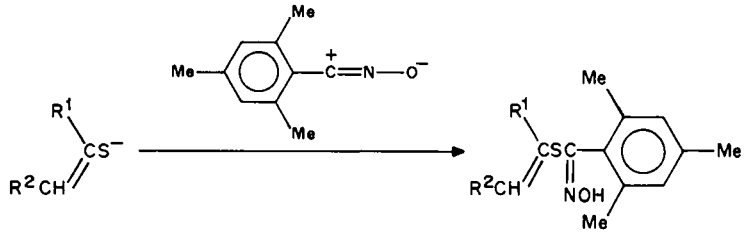
(145)

For carbonyl sulfide (equation 145; X = O), there is an ambiguity as it gives one of the very rare examples of attack on $C_{(\alpha)}$ in the reaction with thiopinakolone ($R^1 = t$-Bu, $R^2 = H$; yield 60%)[469].

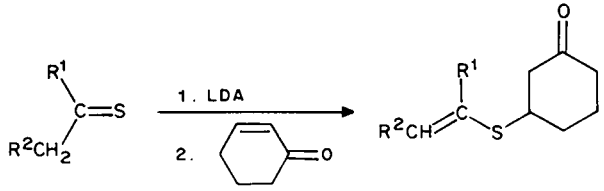
Other electrophilic reagents leading to S—C bond formation in the reaction with enethiolates are epoxides (equation 146)[471], mesitonitrile oxide (equation 147)[374] and enones which give regiospecific 1,4-addition (equation 148)[472].



(146)

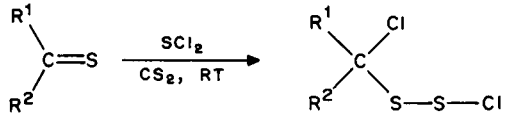


(147)

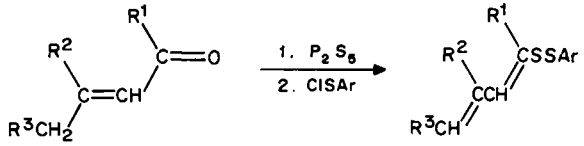


(148)

Besides S—C bonds, S-hetero bonds may be formed in the reaction of thiones with electrophiles. A disulfide moiety is generated by addition of SCl_2 to diaryl- or sterically hindered aliphatic thiones (equation 149)[473,474] and by addition of 2-nitrobenzenesulfenyl chloride, $2\text{-}O_2NC_6H_4SCl$, to enethiones (equation 150)[218]. The latter reaction allows convenient trapping of the thione in cases where it is too unstable to be isolated.



(149)



(150)

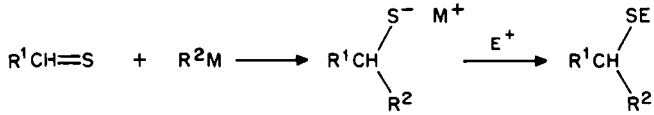
Other options to introduce heteroatoms on the thiocarbonyl sulfur are silylation, for which the enethiolates are usually employed[466,475], or chlorination giving α-chlorosulfenyl chlorides from t-$Bu_2C{=}S$ and hexafluorothioacetone[473,474]. In contrast, chlorine adds to the C=C bond in t-BuCH=C=S to yield an α-chlorothioacyl chloride[98].

C. Nucleophilic Additions

Nucleophilic attack on the electron-deficient carbonyl carbon is the basis for synthetic uses of oxo compounds. Considering the similarities between the C=O and the C=S group, analogous reactions might be expected for their thioxo congeners. However, the chemistry of nucleophilic additions to thioaldehydes or thiones is full of surprises. Thus, in apparent contrast to carbonyl chemistry, nucleophilic attack may occur on the heteroatom end of the C=X bond (see Section IV.C.2), but also the conventional primary attack on carbon gives rise to some unusual reactions (see Section IV.C.1).

1. Addition to the thiocarbonyl carbon

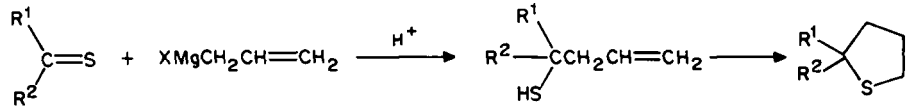
Carbanions, which invariably show carbophilic attack with carbonyl compounds, in thiocarbonyl chemistry do so only under special circumstances; alternatives are thiophilic attack (see Section IV.C.2) or reduction to thiols[101,367,451]. Relatively frequent is carbophilic attack on thioaldehydes (equation 151). It has been reported for the reaction of the stable thioaldehyde **2b** [$R^1 = 2,4,6\text{-}(t\text{-}Bu)_3C_6H_2$] with MeMgI (yield after protic workup 81%)[476] and of thiopivalaldehyde (**4**; $R^1 = t$-Bu) with BuLi (yield after methylation 39%)[101]; however, it should be noted that **2b** gives thiophilic attack with t-BuMgCl and so does **4** with t-BuLi. The emerging rule that t-BuM gives rise to thiphilic rather than carbophilic attack is limited to thials and thiones, e.g. HC(S)OEt adds t-BuLi in the normal way[18].



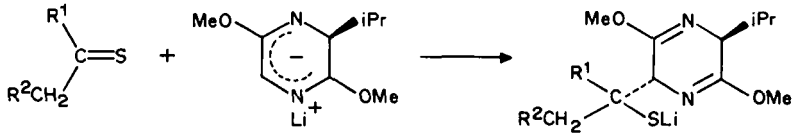
(151)

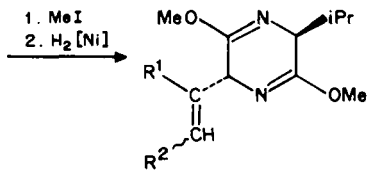
A bond between the thiocarbonyl carbon and $C_{(\alpha)}$ of the heterocycle is also the result of the reaction between thioaldehydes and furans[477].

For thiones, attack by carbanions on the sulfur rather than on the carbon is characteristic. A notable exception was found in the reaction of thiones with allylic Grignard reagents giving homoallyl thiols and subsequently thiolanes (equation 152)[478]. Otherwise, carbophilic attack is characteristic of stabilized carbanions such as cyanide[451], deprotonated α-isocyanopropionate[479] or Schöllkopf's bislactim ether which, after methylation and reductive desulfurization, eventually leads to a Hofmann olefin (equation 153)[480]. An interesting effect of the counterion was reported by Bertz, who found that copper(I) allows clean transfer of the ethyl residue to the thiocarbonyl carbon of thiobenzophenone (**17**; equation 154)[481].

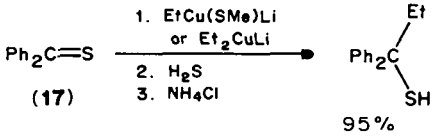


(152)



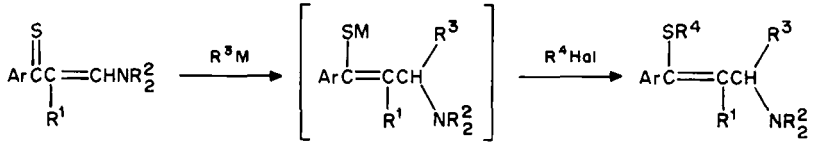


(153)



(154)

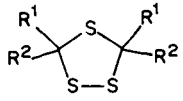
Irrespective of the nature of the carbanion, β-aminoenethiones appear to react via $C_{(\beta)}$ (equation 155)[482].



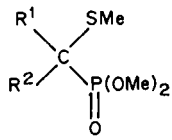
39–96%

(155)

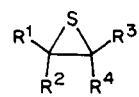
In striking contrast to the reaction of carbonyl compounds with amines, thiobenzophenone or adamantanethione react with amines under ambient conditions to give thioozonides **42** via initial nucleophilic attack on the thione, subsequent oxidative dimerization and finally cyclization[483]. The same products result from the reaction with thiophenol[483].



(42)

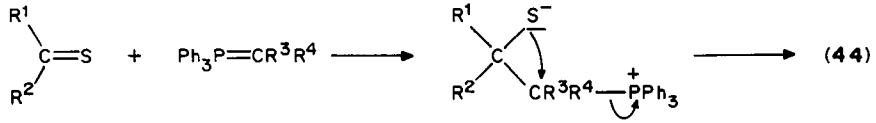


(43)



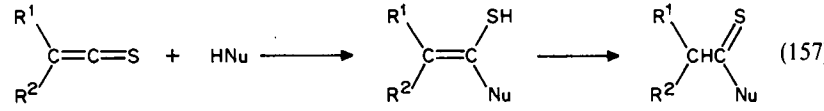
(44)

Trimethyl phosphite, $P(OMe)_3$, reacts with simple alkanethiones[484] or cycloalkanethiones[485,486] to afford α-mercaptophosphonates **43** via a methyl migration. However, on heating thiobenzophenone (**17**) to 100 °C, reductive reaction pathways prevail (cf. Section IV.D)[487], and thioquinone **12** forms a thiirane **44** ($R^1 + R^2$, $R^3 + R^4$ = biphenylene) on treatment with $P(OMe)_3$[28]. Thiiranes **44** are also often found on attempted Wittig olefination of thioaldehydes[101] or stable thiones[488] by ylides $Ph_3P^+C^-R^3R^4$ with the CR^3R^4 moiety being added to the $R^1R^2C{=}S$ bond; a zwitterionic intermediate is invoked to account for the formation of **44** (equation 156)[101,488].



(156)

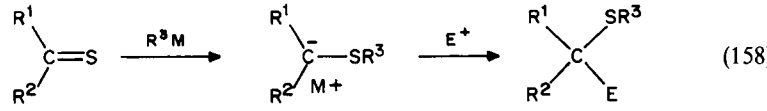
Interestingly, except for the reaction with carbanions (see Section IV.C.2), thioketenes show greater similarity to ketenes than to noncumulated thiones in their behavior toward nucleophiles. For water, alcohols, thiols, ammonia and amines *all* give a clean formation of thiocarboxylic acid derivatives (equation 157)[6]. Considering the high reactivity of the C=S group, the reaction may well proceed through the enethiol with subsequent tautomerization. The reaction with secondary amines is particularly important as it proceeds quantitatively and provides an excellent means to trap unstable thioketenes[6].



(157)

2. Addition to the thiocarbonyl sulfur

Attack of the nucleophile on the thiocarbonyl sulfur is a typical feature of the reaction between thiones and organometallics[489], even though some scattered examples of other nucleophiles have been reported[5,490,491]. The reaction has been recognized by Beak as being part of the family of heterophilic reactions and named accordingly[492]. The basic reaction is given in equation 158; besides carbophilic attack, competing pathways may be reduction to thiols or S-alkylation of the enethiol form to give 1-alkenyl sulfides and these appear to be particularly important for enethiones[493] and aliphatic thiones[451,494,495]. Organolithium compounds allow lower reaction temperatures and apparently give a cleaner reaction than Grignard reagents[492,496] or dialkylcadmium compounds[496].



(158)

Thiophilic attack has been observed for all types of thiocarbonyl compounds as well as for their S-oxides[497], specific examples being thiopivalaldehyde (*t*-BuCH=S)[101], tris(trimethylsilyl)thioacetaldehyde $[(Me_3Si)_3CH{=}S]$[156], silylthioketones[209,498], α-thioxo esters[499] and thioketenes[500].

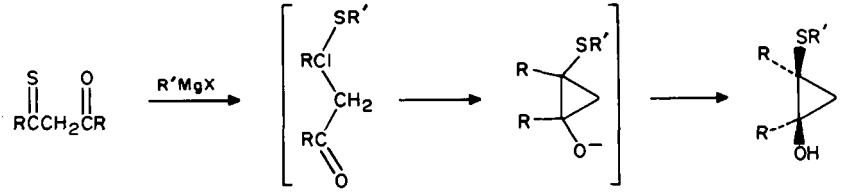
A host of mechanistic investigations have been carried out to find a rationale for thiophilic additions. In a simple picture, this mode of addition may be explained by the inverse polarization of the C=S bond (cf. Sections I and II.C)[501] or by the HSAB principle[502,503]. Support for direct nucleophilic attack by R^3M can be seen in the

retention of configuration, when *Z*- or *E*-2-propenyl Grignard reagents are used[504]. On the other hand, a number of experimental results suggest a radical mechanism[504,505]. Thus, ESR spectroscopy confirmed the presence of a species with unpaired electrons[502,506,507] which, however, does not necessarily imply that the radical is formed along the reaction coordinate to the isolated product. Similarly, the fact that C,S dialkyl products, $R^1R^2C(SR^3)R^3$, have been observed[503] does confirm a nonionic route to this species, but does not clarify the mechanism behind the reaction in equation 158. In any case, taking together the available evidence, the mechanism of equation 159 involving an initial single electron transfer (SET) step and subsequent radical combination gives a satisfactory explanation of the experimental facts, including the solvent effect[505,508,509].

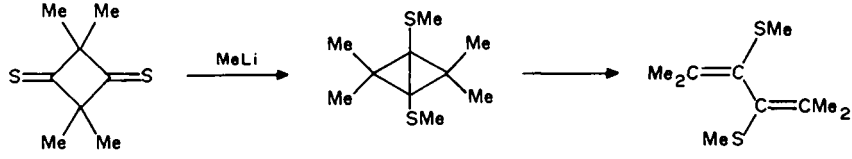
$$R_2C{=}S + R'M \xrightarrow{SET} R_2C^- \text{—} S^{\cdot}M^+R'^{\cdot} \longrightarrow \underset{M^+}{R_2C^-}SR' \longrightarrow \text{products} \qquad (159)$$

For synthetic purposes, use of THF gives the best yields[495,501,508] whereas Et_2O favors carbophilic attack[509].

In some cases, the reactive intermediate of thiophilic attack gives rise to intramolecular cyclization reactions. Illustrative examples are the formation of *cis*-2-(alkylthio)-cyclopropanols from *β*-thioxoketones (equation 160)[510], of bicyclo[1.1.0]butanes and subsequently a diene from dithione **21b** (equation 161)[511,512], and annulation of a thiane ring in thioaldehyde **2b** (equation 162)[476].

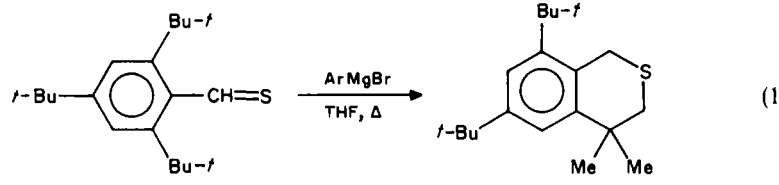


(160)



(21b)

(161)



(2b)

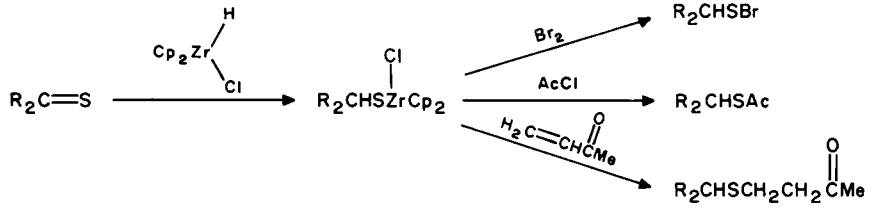
20%

Ar = 2,4,6-*t*-$Bu_3C_6H_2$

(162)

D. Reduction

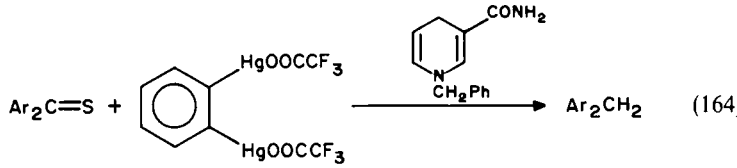
High yields of thiols are obtained from *t*-BuCHS (**4**)[101] or $(Me_3Si)_3CCHS$[497] with $NaBH_4$; for a sterically hindered thione, $LiAlH_4$ has proven to be an efficient reducing agent[513]. Hydride transfer from an organolithium reagent RLi with α-CH_2 offers another convenient approach[101,367,451]. Under the alkaline conditions of these reagents, the primary reaction product is a thiolate salt and this may be used *in situ* as a powerful nucleophile. This possibility has been exploited in the reduction of thiols by a zirconium hydride reagent to give a zirconium thiolate and, subsequently, various sulfur derivatives by addition of electrophiles (equation 163)[514]. A notable feature is the clean 1,4-addition of the thiolate to enones, whereas the reagent gives regiospecific 1,2 attack on enethiones.



(163)

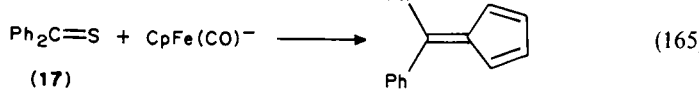
By electrochemical reduction of diarylthiones or *t*-Bu(Ph)C=S, radical anions are generated which react with alkylating agents to yield sulfides along with tertiary thiols resulting from C-alkylation[515].

A benzene bis-mercury derivative reduces thiobenzophenone or adamantanethione to the corresponding thiols; however, electron-rich diarylthiones (Ar = 4-An, 4-$Me_2NC_6H_4$) furnish a complex containing Hg—S bonds and, by treatment with a 1,4-dihydropyridine, eventually diarylmethanes (equation 164)[516].



(164)

The reduction of the thiocarbonyl group in diarylthiones to a methylene moiety is also achieved by $HFe(CO)_4^-$ as generated *in situ* from $Fe(CO)_5$ and base (60–81%)[517] or by P_2I_4 (52–85%)[518]. When used at higher concentrations, the phosphorus reagent gives some reductive coupling to $Ar_2C{=}CAr_2$. These compounds are isolated as main products by the action of alumina-supported $NaBHEt_3/FeCl_2$ on diarylthiones (68–76%); this approach is of interest as a model reaction for desulfurization of crude oil[519]. Similarly, with a cyclopentadienyl(carbonyl)ferrate, formation of a fulvene from thiobenzophenone was achieved (equation 165)[519].



(165)

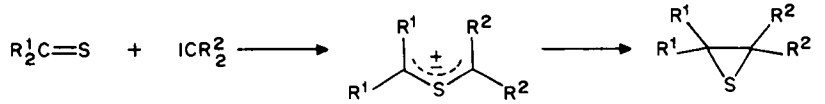
Attempted reductive coupling of diarylthiones with Bu_3P[520] or $P(OR)_3$[487] gives some $Ar_2C{=}CAr_2$ along with other reduction products.

E. Cycloaddition Reactions

Owing to the high-energy CS π bond, thiocarbonyl compounds are excellent reaction partners in all types of cycloadditions. 1,3-Dipolar cycloadditions (Section IV.E.3) and Diels–Alder reactions (Section IV.E.4) are usually particularly efficient and are therefore often employed to scavenge unstable thiocarbonyl derivatives. On the other hand, after photoexcitation, thiocarbonyl compounds display a different reactivity in [2 + 2] cycloadditions and this chemistry will be covered separately in Section IV.G.

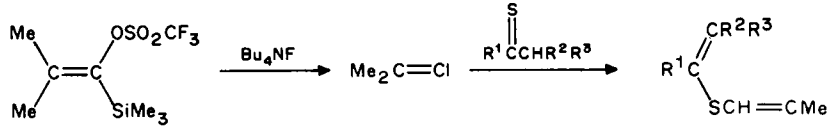
1. [2 + 1] Cycloaddition

Carbenes add to the CS π bond in diarylthiones or sterically hindered aliphatic thiones to give thiiranes **44** by way of a [2 + 1] cycloaddition; depending on the substituents, there may be an equilibrium between the cyclic and the open-chain thiocarbonyl ylide form (equation 166)[521]. The six-electron reagent is generated from a diazo compound (R^2 = Ar)[521,522], by dehalogenation of a chloride [CR^2_2 = CHS(O)Me][523], from an organomercury compound (R^2 = Cl)[524] or from $Me_2S(O)=CH_2$ (R^2 = H)[463]. In accordance with the expected relative reactivity of the two orthogonal π bonds, thioketenes add carbenes across the C=S group[6,525,526].



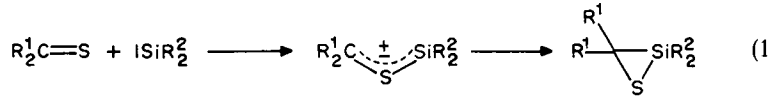
(166)

Contrary to simple carbenes, a vinylidene carbene gives insertion into the SH bond of the enethiol form in the reaction with thiones containing α-hydrogen (equation 167)[527]; yields of divinylsulfides are 26–40%.



R^1 = *i*-Pr, *t*-Bu
R^2, R^3 = H, Me (167)

Besides use of carbenes, [2 + 1] cycloadditions have also been achieved by the reactions of sterically hindered thiones with a silylene SiR_2. By the matrix-isolation technique, a sila thiocarbonyl ylide was detected[528], whereas the actual reaction yields silathiiranes (equation 168)[529].

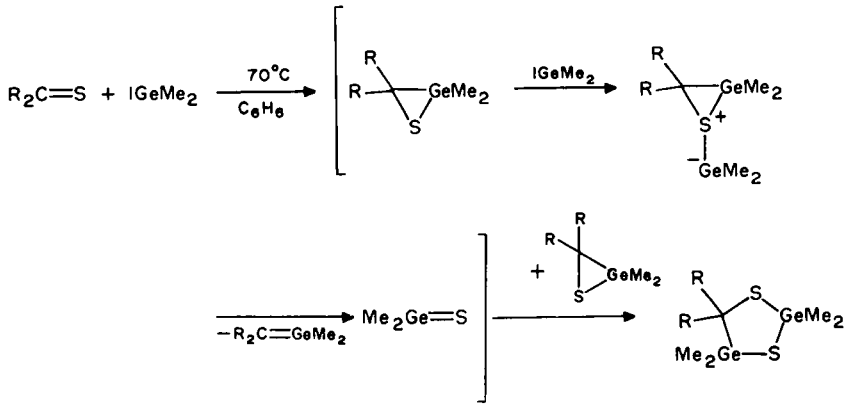


(168)

R^2 = 2,4,6-$Me_3C_6H_2$

The related reaction of thiocarbonyl compounds with a germylene Me_2Ge (generated by retro-Diels–Alder reaction of a 7-germabenzonorbornadiene) takes a more com-

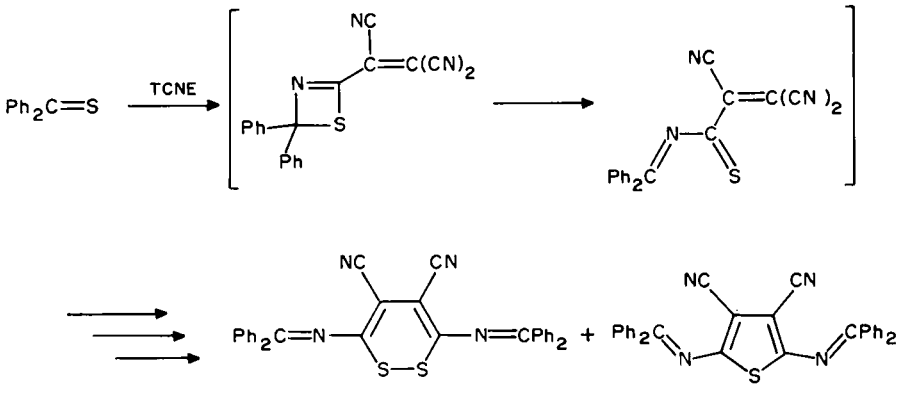
plicated course. Germathiiranes may well be the primary products of a [2 + 1] cycloaddition, but then the intermediate as formed from adamantanethione or 1,1,3,3-tetramethyl-2-indanethione eventually leads to a digermadithiolane (equation 169; 11–38%)[530], whereas t-$Bu_2C{=}C{=}S$ affords a digermathietane[531].



(169)

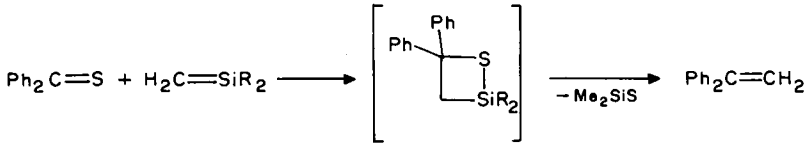
2. Thermal [2 + 2] cycloaddition

A [2 + 2] cycloaddition between a noncumulated thione and another noncumulated π bond system appears to require some special activation of one reaction partner. Thus, the electron-poor thione hexafluorothioacetone, $(F_3C)_2C{=}S$, gives thietanes with enol ethers[338], dimethyl maleate or cyclohexene[339], whereas styrene affords a complicated 2:1 adduct[339]. On the other hand, thietane formation by the reaction of thiocarbonyl derivatives with electron-poor olefins has been reported. Examples are the [2 + 2] cycloaddition between TCNE and thioformaldehyde, and between fumarate of fumarodinitrile with thioacetone[350]. However, thiobenzophenone adds across one C≡N bond of TCNE to give eventually a 1,2-dithiine (21%) and a thiophene (45%; equation 170)[532].



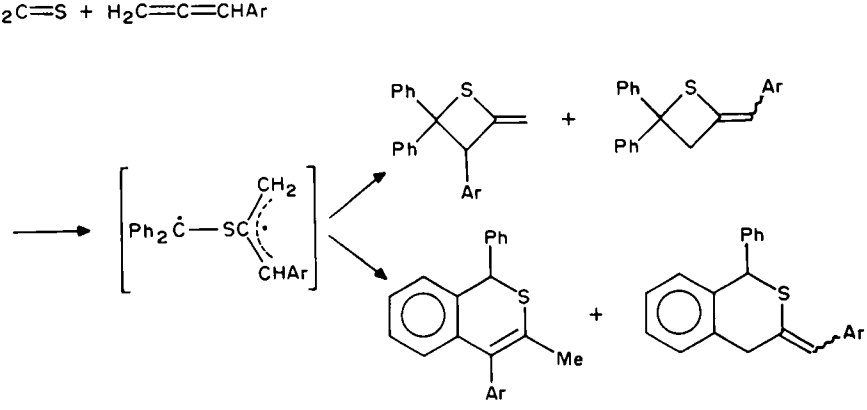
(170)

A silaethene gives an olefination reaction with thiobenzophenone via a sequence of [2 + 2] cycloaddition and cycloreversion (equation 171)[533].



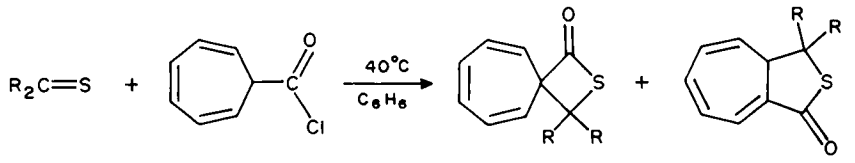
(171)

Various papers deal with the reaction of thiones with cumulated π electron systems. Allenes may give an ene reaction rather than a cycloaddition (cf. Section IV.F)[534], but arylallenes yield regioisomeric thietanes; at the same time, [4 + 2] cycloadducts involving one of the benzene rings of **17** are formed and this points, together with a low Hammett ρ value of -0.36, toward a 1,4-biradical intermediate (equation 172)[535].

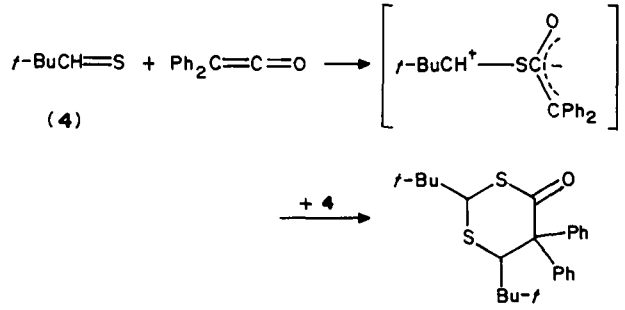


(172)

1:1 Cycloadducts between diarylthiones such as **17** and diphenylketene were first isolated by Staudinger[536], but the correct regiochemistry of β-thiolactones was established only recently[322,537]. The same type of four-membered ring was also isolated from **17** and vinylketenes; surprisingly, the reaction proceeded perispecific without formation of a [4 + 2] cycloadduct involving the diene moiety of the heterocumulene[498,538]. However, in the reaction of adamantanethione with a cycloheptatriene-derived ketene, the formation of a thermolabile [2 + 2] cycloadduct (69%) is accompanied by some [8 + 2] cycloadduct (equation 173)[539]. When thiopivalaldehyde (**4**) is added to diphenylketene, a zwitterionic intermediate is apparently formed and adds a second molecule of the thial (equation 174)[101].

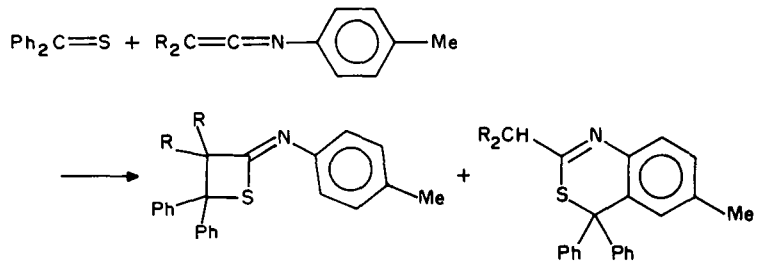


(173)



(174)

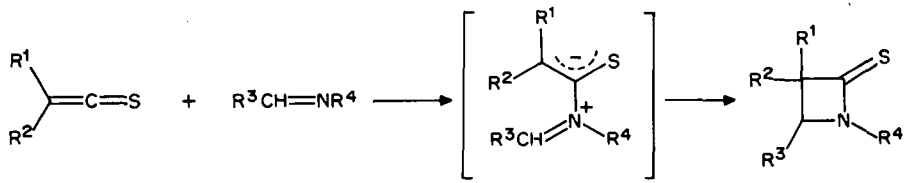
The usual outcome of the reaction between thiones and ketenimines is formation of 2-iminothietanes as [2 + 2] cycloadducts. However, N-aryl ketenimines with unsubstituted 2,6-positions tend to give some [2 + 4] cycloadduct (equation 175)[498,538,540-542].



(175)

Contrary to simple thiocarbonyl derivatives (*vide supra*), thioketenes form [2 + 2] cycloadducts with a large variety of π electron systems[6]. Bis(trifluoromethyl)thioketene, $(F_3C)_2C{=}C{=}S$, is particularly reactive with the cycloaddition occurring across the C=S bond exclusively[102,543,544]. Other thioketenes show this site selectivity in the dimerization reaction to give 2,4-bis(alkylidene)-1, 3-dithietanes (equation 176)[6,178] as well as in the reaction with other thiones[545]. However, there is ample evidence for the formation of β-thiolactams, i.e. of cycloadducts across the C=C bond of the hetero-cumulene, in the reaction of dialkylthioketenes[545,546], allylthioketenes[411], and silyl-thioketenes[427] with C=N systems (equation 177). In contrast, all types of thioketenes appear to react across their C=S moiety in the cycloaddition with the strained C=N bond of 3-amino-2H-azirines[342,547].

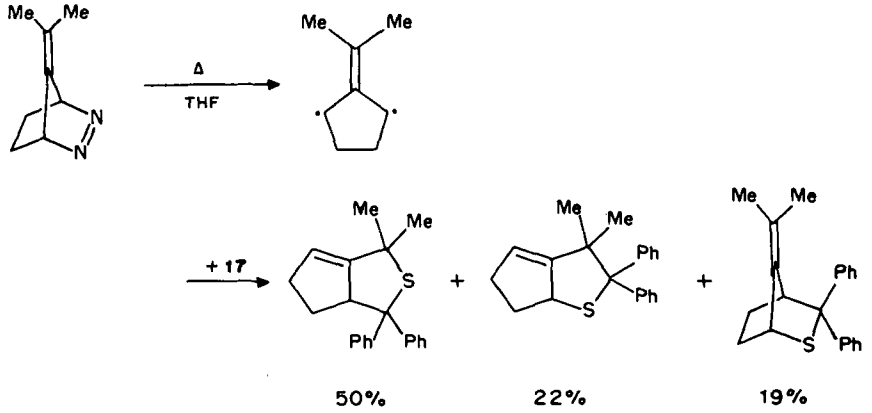
(176)



(177)

3. *[2 + 3] Cycloaddition*

Little and coworkers developed a bicyclic azo compound which, by loss of nitrogen, generates a biradical and thus serves as a substitute for the unknown 1,3-dipole with an all-carbon framework; on reaction with thiobenzophenone (**17**), the species gives rise to regioisomeric [2 + 3] cycloadducts (equation 178)[548].



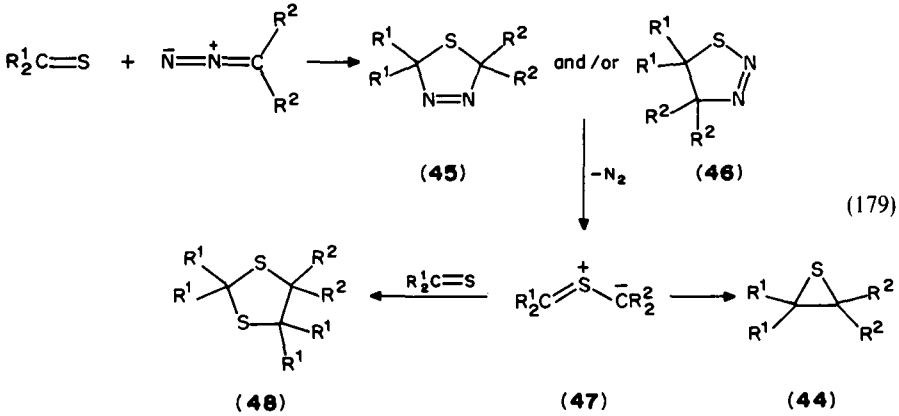
(178)

Via reaction with conventional 1,3-dipoles, thioaldehydes[18,101], thioketenes[6] and particularly thioketones have been widely used in heterocyclic synthesis. Usually, 1,3-dipoles with octet stabilization are employed. Among 1,3-dipoles of the linear allenyl-propargyl type, diazo compounds are the most popular example. This reaction was studied intensively by Schönberg[549], who isolated either thiiranes **44** or 1,3-dithiolanes **48**, but never mixtures of the two. Later work provided additional examples for thiirane formation from *t*-Bu-substituted thiones, *t*-BuC(S)R (R = Me, Ph)[550], enethiolizable thiones (along with S-alkylation by the diazo compound, cf. Section IV.B)[551], the S,S-dioxide of thietanethione **36**[552], enethiones[553], oxothione **21a**[554], thioquinone **12**[28] and silylthiones, $PhC(S)SiR_3$ (48–100%)[208]. At the same time, additional evidence for dithiolanes **48** was obtained[553]. Tropothione (**14**) provides a dithiepine derivative in the reaction with diazomethane[555,559].

Careful investigations, using in particular sterically hindered thiones, allowed isolation or at least detection of the primary cycloadducts from thiones and diazo compounds, which proved to be 1,3,4-thiadiazolines **45** starting from thionated **27**[556], or dialkylthioketenes[429], while dithione **21b** even gave a bis-adduct[202]. A chemical proof of the symmetrical structure **45** rather than **46** comes from the fact that the reaction of *t*-Bu_2C=S with diphenyldiazomethane (R^2 = Ph) affords the same adduct as formed from **17** (R^1 = Ph) and di-*t*-butyldiazomethane (R^2 = *t*-Bu)[358]. Also a vinyl diazo compound, fluorenylidenediazomethane, was used and gave, in the reaction with thiobenzophenone (**17**), 25% of a 2-*fluorenylidene*-1,3,4-thiadiazoline[557]. In another case, the adduct was too labile to allow unambiguous structure assignment[554]. On the other hand, some thiones give mixtures of thiadiazoline **45** and its regioisomer **46** with the ratio being solvent dependent[558]. This was observed for adamantanethione using diazomethane[558,559] or other diazo compounds[560], for thiopivalaldehyde (**4**)[18] and bis(trifluoromethyl)-thioketene[102].

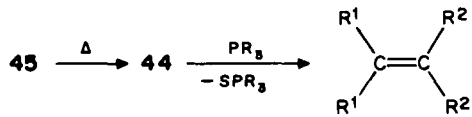
A consistent mechanistic picture for the reaction of thiocarbonyl compounds with diazo derivatives was developed by the recent intensive work of Huisgen and collaborators

(equation 179)[559,561-565]. By working below −45 °C, the Munich group was able to isolate a primary cycloadduct of type **45** even from thiobenzophenone and diazomethane, and study its subsequent reactions[561,562]. Obviously, loss of nitrogen leads to a thiocarbonyl ylide **47** as the crucial intermediate. From here, cyclization provides thiiranes **44**, but trapping of **47** by a second equivalent of the thione is possible and furnishes dithiolanes **48**. This [3 + 2] cycloaddition between ylide **47** and thiones is not necessarily regiospecific but, using **17** and diazoacetate, provides mixtures of **48** and its regioisomer[566]. On the other hand, thiocarbonyl ylides **47** may be trapped by thiones other than the one used in the primary cycloaddition step, providing dithiolanes **48** with a more complex substitution pattern[565], or by acetylenedicarboxylate giving a dihydrothiophene, albeit in low yield[567].



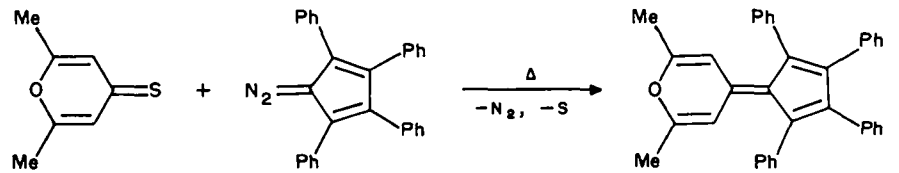
(179)

Besides the mechanistic complexity, the reaction between thiones and diazo compounds holds interest from a synthetic point of view. The main use is twofold extrusion of nitrogen and sulfur from thiadiazolines **45** (equation 180). When thiones with bulky substituents and hindered diazo compounds are employed, this reaction sequence offers a route to very hindered olefins. Following some earlier work[550,554,568], the approach was first exploited by Barton[358] and later by some other groups in the—so far unsuccessful—quest for tetra-*t*-butylethylene and related olefins[208,355,552,556,569-571].



(180)

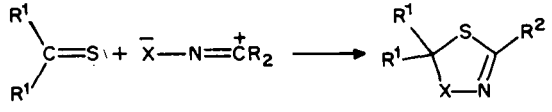
Another aspect is use of the twofold extrusion from thiadiazolines **45** to obtain highly conjugated systems[572] as in equation 181, where a **45**-type cycloadduct is formed *in situ*[573].



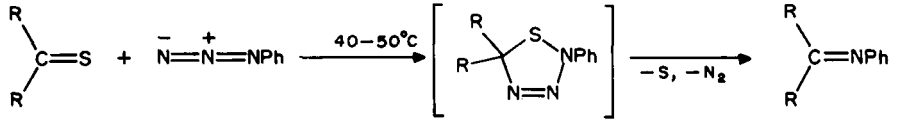
(181)

Finally, the extrusion sequence from **45** is used in the generation of trimethylenemethanes[571].

Other 1,3-dipoles of the allenyl-propargyl type that give a smooth reaction with thiocarbonyl compounds are nitrile oxides, imines and sulfides (equation 182; X = O, NR^3, S) as well as some azides (equation 183). In particular, thiobenzophenone and other diarylthioketones have been reacted with nitrile oxides (X = O)[374,560,574,575] or N-phenylnitrile imine ($R^2 = R^3 = Ph$)[560,575], but also thioaldehydes[101,373], aliphatic thiones[560,575] and thioketenes[177,345] have been employed in the cycloaddition with nitrile oxides (X = O). The adducts from adamantanethione and nitrile oxides with R^2 = Ar, 1-adamantyl, or PhC=O are thermolabile and tend to decompose in a [3 + 2] cycloreversion, giving adamantanone and isothiocyanates R^2NCS (71–93%)[560,575]. The reaction with nitrile sulfides (X = S) has been studied for thiobenzophenone and PhC(S)Bu-*t*[576] (yield 17–65%). To achieve a cycloaddition between thiones with bulky alkyl substituents and phenyl azide, some heating is required leading to *in situ* decomposition of the primary adduct and eventually providing Schiff bases (equation 183).

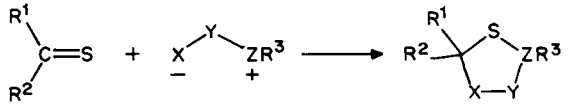


(182)



(183)

Relatively few examples have been studied for the reaction of thiocarbonyl compounds with 1,3-dipoles of the bent allyl anion type (equation 184). A case of this cycloaddition mode was mentioned above (equation 179; step **47** → **48**). Similarly, a thiocarbonyl sulfide (X = Y = S, $ZR^3 = CPh_2$) is generated by heating trithiolane **42** ($R^1 = R^2$ = Ph) to 80 °C and can be trapped by alkynes or adamantanethione[577]. A related example is the reaction of a thiocarbonyl imide (X = NTos, Y = S, ZR = fluorenylidene) with diarylthiones to give 1,4,2-dithiazolidines (13–88%)[578].

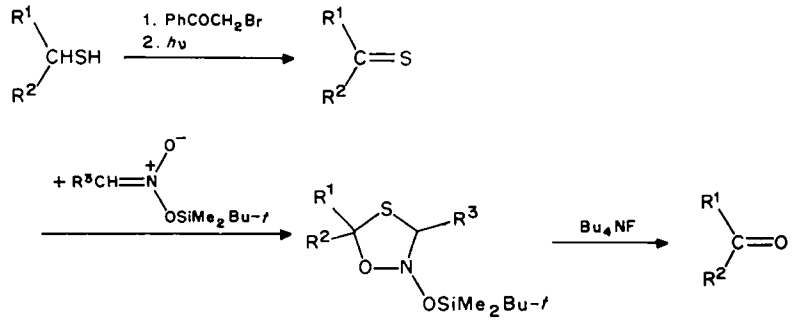


(184)

An azomethine ylide (equation 184; X = $ZR^3 = CH_2$, Y = NMe) provides thiazolidines in the reaction with adamantanethione (16%) or thiobenzophenone (72%)[579]. Azomethine *imines* (equation 184; X = NR^4, Y = NR^5, $ZR^3 = CR_2^5$) were used to synthesize heterocycles by reaction with thiopivalaldehyde[580] or allyl(*t*-butyl)thioketene (30%)[581].

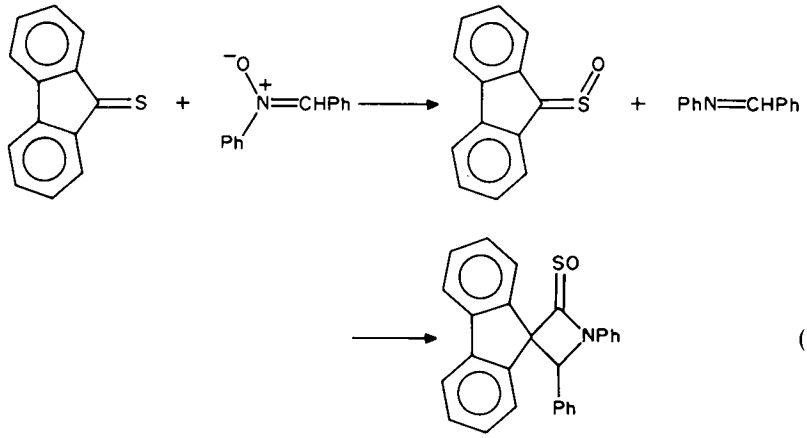
Several papers deal with the cycloaddition between thiocarbonyl compounds and nitrones (equation 184; X = O, Y = NR^4, $ZR^3 = CR_2^4$). In most cases, the expected oxathiazolidines are isolated[101,275,575,580,582]. In combination with the thiocarbonyl synthesis of equation 69 and with desilylation of the cycloadduct, use of a nitronate ester provides a method to oxidize a thiol to a carbonyl compound (equation 185)[275].

In striking contrast to the chemistry of equations 184 and 185, nitrones may behave as oxidizing agents in their reaction with thiocarbonyl compounds. This became apparent in



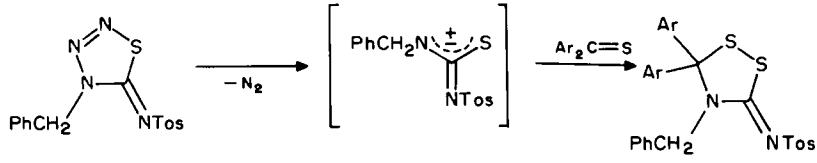
(185)

the attempted [3 + 2] cycloaddition of fluorenethione (**18**) with a particular nitrone (X = O, Y = NPh, ZR^3 = PhCH) giving a β-thiolactam S-oxide; the mechanistic rationale is oxidation of the thione to the corresponding sulfine and subsequent [2 + 2] cycloaddition of this species with the deoxygenated nitrone (equation 186)[583]. Even more noteworthy is the oxidation of thioketenes to α-thiolactones by the action of nitrones (equation 139)[323,324].



(186)

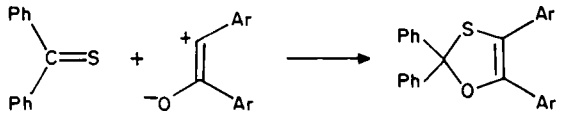
L'abbé generated an interesting 1,3-dipolar species by thermolysis of a thiatriazoline and was able to trap it with a diarylthione (equation 187)[584].



(187)

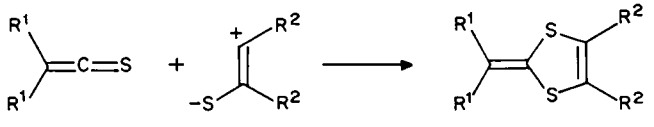
Only three examples appear in the literature for [2 + 3] cycloaddition of thiocarbonyl compounds with 1,3-dipoles lacking octet stabilization. Thus, copper-induced decomposition of α-diazoketones generates a four-electron species which adds to **17** in a 1,3-dipolar

fashion (equation 188) along with some [2 + 2] cycloadduct (cf. equation 173)[585]. Similarly, intermediate **38** may add to thioketenes providing dithiafulvenes (equation 189), and a vinylnitrene as generated by thermolysis of an 2*H*-azirine forms regioisomeric [3 + 2] cycloadducts with diarylthiones in modest yields (equation 190)[586].



(188)

(17)



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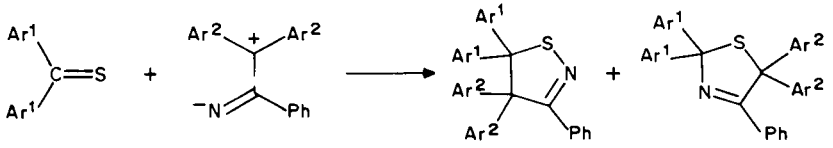
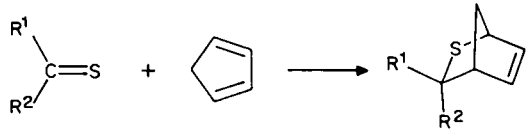


(190)

Hydrazones and oximes may exhibit 1,3-dipolar reactivity through a tautomeric form[587] and, in fact, [3 + 2] cycloadducts have been isolated by their reaction with thioketenes[6,102]. Thioketenes may also undergo 1,3-anionic cycloadditions with the 2-azaallyl[588] or the azide anion[589].

4. *[2 + 4] Cycloaddition*

Diels–Alder chemistry is one of the standard reactions to scavenge or identify unstable thiocarbonyl compounds. Cyclopentadiene is the diene that is used most frequently; applications include trapping of thioformaldehyde[304,334], higher alkanethials (58–94%)[241,304], arylthioaldehydes (80–97%)[241,304], thioaldehydes with electron-withdrawing substituents (51–100%)[284,291,302] and thioketenes[6]. In the thioaldehyde reactions, the *endo* isomer (equation 191; $R^1 = H$) is preferred over the *exo* form ($R^2 = H$) by a ratio of 3 to > 50:1[241,276], e.g. 3:1 for $R^2 = R^3C(O)$, 6.6:1 for $R^2 = AcOCH_2$, 16:1 for $R^2 = i$-Pr, > 50:1 for $R^2 = t$-Bu[276]. With the acetonide of thioglyceraldehyde, useful thioformyl face selectivity is observed (ratio of diastereomers 82:18)[276].



(191)

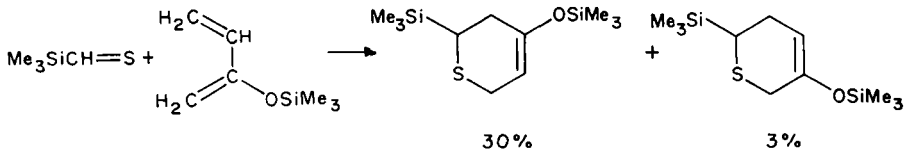
Owing to its convenience, the [2 + 4] cycloaddition of thiocarbonyl compounds with cyclopentadiene has also been employed to characterize fairly stable C=S derivatives

such as thioacetophenone, PhC(S)Me[271], adamantanethione[590] or monothiobenzil (15%)[591]. Silylthioketones give the cycloadduct with the silyl group being in the *endo* position ($R^2 = SiR^3_3$ with R^3 = Me, Ph)[592].

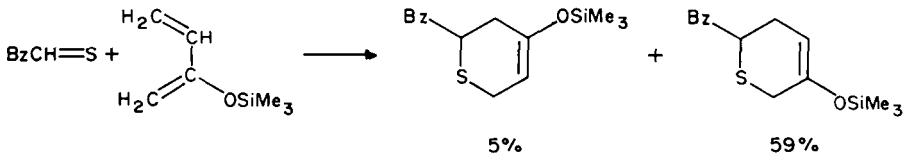
Another frequently used diene is anthracene which reacts smoothly with thioaldehydes[284,289,350], thioacetone[350] or hexaflurothioacetone (82%)[338,339] via carbons $C_{(9)}$, $C_{(10)}$. 9, 10-Dimethylanthracene is considerably more efficient[350].

A number of other symmetrical (cyclo)alkadienes are sufficiently reactive to give [4 + 2] cycloadducts with electron-poor thioaldehydes (48–88%)[302,320,380], adamantanethione[575], fluorenethione[336b] and bis(trifluoromethyl)thioketene[102,593] as well as bis(trimethylsilyl)thioketone[290] and thioquinone **12** (46 and 89%, respectively, with 2, 3-dimethylbutadiene)[28]. The silylthioketone, PhC(S)SiMe(Ph)α-Naph, with an optically active silyl residue gives rise to 50% diastereomeric excess in the formation of the Diels–Alder adduct with butadiene[209].

A prerequisite for synthetic applications of the [2 + 4] cycloaddition between thiocarbonyl compounds and asymmetrical dienes is the knowledge and predictability of the regioselectivity. Based on the experimental evidence[101,274,447] and MO calculations[447,594] the rules have emerged that donor-substituted thioaldehydes RCH=S (R = H, Alk, Ph, Me_3Si) are reactive toward electron-rich dienes and [2 + 4] cycloadducts with a regiochemistry corresponding to advanced CC bonding in the transition state are observed (major formation of the '*meta*' product; equation 192), whereas acceptor-substituted thioaldehydes (R = e.g. ROOC, NC, Bz) react in the opposite regiochemical sense with CS bonding being advanced (major formation of the '*para*' product; equation 193).



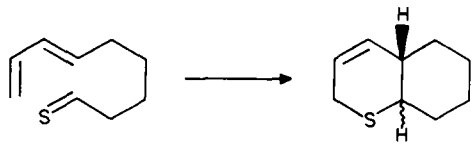
(192)



(193)

Similar rules as for thioaldehydes seem to hold for thiones, since thiobenzophenone reacts with the electron-rich isoprene preferentially to '*meta*' adducts (ratio 1.5:1), but with chloroprene to '*para*' adducts (ratio 1.8:1)[595]. In contrast, the corresponding ratios for thioacetone are 1:1.2 and 1:2, respectively[595].

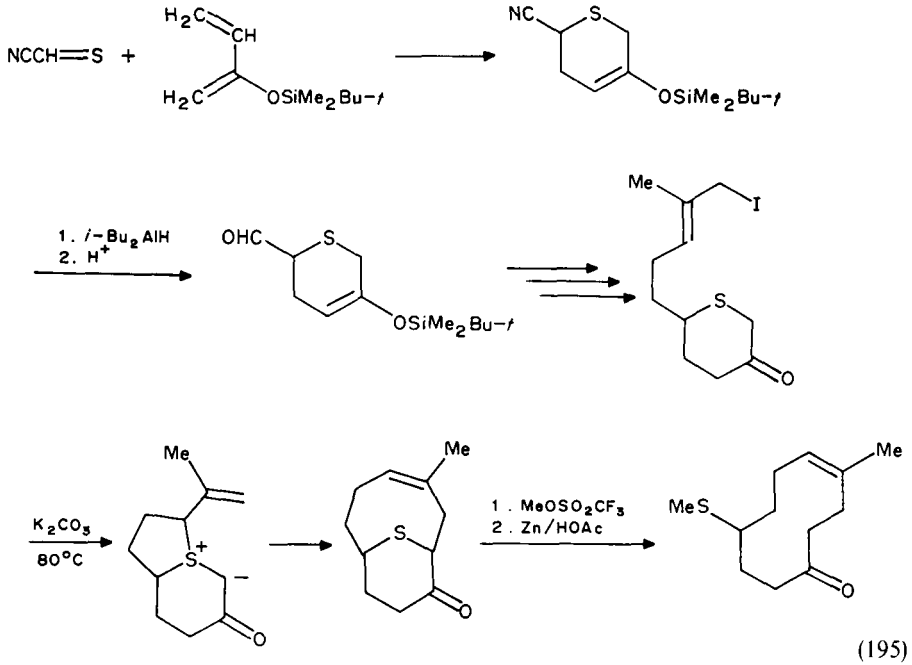
Also in accord with the selectivity of equation 192, thiopivalaldehyde[101] and MeOCH=CH—$C(OSiMe)_3CH_2$ (Danishefsky's diene) yield a 'bis-*meta*' adduct and, after work-up, 25% of a 2-*t*-butyl-2, 3-dihydrothiane-4-one[101]; the same selectivity is found for adamantanethione, whereas thiobenzophenone shows a preference for the '*ortho/para*' product[590]. However, in an intramolecular Diels–Alder process, the conformational constraints give rise to exclusive formation of the '*ortho*' adduct in a *cis/trans* ratio of 2:1 (equation 194)[596].



(194)

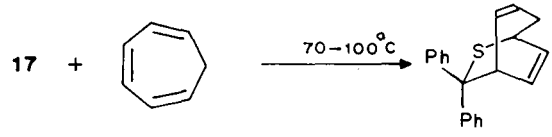
Thiomesoxalate, $(ROOC)_2C{=}S$, and 1-acetoxybutadiene give an '*ortho*' adduct which, by further elaboration, is of interest for the synthesis of thiathromboxanes[212].

Adducts of the type obtained in equation 192 are important intermediates in the total synthesis of natural products[597,598] such as carbocyclic cytochalasans[275,599] and zygosporin E[600]. After the Diels–Alder step, formation of an S-ylide and subsequent 2,3-sigmatropic rearrangement are key reactions. The underlying principle is illustrated by equation 195[597].



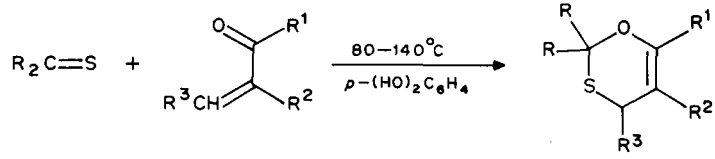
(195)

In addition to conventional dienes, some more unusual dienes have been employed in [4 + 2] cycloadditions to thiones. In the reaction of 1,3,5-cycloheptatriene with thiobenzophenone (**17**), two of the three π bonds react in a regiospecific way (yield 40%; equation 196)[601].



(196)

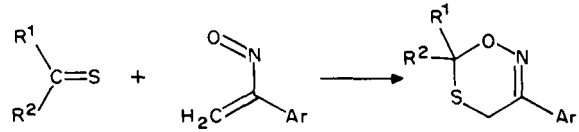
Enones give rise to 1,3-oxathiane derivatives in their reaction with thiones. Using adamantanethione, yields of 23–94% are obtained (equation 197)[575,602].



(197)

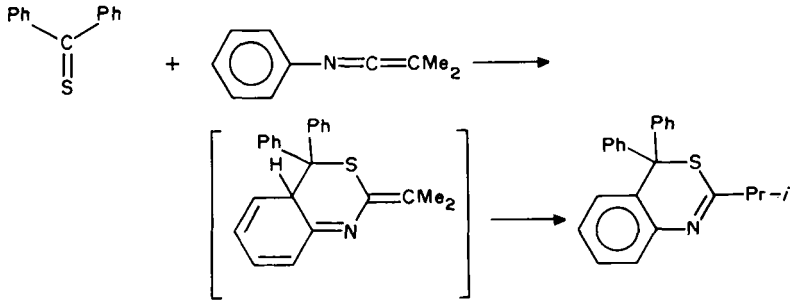
o-Quinone methides (yields 40–90%) show the same regioselectivity[603].

The reaction of silylthioketones or fluorenethione (**18**) with nitrosoalkenes furnishes 1,3,6-oxathiazine derivatives in 60–94% yield (equation 198)[84,604].



(198)

In a few instances, thiones add to dienes with one π bond being incorporated into a benzene ring. This behavior is found in the reaction of hexafluorothioacetone with styrene giving eventually a 2:1 adduct[339], in some photocycloadditions (see Section IV.G, equation 219) and in cycloadditions between thiones and N-arylketenimines with unsubstituted 2,6-positions on the aromatic ring; [2 + 2] cycloadditions are competing processes (cf. Section IV.E.2)[84,498,538,540,541]. Equation 199 shows an illustrative example (yield 80%)[541]. On the other hand, *N*-(mesityl)vinylketenimines are excellent dienes in the reaction with thiones[498,538,540].



(199)

An attempt to add diarylthioketones to dehydrobenzene as generated from benzenediazonium-*o*-carboxylate gave trapping of the 1,4-dipolar intermediate, which is formed after loss of nitrogen[605].

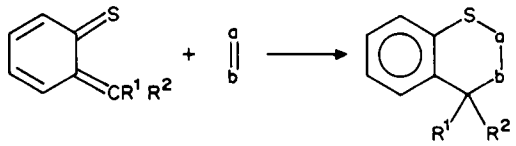
Contrary to the chemistry of equations 191–199, where the thiocarbonyl compound serves as dienophile, α,β-unsaturated thiocarbonyl derivatives may act as diene component in Diels–Alder reactions (equation 200).

(200)

Many examples are known for the reaction of equation 200 with X = carbon. In the dimerization of enethials or enethiones, the thiocarbonyl compound serves both as diene

and as dienophile (cf. equation 20)[302,594], but mixed Diels–Alder reactions are possible between thioacrolein and HC≡CCH=S[269], as well as between enethiones and electron-poor olefins[220,606] or (hetero)allenes[607]. β-Amino-substituted enethiones (vinylogous thioamides) are particularly reactive and give a smooth [4 + 2] cycloaddition with various double-[608–610] and triple-bond systems[608].

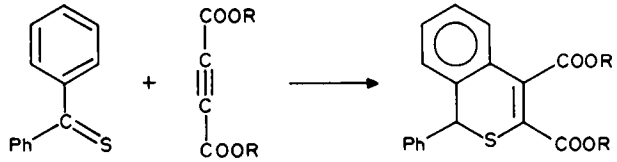
Another modification that favors Diels–Alder reactions according to equation 200 is use of *o*-thioquinone methides (equation 201)[57,58,325,420,421,423,424,611,612]. Here, the fact that the [4 + 2] cycloaddition generates an aromatic ring supplies a special driving force.



(201)

Among the dienophiles that react according to equation 201 are cycloalkenes[424], electron-deficient alkenes[421], enamines[612], N-phenylmaleinimide[325,423], alkynes[421], thioketones[420], Schiff bases[57], azo compounds[57], mesoxalate[57] and diphenylketene[421]. Use of maleate or *cis*-1,2-dimethoxyethylene gave stereoisomeric cycloadducts, indicating that the cycloaddition is a two-step process[58].

Interestingly, in arylthiones the C=S and one π bond of the aromatic ring may also react as diene[577,613,614]. Equation 202 gives an illustrative example (yield 68%)[577,613].

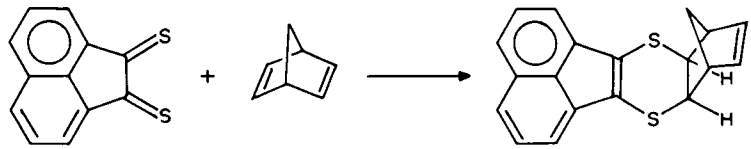


(17)

(202)

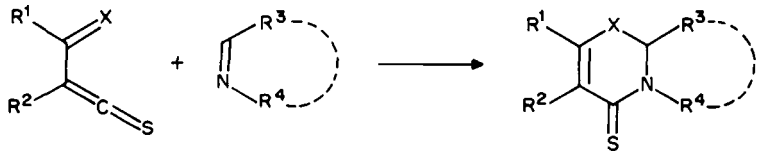
Similarly, together with a thioxo group, one π bond of a heteroaromatic ring may form part of a diene system[615,616].

By analogy with equation 202 and as an example of equation 200 (X = O), an *o*-thioquinone readily adds a vinyl ether to give a Diels–Alder adduct[59]. Finally, α-dithiones may react as dienes and do so with strained cycloalkenes[329,383], with 1,2-dimethoxyethylene[65] or with acetylene dicarboxylate[277], e.g. equation 203 (yield 60%)[329].



(203)

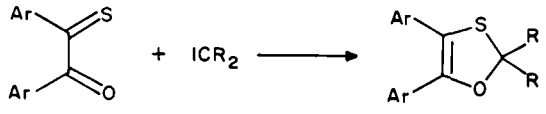
Also acyl[376] (X = O) and thioacyl thioketenes (X = S)[6,306] may serve as 4π electron components in Diels–Alder cycloadditions; Schiff bases are convenient reaction partners (equation 204).



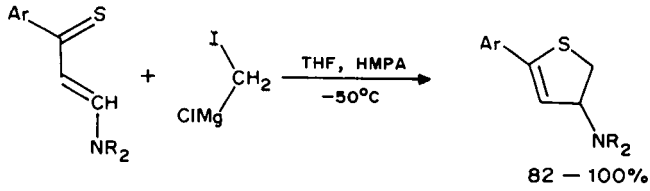
(204)

F. Other Pericyclic Reactions

Some less common types of cycloadditions are worth mentioning. Monothiobenzils give a [4 + 1] cycloaddition with carbenes as generated from diazo compounds (equation 205)[293,295], and the same type of cycloaddition occurs between vinylogous thioamides and a Simmons–Smith type reagent (equation 206)[617].

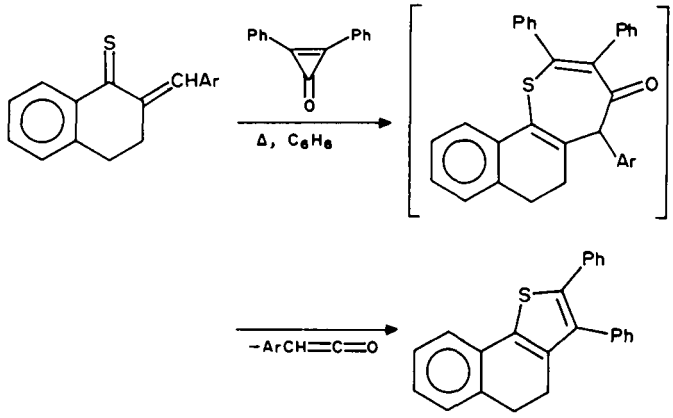


(205)



(206)

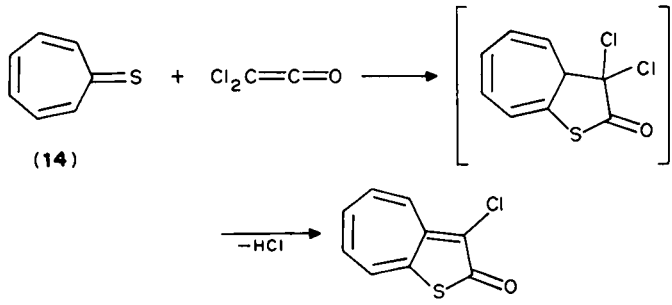
A [4 + 3] cycloaddition was observed between an enethione and diphenylcyclopropenone; the intermediate cleaves with loss of a ketene to give an annulated thiophene (yield 57%; equation 207)[618].



(207)

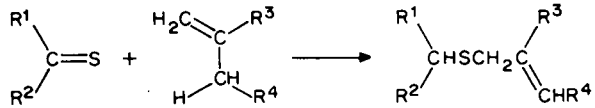
For an *o*-thioquinone methide, dimerization in a [4 + 4] cycloaddition to give an eight-membered ring was reported[57].

Tropothione (**14**) undergoes [8 + 2] cycloadditions with C=C or C≡C systems such as maleic anhydride[619], acetylene dicarboxylate[619] or ketenes[620,621] (cf. equation 173), such as equation 208[621].



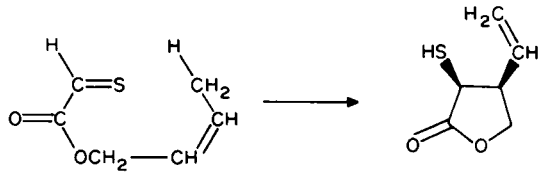
(208)

Ene reactions are frequently encountered on adding thioaldehydes[289,320,596,622] [except for thiopivalaldehyde (4)][596], thiobenzil[623], diarylthiones[534] or bis(trifluoromethyl)thioketene[624] to alkenes, in particular β-pinene[289,320,596] or tetramethylallene[534] (equation 209).



(209)

Also, intramolecular ene reactions have been reported; they give CC bond formation, i.e. the opposite regiochemistry from the intermolecular process[320,596], (e.g. equation 210)[320].



(210)

Though tris(trimethylsilyl)thioacetaldehyde is thermally more stable than the corresponding aldehyde, it isomerizes on heating in a 1,3 silyl shift to a vinyl sulfide (equation 211)[497].

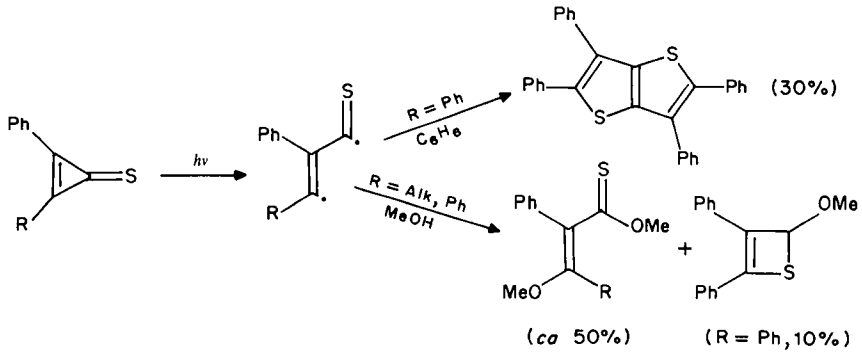
$$(Me_3Si)_3CCH{=}S \xrightarrow{80\,^{\circ}C} (Me_3Si)_2C{=}CHSSiMe_3 \qquad (211)$$

G. Photochemistry

While the study of carbonyl photochemistry has a long tradition, thiocarbonyl compounds have only recently emerged as chromophores of particular interest[625,626]. Basically, irradiation of thiocarbonyl derivatives induces the same types of reactions as with their carbonyl congeners, i.e. α-cleavage, hydrogen abstraction and cycloadditions[627], but a number of special features are noteworthy.

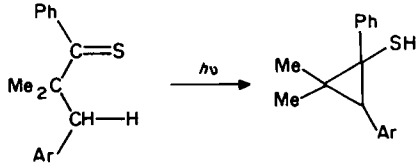
Contrary to carbonyl photochemistry, α-cleavage (Norrish type I) is quite exceptional. It has only been reported to occur on n,π^* excitation of cyclopropenethiones giving, depending on the substituents and the solvent, various products (equation 212)[96].

Intramolecular hydrogen transfer to a photoexcited thiocarbonyl group may occur from the β, γ or δ position. The first-mentioned possibility is found with β-substituted

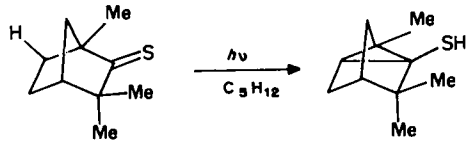


(212)

aralkyl thiones yielding cyclopropanethiols (equation 213)[94]. A careful study revealed that the three-membered ring is either formed via $^1(n, \pi^*)$ excitation and intersystem crossing to the $^3(n, \pi^*)$ state or directly from the S_2 (π, π^*) state[94]. Similarly, thiofenchone and similar rigid compounds undergo intramolecular β-hydrogen abstraction on irradiation (254 nm; equation 214)[628].

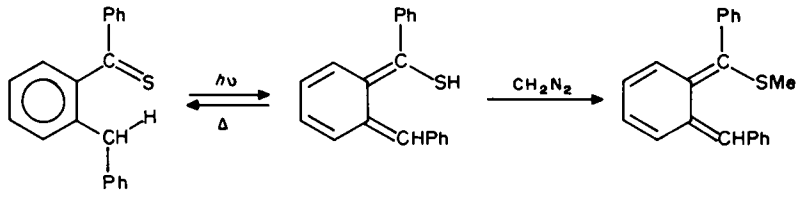


(213)

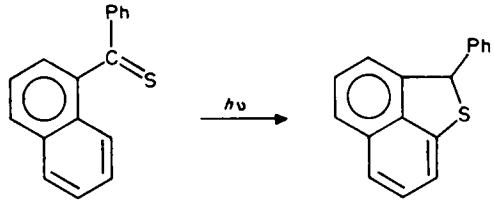


(214)

With rigid aromatic systems, hydrogen abstraction from the γ position has been observed. Thus, *o*-benzylthiobenzophenone furnishes an enethiol on photoexcitation by 589 nm, which can be captured by addition of diazomethane (equation 215)[629], and PhC(S)α-Naph cyclizes with formal hydrogen abstraction from the peri position, but deuteration confirmed an intermolecular pathway (equation 216)[206].

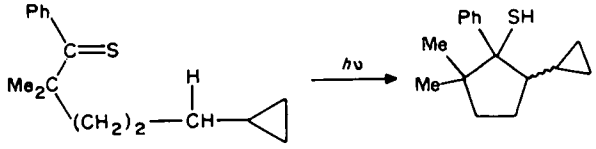


(215)



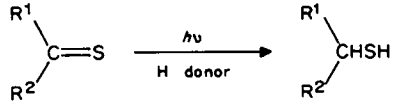
(216)

If possible, the preferred reaction in thioketones involves abstraction from the δ position[630]. This is a reaction of the S_2 (π,π^*) state and does not occur with long-wavelength light. A typical example is shown in equation 217 (yield 65%).



(217)

Diarylthiones and sterically hindered aliphatic thiones are photoreduced by intermolecular hydrogen transfer. Thus, irradiation of a solution of thiobenzophenone in methanol yields diphenylmethanethiol, Ph_2CHSH (63%), and acetone (88%)[631]. Similarly, di-*t*-butylthioketone[632,636], adamantanethione[633] and 2,2,4,4-tetramethyl-1,3-cyclobutanedithione (**21b**)[103] yield the corresponding thiol or, as a secondary product, the disulfide on irradiation (equation 218).

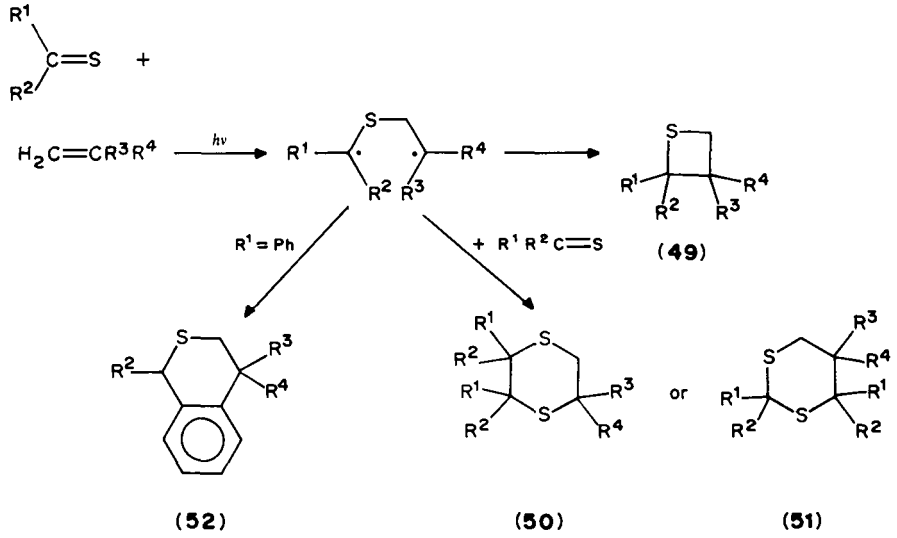


(218)

[2 + 2] Photocycloaddition of thiones with C=C systems has been studied intensively. Products are thietanes (**49**), 1,4- (**50**) or 1,3-dithianes (**51**), and tetrahydrothianaphthalenes (**52**; equation 219). Formation of heterocycles **44** is the usual outcome on irradiation of thioketones in the presence of electron-rich or electron-poor alkenes. With electron-rich alkenes (e.g. $R^3 = Alk$[634,635], $R^3 = OR$[636-640], $R^3 = R^4 = OR$[641]) the cycloaddition occurs via the S_1 (n,π^*) state; increasing amounts of dithianes **50** may be formed with higher concentrations of the thioketone, as expected for a reaction through a diradical intermediate which can be trapped by ground-state thioketone (equation 219)[639,640,642]. Also in accord with the intermediate diradical, 1,2-dimethoxyethylene of defined configuration gives a nonstereospecific reaction[643]. When an alkene with an optically active residue R^3 is employed, up to 17% asymmetric induction is observed[635].

The reaction of diarylthioketones with electron-deficient C=C components (R^3 = CN[644,645], COOR[646]) is wavelength-dependent. After excitation of the thione to the S_2 state, thietanes **49** are formed in a stereospecific and regioselective cycloaddition. An enethione was found to react in an analogous way[594,640,647]. However, in the reaction of thiobenzophenone with acrylonitrile, the thietane **49** formed arises from thermal decomposition of a 1,3-dithiane **51**[644,645]. At long wavelengths ($\approx$ 550 nm), 1,4-dithianes **50** and benzo-annulated thiapyrans **52** are obtained[645,648]. Although **52** is a 1:1 adduct, a second molecule of ground-state diarylthioketone is involved in its formation[645].

The reaction of dialkylthioketones such as adamantanethione with electron-deficient C=C systems is possible both from the S_2 (π,π^*) and T_1 (n,π^*) states to give thietanes

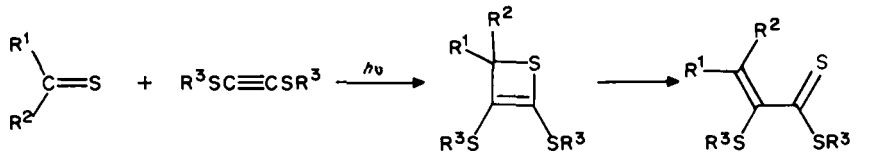


(219)

49[636,637,649,650]. Cycloadditions originating from the T_1 state are nonstereospecific, but regioselective[650], whereas reactions from the S_2 state are stereospecific, but not regiospecific[637].

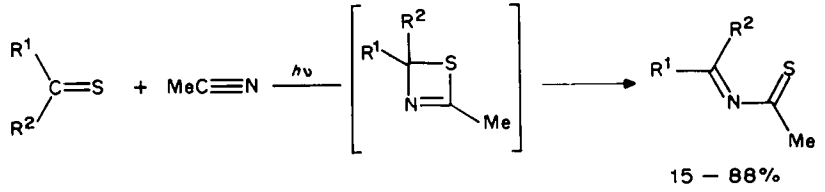
Besides simple C=C systems, various cumulated derivatives have been used in the photocycloaddition to thiocarbonyl compounds. Monosubstituted allenes react with thioaldehyde **2b** to give thietanes **49** with the substituent being on the four-membered ring[651]. However, the analogous reaction of xanthione is not site-specific[652], and thiobenzophenone gives rise to some product **52** with $CR^3R^4 = C = CHOMe$[653]. Also, tetramethylallene has been studied[654] and so have heteroallenes such as diphenylketene[655] and ketenimines[655,656]. Even cycloadditions of butatrienes to aromatic thiones have been examined[657].

Bis(alkylthio)acetylene reacts with diarylthioketones to give thietes as primary products and subsequently, via electrocyclic ring-opening, unsaturated dithioesters (equation 220)[658-661]. The thiete intermediate could be isolated starting from xanthione and for $R^3 = t$-Bu[658]. Furthermore, [4 + 2] cycloadducts of type **52** are found in some instances[659,662,663].



(220)

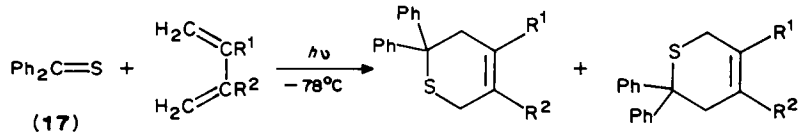
[2 + 2] Photocycloadditions are also possible between thiones and carbon-hetero π bonds. A simple example is the photoinduced dimerization which has been seen for dibenzylthioketone[455] and adamantanethione[634,637,650]. Thiobenzophenone and a Schiff base react to yield 2:1 cycloadducts[664], and several thiones add to the C≡N bond in acetonitrile (equation 221)[665].



(221)

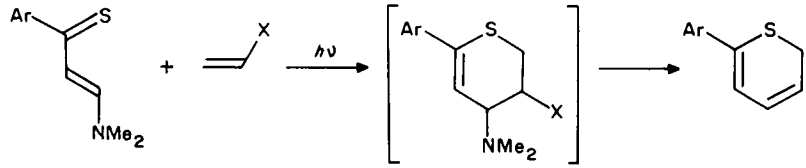
With simple alkenes, di-*t*-butylthioketone undergoes a substitution reaction to give *t*-$Bu_2CHSCH{=}CR_2$ rather than a cycloaddition[666].

In the case of 1, 3-dienes as reaction partners, 1, 4 addition of thiobenzophenone (**17**) to the diene system is most often observed, with thietanes **49** being found in some instances (equation 222)[667]. Mixtures of regioisomers are formed, which could not be separated. The product ratio is the same as in the thermal (100 °C) [2 + 4] cycloaddition of **17** to dienes (cf. equation 191). Similarly, a [2 + 4] cycloadduct is formed in the reaction of **17** with cyclooctatetraene[668].



(222)

By analogy with the thermal reaction (equation 200), vinylogous thioamides may act as dienes in the photoinduced cycloaddition to electron-deficient dienes giving thiapyrans (equation 223; X = CN, COOMe)[610].

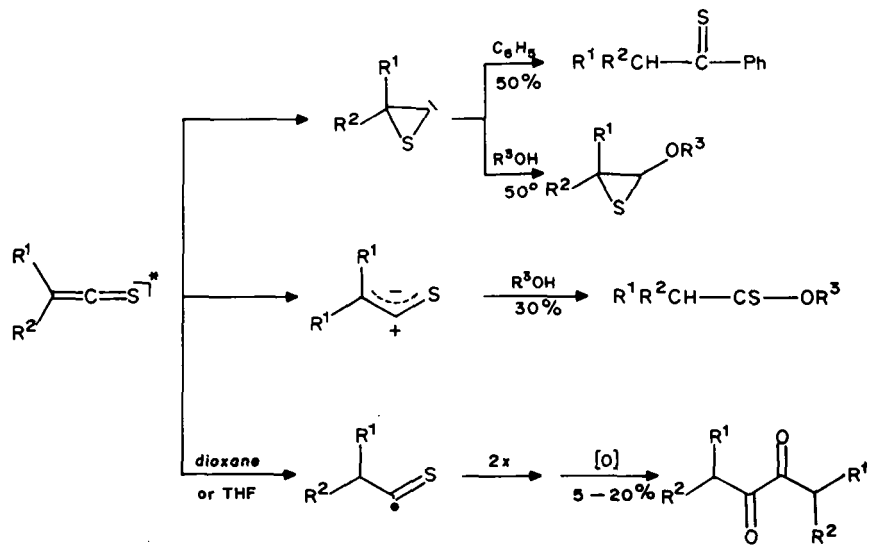


(223)

Insights into the photochemistry of thioketenes were obtained with the aid of sterically stabilized representatives[6]. The compounds proved unreactive upon excitation to the S_1 state (wavelengths > 480 nm) but, from the S_2 state, they produce thiiranylidene carbenes and zwitterionic intermediates which are trapped by the solvent (equation 224)[669].

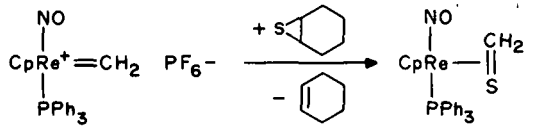
H. Coordination Chemistry

Coordination of thiocarbonyl compounds to metals holds interest for the stabilization of labile derivatives or for the modification of thiocarbonyl reactivity.

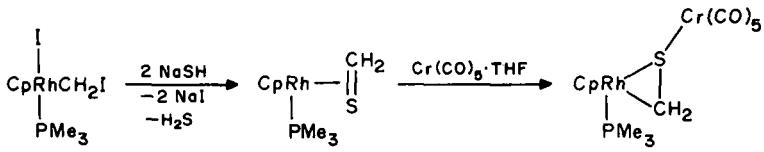


(224)

Several routes have been developed for the synthesis of metal-coordinated thioaldehydes. Coordination compounds with η^2 (CS)-bound thioformaldehyde ligands were isolated from the reaction of a rhenium–carbene complex with cyclohexene sulfide as a sulfur transfer reagent (85–95%; equation 225)[670], or of an iodomethyl rhodium derivative with diazomethane (48%; equation 226)[671]. In the last-mentioned case, subsequent reaction with $Cr(CO)_5 \cdot THF$ gives a coordination compound with mixed η^2 (CS) and η^1 (S) bonding (equation 226)[672]. Another complex with a thioformaldehyde bridge is obtained on reacting a manganese sulfide with diazomethane[673].

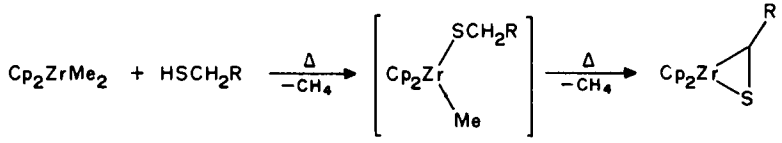


(225)

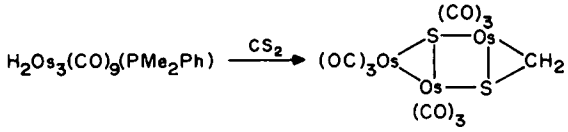


(226)

The first thioaldehyde complexes of an early transition metal were isolated from the redox reaction of a dimethylzirconium compound and thiols RCH_2SH (R = Me, Ph; 85–90%; equation 227)[674]. Besides the final product of equation 226, a similar way of simultaneous η^1 (S) and η^2 (CS) bonding is encountered in an osmium coordination compound (equation 228)[675].



(227)

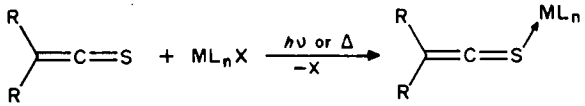


(228)

Besides generation of thiocarbonyl compounds on the metal (equations 225–228), reactive thioaldehydes may be trapped by an appropriate coordination compound. Thus, the highly reactive *t*-butyldithioglyoxal, *t*-BuC(S)CH=S, is scavenged by addition of $Ni(CO)_4$[277].

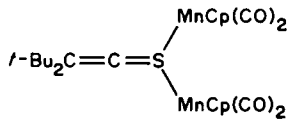
A remarkable case of stabilization of an otherwise elusive thioketone by metal coordination was possible for an α-diazothione[676]. Contrary to their oxo analogs, these compounds inevitably cyclize to thiadiazoles **39** in the absence of a metal.

The coordination chemistry of thioketenes has been intensively studied by Behrens and his group[677–9,682,684–8] especially for sterically hindered representatives[6]. A common feature with the above-mentioned thioaldehyde complexes is dihapto coordination of the type of equation 225 as observed for MCp_2 (M = Ti, V)[677], $FeCp(CO)_2Fe(CO)Cp$[678], MCpL (M = Co, Rh; L = CO, PMe_3)[679,680], $Ir(CO)Cl(PR_3)$[681], $Pt(PPh_3)_2$[678,681], VCp_2[682] and $MCp(Pi\text{-}Pr)_3$ (M = Rh, Os)[683]. On the other hand, the thioketene may coordinate to the metal via an η^1 (S) bond as seen for $M(CO)_5$ (M = Cr, W)[684,685], $MnCp(CO)_2$[685] and $\frac{1}{2}$ $PdCl_2$[678] (equation 229).

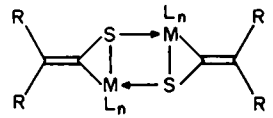


(229)

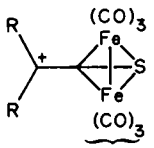
Very recently, a dinuclear Mn complex **53** was isolated, which shows bonding of both metal atoms to the lone electron-pairs on sulfur[686]. Several examples of dimeric coordination compounds **54** have been reported [$ML_n = M(CO)_3$ with M = Fe[687], Ru, Os[688]; $Co(CO)_2$[679]]. With iron, even η^6 coordination as in **55** is possible.



(53)



(54)



(55)

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The Chemistry of Double-bonded Functional Groups
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CHAPTER **18**

Cycloadditions of enones

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I. INTRODUCTION

A. Scope of the Review

Like all molecules possessing at least one π function, enones can undergo cycloadditions, i.e. reactions forming cyclic compounds via the creation of two new σ bonds. We shall be concerned mostly with conjugated enones, i.e. α,β-unsaturated ketones (and aldehydes). The cycloadditions of dienones, benzoquinones, trienones and tropones will not be treated systematically. A few cases of cycloadditions involving β,γ-unsaturated ketones will also be presented. The reactions of γ,δ-, δ,ε- etc. unsaturated ketones will not be discussed, since these molecules can be assumed to behave similarly to alkyl substituted alkenes or ketones.

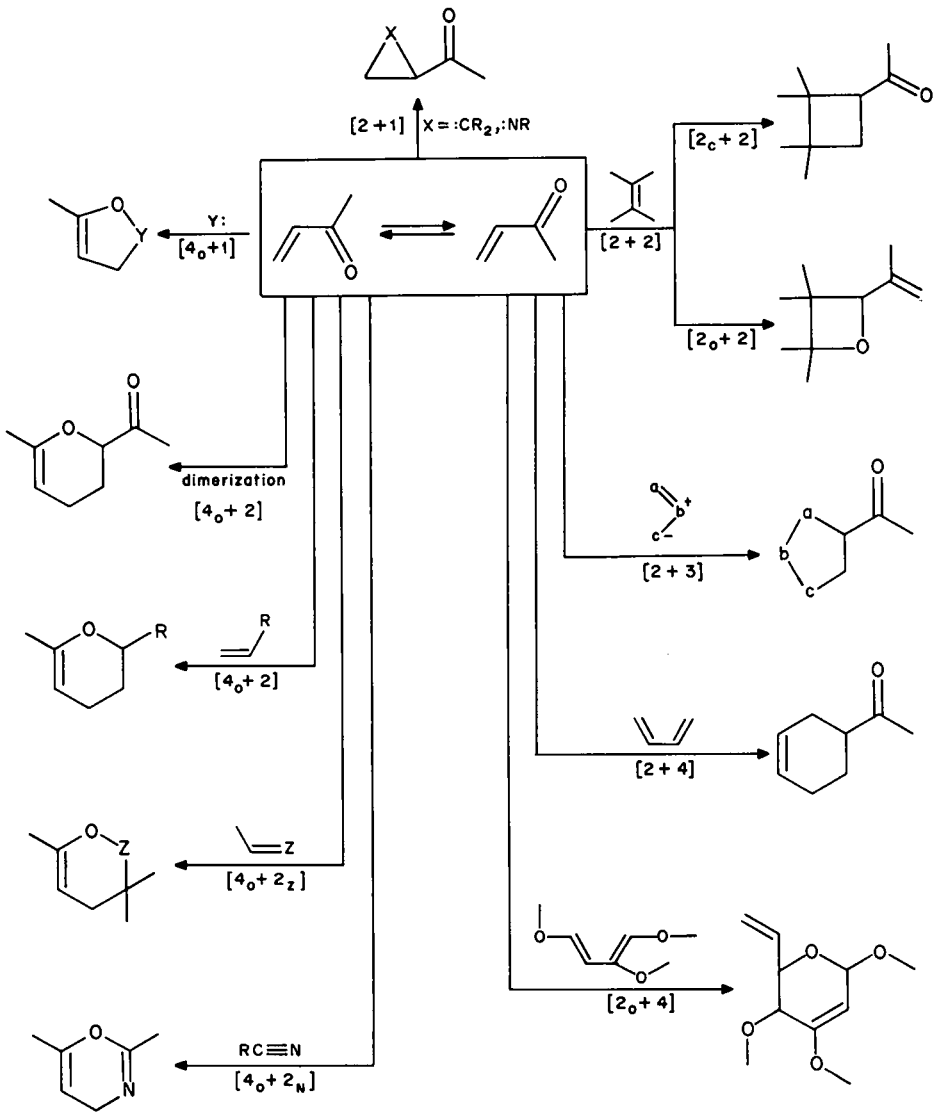
B. Classification of the Cycloadditions

The physical and chemical properties of α,β-unsaturated ketones are, to a first approximation, those of their alkene and carbonyl moieties. If their conformation is s-*cis* (dihedral angle between the C=C and C=O axis near 0°) or s-*trans* (dihedral angle near 180°), π conjugation intervenes and may dominate the reactivity of the conjugated enones. In the case of β,γ-unsaturated ketones, homoconjugation may occur and affect their physical and chemical properties.

The alkene moiety of α,β- and β,γ-unsaturated ketones (and aldehydes) can undergo [2 + 1] cycloaddition (e.g. cyclopropanation), [2 + 2] cycloaddition induced thermally or photochemically, dipolar [2 + 3] cycloaddition or a [2 + 4] cycloaddition (e.g. Diels–Alder addition). In these cycloadditions the carbonyl group is a substituent that activates or retards the reactions in comparison with the cycloadditions of analogous alkyl-substituted olefins, but does not intervene directly in the process that leads to the two

newly formed σ bonds. However, we shall see it can play a directing role on the stereoselectivity of the cycloadditions. Furthermore, because of the Lewis base character of the C=O group, it may be protonated or may form a coordination complex with a Lewis acid and thus modify the properties of the enone and its reactivity in a favourable fashion.

In some rare instances, the enones can undergo [2 + 2] and [2 + 4] cycloadditions involving the carbonyl group only in reactions typical of saturated ketones (or aldehydes). Alternatively, and provided that the s-*cis* conformation is accessible, α,β-unsaturated

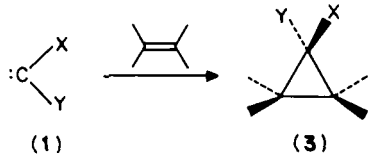


SCHEME 1

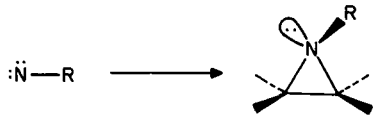
ketones may react as oxabutadiene moieties, undergoing $[4_o + 1]$ cycloadditions, or, more commonly, $[4_o + 2]$ cycloadditions (e.g. hetero Diels–Alder addition) as illustrated in Scheme 1.

II. [2 + 1] CYCLOADDITIONS

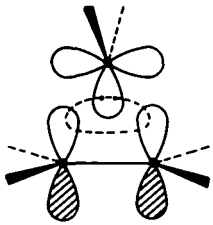
Carbenes (**1**) and nitrenes (**2**) are typical unsaturated, sextet species that can add to unsaturated hydrocarbons and generate the corresponding cyclopropanes (**3**)[1] and aziridines (**4**)[2]. These reactions can be classified as [2 + 1] cycloadditions[3]. Woodward and Hoffmann[4] define a cheletropic reaction as 'a process in which two σ bonds which terminate at a single atom are made, or broken, in concert'. Insofar as the addition of singlet methylene, $:CH_2(^1A_1)$[5], to a double bond adheres to this definition it can be treated by the selection rules. The methylene (and other carbenes, or nitrenes) can approach a double (or triple) bond in either a linear (see **5**) or non-linear manner (see **6**). In the former, the reaction must be designated as a $[{}_\pi 2_s + {}_\omega 2_s]$ cycloaddition and, by selection rules, is not allowed. On the other hand, in the non-linear case, the reaction must be designated as a $[{}_\pi 2_s + {}_\omega 2_s]$ reaction and, by selection rules, is allowed[3].



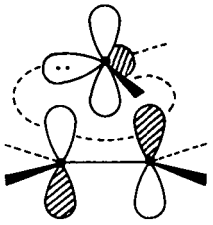
(1) (3)



(2) (4)

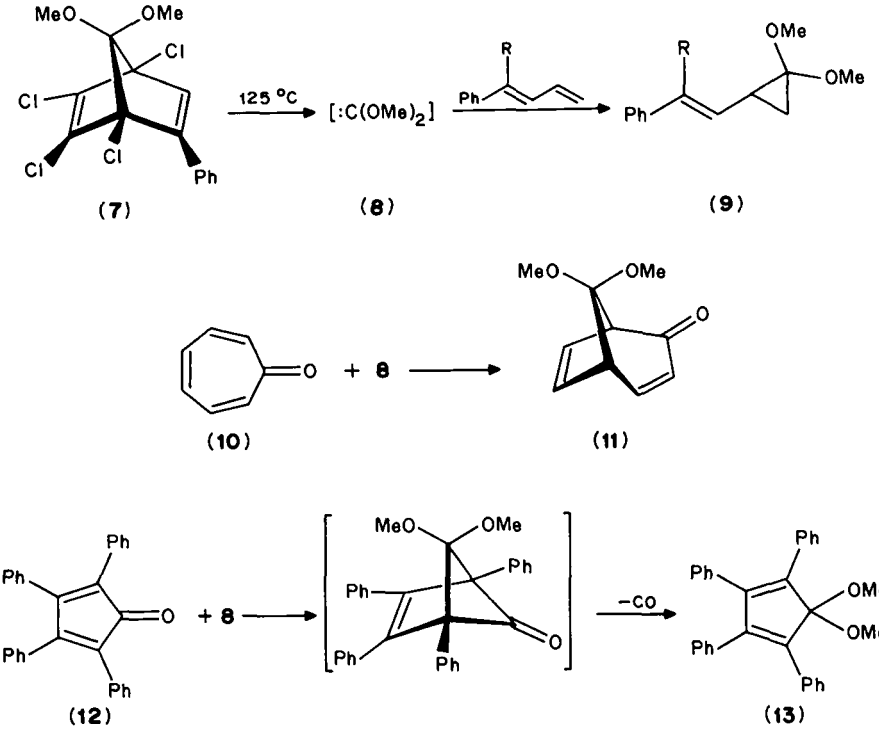


(5) $[{}_\pi 2_s + {}_\omega 2_s]$



(6) $[{}_\pi 2_s + {}_\omega 2_a]$

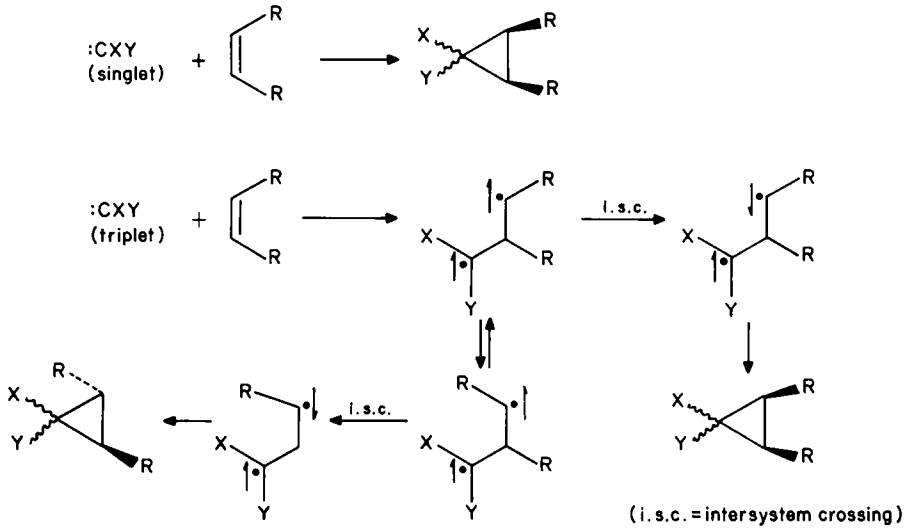
In general, carbenes and nitrenes add to enones selectively onto the C=C double bond, leading to derivatives of **3** and **4**, respectively. In theory, a s-*cis* enone could undergo a $[4_o + 1]$ cycloaddition giving five-membered ring systems (see Scheme 1). Such reactions have not been reported yet for the reactions of carbenes and nitrenes (however, see Section IV). Interestingly, the addition of dimethoxymethylene (**8**) generated by thermal decomposition of **7** was found to give [4 + 1] adducts (see **11**, **13**) with tropone (**10**) and tetraphenylcyclopentadienone (**12**)[6]. In these cases, the cyclopropanation was not observed contrastingly with the addition of **8** to 1-phenyl substituted butadiene, which gave exclusively product of cyclopropanation **9** of the less substituted double bond[6].



A. Properties of Carbenes

Buchner and Curtius (1885)[7], Staudinger and Kupfer (1912)[8], Rice and Glasebrook (1934)[9] and Meerwein and coworkers (1942)[10] are the more prominent names associated with the discovery of carbene chemistry[11]. In 1950, Hine proposed that alkaline hydrolysis of $CHCl_3$ proceeds by a two-step α-elimination involving a new intermediate, $:CCl_2$[12]. Doering and Hoffmann[13] developed later an efficient method for the preparation of 1, 1-dihalocyclopropanes based on that hypothesis (see Section II.C). In 1956, Skell and Woodworth[14] postulated that the addition of methylene, $:CH_2$, in its singlet state ($^1A_1$) is a one-step process in which the two σ C—C bonds are formed simultaneously, whereas that of the more stable triplet $:CH_2$ ($^3B_1$) is a non-concerted, two-step process (Scheme 2) involving a 1, 3-diradical whose life-time allows for rotation about the C—C bond of the olefin. As a consequence, the additions of singlet carbenes (and nitrenes) are stereospecific with retention of the configuration at the centres originating from the alkene (suprafacial mode of cycloaddition), whereas the reactions of triplet carbenes (and nitrenes) are not (Skell's rule). While this rule has not been entirely supported by theoretical studies[15,16] it provides a simple explanation for the observed behaviour. Evidence for intermediates in the cycloaddition of singlet carbenes has also been presented[17].

Singlet methylene is very highly reactive, allowing its detection even in a large excess of the triplet species. The energy gap between the singlet and triplet $:CH_2$ is estimated to be *ca* 9 kcal mol^{-1}[5]. The latter is singularly unreactive for a biradical, except in some additions with unsaturated hydrocarbons[1]. In reactions with saturated hydrocarbons, singlet $:CH_2$



SCHEME 2

inserts in σ bonds (see e.g. equation 1) while the triplet abstracts a hydrogen atom (see e.g. equation 2). These reactions are concurrent with the cyclopropanations of olefins.

$$:CH_2(^1A_1) + R{-}H \longrightarrow R{-}CH_3 \quad (1)$$

$$:CH_2(^3B_1) + R{-}H \longrightarrow CH_3\cdot + R\cdot \quad (2)$$

It has long been known that most carbenes are electrophilic species which react faster with electron-rich alkenes than with electron-deficient alkenes (e.g. α,β-unsaturated ketones)[1,18-20]. Thus, halocarbenes and most substituted carbenes have negative Hammet ρ values in reactions with substituted styrenes, and more highly alkylated alkenes react faster than less alkylated alkenes with most carbenes. Only potent electron-donor substituents can render the carbene ambiphilic or even nucleophilic (see Table 1 below).

By comparing the selectivities $(k_i/k_o)_{CXY}$ of the cycloadditions of carbenes :CXY to a set of standard alkenes ($Me_2C{=}CH_2$ being chosen as reference alkene defining k_o) with those, $(k_i/k_o)_{CCl_2}$, of $:CCl_2$ (reference carbene) to the same set of alkenes, the 'carbene selectivity index' $m_{CXY} = \log(k_i/k_o)_{CXY}/\log(k_i/k_o)_{CCl_2}$ was proposed by Moss and coworkers[19,20] for reactions at 25 °C. Multiple linear regression analysis of the dependence of m_{CXY} on the substituent constants σ_R^+ and σ_I afforded the dual substituent parameter correlation (equation 3) in which $\sum_{X,Y}$ represents the sum of the appropriate σ constants[21] for the

$$m_{CXY} = -1.10 \sum_{X,Y} \sigma_R^+ + 0.53 \sum_{X,Y} \sigma_I - 0.31 \quad (3)$$

substituents of :CXY[19,20]. Relation 3 can be used to estimate selectivities of the cycloadditions of unknown carbenes and to determine whether a carbene :CXY is electrophilic (reacts faster with electron-rich olefins), nucleophilic (reacts faster with electron-poor olefins) or ambiphilic, i.e. it behaves as an electrophile toward electron-rich alkenes (viz. isobutene > hex-1-ene) but as a nucleophile toward electron-poor alkenes (α,β-unsaturated ketones > hex-1-ene). Houk and coworkers[22] showed that the selectivities m_{CXY} were correlated with the carbene stabilities. Thus, whereas:CH_2 is unselective, donor substituents stabilize carbenes and increase their selectivities. This normal

reactivity–selectivity relationship implies that activation enthalpy variations control selectivity.

However, Skell and Cholod[18] reported that the relative rates of $:CCl_2$ cycloadditions to alkylethylenes were paralleled by the differences in entropies, not enthalpies, of activation. It was proposed that more reactive alkenes have earlier transition states. Earlier transition states have lower vibrational frequencies and thus have less negative entropies than late transition states. Accordingly, for highly reactive alkenes the selectivity is controlled by the $-T\Delta S^{\ddagger}$ term whereas for less reactive alkenes (e.g. α,β-unsaturated ketones) the $\Delta H^{\ddagger}$ term predominates[16]. Giese and coworkers[23] have observed that selectivities of the cycloadditions of halocarbenes, $:CF_2$, $:CFCl$, $:CCl_2$, $:CClBr$ and $:CBr_2$ to alkyl-substituted olefins depend on the temperature. All halocarbenes were found to be equally selective at 90 $\pm$ 10 °C (isoselective temperature) toward isobutene and 2,3-dimethylbut-2-ene. Below 90 °C the 'normal' selectivity is observed, but a reversal in selectivity occurs above 90 °C[23]. The selectivity of $:CF_2$ is 'normal' and controlled by the $\Delta H^{\ddagger}$ term. $:CF_2$ is more selective at low temperatures than at high ones, and the entropy works against the enthalpy, favouring the less substituted alkene. The selectivity of $:CCl_2$ is temperature independent, indicating that the relative rates of reaction are controlled by entropies of activation, since $\Delta H^{\ddagger}$ is essentially identical for both alkenes. The selectivity of $:CBr_2$ shows an inverse

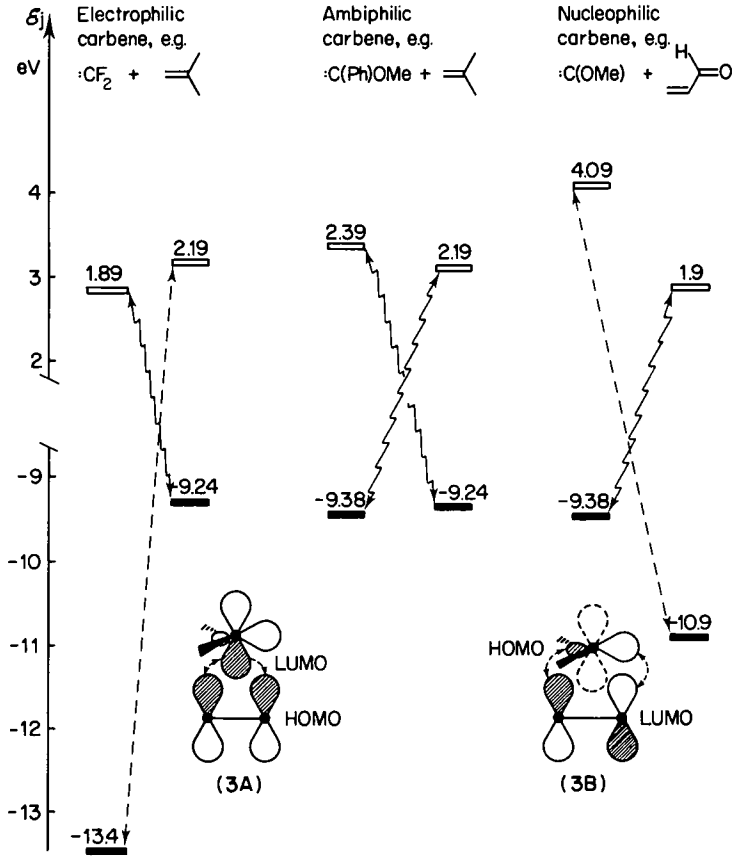


FIGURE 1. (Orbital energies are taken from References 20 and 26)

temperature dependence. Here, the $-T\Delta S^{\ddagger}$ term favours the more alkylated alkene, while enthalpy has a small influence in the opposite direction. :CFCl and :CBrCl are intermediate cases.

Frontier molecular orbital (FMO) theory has been applied successfully to the rationalization and prediction of electrophilic, nucleophilic and ambiphilic behaviour in 1,3-dipolar cycloadditions (see Section V) and Diels–Alder additions (see Section VI)[24]. Calculations of orbital energies for a variety of substituted carbenes[22] lend themselves to a similar rationalization of carbenic selectivity controlled by the enthalpy of activation of the concerned [2 + 1] cycloadditions. The addition of a singlet carbene to an alkene involves simultaneous interactions of the vacant carbenic p orbital (LUMO) with the filled alkene π orbital (HOMO) and the filled carbenic σ orbital (HOMO) and the vacant alkene π^* orbital (LUMO) as shown in Figure 1[20,25]. Although a singlet carbene is inherently both an electrophile and a nucleophile, behaviourally decisive is whether, in the transition state of the [2 + 1] cycloaddition, it is the LUMO(carbene)–HOMO(alkene) (see **3A**) or the HOMO(carbene)–LUMO(alkene) (see **3B**) interaction which is stronger and determines the electronic distribution. The dominant orbital interaction depends both on the differential energies of the FMOs and on their overlaps. The orbital overlaps can be estimated as overlap integrals derived from calculated geometries and orbital coefficients for the :CXY + alkene transition states. If one neglects the overlap and concentrates on the energies of the FMOs only, from the values given in Table 1, carbenes like :CF_2 or :CCl_2 must be considered to behave as electrophiles towards common olefins, since the dominant interaction is LUMO(CXY)–HOMO(alkene) (see **3A**). Alternatively, for :$C(OMe)_2$[27] the LUMO(alkene)–HOMO(carbene) interaction dominates (see **3B**) and this carbene behaves as a nucleophile, as observed. Finally, if the HOMOs and LUMOs of a carbene and a simple alkene are such as to afford comparable differential energies for both sets of orbital interactions, and assuming similar orbital overlap integrals, then ambiphilic carbene reactivity should obtain. This was proved to be the case experimentally

TABLE 1. Carbenic philicity of selected carbenes[a]

:CXY	m_{CXY} (obs.)[b]	m_{CXY} (calc.)[c]	ε(HOMO)[d]	ε(LUMO)[d]	Observed philicity[e]
:C(Me)Cl	0.50	0.58	−10.28	1.61	E
:C(Ph)Br	0.70	0.64	*f*	*f*	E
:C(Ph)Cl	0.83	0.71	*f*	*f*	E
:CBr_2	0.65	0.82	*f*	*f*	E
:C(Ph)F	0.89	0.96	−10.23	1.51	E
:CCl_2	(1.0)	(1.0)	−11.44	0.31	E
:CFCl	1.28	1.22	−11.98	1.03	E
:C(Ph)OMe		1.34	−9.38	2.39	A
:CF_2	1.48	1.47	−13.38	1.89	E
:C(OPh)Cl		1.49	−10.78	2.02	A
:C(OMe)Cl		1.59	−10.82	2.46	A
:C(OPh)F		1.74	−11.81	2.56	A
:C(OMe)F		1.85	−11.81	3.19	*f*
:$C(OMe)_2$		2.22	−10.81	4.09	N

[a] Taken from Reference 26.
[b] Taken from Reference 20.
[c] Calculated from equation 3.
[d] Orbital energies in eV at the *ab initio* 4.31 G level; Reference 26.
[e] Philicity based on experiments, E = electrophilic, A = ambiphilic, N = nucleophilic.
[f] Not available.

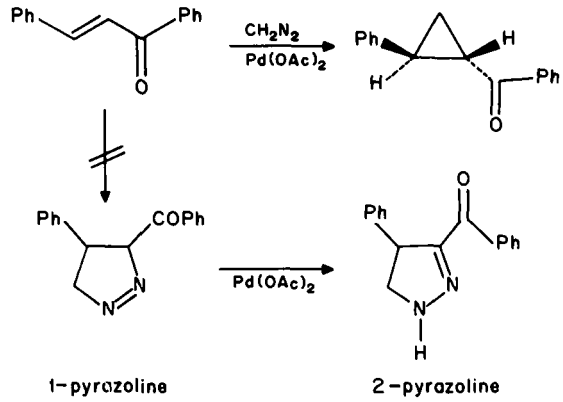
for MeOCPh, :C(Ph)OMe, :C(OPh)Cl, :C(OMe)Cl and :C(OPh)F[26,28]. Thus, these carbenes are the best candidates for cyclopropanation of α,β-unsaturated ketones, in theory at least.

B. Cyclopropanation of Conjugated Enones

There are several methods for converting the C=C double bond of α,β-unsaturated ketones and aldehydes into cyclopropane derivatives (equation 4). For instance, in Corey's method[29] sulphur methylides or dimethylsulphoxonium methylide[30] are condensed to the enones. In the presence of diazomethane, CH_2N_2, enones undergo readily 2,3-dipolar cycloadditions (see Section V) giving the corresponding 1-pyrazolines which, depending on the substitution pattern, may decompose thermally or photochemically into cyclopropane derivatives[31]. These reactions are not cheletropic reactions of the C=C double bonds with methylene, $:CH_2$, but multi-step processes and thus will not be treated further.

(4)

Diazomethane can be decomposed thermally or photochemically into N_2 and $:CH_2$. The latter carbene can be trapped by the enones, giving usually products of cyclopropanation in low yields. Vorbrüggen and coworkers[32] showed that cyclopropanation of α,β-unsaturated carbonyl compounds can be achieved in high yield by treatment of the enone with CH_2N_2 in the presence of $Pd(OAc)_2$ (catalyst), as exemplified below.



$PdCl_2$ and Pd(II) acetylacetonate were also catalysts for the decomposition of CH_2N_2, but were not as efficient as $Pd(OAc)_2$. Since the corresponding 1-pyrazoline prepared independently is isomerized readily into the corresponding more stable 2-pyrazoline, it was suggested that methylenation does not proceed through the intermediacy of the former but is a direct process involving either transfer of 'free' $:CH_2$ to the C=C double bond of the enone, or the intervention of a transition metal carbenoid[33,34].

The reaction of Simmons–Smith[35] allows the cyclopropanation of a large variety of alkenes under relatively smooth conditions. It involves the treatment of the olefin and CH_2I_2 with the Zn/Cu couple. The transfer of $:CH_2$ is facilitated for alkenes with adjacent alcohol, ester, ether or amine functions[36a]. When applied to difficult enolizable conjugated

TABLE 2. Simmons–Smith methylenation of α,β-unsaturated ketones showing number of equivalents of CH_2I_2–Zn/Cu, reaction time and isolated yields

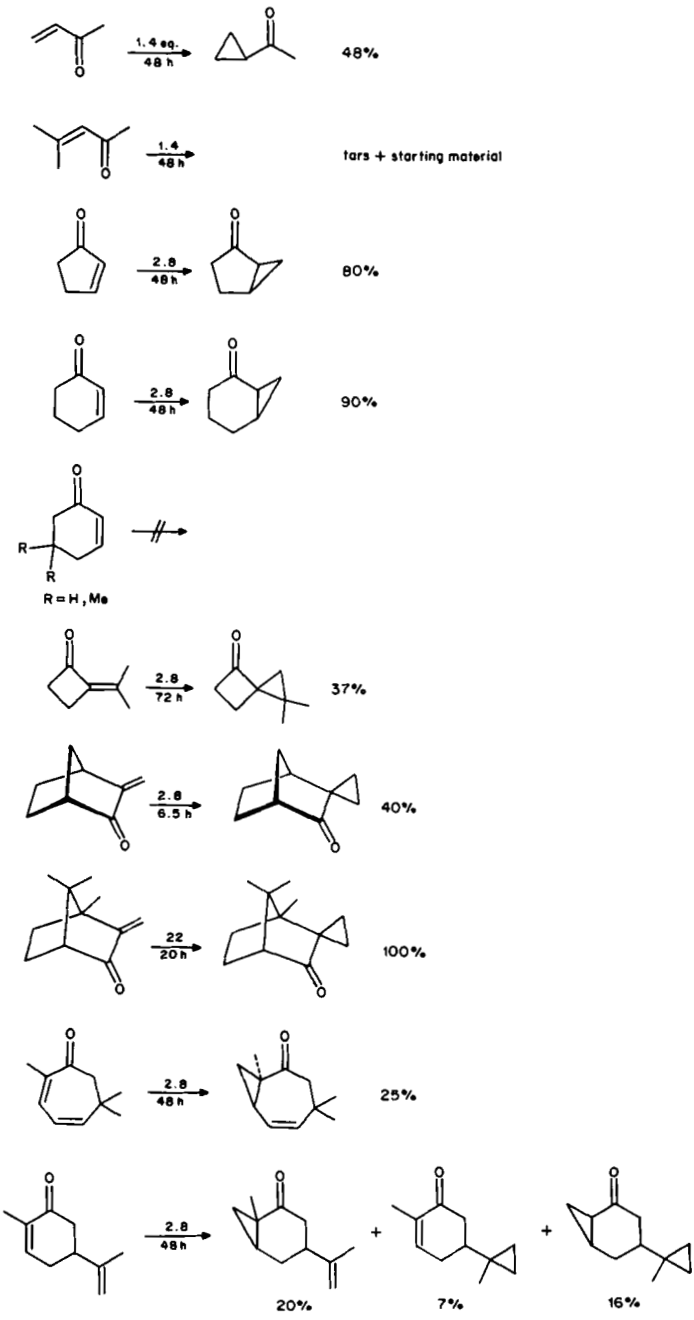
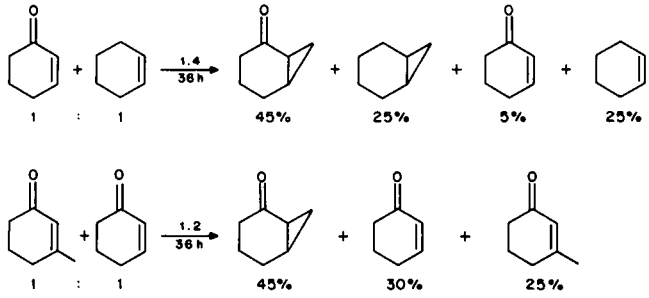
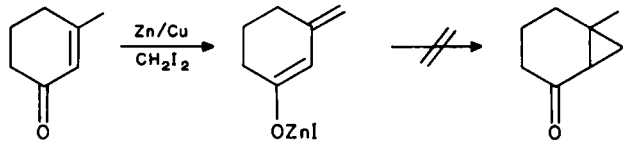


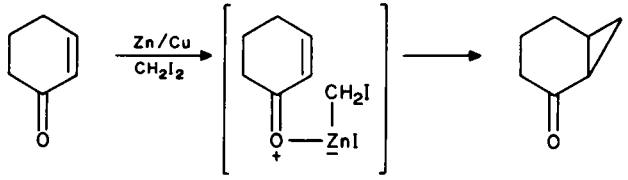
TABLE 2. (*continued*)



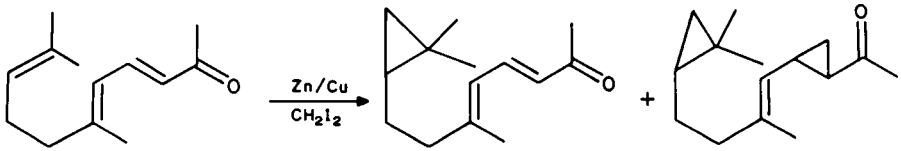
enones, this technique affords the corresponding cyclopropyl ketones in good yield as shown by Conia and coworkers[36b] (see Table 2). Readily enolizable enones lead to the production of tars, probably because of the formation of dienolates as shown below:



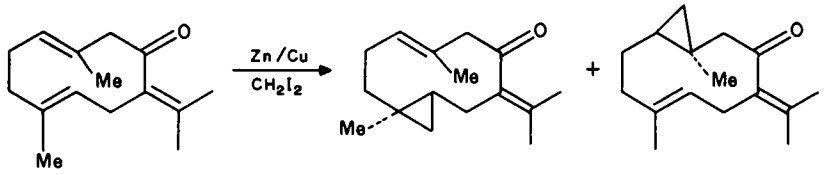
Competitive cyclopropanation of cyclohex-2-enone and cyclohexene suggested (Table 2) that the transfer of:CH_2 to the enone might be assisted by the carbonyl group, as interpreted by the following reaction:



The Simmons–Smith procedure is not strongly affected by the degree of substitution of the alkene. For instance, *trans*-pseudojonone (**14**) reacted with 2-equiv. of CH_2I_2/Zn/Cu to give a mixture of products containing 70–80% of **15** resulting from the cyclopropanation of the non-conjugated, trisubstituted C=C double bond and only 5–15% of **16**, resulting from the cyclopropanation of the conjugated enone moiety in **15**[37].



The cyclopropanation of 8-oxo-germacrene B (**17**) with the Simmons–Smith reagent afforded a 7:3 mixture of the products of monocyclopropanation **18** and **19**. The tetrasubstituted double bond in **17** conjugated in this case, probably because of the greater steric hindrance to the methylene transfer than for the other trisubstituted double bond[38].

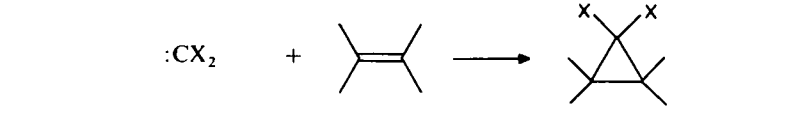


(**17**) (**18**) (**19**)

A variant of the Simmons–Smith method replaces the expensive CH_2I_2 by CH_2Br_2[39]. The latter implies the formation of bromomethylzinc bromide from CH_2Br_2 and Zn in anhydrous tetrahydrofuran. With CH_2I_2, the Zn/Cu couple can be replaced by EtZnI[40], Et_2Zn[41], by the Zn/Ag couple[42] or by Cu powder[43,44].

C. Reactions with Substituted Carbenes

In 1954, Doering and Hoffmann[13] showed that *gem* dihalocyclopropanes can be obtained readily by treatment of an olefin and the corresponding trihalogenomethane with *t*-BuOK. The reaction (Scheme 3) is interpreted in terms of the formation of dihalocarbene, $:CX_2$, which undergoes a [2 + 1] cycloaddition with the alkene. This procedure and several of its variants[45] necessitates the use of a strong base that destroys or interferes with sensitive substituents of the alkene, such as the carbonyl group of enones, thus leading to low yields of cyclopropanation. Furthermore, the trihalogenomethide ion intermediate, CX_3^-, can be intercepted in a Michael type of addition before it has time to decompose to the corresponding dihalogenocarbene, $:CX_2$. (See however the reaction of tetrasubstituted cyclopentadienones with dichlorocarbene and dibromocarbene[45b].)

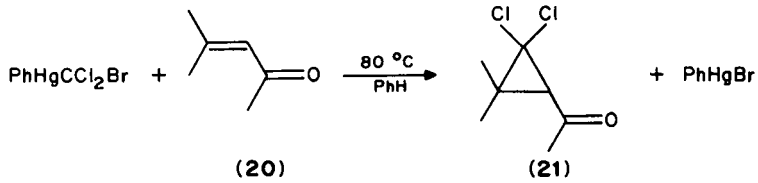


SCHEME 3

The Wagner[46] procedure which involves the decomposition of trihaloacetate ions (equation 5), or the method using preformed $LiCCl_3$ at low temperature (equation 6)[47], are not much better for the dihalocyclopropanation of conjugated enones (however, see below the preparation of difluoromethylene steroids). Seyferth and coworkers[48] have discovered that heating phenyl(trichloromethyl)mercury or phenyl(tribromomethyl)mercury with cyclohexene in excess when refluxing benzene yielded the corresponding 7,7-dihalogenonorcarane in good yield. Under similar conditions, they found that $PhHgCCl_2Br$ in the presence of three equivalents of mesityl oxide (**20**) gave the dichlorocyclopropane derivative **21** in 62% yield[48].

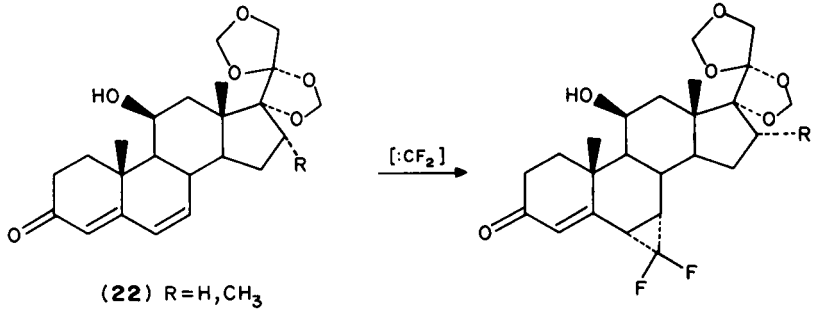
$$CX_2ClCOONa \xrightarrow{\Delta} :CX_2 + CO_2 + NaCl \quad (5)$$

$$LiCCl_3 \longrightarrow :CCl_2 + LiCl \quad (6)$$



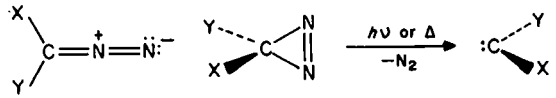
(20) (21)

Since the conversion of *cis* and *trans* olefins to *gem* dihalocyclopropanes by the mercurial route occurred with retention of configuration, it was proposed that dichlorocarbene, $:CCl_2$, is a true intermediate which undergoes the [2 + 1] cycloaddition in a concerted manner (see below)[1,3,20]. Fried and coworkers have reported an efficient method for the preparation of a 6,7-difluoromethylenesteroid[49]. For instance[50], $:CF_2$ generated by thermolysis of $ClF_2CCOONa$ in diglyme at 190 °C added to dienones **22** and gave mixtures of products from which the 6α,7α-difluoromethylene adducts **23** were isolated.



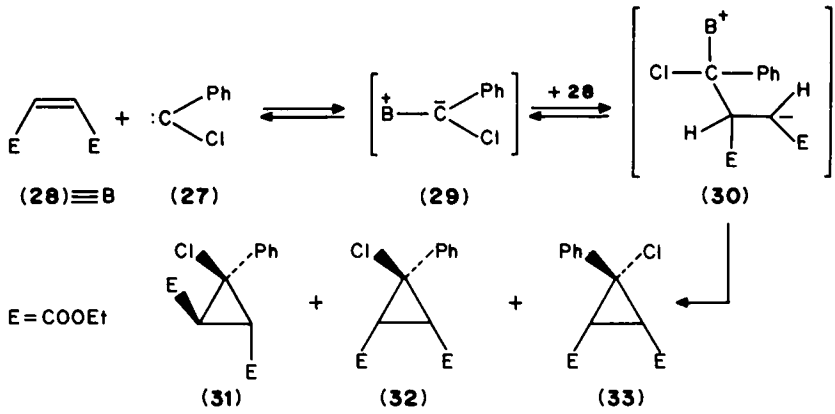
(22) R=H,CH_3 (23)

As for the parent carbene, $:CH_2$, substituted carbenes :CXY (**26**) can be generated by photochemical decomposition of the corresponding diazoalkane (**24**) or diazirine (**25**)[20,26,51]. Moss and Pilkiewicz[28] have demonstrated that :C(Ph)Br and :C(Ph)Cl were generated as free carbenes from *t*-BuOK and the corresponding benzal halide if the macrocyclic polyether, 18-crown-6, was added to preclude carbenoid formation. The crown ether-base engendered species had selectivities for their cycloadditions to various alkenes identical with those of the corresponding diazirine-photogenerated carbenes. Equivalence between thermally (KX leaving group) and photolytically (N_2 leaving group) generated species implies a common intermediate that is the free, non-excited, singlet carbene.

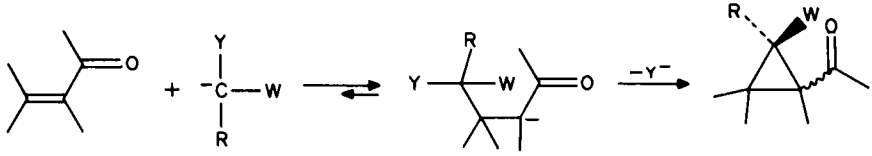


(24) (25) (26)

Chlorophenylcarbene (**27**) is classified as an electrophilic species (see Table 1). Nevertheless, Doyle and coworkers[52] have reported that vinyl ethers, α,β-unsaturated esters and nitrile exhibit similar reactivity toward :C(Ph)Cl generated by thermal (80 °C) decomposition of 3-chloro-3-phenyldiazirine. Since the reaction of :C(Ph)Cl with diethyl maleate (**28**) gave the three possible stereoisomeric substituted cyclopropanes (**31**–**33**), it

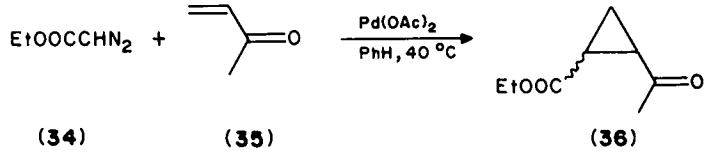


was proposed that the reaction is not a concerted [2 + 1] cycloaddition but a multistep process involving the intermediacy of an ylide (**29**), resulting from the condensation of an ester group of **28** onto the electrophilic carbene which, in turn, can add in a 1,4-fashion to diethyl maleate (**28**) giving intermediate **30** whose lifetime allows bond rotation to occur and formation of the products **31**–**33**. Many multi-step cyclopropanation methods are based on the principle of the intermediacy of species similar to **30**. They imply a first step that is the Michael addition of a stabilized, substituted methyl anion leading to an enolate that undergoes an intramolecular displacement, as summarized in Scheme 4[53].



SCHEME 4

As for the cyclopropanation of enones with diazomethane[32], the transfer of substituted carbenes to olefins can be catalyzed by transition metal salts or complexes[54]. For instance, in the presence of $Pd(OAc)_2$, ethyl diazoacetate (**34**) reacts with methyl vinyl ketone (**35**) already at 40 °C in benzene to give the corresponding cyclopropylketone (**36**) in 76% yield[55]. Copper[56] and rhodium catalysts[57] were also found to be useful in cyclopropanations with **34**. The reaction can be rendered enantioselective by complexation of the metal with optically active ligands[58]. Cyclopropanations of olefins with diazoalkanes have been also found to be catalyzed by single electron acceptors such as tris(2,4-dibromophenyl)aminium hexachloroantimoate. These reactions are mechanistically cation–radical chain processes in which the olefin is ionized first, before ethyl diazoacetate (**34**)[59]. This fact thus suggests that conjugated enones should be less likely than electron-rich olefins to undergo the radical-cation catalyzed/initiated cyclopropanation.



D. Reactions with Nitrenes

Nitrenes[2,60], :NR, are the nitrogen analogs of carbenes, and most of the properties presented for the carbenes also apply to them. Nitrenes are too reactive for isolation under normal conditions. Alkylnitrenes have been isolated by trapping in matrices at 4 K[61] while aryl nitrenes, which are less reactive, can be trapped at 77 K[62]. The ground state of :NH, and probably of most substituted nitrenes, is a triplet.

Fast equilibria between singlet and triplet spin states of nitrenes has also been noted[63,64]. By analogy with Skell's rule involving carbenes, the singlet nitrenes are supposed to add stereospecifically to an olefin whereas the triplet nitrenes give stereoisomeric adducts. Because of the intrinsic greater electronegativity of the nitrogen atom compared to the carbon atom, nitrenes, :NR, are expected to be more electrophilic than the corresponding carbenes, :C(H)R, and thus will be reluctant to add to electron-poor alkenes such as the conjugated enones. Therefore, the best chances for observing cheletropic reactions of enones with nitrenes imply that the latter bear electron-releasing substituents such as in :N-OMe[65] or N-nitrenes[66,67]. These species have probably singlet ground states which means that their additions to alkenes are stereospecific and, unlike most other nitrenes, do not insert readily into C—H bonds[67].

As for the generation of carbenes, nitrenes can be generated by either α-elimination (e.g. equation 7)[63] or by thermal or photolytic decomposition of azides (e.g. equation 8)[60,68]. A third method, specific for the generation of S-, O- or N-nitrenes, involves the oxidation of the corresponding sulphenamide[64], alkoxyamine[65] or dialkylhydrazine[66], respectively, with lead tetraacetate (see equation 9).

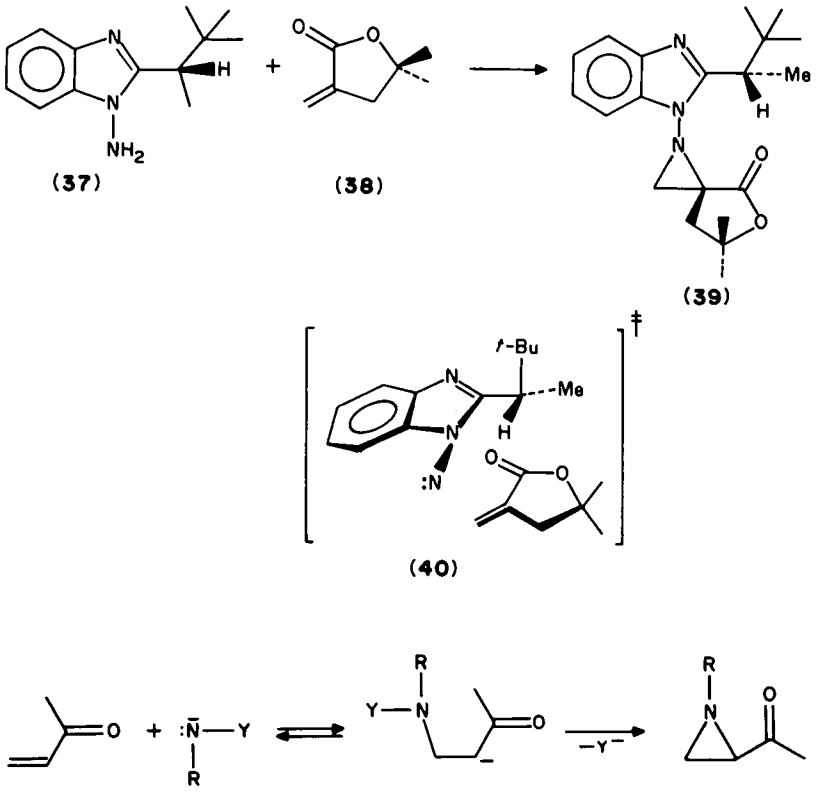
$$ArSO_2NHCOOEt \xrightarrow{base} :NCOOEt + ArSO_2H \tag{7}$$

$$R\bar{N}—\overset{+}{N}{\equiv}N: \xrightarrow[\text{or } \Delta]{h\nu} :NR + N_2 \tag{8}$$

$$ZNH_2 + Pb(OAc)_4 \longrightarrow :NZ + Pb(OAc)_2 + 2AcOH \tag{9}$$
$$(Z = ArS,\ MeO,\ R_2N)$$

The latter procedure (equation 9) has been applied in the chiral aziridination of alkenes, and particularly of γ,γ-dimethyl-α-methylene-γ-butyrolactone (**38**)[68]. Oxidation of N-aminobenzimidazole (**37**) with lead tetraacetate in CH_2Cl_2 in the presence of **38** led to the formation of one single stereoisomer (**39**) isolated in 69% yield. The results were interpreted in terms of 'syn-selectivity' typical of singlet nitrene additions to alkenes[69]. Attack of the N-nitrene derived from **37** with **38** is believed to occur via a transition state geometry as shown in **40**, in which the benzimidazole and butyrolactone are contained in parallel planes.

Although no examples have yet been reported, this method of chiral aziridination should be applicable to enones. Finally, one should mention that, as for their cyclopropanation (see Scheme 4), Michael acceptors such as α,β-unsaturated ketones (and aldehydes) can be converted into the corresponding aziridines without the generation of nitrenes via two step processes as summarized in Scheme 5[70].

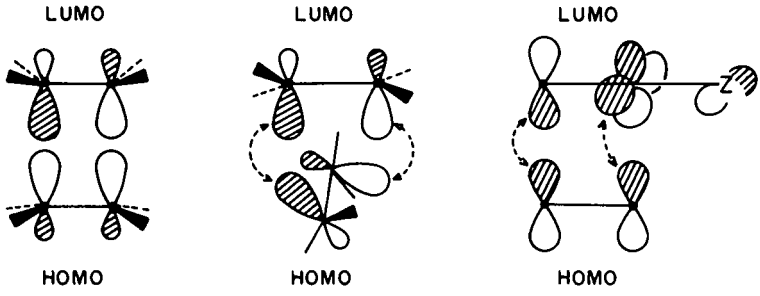


SCHEME 5

III. [2 + 2] CYCLOADDITIONS

According to the Woodward–Hoffmann rules[4], the concerted suprafacial $[{}_{\pi}2_s + {}_{\pi}2_s]$ cycloaddition (C_{2v} transition state) of two olefinic moieties is thermally forbidden. This is also true for the reverse reaction, called a cycloreversion. The same rules predict that the concerted suprafacial, antarafacial $[{}_{\pi}2_s + {}_{\pi}2_a]$ mode of addition (C_2 transition state) is thermally allowed. The frontier molecular orbital (FMO) theory[24] applied to these reactions states that no stabilizing LUMO–HOMO interactions are possible between the two reacting alkenes in the $[{}_{\pi}2_s + {}_{\pi}2_s]$ mode (see **41**), whereas such stabilizing interactions are possible for the $[{}_{\pi}2_s + {}_{\pi}2_a]$ mode of cycloaddition (see **42**). The latter mode, however, requires a significant distortion of the two ethylene units to reach significant overlap between their FMOs, thus making the thermal reaction less facile, expect for cycloadditions involving allenes, cumulenes of ketenes[4,24] (see **43**)[71].

The relatively high energy barrier of $[{}_{\pi}2_s + {}_{\pi}2_s]$ cycloadditions is due to the lack of efficient assistance between the bond breaking (two π bonds) and bond forming (two σ bonds) processes. The correlation diagram reproduced in Figure 2 illustrates this fact. Indeed, the ground state configuration ϕ_0 of two ethylene molecules approaching the C_{2v} symmetrical transition state of the concerted $[{}_{\pi}2_s + {}_{\pi}2_s]$ cycloaddition does not mix with any of the singly excited configurations ϕ_1, ϕ_2, ϕ_3 or ϕ_4 for reason of symmetry. However,



(41) $[{}_{\pi}2_s + {}_{\pi}2_s]$ (42) $[{}_{\pi}2_s + {}_{\pi}2_a]$ (43)

interaction between ϕ_0 and the doubly exbited configuration ϕ_5 is possible. As the latter is very high in energy, the resulting energy barrier of the thermal reaction remains relatively high. The $[{}_{\pi}2_s + {}_{\pi}2_a]$ cycloaddition in said to be 'photochemically allowed' since the first excited configurations of reactants (ϕ_1) and products (ϕ'_1) have the same symmetry.

Substitution of the reactants introduces two important modifications. First, the geometry of the transition state of the $[{}_{\pi}2_s + {}_{\pi}2_s]$ cycloaddition may deviate from the C_{2v} symmetry, i.e. the two σ bonds are no longer generated in a synchronous fashion, and second, the substituents may stabilize charge-transfer configuration $\phi_{C.T.}$, $\phi'_{C.T.}$ which can

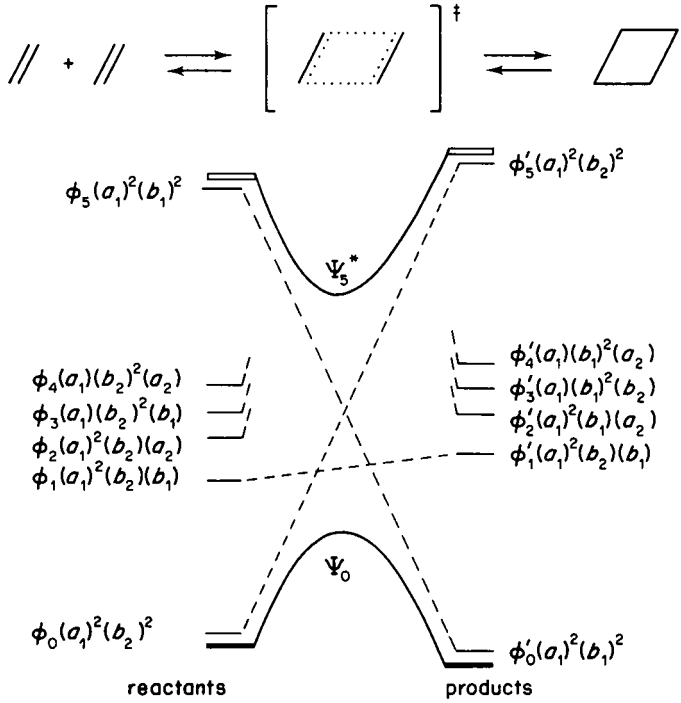


FIGURE 2. Correlation diagram for the $[{}_{\pi}2_s + {}_{\pi}2_s]$ cycloaddition (C_{2v} transition state)

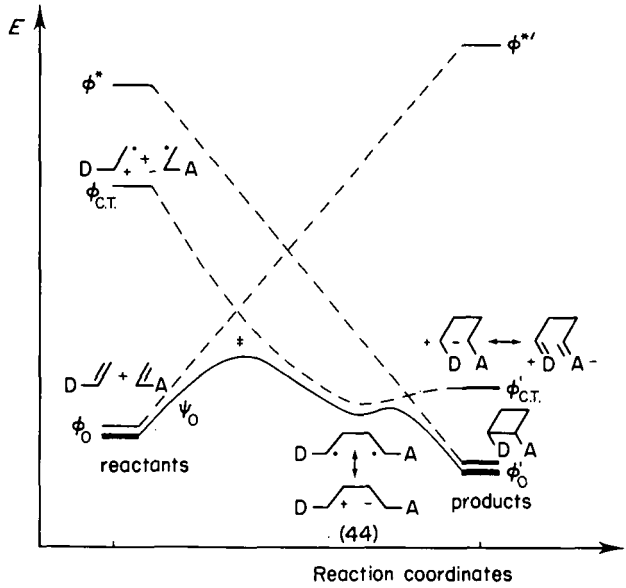
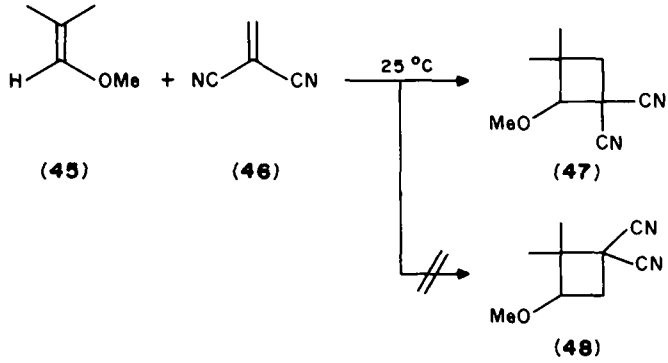


FIGURE 3. Energy diagram representing various electronic configurations of a [2 + 2] cycloaddition involving non-symmetrical reactants and products. The energy of the charge-transfer configuration of the reactants is given by $E_{C.T.}$ = IE(electron-rich olefin) − EA(electron-poor olefin) where IE denotes ionizing energy and −EA denotes electron affinity; ϕ_0 and ϕ_0' denote the ground state configurations of reactants and products, respectively; ϕ^* and ϕ'^* denote electronically excited configurations; $\phi_{C.T.}$ and $\phi'_{C.T.}$ denote charge-transfer configurations that can mix with ϕ_0 and ϕ'_0, respectively, to give the reaction hypersurface Ψ_0. In the early stage of the cycloaddition, the charge-transfer configuration $\phi_{C.T.}$ follows a descending hypersurface as the chemical process corresponds to the collapse of two species with opposite charges. In the early stage of the cycloreversion, the charge-transfer configuration $\phi'_{C.T.}$ also follows a descending hypersurface as the bond-breaking process relieves some steric strain between the substituents A and D. The solvent may also intervene and affect the shape of the hypersurface $\phi_{C.T.} \leftrightarrow \phi'_{C.T.}$

mix with the ground state configuration ϕ_0, ϕ'_0, and thus reduce the energy barrier of the overall thermal reaction. This is illustrated by the energy diagram of Figure 3 for the [2 + 2] cycloaddition of an electron-rich olefin (substituted by a donor substituent D) and an electron-poor olefin (substituted by an electron-attracting group A). Depending on the type of substituents A and D, the cycloaddition of the unsymmetrical reactants may go through one or two reactive intermediates. One can imagine the intervention of a charge-transfer complex preceding the transition state or a diradical-zwitterion intermediate (**44**) following the rate-determining step, as shown in Figure 3.

The thermal additions of alkoxy-substituted olefins to electron-poor olefins are very facile. For instance, 1-methoxy-2-methylpropene (**45**) adds to ethylene-1, 1-dicarbonitrile (**46**) in benzene at 25 °C ($k = 3.16 \times 10^{-4}\,dm^3\,mol^{-1}\,s^{-1}$) and gives the cyclobutane derivative **47** with high regioselectivity[72].

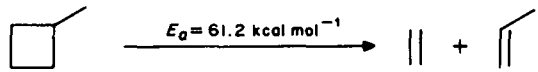


Substituent effects on thermal pericyclic reactions can be interpreted in terms of substituent effects on the stability of ionized species. Thus, predictions on the reactivity (rate) and regioselectivity (product distribution under conditions of kinetic control) can be made simply by examining the substituent effects on the charge-transfer configurations that can be written for the transition states of these reactions [e.g. diradical↔zwitterion (**44**), Figure 3]. If the substituents do not stabilize charge species efficiently they will offer little assistance to the reaction which will therefore have little solvent dependence. In contrast, if the substituents strongly stabilize the charge-transfer configurations, the rate of the pericyclic reaction may be solvent-dependent. For instance, the addition of ethylenetetracarbonitrile to verbenene is about 800 times faster in 1,2-dichloroethane than in butyl ether at 60 °C[73].

At the limit, a diradical↔zwitterion transition state can be sufficiently stabilized by substitution and solvation to become a true reactive intermediate[74]. Under these circumstances, the reactive intermediates can be considered as ion-pair intermediates. In these, the rotation about the σ bonds might be partly blocked owing to electrostatic interactions, thus maintaining a stereocontrol in the [2 + 2] cycloaddition.

A. Thermal and Lewis Acid Catalyzed [2 + 2] Cycloadditions

Conjugated enones are olefins substituted with an electron-withdrawing group (A = COR) and, as such, are expected to add to electron-rich alkenes in a [2 + 2] fashion under thermal conditions. The activating effect of the carbonyl function is illustrated by comparison of the energy barriers of the [2 + 2] cycloreversions of the substituted cyclobutanes shown in equations 10–13[75].



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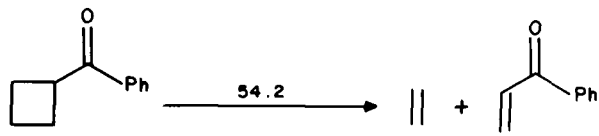

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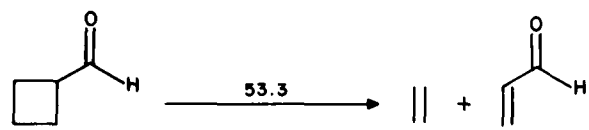

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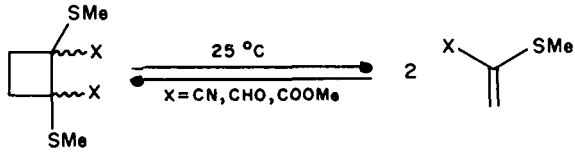
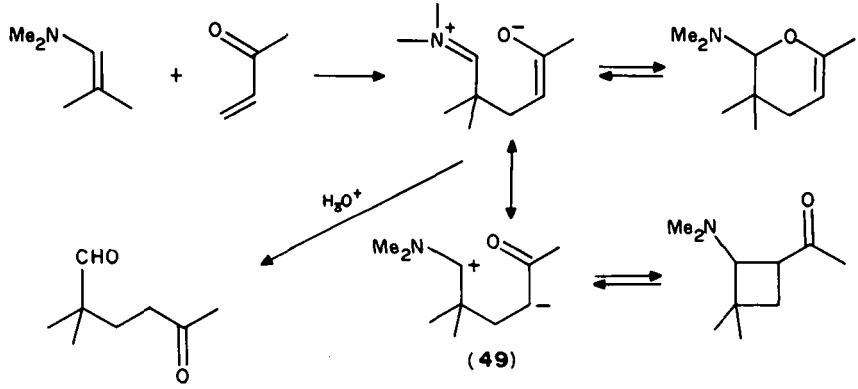


(13)

One of the earliest examples of a thermal cycloaddition of an enone to an olefin was reported by Fleming and Karger (Scheme 6)[76]. They found that the reaction of *N*,*N*-dimethylisobutenylamine with methyl vinyl ketone gives 2-dimethylamino-3,3,6-trimethyl-3,4-dihydro-2*H*-pyran as the first-formed product. The reaction of this adduct, however, indicated a ready equilibration of the dihydropyran with methyl 2-dimethylamino-3, 3-dimethylcyclobutyl ketone through the ammonium enolate intermediate **49**. Other enamines and methyl vinyl ketone were found to behave similarly[76].



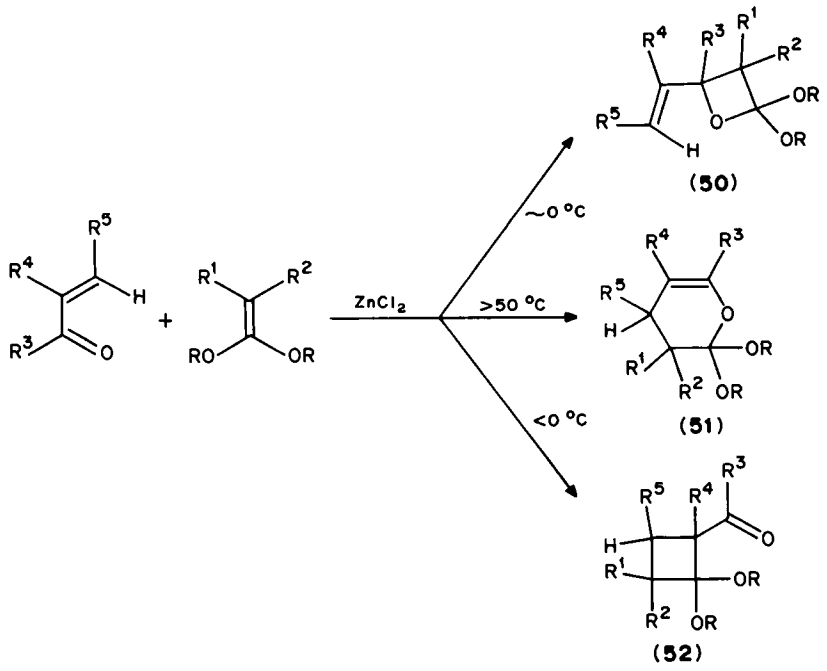
SCHEME 6

A priori, α,β-unsaturated ketones (and aldehydes) can add to ketene acetals (1,1-dialkoxyethylenes) and give three different types of cycloadduct (Scheme 7)[77]. In general, at low temperature and in the presence of Lewis acid catalysts such as $ZnCl_2$, capable of coordinating to the carbonyl group of the enone, oxetanes (**50**) are the main products[78]. In terms of FMO theory, complexing with the carbonyl oxygen of the Lewis acid catalyst not only lowers the energy of the LUMO of the enone, but also leads to an increased atomic coefficient at the carbon atom of the carbonyl group for that LUMO, thus making the carbonyl group more electrophilic than the conjugated C=C double bond and favouring the oxetane formation. At higher temperature, the oxetane formation is reversible and the dihydropyrans (**51**), which are thermodynamically more stable, are the ultimate products. Cyclobutanes (**52**) are only partly formed when tetramethoxyethylene is reacted with α,β-unsaturated carbonyl compounds having no β-substituents. The formation of cyclobutanes is favoured when ketene acetals react with α,β-unsaturated aldehydes under high pressure without a Lewis acid catalyst (see e.g. equation 14)[79].

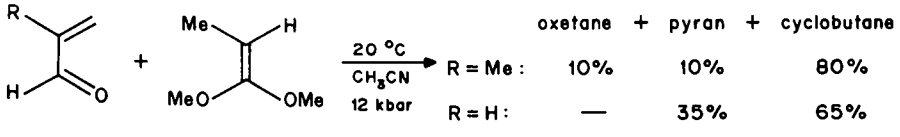
At high pressure and in the absence of Lewis acid, α,β-unsaturated ketones undergo exclusively 1,4-alkylation (equation 15)[80].

2-Phenylthiocyclobutenyl ketones were produced by the polar [2+2] cycloadditions of alkenyl sulphides to α,β-unsaturated ketones, in the presence of $AlCl_3$ or $TiCl_4$ as catalyst, at −78 °C to −30 °C (equation 16)[81].

Ficini and Krief[82] studied the reactions of acyclic conjugated enones and ynamines. Under thermal conditions they form generally 2-amino-γ-pyrans (equation 17). With α,β-



SCHEME 7



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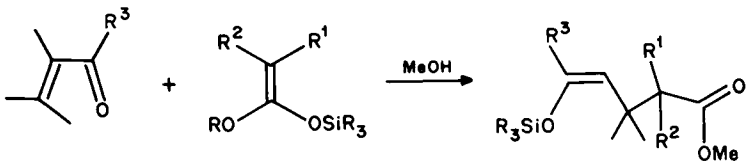

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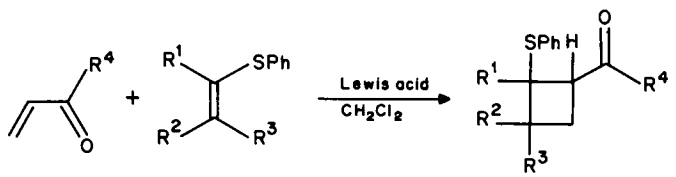
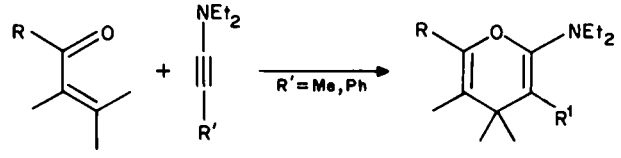


(16)

unsaturated aldehydes, the reactions with diethylaminoacetylenes give mixtures of the corresponding γ-pyranes (**53**) and dienecarbamides (**54**). The latter result probably from initial [2+2] addition of the ynamines to the carbonyl group (equation 18).



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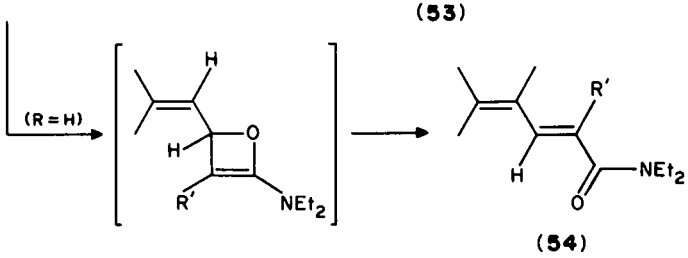
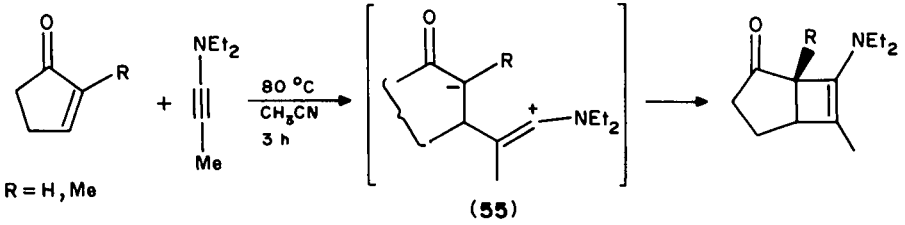


(54)

(18)

With cyclopent-2-en-1-one (equation 19) and carvone (equation 20) the corresponding [2+2] cycloadducts are obtained in good yield and with high regioselectivity[83]. The latter can be interpreted in terms of a zwitterion intermediate of type **55**, analogous to **44** shown in Figure 3, and in which the carbonyl group plays the role of an electron-withdrawing substituent and the diethylamino group that of an electron-releasing substituent.



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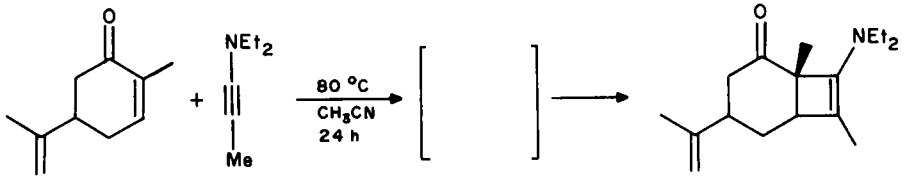

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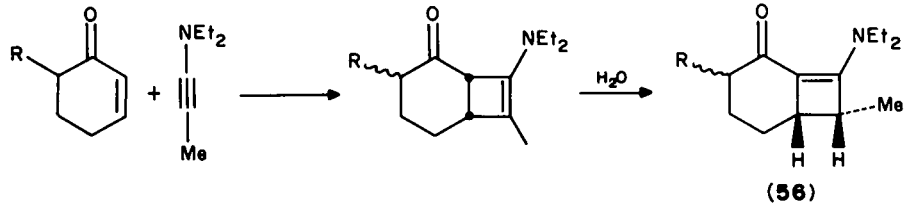
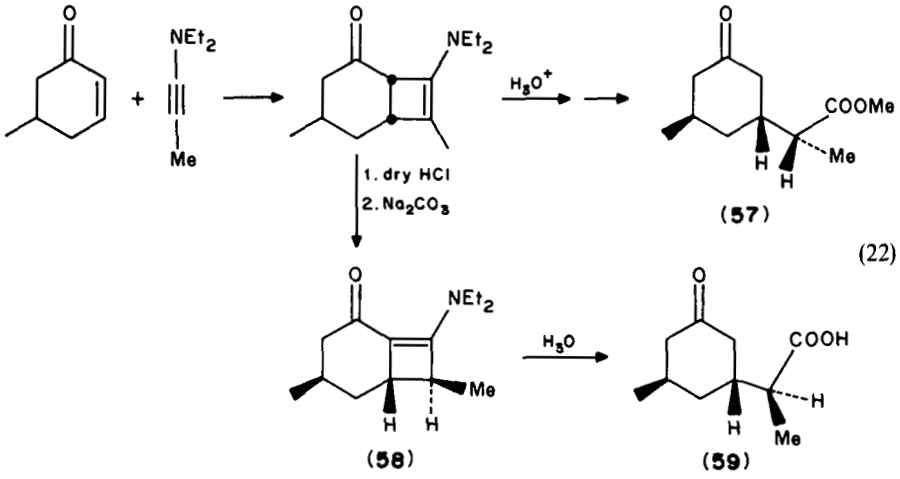


(56)

(21)

The aminocyclobutenes so obtained are useful synthetic intermediates. For instance, in the presence of acids, they can be isomerized into their more stable conjugated enones derivatives (see e.g. **56**, equation 21[84] and **58**, equation 22[85]). The latter can be hydrolyzed stereoselectively into the corresponding carboxylic derivatives[83] (e.g. **57**, **59**). Interestingly, the [2+2] cycloadditions of 5-methyl- (equation 22) and 4-methylcyclohex-2-en-1-one (equation 23)[86] are highly facial selective, the ynamine attacking preferentially the face of the enone *anti* with respect to the remote methyl substituent.



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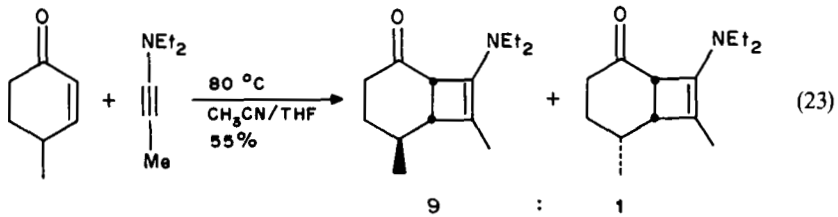
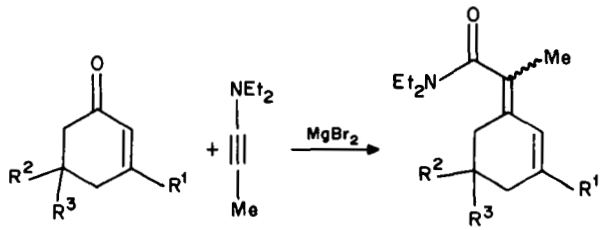


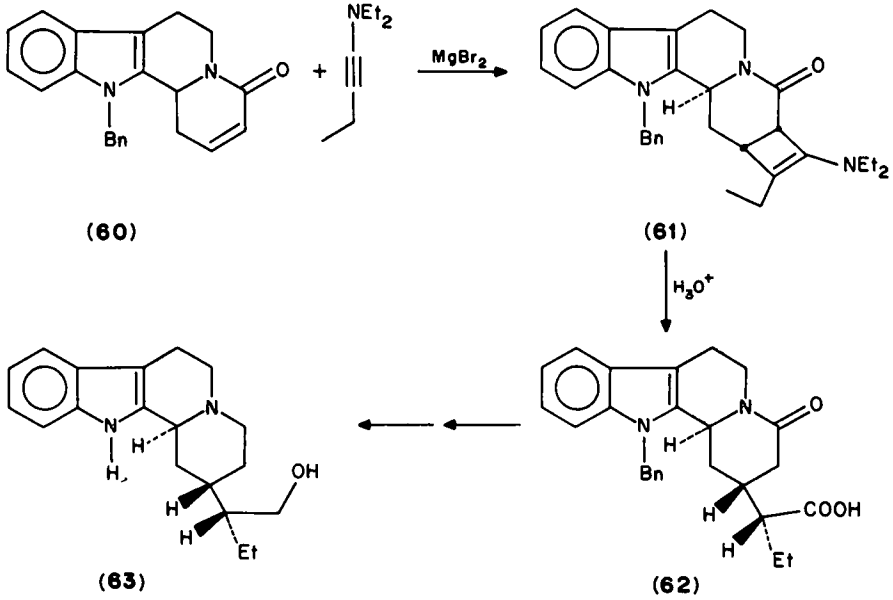
(23)

The influence of $MgBr_2$ on the regioselectivity of the cycloaddition of ynamines to cycloalkenones has been explored[87]. The reaction of various cyclohex-2-en-1-ones in the presence of $MgBr_2$ does not afford the corresponding cyclobutene derivatives, but proceeds by attack of the ynamine onto the carbonyl group, giving the corresponding dienecarbamides (equation 24). In contrast, cyclopent-2-en-1-one and 2-methylcyclopent-2-en-1-one add to ynamines giving the corresponding cyclobutene derivatives both in the presence and absence of the Lewis acid catalyst[87].

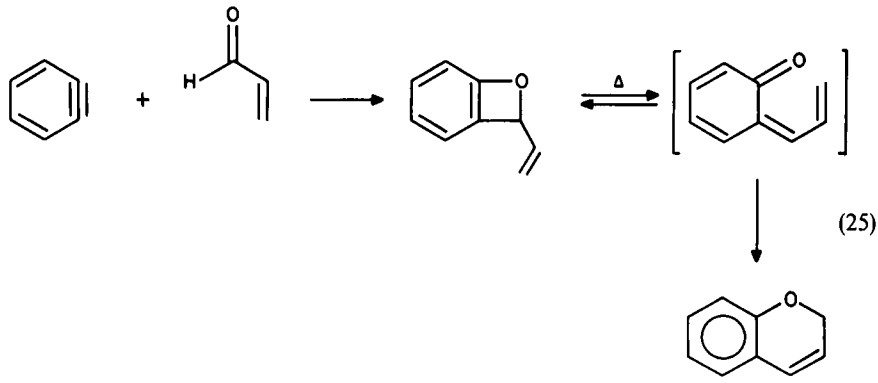


(24)

A stereoselective synthesis of (±)-dihydroantirhine (**63**) based on the facial selective [2 + 2] addition of 1-(*N*, *N*-diethylamino)butyne to lactame **60** has been realized[88]. In this case, $MgBr_2$ was used as a catalyst and the reaction performed in boiling tetrahydrofuran. Hydrolysis of adduct **61** with 10% aqueous HCl to 20 °C gave the acid **62**, which was then transformed into the corresponding methyl ester. Reduction with $LiAlH_4$ followed by debenzylation of the indole gave **63**[88].

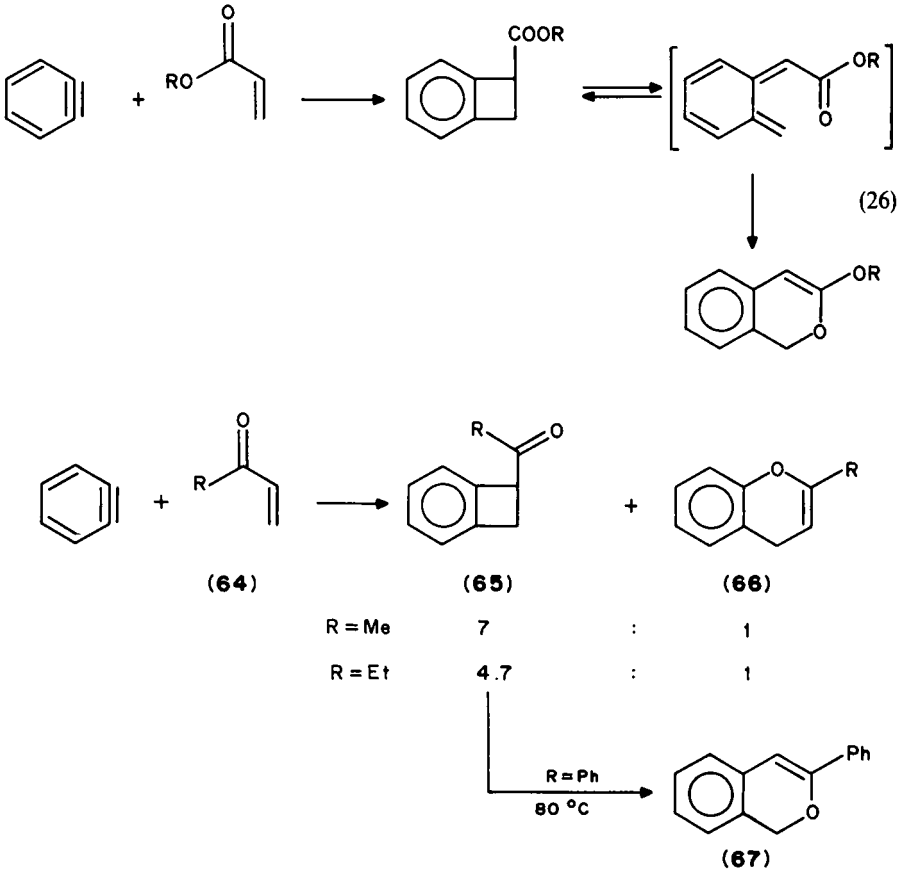


The reaction of benzyne with α,β-unsaturated aldehydes gives mostly products derived from initial [2_O+2] cycloaddition of the carbonyl group (equation 25)[89]. In contrast, α,β-unsaturated esters, products resulting from initial [2+2] cycloaddition of the C=C double bond, are preferred (equation 26)[90]. Interestingly, the reaction of benzyne (generated by thermal decomposition of benzenediazonium-2-carboxylate) with α,β-unsaturated ketones (**64**, R = Me, Et) gave mixtures of adducts resulting from the concurrent [2+2] (**64** → **65**) and hetero Diels–Alder [$2+4_O$] (**64** → **66**) cycloadditions.

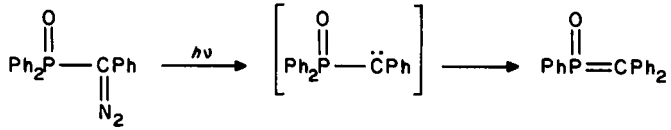


(25)

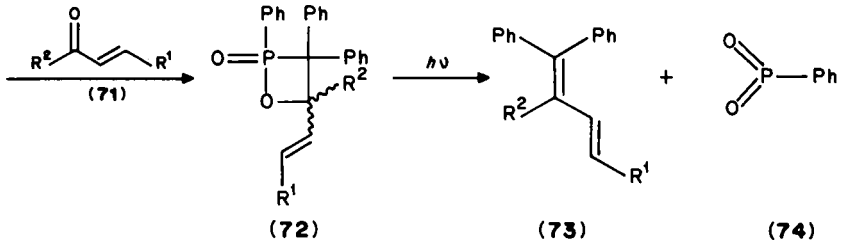
With phenyl vinyl ketone (**64**, R = Ph) only product **67** was isolated. It arises from [2 + 2] cycloaddition of the C=C double bond of the enone, giving the corresponding benzocyclobutene derivative (**65**, R = Ph) which is isomerized into the more stable system **67** under the conditions of its formation[91].



Photolysis of **68** produces the carbene **69**, which is transformed into the short-lived phosphene **70** by phenyl group migration. **70** reacts with α,β-unsaturated ketones (**71**) in a [2 + 2] cycloaddition and gives the corresponding $1,2\lambda^5$-oxaphosphetanes (**72**). No products arising from the cycloaddition of the C=C double bond of **71** are observed consistently with the higher affinity of phosphor atom for oxygen than for carbon atom. The heterocycles **72** undergo a photofragmentation, which leads to olefins **73** and heterocumulene **74**[92].

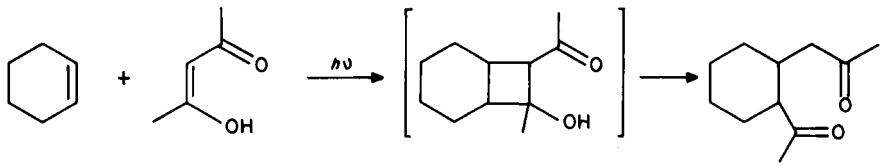


(**68**) (**69**) (**70**)

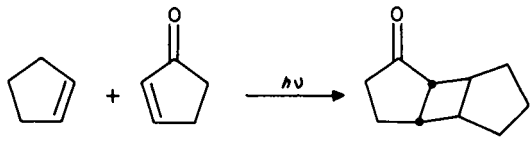


B. Intermolecular [2 + 2] Photocycloadditions

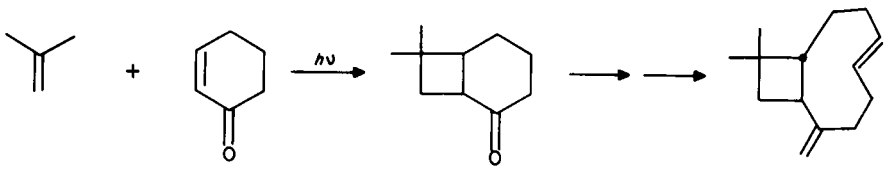
Prior to 1962 few examples of the photochemical addition of an enone to an olefinic moiety were found in the literature, and these were concerned either with dimerization or with intramolecular photoaddition (see Section III.C). In 1962, de Mayo and coworkers[93] reported on the photoreaction of cyclohexene with enolized acetylacetone (equation 27); within months, Eaton[94a] published the related photocycloaddition of cyclopent-2-en-1-one to cyclopentene (equation 28) and pointed out the potential of this enone photoannelation procedure in synthesis[94]. This estimate was correct and the de Mayo photocycloaddition[95] has been widely used for the construction of complex polycyclic compounds which could be transformed in several instances, into natural products[95,96]. The earlier examples include the synthesis of caryophyllene (equation 29)[97,98] and α-caryophyllene alcohol (equation 30)[99] by Corey and coworkers, of bourbonenes (equation 31) by White and Gupta[100], of γ-tropolone (equation 32) and β-himachalene (equation 33) by de Mayo and coworkers[101], of atisine (equation 34) by Guthrie and collaborators[102], of loganin (equation 35) by the group of Büchi[103] and of the prostanoic acid skeleton (equation 36) by Bagli and Borgi[104].



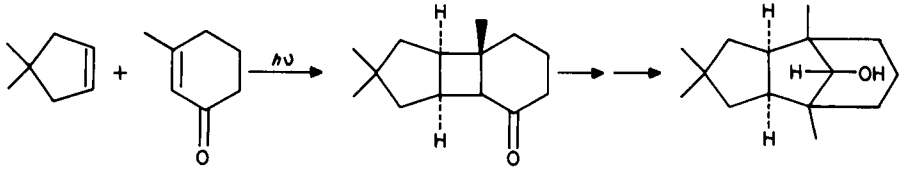
(27)



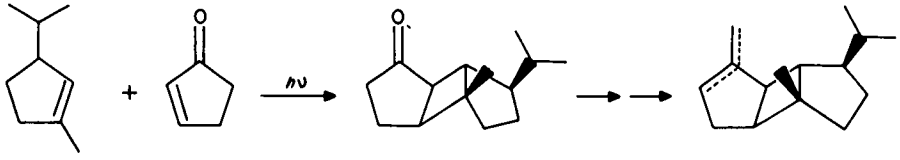
(28)



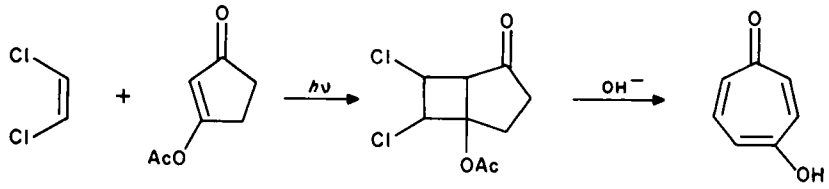
(29)



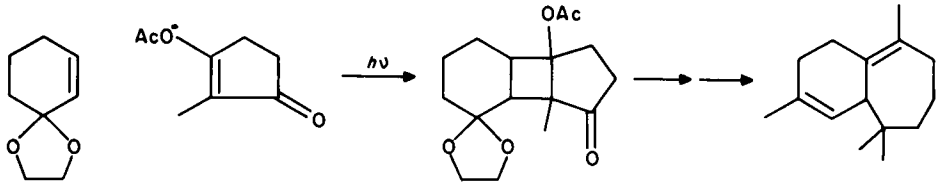
(30)



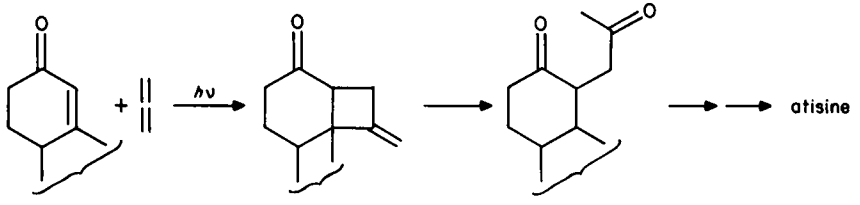
(31)



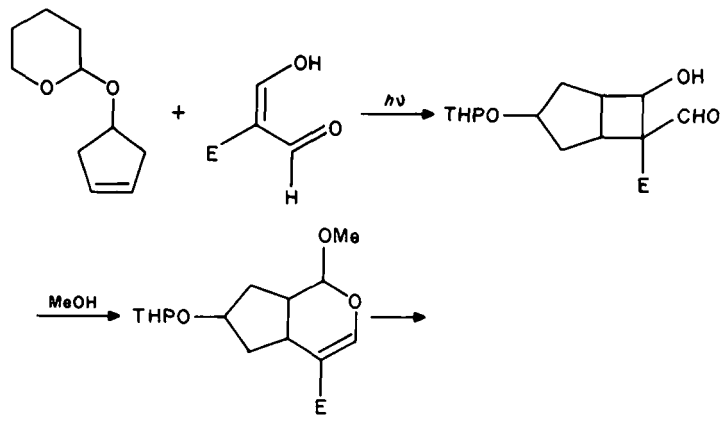
(32)

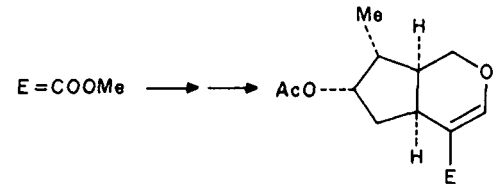


(33)

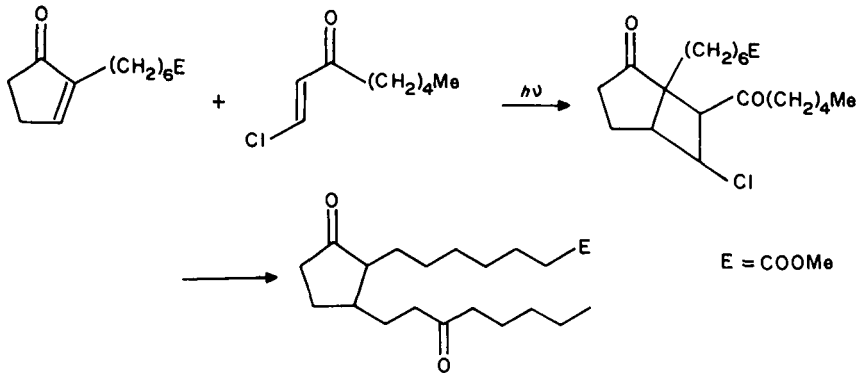


(34)





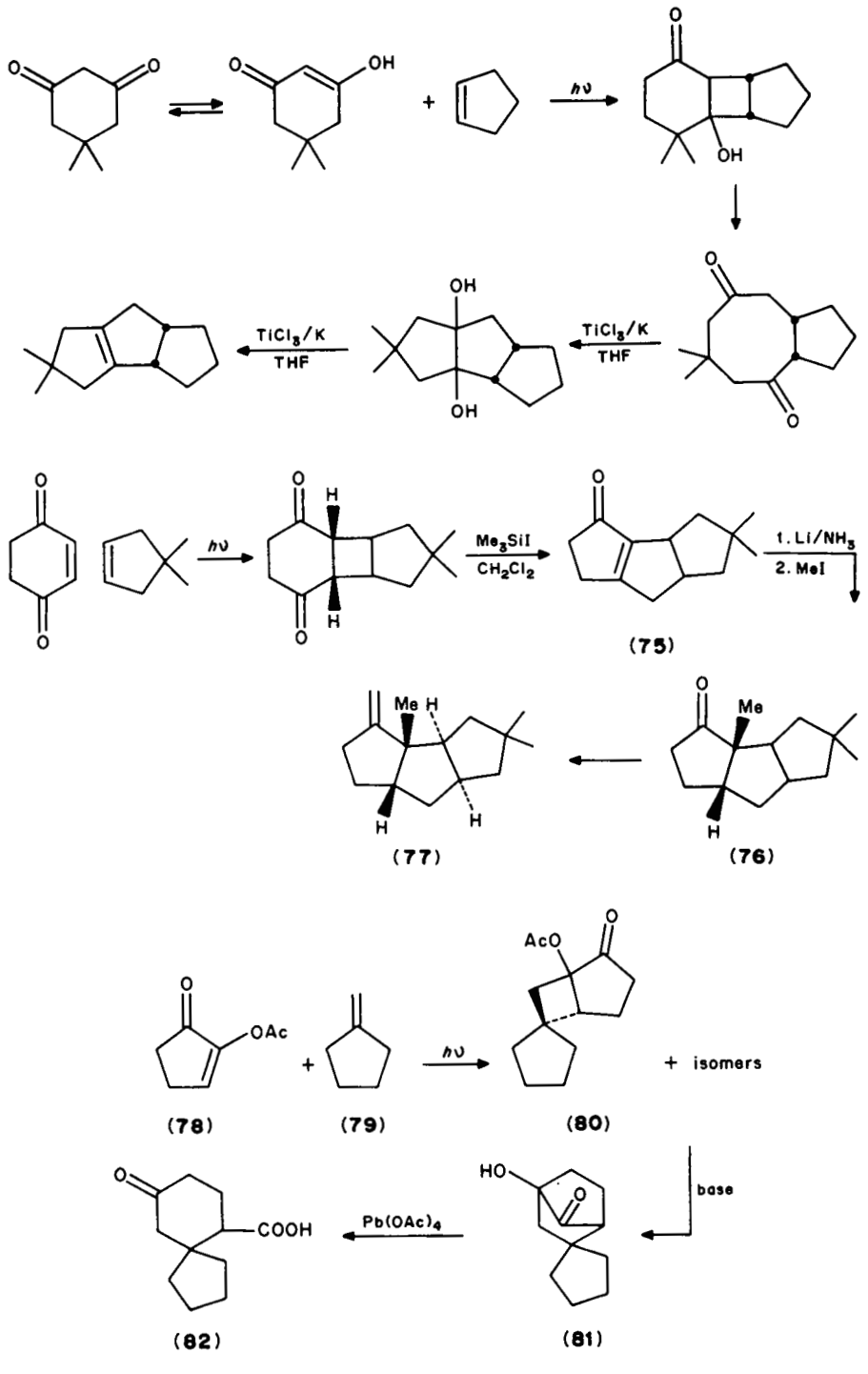
(35)

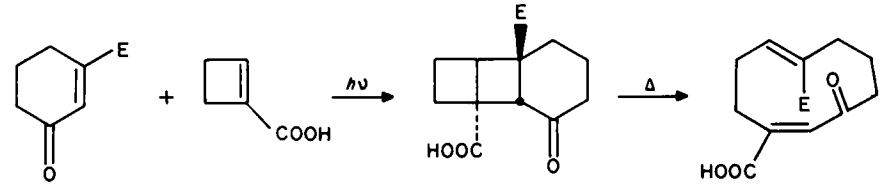


E = COOMe (36)

More recently, an efficient synthesis of the tricyclo[6.3.0.0^{2,6}]undecane systems has been described[105]. It features a photochemical annelation of dimedone, an enolizable β-diketone[105], to produce the corresponding 1,5-diketone (see below). Subsequent intramolecular reductive coupling with $TiCl_3$/K in THF produced the tricyclic systems shown. The *cis, anti, cis*-tricyclo[6.3.0.0^{2,6}]undecane system is found in the carbon skeleton of the hirsutane group of sesquiterpenes. An extremely short synthesis of hirsutene (**77**) has been described[106] starting from the [2+2] photocycloaddition of cyclohex-2-ene-1,4-dione to 4,4-dimethylcyclopentene. The cyclobutane derivative so obtained was treated with Me_3SiI in CH_2Cl_2, leading to **75**. Reduction with Li in NH_3 followed by addition of MeI gave **76** and treatment with $Ph_3P{=}CH_2$ afforded hirsutene (**77**).

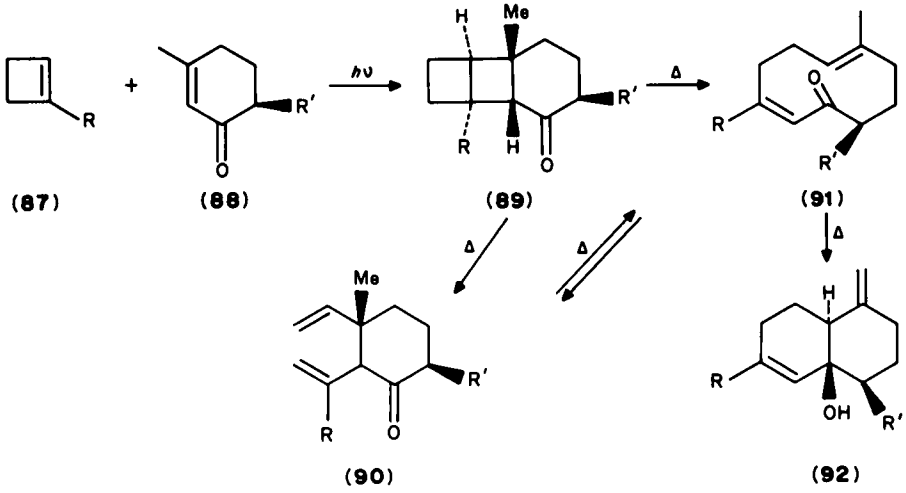
An approach to spiro[4.5]decan-7-ones and the acorenones based on the photoaddition of enone **78** to **79** has been proposed by Lange and Otulakouski[107]. It features the base-induced transformation **80** → **81** and oxidation **81** → **82**. The same group[108] has developed a useful procedure for the synthesis of cyclodeca-1,5-diene systems (e.g. **86**) based on the photocycloaddition of enone **83** to **84**. The photoadduct **85** was esterified and then thermolyzed (164 °C) into **86**.

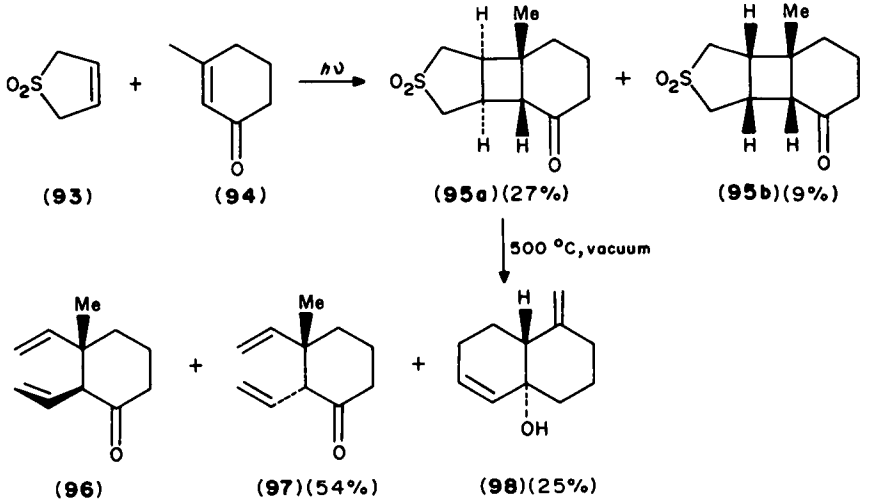

hν
TiCl3/K
THF
TiCl3/K
THF
Me3SiI
CH2Cl2
1. Li/NH3
2. MeI
(75)
(77)
(76)
(78)
(79)
(80)
+ isomers
base
Pb(OAc)4
(82)
(81)



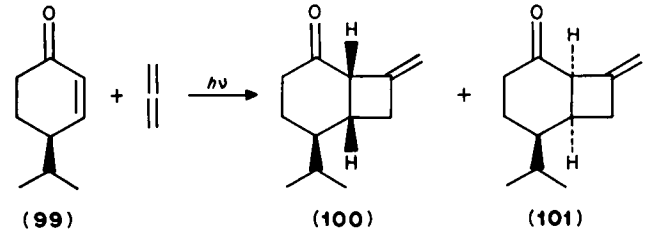
(83) (84) E=COOMe (85) (86)

The [2+2] photocycloaddition between the substituted cyclobutene **87** and chiral cyclohexenones **88** has afforded a convenient entry into the stereospecific synthesis of elemane (**90**), germacrane (**91**) and cadinane (**92**) sesquiterpene skeleton containing a 1,5-diene unit. In these reactions the cyclobutene plays the role of a 1,2-divinyl synthon[109]. The same is true with 2,5-dihydrothiophene 1,1-dioxides(sulpholenes), as illustrated by **93** + **94** → **95a** + **95b** → **96** + **97** + **98**[110].



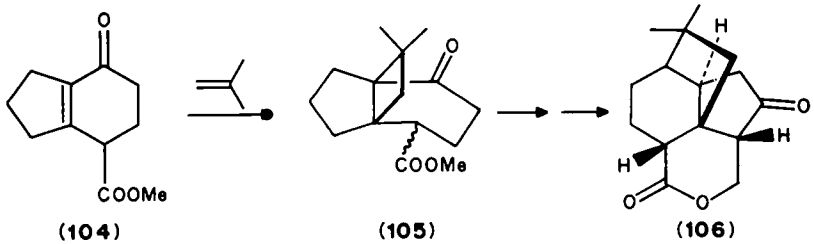


The photoaddition of allene to enone **99** yields a 2:1 mixture of adducts **100** and **101**, which were converted to diene **102**. Irradiation of **102** yielded the *trans* isomer **103**, which was subsequently transformed into a pheromone of the American cockroach[111].

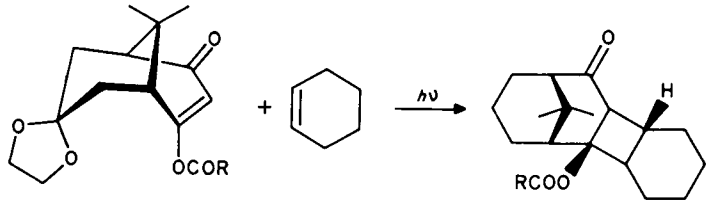


(99) (100) (101) (102) (103)

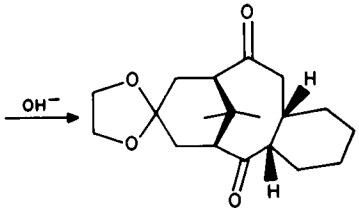
Irradiation of enone **104** with 2-methylpropene afforded a 2:1 mixture of the *syn* and *anti* isomeric adducts **105**, which were then transformed into quadrone **106**[112].



(104) (105) (106)

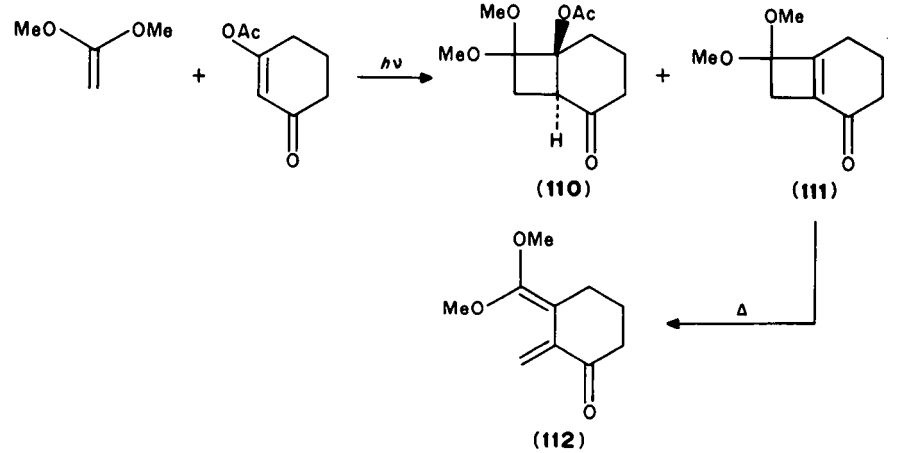


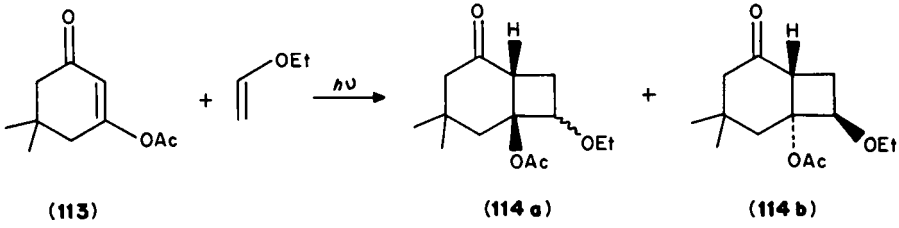
(107) (108)

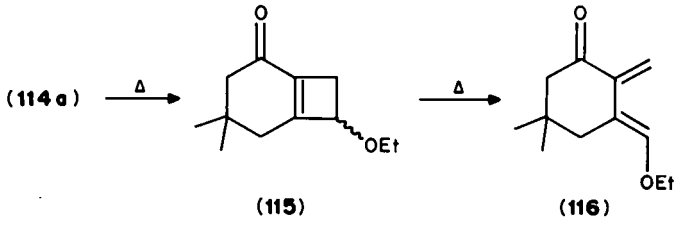


(109)

The tricyclic compound **109**, which possesses the taxane skeleton, has been prepared from **107** and cyclohexene via the photoadduct **108**[113]. Photochemically induced [2+2] cycloadditions of cycloalk-2-en-1-ones have also been the key step in the total syntheses of grandisol[114], lineatin[115,116] and stemarin[117]. Irradiation of ketene dimethyl acetal (1, 1-dimethoxyethylene) and 3-acetoxycyclohex-2-en-1-one in ether produced a mixture of *trans*-fused adduct **110** and cyclobutene **111**. The latter substance arose probably from facile elimination of AcOH from the *cis*-fused isomer of **110**. **110** and **111** treated with alumina produced **111** (60% yield), a useful synthon for the preparation of polycyclic systems via Diels–Alder addition of dienones **112** engendered through thermolysis of **111**[118].

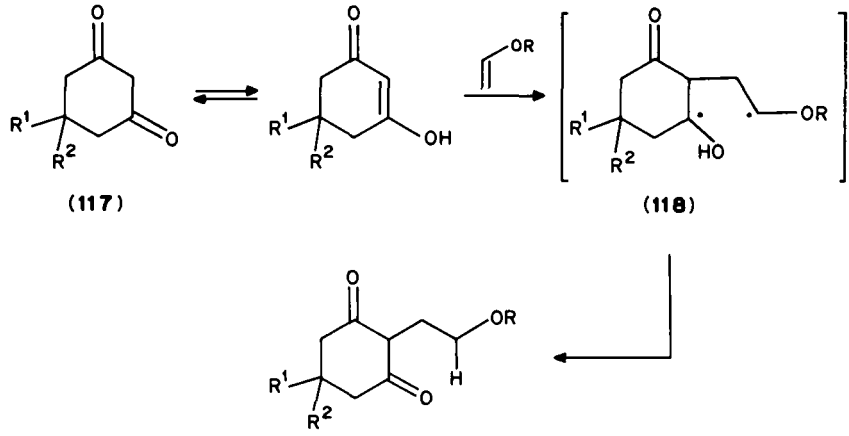






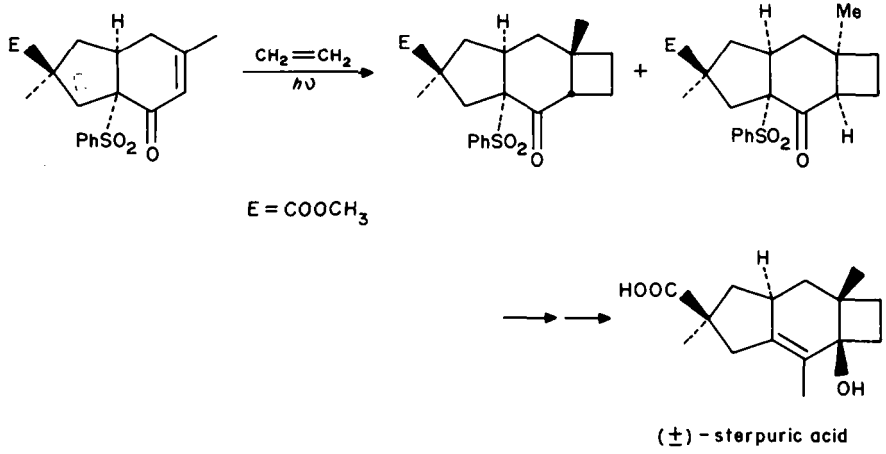
Similarly, the adducts **114** obtained from [2 + 2] photocycloaddition of ethyl vinyl ether to 1,3-dione enol acetate (**113**) rapidly loses AcOH, producing the ethoxycyclobutene **115** on heating. The latter undergoes ring opening to the substituted diene **116**, which reacts readily with a variety of dienophiles to afford polycyclic, polyfunctional systems[119a].

Cyclohexane-1,3-diones **117** may be photochemically 2-alkylated with enol ethers through a process that involves probably the intermediacy of 1,4-diradicals (**118**) as shown in Scheme 8[119b].



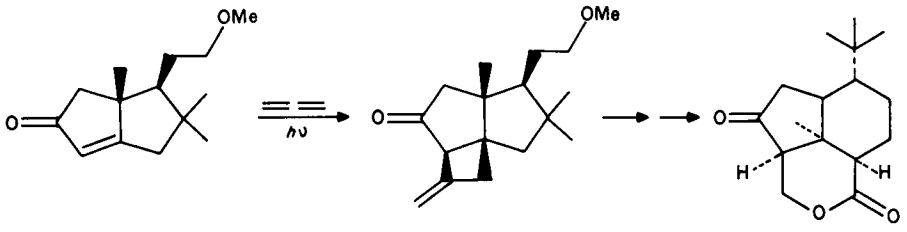
SCHEME 8

Paquette and coworkers[120a] reported recently a total synthesis of (±)-sterpuric acid featuring a photocycloaddition of ethylene to a cyclohex-2-en-1-one derivative. The reaction gave a 71:23 mixture of the two possible *cis*-fused cycloadducts shown.

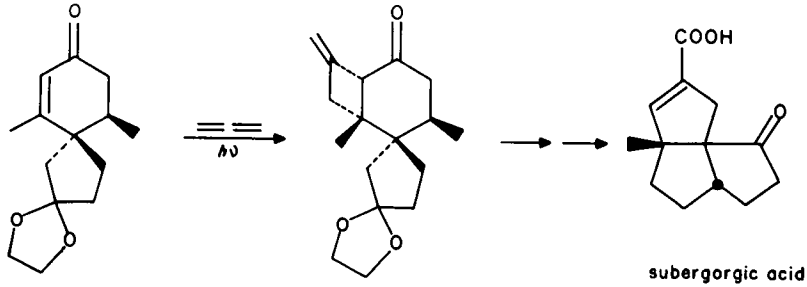


Elegant syntheses of (−)-quadrone[120b] and (±)-subergorgic acid[120c] based on the

[2 + 2] photocycloaddition of allene to conjugated enones have been presented recently:



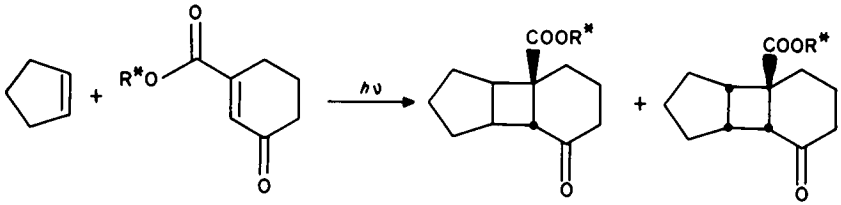
(−)-quadrone



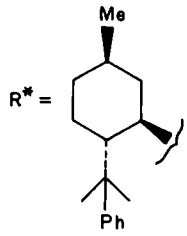
subergorgic acid

1. Asymmetric induction

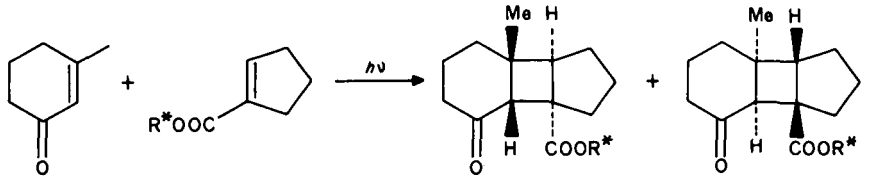
Irradiation ($\lambda_{irr} = 350$ nm) of a toluene solution of cyclopentene with optically pure enone esters (**119**) gave mixtures of *cis-anti-cis* adducts (**120a**) and *cis-syn-cis* adducts (**120b**) in varying proportions. For the chiral auxiliary group R* = (−)-8-phenylmethyl a 3:2 mixture of **120a** and **120b** was obtained with diastereomeric excesses (d.e.) of 30 and 79%, respectively[121]. In AcOH/MeOH 95:5, the photoaddition led to d.e. values of 68 and 76% for **120a** and **120b**, respectively[122].



(119) (120a) (120b)

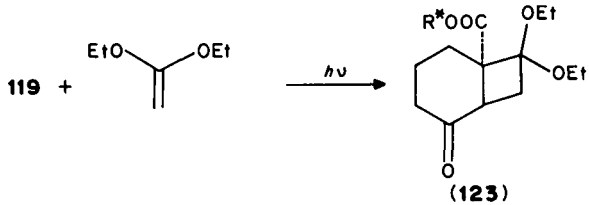


Irradiation of excess of 3-methylcyclohex-2-en-1-one with chiral enoates (**121**) gave the *cis-anti-cis*, head-to-head adducts as inseparable mixtures of diastereomers **122a** and **122b**. For R* = (−)-8-phenylmethyl, (−)-menthyl and (−)-bornyl, the diastereomeric excess (d.e. = % of **122a** minus % of **122b**) was 56, 13 and 19%, respectively[123].



(121) (122a) (122b)

Interestingly, the irradiation of **121** (R* = (−)-8-phenylmenthyl) with 3-methylcyclohex-2-en-1-one gave the corresponding adduct **122a** with d.e. values strongly dependent on the solvent. While the (6*R*)-configurated isomer **122a** was obtained with d.e. values of 62, 52, 56 and 30% in cyclohexane, CH_2Cl_2, toluene and MeOH, respectively, the (6*S*)-configurated isomer **122b** with a d.e. of 12% was found for the irradiation in CF_3CH_2OH[122]. It was also observed that temperature had a marked effect on the extent of asymmetric induction[122].



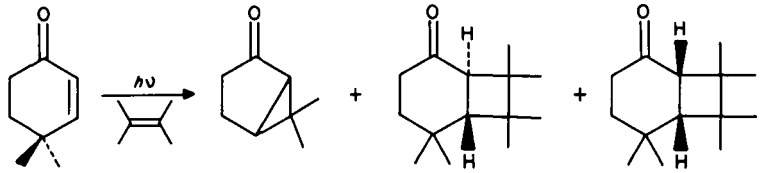
(123)

(−)-8′-Phenylmethyl 3-oxocyclohexene-1-carboxylate (**119**) added to 1,1-diethoxyethylene giving one major regioisomeric adduct (**123**). The diastereomeric excess was *ca* 56% for irradiation in toluene at −40 °C[124].

Diastereomeric excesses as high as 84% were achieved in the photoaddition of methyl 3-oxocyclohex-2-ene-1-carboylate with α,β-unsaturated homochiral acetals prepared from 2-cyclopent-2-en-1-one and (2*R*,3*R*)-tartarate esters[125,126].

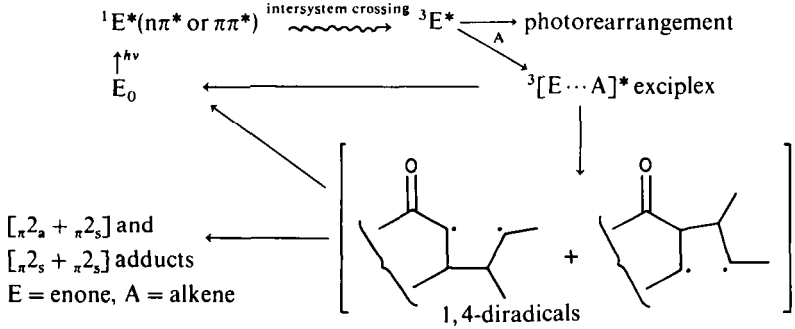
2. *Mechanisms of photochemical [2+2] cycloadditions*

In the photocycloaddition of cyclohex-2-en-1-one to acyclic alkenes, *trans*-fused bicyclo[4.2.0]octanes are generally the major products.[97,98,127,128] For instance, alkenes such as 2,3-dimethylbut-2-ene quench the photorearrangement of enone **124** to the bicyclic ketone (**125**: luminoketone) concomitant with formation of the [2+2] cy-



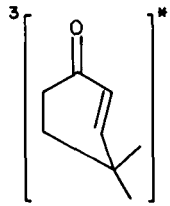
(124) (125) (126) (127)

cloadducts **126** (*trans*-fused, major) and **127** (*cis*-fused, minor)[128]. This implies a common intermediate on the two reaction pathways. In their pioneering studies, Corey and coworkers[97,98] suggested that the reactions involve a triplet excited state of the enone, which forms an 'oriented π complex' with the alkene. This species, an exciplex[129,130] (see Scheme 9), was proposed to give one or two 1,4-diradical intermediates resulting from C—C bond formation at the α- or/and β-positions of the enone. While (*Z*)- and (*E*)-but-2-enes give, with cyclohexenone derivatives, mixtures of the stereoisomers with almost identical relative ratios from either olefin[97,131], suggesting rotational equilibration of the 1,4-diradical intermediates, photoaddition of cyclopent-2-en-1-one to *cis* and *trans* dichloroethylenes afforded four stereoisomers whose proportions could not be rationalized in terms of rotational equilibration of the corresponding 1,4-diradical intermediates[132].



SCHEME 9. Corey's and de Mayo's mechanism

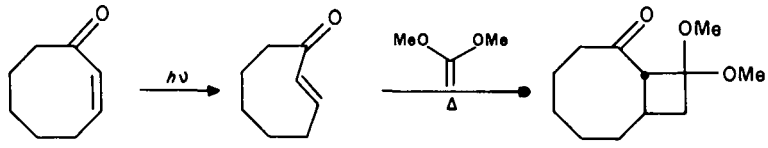
The diradical intermediates can account for the olefinic by-products that are observed for some photoannelation of conjugated enones. However, the favoured formation of strained *trans*-fused adducts (or $[_\pi 2_s + _\pi 2_a]$ adducts) in the photoaddition of cyclohex-2-en-1-ones to alkenes makes the hypothesis of freely rotating 1,4-diradical hardly acceptable. It was thus proposed that a twisted enone triplet (e.g. **128**) is formed first as an intermediate, which then interacts with the alkene to give *cis*- and *trans*-fused adducts (e.g. **126,127**) or the corresponding bicyclo[3.1.0]hexan-2-one (see e.g. **124** → **125**). Using pulsed



(128) 'twisted enone'

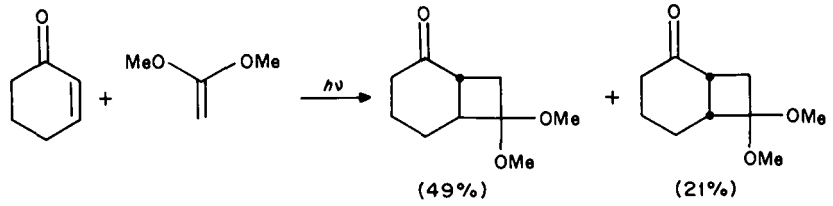
laser technique, Bonneau[133] has observed transient absorptions near 280 nm assigned to the twisted triplet π,π^* excited state for a number of conjugated enones. The triplet state can relax by rotation about the C(2)—C(3) bond and this rotation allows the excited triplet and ground-state singlet hypersurfaces to cross. This can explain why acyclic

enones in flexible systems do not give [2+2] adducts readily on irradiation (energy waste through the 'free rotor effect'[134]). Eaton and Lin[135] have shown that (*Z*)-cyclooct-2-en-1-one (**129**) can be isomerized to the *trans* enone **130** by irradiation at wavelengths greater than 300 nm. Similar results were obtained for (*Z*)-cyclohept-2-en-1-one[136] and 2-phenylcyclohex-2-en-one[137]. The *trans* cycloenones are reactive species that dimerize on warming, concurrently with their isomerization to the *cis* enones; they can be trapped in the dark by electron-rich olefins[94,95], dienes, giving *trans* Diels–Alder adducts[135,138], or by oxygen and nitrogen nucleophiles[139].



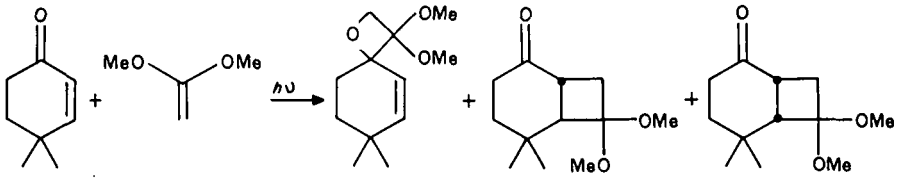
(**129**) (**130**) (**131**)

Recently, Schuster and collaborators[140] have suggested that the photoadditions of cyclohex-2-en-1-one to olefins imply the ground state rather than the triplet excited state of the twisted enone intermediate. It should be noted, however, that in their ground state, (*E*)-cyclooct-2-en-1-one and (*E*)-cyclohept-2-en-1-one add to electron-rich olefins such as 1,1-dimethoxyethylene, to give head-to-head *trans*-fused adducts (see e.g. **130** → **131**), a regioselectivity opposite to that observed for the photocycloaddition of cyclohex-2-en-1-one to 1,1-dimethoxyethylene (see equation 37).

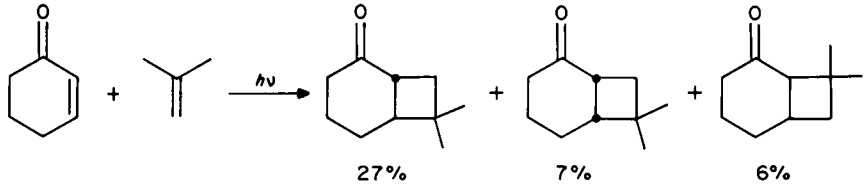


(37)

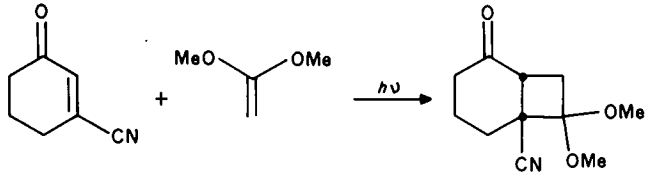
Epiotis and Shaik[141] proposed that triplet [2+2] photoaddition of enone–alkene pairs occur preferentially in a concerted $[_{\pi}2_s + _{\pi}2_a]$ manner, the enone playing the role of the antarafacial component. Shaik[142] further elaborated this hypothesis, indicating that the stereochemistry of olefin + olefin [2+2] photoadditions varies depending on the polarity (donor–acceptor relationship) of the olefin pair. When the olefin pair is non-polar (i.e. both olefins are electron donors or electron acceptors) the *cis*-fused, or $[_{\pi}2_s + _{\pi}2_s]$ adduct is formed preferentially. When the olefin pair is polar (see e.g. equations 37[98], 38[143] and 39)[98] the *trans*-fused, or $[_{\pi}2_s + _{\pi}2_a]$ adduct becomes the major adduct. When the olefin pair is very polar (see e.g. equations 40 and 41), the $[_{\pi}2_s + _{\pi}2_s]$ adduct is again preferred[98,144,145].



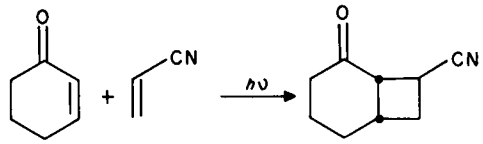
(**124**) (38)



(39)



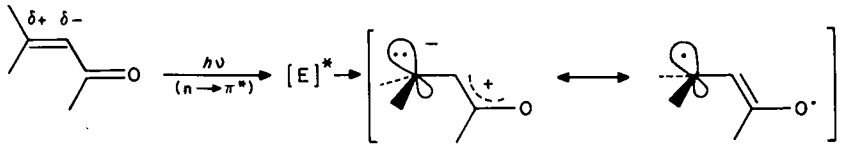
(40)



(41)

Interestingly, when the enone is substituted at C(4) by bulky groups, steric hindrance retards the cycloaddition of the C=C double bond and makes the [2+2] photocycloaddition of the carbonyl moiety (Büchi–Paterno reactions) competitive (see equation 38)[95].

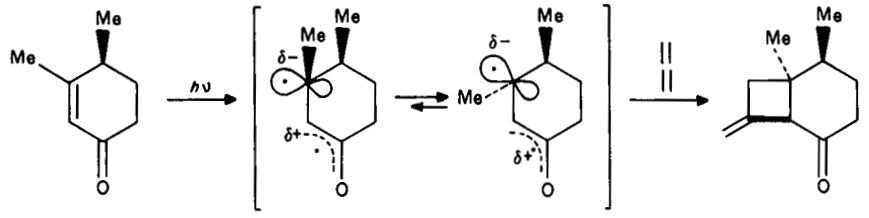
The importance of polar effects has been evidenced by studies on the stereo- and regioselectivity of [2+2] photocycloadditions of enones to olefins in biphasic media (micellar control[146], or surface control by silica gel)[147]. According to Wiesner's groups[148] the relative configuration of the major cycloadduct is determined by the geometry of the excited enone which features essentially a trigonal, slightly positive α-carbon atom and a pyramidal, slightly negative β-carbon atom[149], as shown in **133**. The reactive excited state (**133a**) of the enone has a dipole moment oriented in the opposite direction to that of its ground state (**132**). This explains the opposite regioselectivity observed between the thermal [2+2] cycloaddition **130**→**131** and that of the photochemical [2+2] cycloadditions of equations 37–40. This model (**133a**↔**133b**) also explains the reversal of regioselectivity between the photocyclizations involving olefins with electron-releasing substituents (equations 37–40) on the one hand, and photocyclizations of enones to olefins substituted with electron-attracting groups (see e.g. equation 41) on the other hand[98].



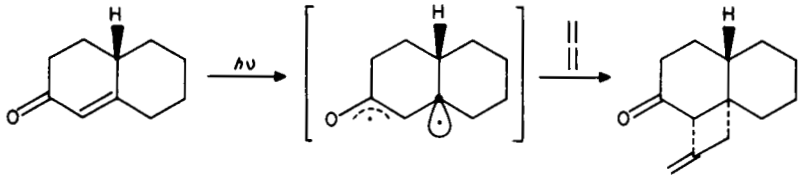
(**132**) (**133a**) (**133b**)

The model of Wiesner[148] allowed one to interpret the stereoselectivity (facial selectivity) of [2+2] photocycloadditions of chiral enones to alkenes and allenes. Pyramidalization of

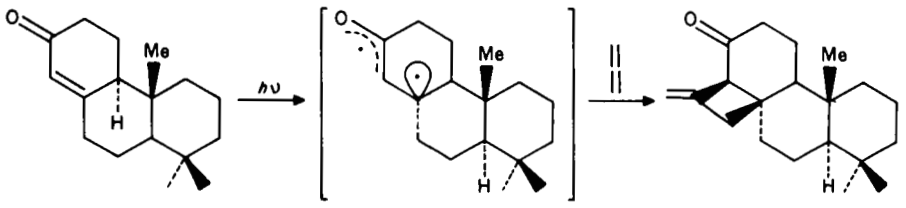
carbon atom C(3) leads to two possible diastereomeric species, the most stable of which adds to the olefin. Typical examples are shown in equations 42–45[148].



(42)



(43)



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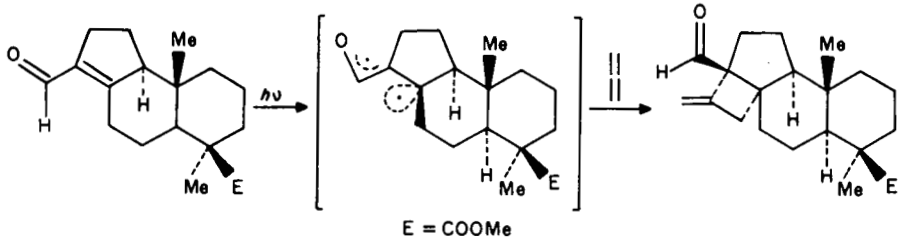
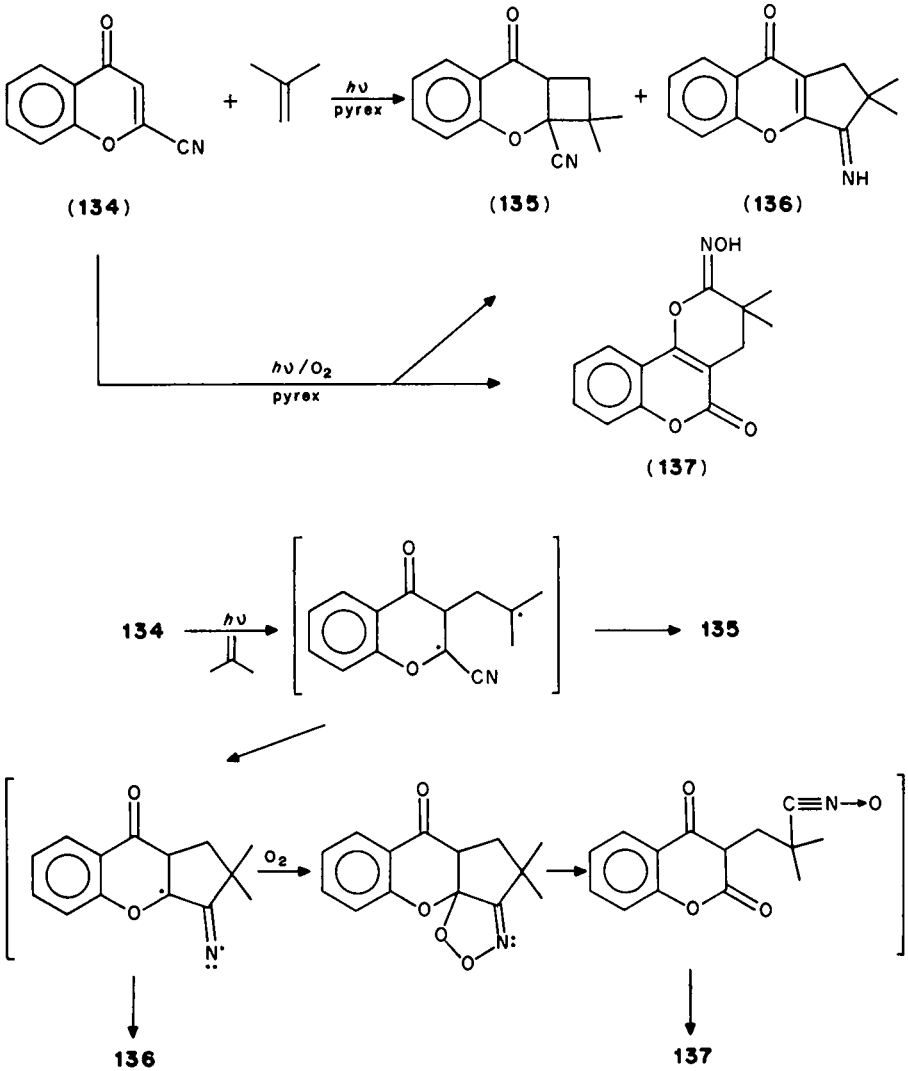


E = COOMe

(45)

The model of Wiesner has not been fully accepted[129]. 1,4-diradical intermediates (see e.g. Scheme 10) involving bond formation at both C(2) and C(3) of the conjugated enone are quite often invoked to interpret the results[150]. In some instances it has been shown that such diradicals have very short lifetimes since they could not be trapped by molecular oxygen[151]. For example, irradiation (pyrex) of **134** with 2-methylpropene gave 12% of the [2+2] adduct (**135**) and 81% of the [3+2] adduct (**136**)[152]. The same irradiations under

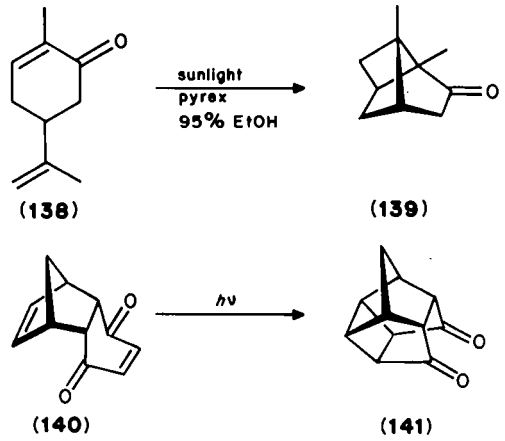
O_2 bubbling yielded 13% of **135** and 55% of **137** whose formation is believed to follow the mechanism outlined in Scheme 10[151].



SCHEME 10

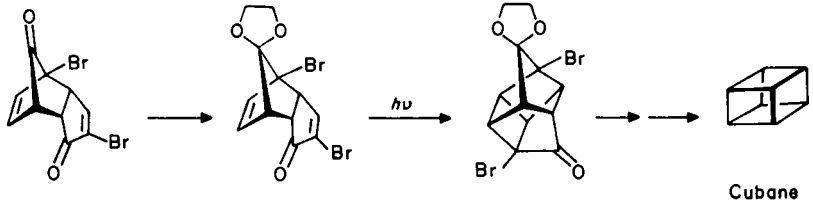
C. Intramolecular [2+2] Photocycloadditions

Although the intramolecular photoaddition of carvone (**138**), leading to carvonecamphor (**139**), was first described by Ciamician[153] in 1908, little attention was paid to this type of reaction until 1957[154]. Cookson and coworkers[155] showed in 1958 that cage compounds such as **141** were readily attained through intramolecular [2+2] photocy-



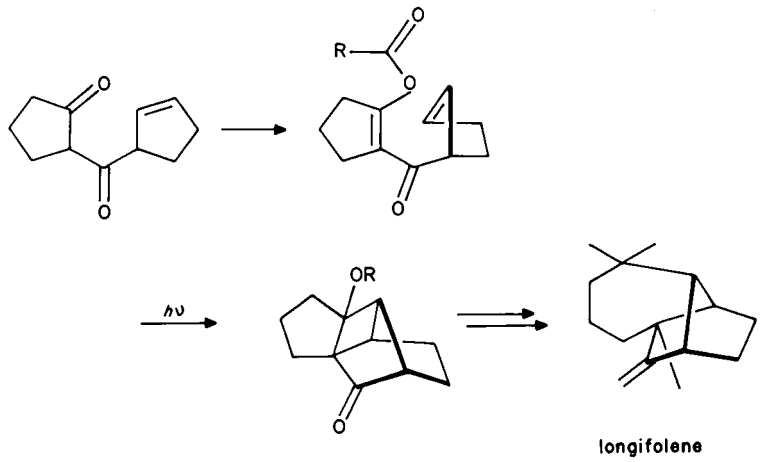
(138) (139) (140) (141)

cloaddition of the Diels–Alder adduct of cyclopentadiene and benzoquinone (**140**). The possibility of creating unusual, polycyclic structures by intramolecular [2+2] photocycloaddition was brilliantly demonstrated in 1964 by Eaton and Cole[156] with the synthesis of cubane (equation 46).

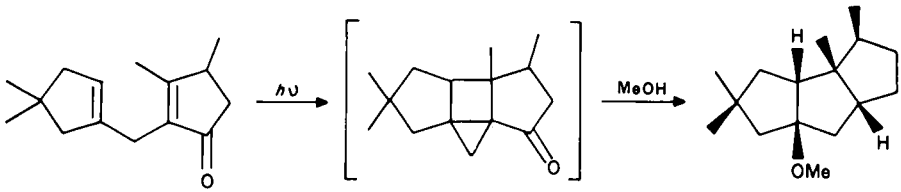


(46)

During 1978, the groups of Oppolzer[157] and of Pattenden[158] demonstrated independently the synthetic utility of the intramolecular variant of the de Mayo reaction during synthetic investigations amongst the terpenes longifolene (see Equation 47)[157] and

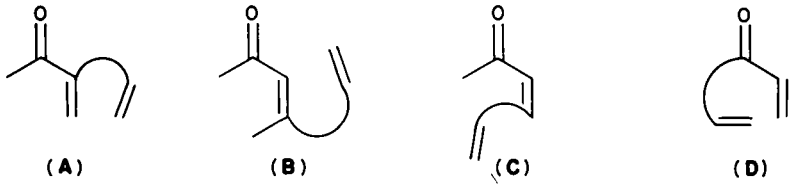


(47)

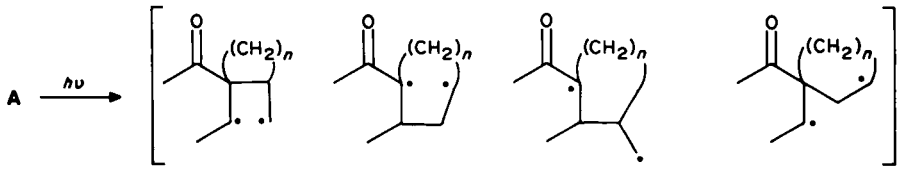


(48)

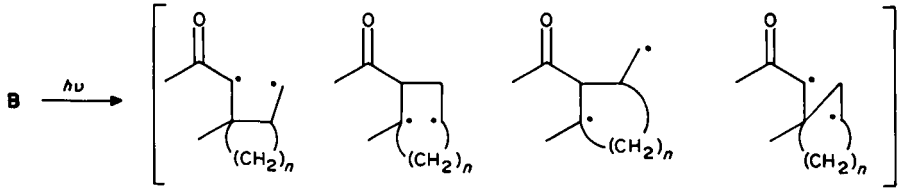
hirsutane derivatives (see equation 48)[158], respectively. Since then, an impressive number of syntheses of difficult, accessible fused ring systems and natural products have been reported[159–167]. The selected examples reviewed below will be arranged according to type **A**, **B**, **C** or **D** of the polyenones which distinguish the different possibilities for connecting the enone moiety with an alkene, allene or alkyne unit. Sections III.C.1 and III.C.2 will discuss the photocyclizations of 2-(alkenyl)enones (**A**) and (*E*)-3-(alkenyl)enones (**B**), respectively. The photolysis of (*Z*)-3-(alkenyl)enones will be treated in Section III.C.3 and of hexa-1,4-dien-3-ones (type **D** of dienones) in Section III.C.4.



An important problem with the intermolecular [2 + 2] photocycloaddition of enones is their stereo- and regioselectivity. Except for reactions of allenes and of olefins mono- or 1,1-disubstituted with strongly polar groups (see e.g. **119** → **123**, equations 37–45), unpredictable mixtures of regioisomers are obtained. In this respect, intramolecular [2 + 2] photocycloaddition permits, in general, a good and predictable control of the regioselectivity. In the absence of special constraints and for systems of type **A** and **B** with connecting chain of two to four atoms, the photocycloaddition is regioselective. The favoured polycyclic system will be that derived from an initial attack of the excited α,β-unsaturated ketone moiety onto the olefinic (or acetylenic) unit to form a 1,4-diradical **A1**, **A2**, **A3** or **A4** and **B1**, **B2**, **B3** or **B4**, respectively, possessing a five-membered ring. This empirical rule, known as the 'rule of five', noted first by Scrinivasan[168] and Hammond[169] and further established particularly by Wolff and Agosta[170], resides on entropic factors. Furthermore, the diradical reversion process is disfavoured entropically as compared to the bimolecular process, which decreases energy dissipation. If the five-membered ring formation is impossible, a six-membered ring is next favoured. Deviations from the 'rule of five' have been observed and will be presented below.

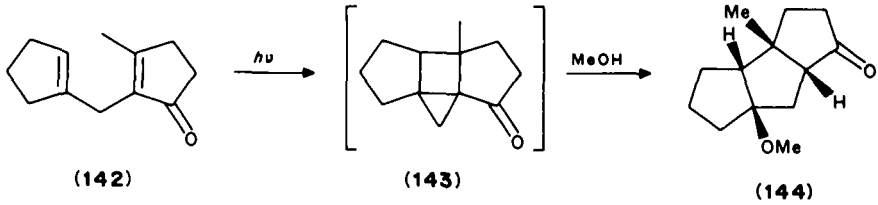


Type	(A1)	(A2)	(A3)	(A4)
Favoured for	$n=3$	$n=1$	$n=2$	$n=2$

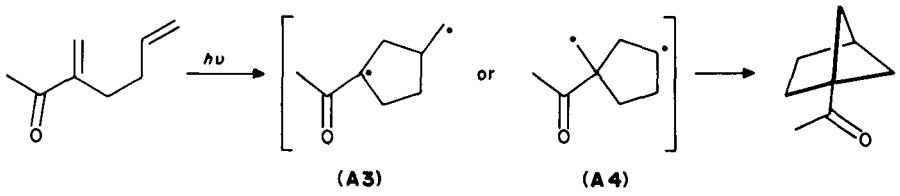


1. Photocycloadditions of 2-(alkenyl)enones and analogues

Irradiation of **142** in MeOH, through a Pyrex filter using a medium-pressure 100-W Hg lamp, resulted in the formation of the tricyclo[6.3.0.$0^{2,6}$]undecanone derivative (**144**). The *cis*-cisoid-*cis* product (**144**) appears to result from a rapid nucleophilic ring opening by the solvent of the presumed highly strained intermediate (**143**).[158] The same approach has been used in the synthesis of the hirsutane carbon skeleton (equation 48)[158].



The photocycloaddition of **142** is typical of a 2-acylpenta-1,4-diene system and gives a head-to-head adduct (e.g. **143**). It implies probably the intermediacy of a 1,4-diradical of type **A2**. The 'rule of five' was also nicely obeyed for the intramolecular [2+2] photocycloaddition of 2-acylhexa-1,5-dienes, as illustrated below in equations 49–54. In this case the corresponding head-to-tail adducts are favoured[170c].



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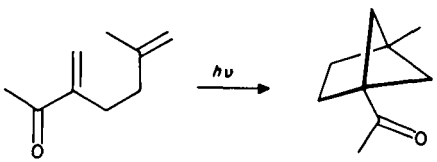
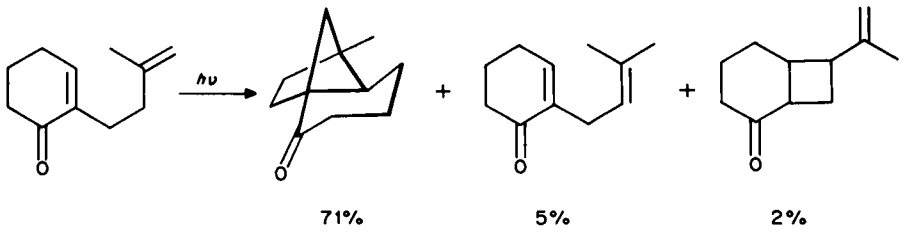
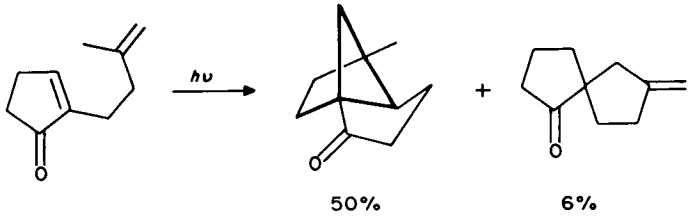


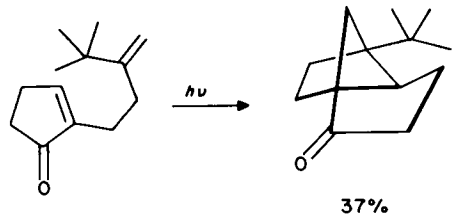
(50)



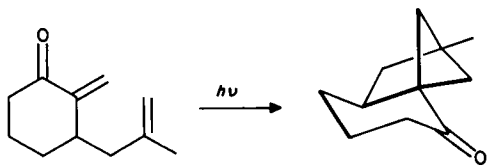
(51)



(52)

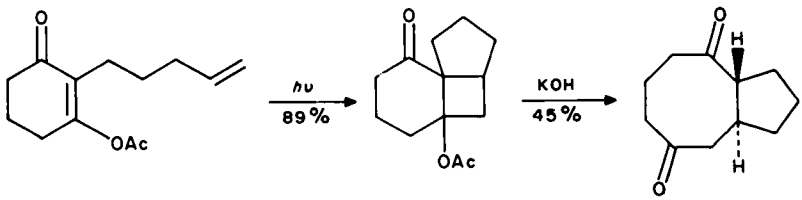


(53)

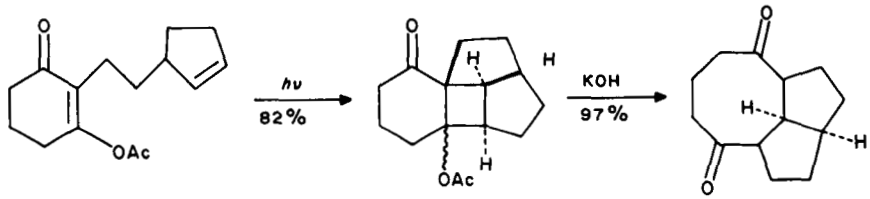


(54)

According to the 'rule of five' the irradiation of 2-acylhepta-1,6-diene derivatives should generate diradical intermediates of type **A1** and give the corresponding head-to-head cycloadducts. The [2+2] photocycloaddition, hydrolysis, retro-aldol sequences **145** → **146** → **147**[171] and **148** → **149** → **150**[171a] reported below are in accord with that prediction.

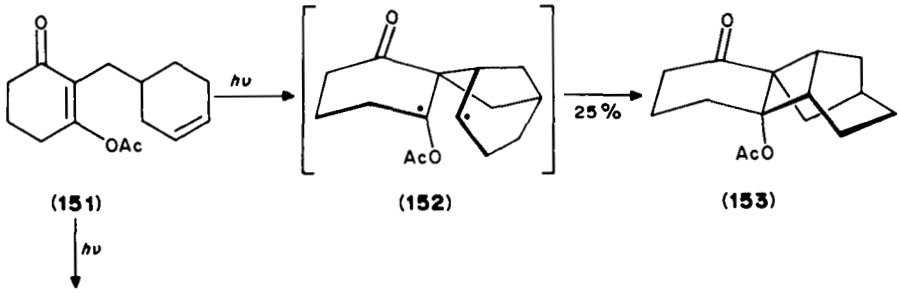


(145) **(146)** **(147)**

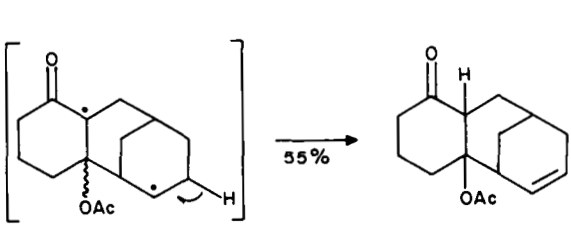


(148) (149) (150)

A limit of the 'rule of five' was demonstrated by irradiation of **151**. The expected adduct **153** was obtained in 25% yield only, together with the major product **155** (55%), which probably arises from a hydrogen shift in the diradical intermediate **154**[171a].



(151) (152) (153)

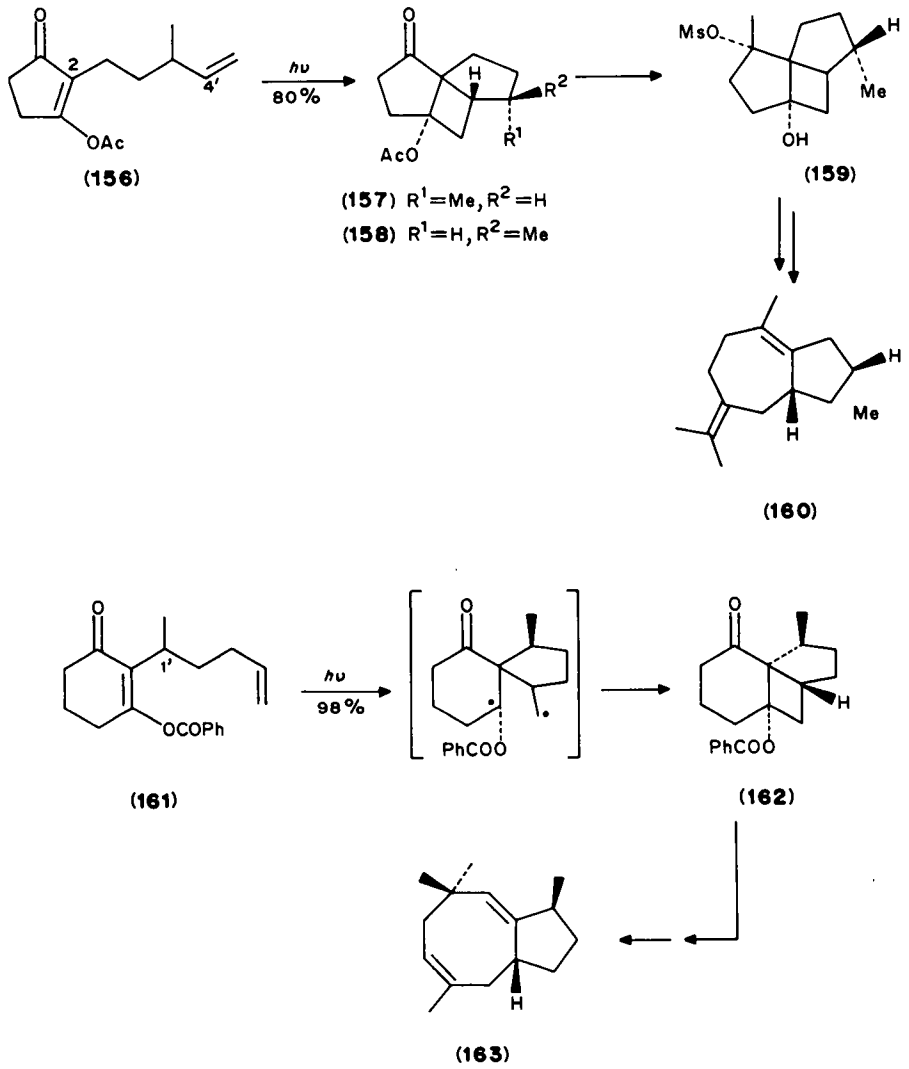


(154) (155)

Irradiation of **156** gave a 1:3 mixture of adducts **157** and **158** in 80% yield. This selectivity in favour of the least sterically crowded product may be kinetically controlled during the bond formation between C(2) and C(4'). Adduct **157** was transformed into (±)-bulnesene (**160**) via fragmentation of the tricyclo[5.3.0.0^{1,5}]decane system **159**[172].

A more pronounced stereoselectivity was found in the photocycloaddition of **161** containing a chiral center at C(1'), as the sole product obtained in 98% yield was the *cis*-fused tricyclic system **162**. This result was interpreted in terms of avoided steric hindrance between the methyl and benzoate groups. Adduct **162** was transformed into 11-epi-precapnelladiene (**163**)[160e,173].

The 'rule of five' was followed nicely in the case of intramolecular [2+2] photocycloadditions of 2-(2-propenyloxy)cyclohex-2-enones (**164**) which gave the corresponding 2-oxabicyclo[2.1.1]hexanes (**165**) in good yields (head-to-tail adducts)[174]. In contrast, the 2-(3-butenyloxy) derivative **166** gave the head-to-head adduct **167** as the major product. This observation suggests the preferred formation of the six-membered diradical **169** over the five-membered diradical **170**[174]. In this context, it is of interest to note that the closely related 2-(4-pentenyl)[175] and 2-(3-butenoyloxy)cyclohex-2-enones[176] gave exclusively



(156)

(157) R^1=Me, R^2=H

(158) R^1=H, R^2=Me

(159)

(160)

(161)

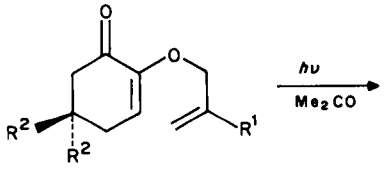
(162)

(163)

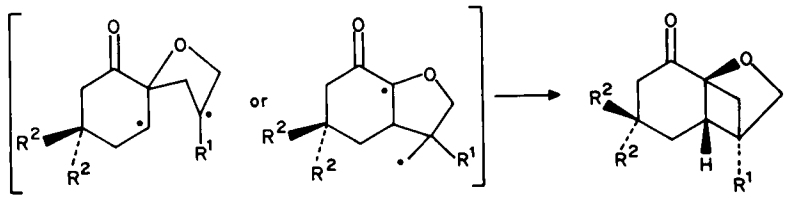
head-to-head adducts (see **173** → **174** → **175**) in accord with the 'rule of five'. Deviations from this rule have been attributed to special substituent stabilizing effects on the diradical intermediates[174,176].

The intramolecular [2+2] photocycloaddition of 2-(*N*-acyl-*N*-allylamino)cyclohex-2-enone (**169**) gave the expected adduct **170** together with the spiro-β-lactam **171** which arises probably from hydrogen transfer to give the intermediate diradical **172**[177]. Photoirradiation of 2-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones in acetone was also found to give the corresponding *N*-alkyl-1-azaspiro[3.5]nonane-2,5-diones in moderate yields[178].

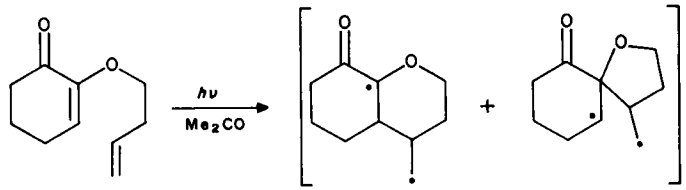
Becker and coworkers[179] have studied the stereoselectivity of the intramolecular [2+2] photoadditions of 2-(pent-4'-enyl)cyclohex-2-en-1-ones (**173**) substituted at C(4), and at



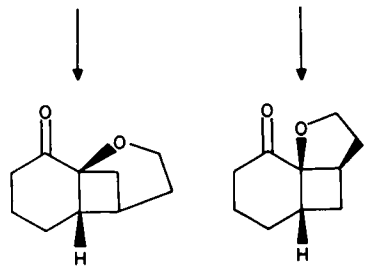
(164)



(165)



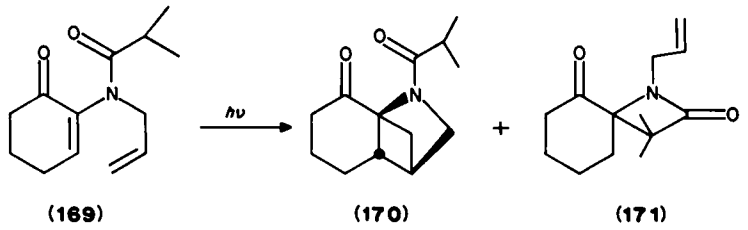
(166) (169) major (170) minor



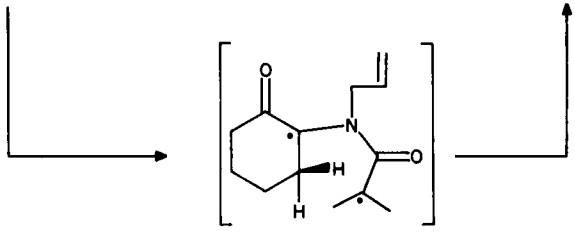
(167) (168)

C(1'), C(2'), C(4') and C(5') of the side-chain. While for the unsubstituted system **173** ($R = R^1 = R^2 = R^4 = R^5 = R^6 = H$) a 2.3:1 mixture of adducts **174/175** was obtained[175], irradiation (uranium glass filter, $\lambda_{irr} > 330$ nm, cyclohexane, 20 °C) of derivatives **173** with R = *t*-Bu led to selectivities higher than 94% in favour of the corresponding adducts **174** resulting from the olefin addition to the enone moiety on its face *anti* to the bulky substituent at C(4)[179].

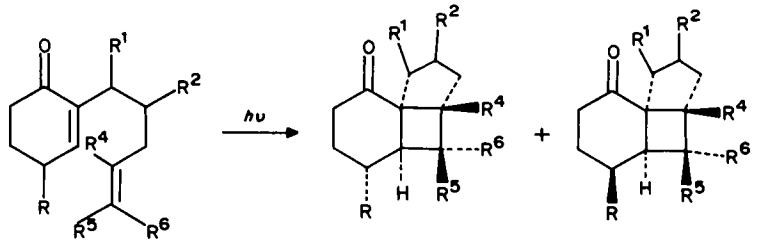
The photocyclization of enone **177**, obtained by silylation of diketone **176**, results in the formation of adduct **178** in 81% yield. This compound was subsequently transformed into the racemic pentalenene **179**[160g].



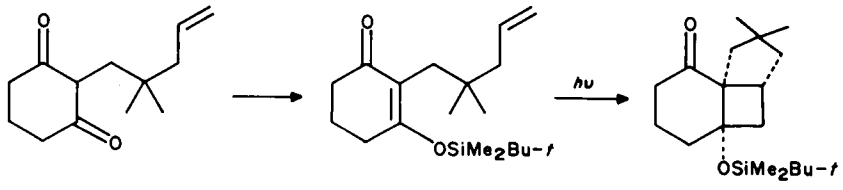
(169) (170) (171)



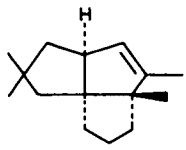
(172)



(173) (174) (175)

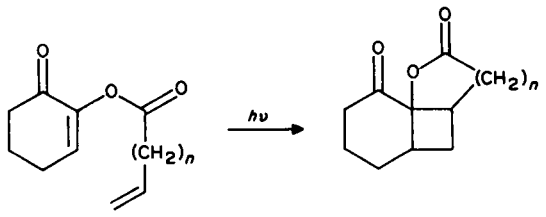


(176) (177) (178)

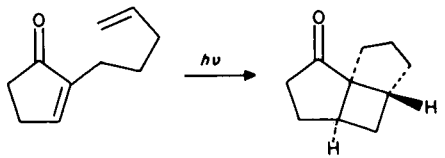


(179)

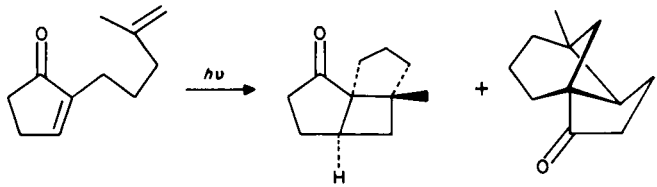
The head-to-head adducts (**181**, $n = 1,2$) were obtained in good yields on irradiating the enones **180**[177]. Examples of intramolecular [2 + 2] photocycloaddition of 2-(4-alkenyl)-cyclopent-2-en-1-ones are given in equations 55–58[170d].



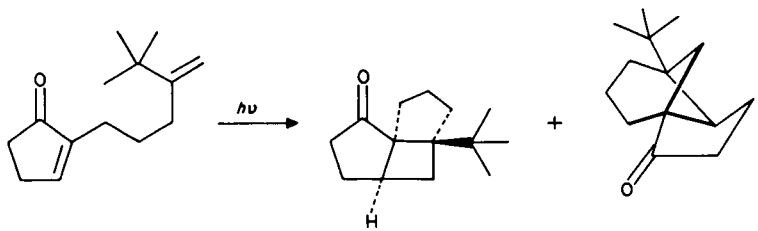
(180) **(181)**



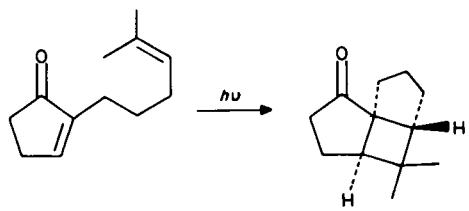
82% (55)



46% 17% (56)



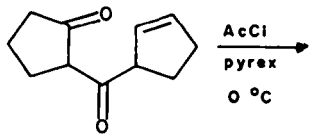
73% 18% (57)



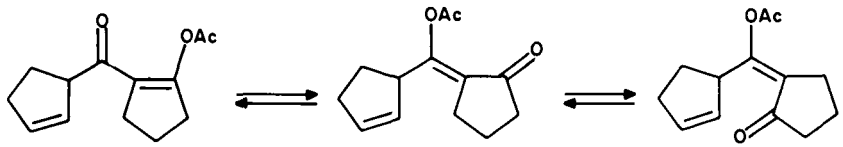
88% (58)

2. Photocyclization of (E)-(3-alkenyl)enones and analogues

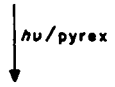
An example of intramolecular [2 + 2] photocycloaddition of dienone of type **B**, i.e. 3-(alkenyl)enone in which the non-conjugated alkene moiety is attached at C(3) of the enone unit through a spacer of one carbon atom, is given with the irradiation of the equilibrating enol acetate mixture (**183a**, **183b**, **183c**), derived from acylation (AcCl/pyridine) of the 1,3-dione **182**, which gave adduct **185**[161a].

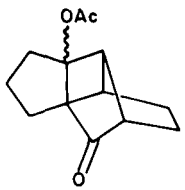


(182)



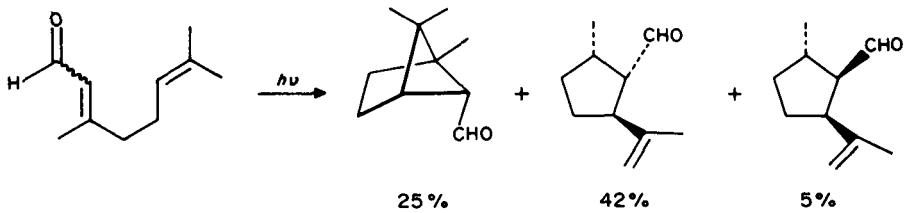
(183a) (183b) (184c)



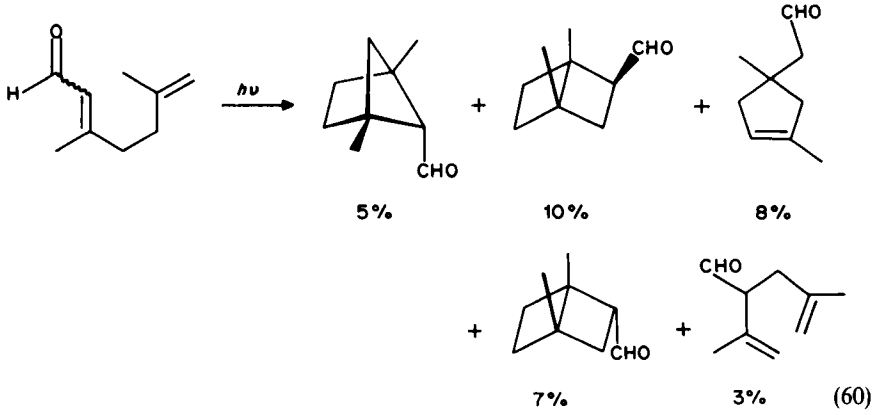


(185)

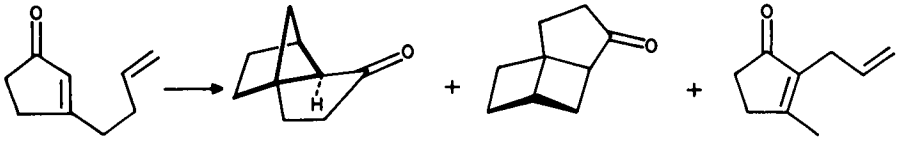
Examples of intramolecular [2+2] photocycloadditions of dienones of type **B**, i.e. 3-(alkenyl)enones in which the non-conjugated olefinic moiety is attached at C(3) of the enone through a spacer of two atoms, are given in equations 59–66[170b,c,180].



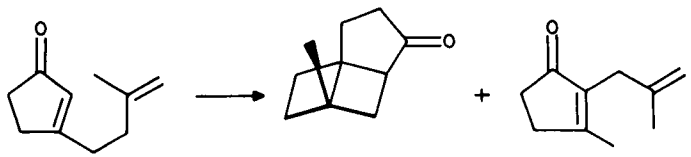
(59)



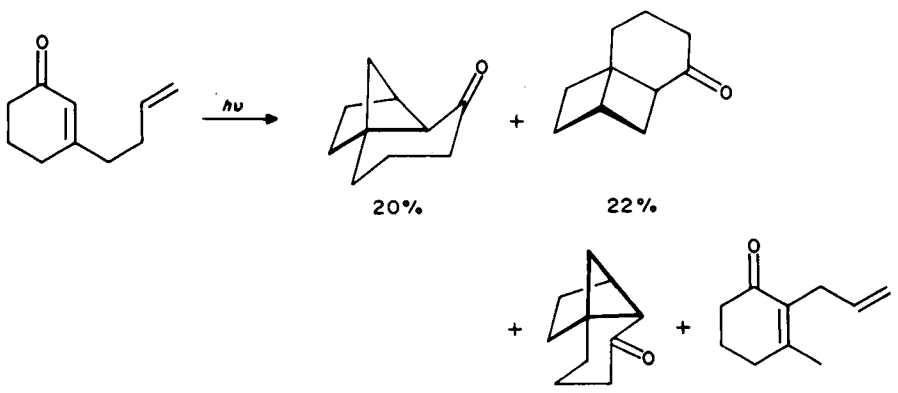
(60)



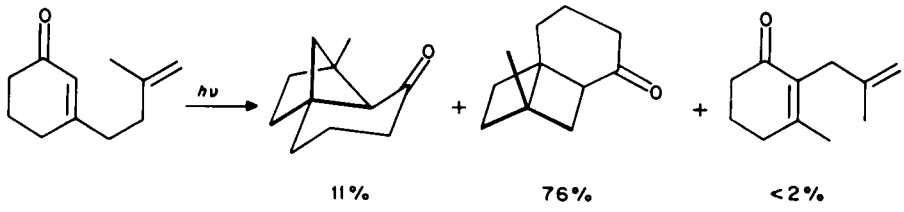
(61)



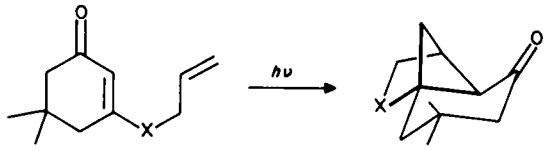
(62)



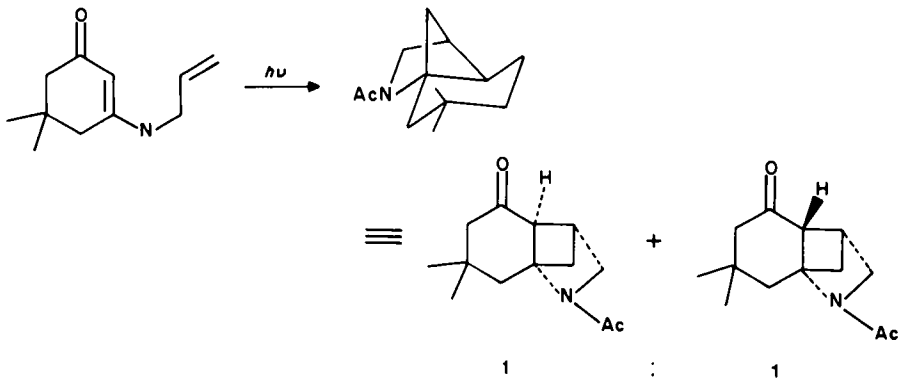
(63)



(64)



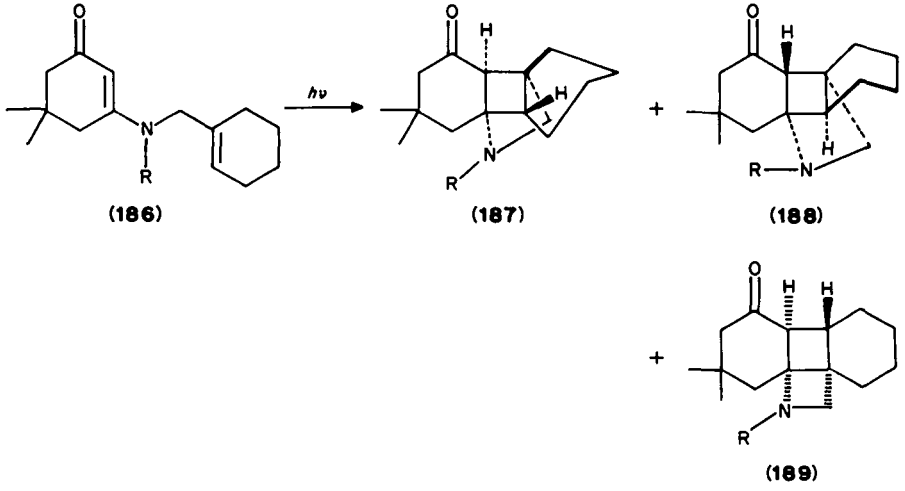
(65)



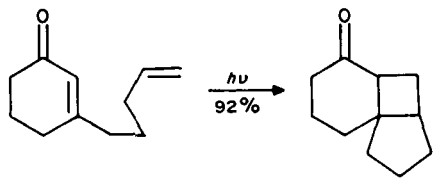
(66)

According to the 'rule of five', the diradical intermediate of type **B3** and **B4** should be favoured and lead to the corresponding head-to-tail adducts with a bicyclo[2.1.1]hexane skeleton. This regioselectivity is indeed observed for the acyclic system of equation 59. In the other cases, head-to-head adducts with the bicyclo[2.2.0]hexane skeleton (and the products derived therefrom) are also formed concurrently. They imply 1-acylhexa-1, 5-diene systems with alkyl substituents at C(5) (see equations 60 and 64) or with the conjugated double bond of the enone moiety being part of a five- (see equations 61 and 62) or six-membered ring (see equations 63 and 64)[170b]. However, when the side-chain is an allyloxy or allylamino group, the 'rule of five' is followed (see equation 65 and 66)[180].

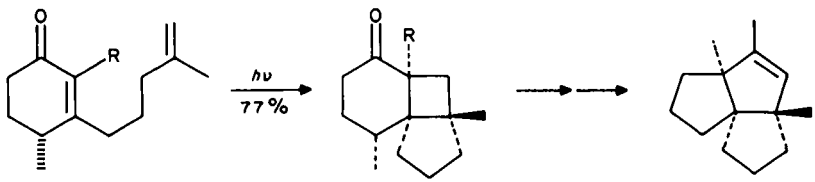
Schell and coworkers[181] reported the photochemical cyclization of imide (**186**, R = $COCH_3$) to yield the expected head-to-tail adduct (**187**, R = $COCH_3$). Swindell and coworkers[182] have re-examined this reaction and found that product **187** is formed in 70% yield together with significant amounts of the corresponding isomer **188** (8%) and the head-to-head adduct **189** (13%). Analogous product mixture was obtained from irradiation of imide (**186**, R = CHO)[182].



A large number of photochemically induced cyclizations of 1-acylhepta-1,6-diene systems have been reported. Most of the cases studied follow the 'rule of five'[170] and give the corresponding head-to-head cycloadduct[159], as illustrated in equations 67–69. In several instances, the photoadducts could be derived into natural products (see e.g. equations 68, 69 and 74). A detailed study of the intramolecular cycloadditions of (*E*) and (*Z*) olefins **190** and **191** has shown that the bond of C(3) of the cyclohexenone moiety is formed first and leads to the equilibrating diradical intermediates **192** and **193** giving mixtures of products **194** and **195**[188]. Similarly, the intramolecular [2 + 2] photocycloaddition of substituted allenes to conjugated cyclohexenones gave mixtures of the two possible stereoisomers (equation 75)[189].

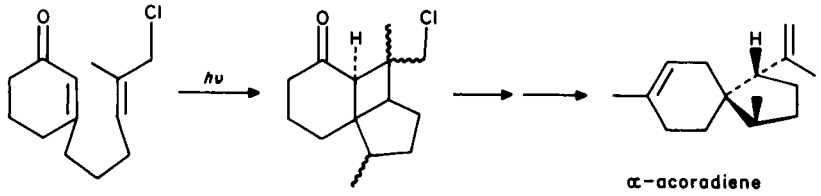


(67)[137]

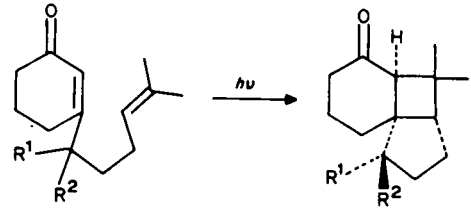


(±)-isocomene

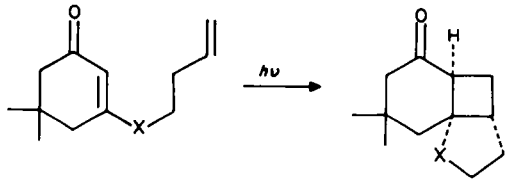
(68)[183]



(69)[16fb]

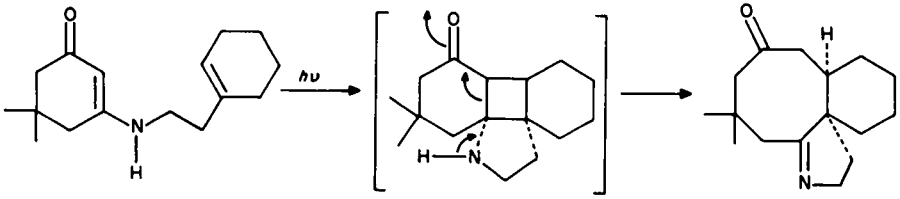


(70)[184]

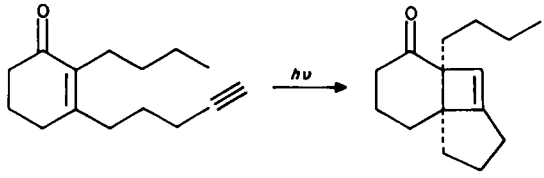


X=O, NAc

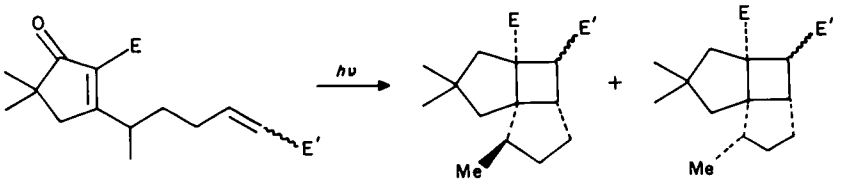
(71)[185]



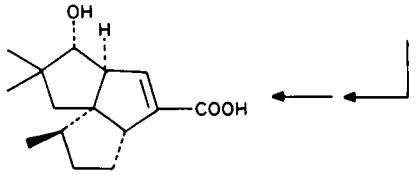
(72)[186]



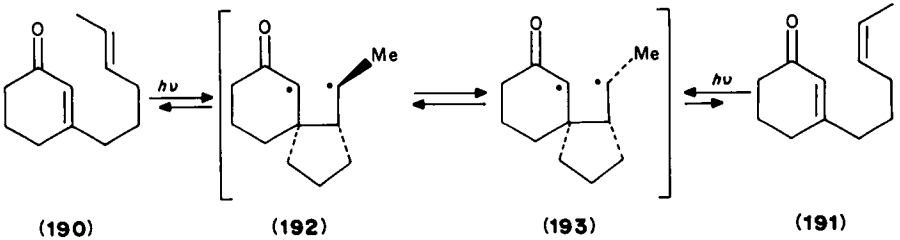
(73)[187]



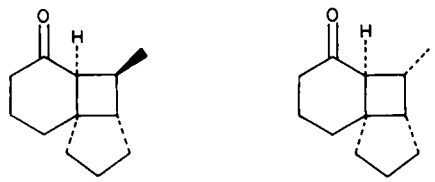
E=COOMe, E'=COOEt 13 : 1



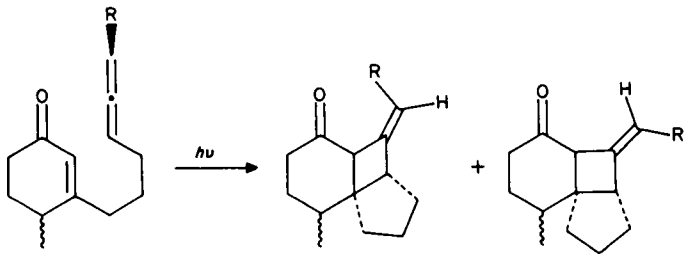
(±)-pentalenic acid (74)[160f]



(190) (192) (193) (191)

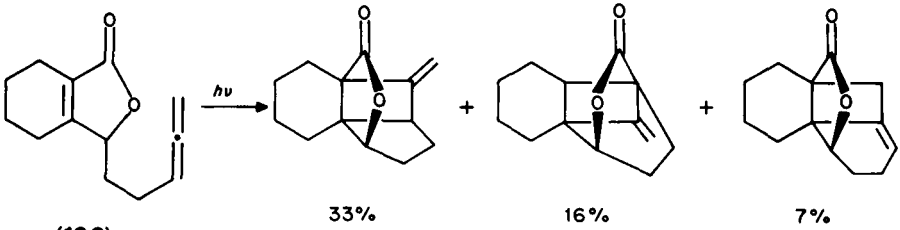


(194) (195)



R=Me, *t*-Bu (75)

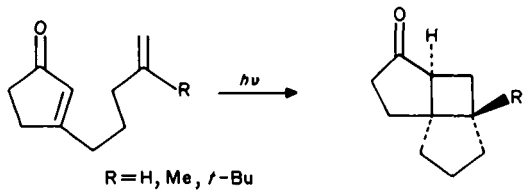
While the 'rule of five' is followed nicely for the intramolecular [2+2] cycloadditions of acetylene (equation 73) and allene moieties (equation 75) attached to cyclohex-2-en-1-one at C(3), the irradiation of allene **196** gave a mixture of adducts showing that 1,4-diradical intermediates with a six-membered ring are formed concurrently with the diradical with a five-membered ring (see equation 76)[190].



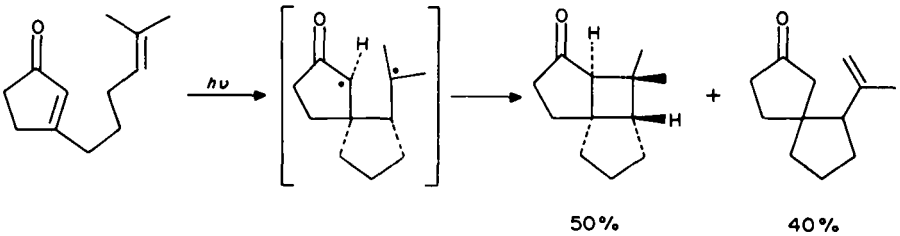
(196)

(76)

Irradiation of 3-(4-alkenyl)cyclopent-2-en-1-ones gives exclusively head-to-head adducts as predicted by the 'rule of five' (see equation 77). In some cases, however, products resulting from hydrogen shift in the hypothetical diradical intermediate are observed (see equation 78)[170d].

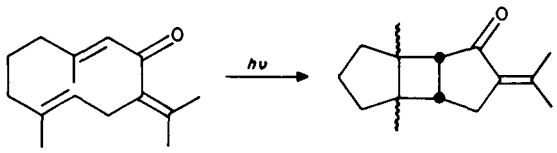


(77)

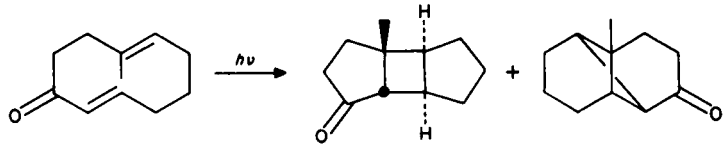


(78)

Scheffer has shown that photolysis of isogermacrone (**197**) gives a mixture of bicyclo[5.3.0.0^{2,6}]decanones (**198**)[191]. Similarly, Heathcock has shown that 6-methyl-1, 6-cyclodecadien-3-one (**199**) gives a mixture of bicyclo[5.3.0.0^{2,6}]decanone (**200**) and bicyclo[4.4.0.0^{2,7}]decanone (**201**)[192].

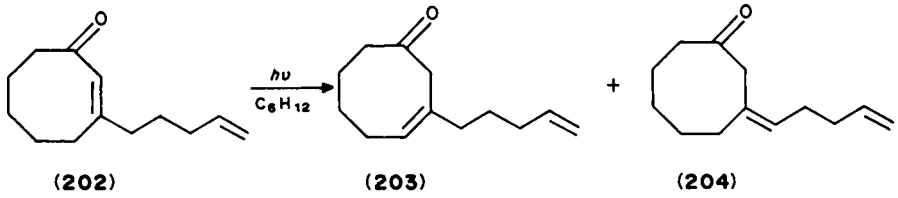


(197) (198)

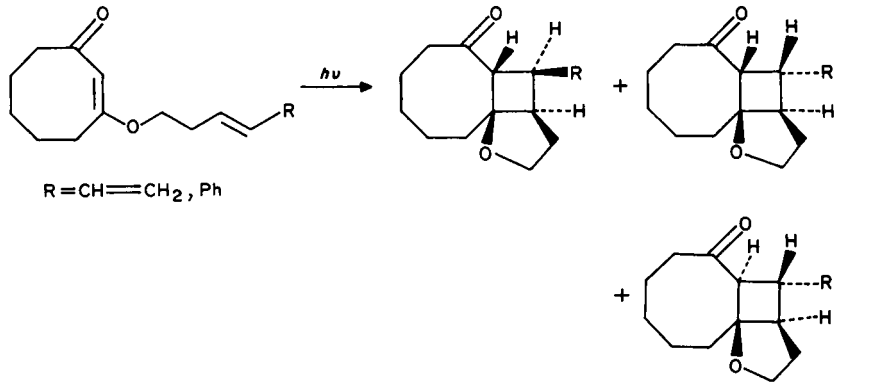


(199) (200) (201)

Eaton has shown that (*Z*)-cyclooct-2-en-1-one (**129**) is isomerized into the (*E*)-isomer **130**[135] on irradiation with UV-light filtered with pyrex. Pirrung and Webster[193] showed that intramolecular [2+2] photocycloaddition does not occur with **202** but rather gives a mixture of the β,γ-enones **203** and **204**. In contrast, irradiation of cyclooct-2-en-1-ones shown in equations 79–83 leads to products of intramolecular cycloaddition[193].

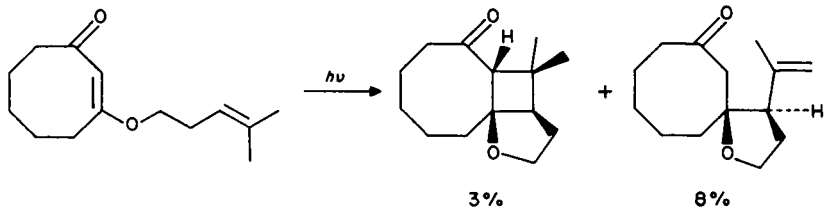


(202) (203) (204)



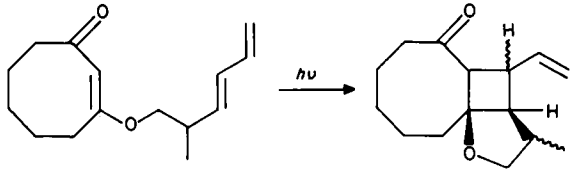
R=CH=CH$_2$, Ph

(79)

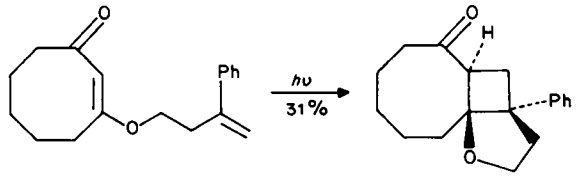


3% 8%

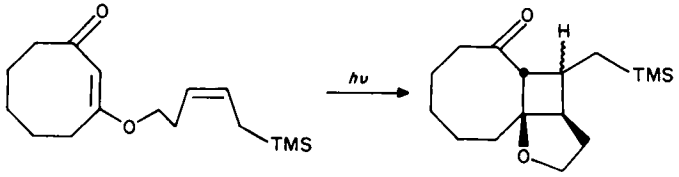
(80)

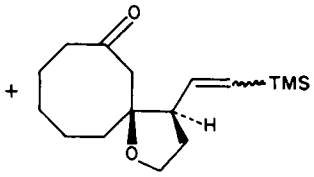


(5 isomers) (81)



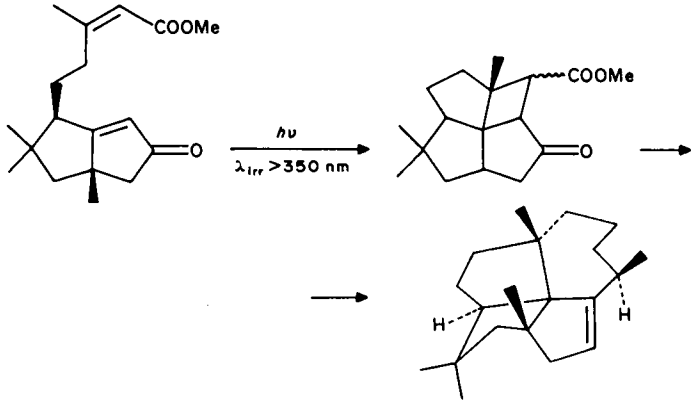
(82)





(83)

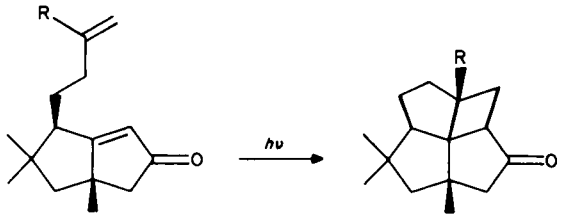
A total synthesis of (±)-laurenene based on an intramolecular [2+2] photocycloaddition (equation 84) has been reported recently by Crimmins and Gould[194]. This crucial reaction establishes the three contiguous quaternary centres required for the sterically congested central portion of (±)-laurenene, an example of angular fused triquinane.



(±)-laurenene

(84)

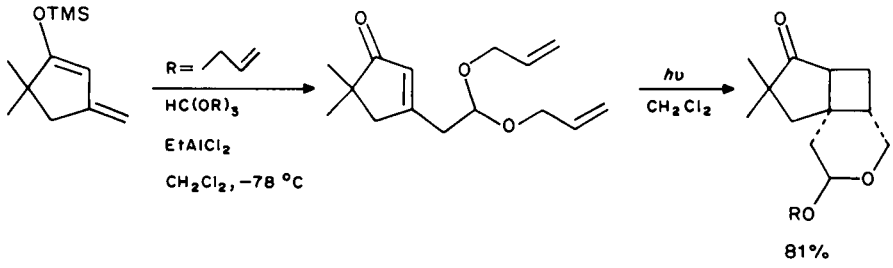
Crimmins and coworkers[165] have also reported the synthesis of fenestrane **206b** by the photocyclization of enone **205a**. The reaction is efficient and yields the product in 90% yield when the irradiation is carried out in hexane. Under identical conditions, the methyl substituted derivative **205b** is inert. However, cycloaddition can be brought about by irradiation in chlorobenzene at 110 °C, giving the fenestrane **206b** in 65% yield.



(205) (a) R=H
(b) R=Me

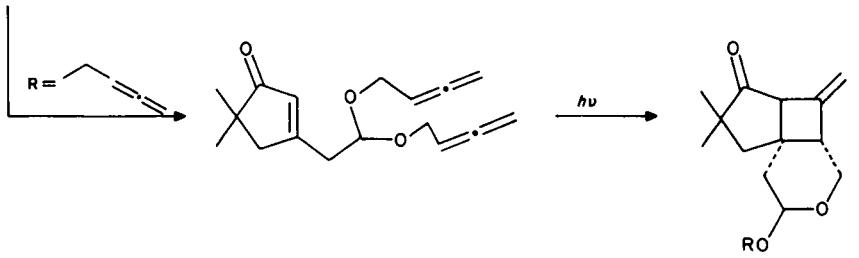
(206)

Lewis-acid catalyzed condensation of unsaturated orthoformates $HC(OR)_3$ with dienol silyl ethers gives enone acetals suitable for intramolecular [2+2] photocycloadditions, yielding heterocyclic precursors to sesquiterpene lactones (equations 85–88). The ease of the photocyclizations shown in equations 85–88 contrasts with the photostability of esters **207** shown in equation 89[195].



81%

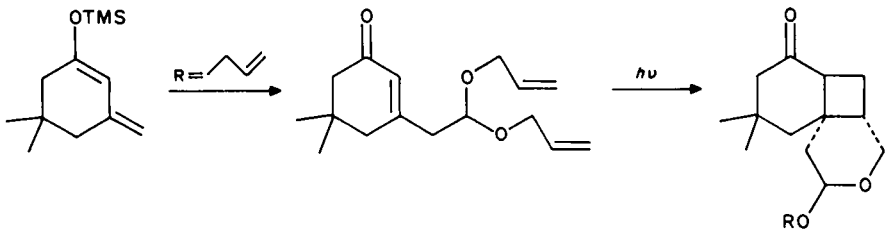
(85)



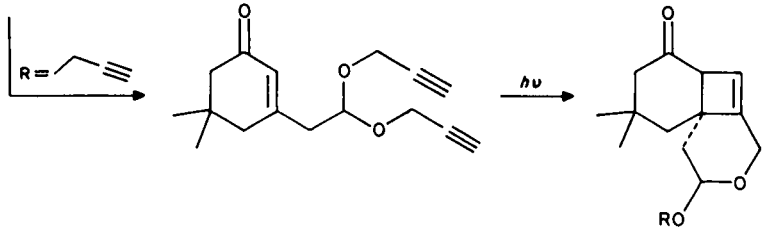
70%

(86)

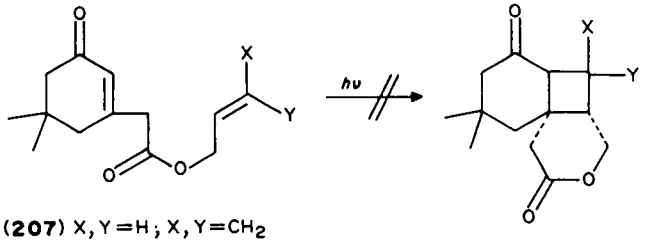
A synthesis of *trans*-bicyclo[5.3.1]undecan-11-one (**211**) based on the intramolecular photocyclization of the dioxolenone **208** into **209** has been reported[196]. The stereochemistry of the bicyclo[5.3.1]undecane produced is *trans*-bridged, making **210** (and **211**) the smallest known bicyclic cycloalkane to exhibit inside–outside stereoisomerism[197].



(87)



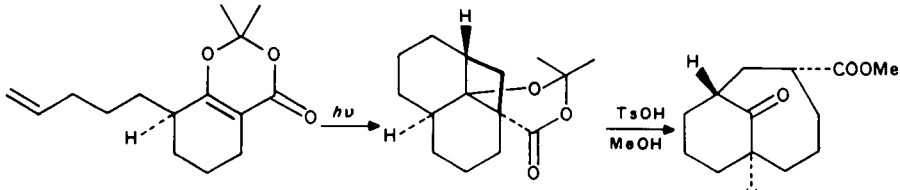
(88)



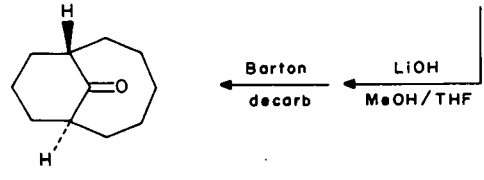
(89)

(207) X, Y=H; X, Y=CH_2

X=H, Y=CO_2R



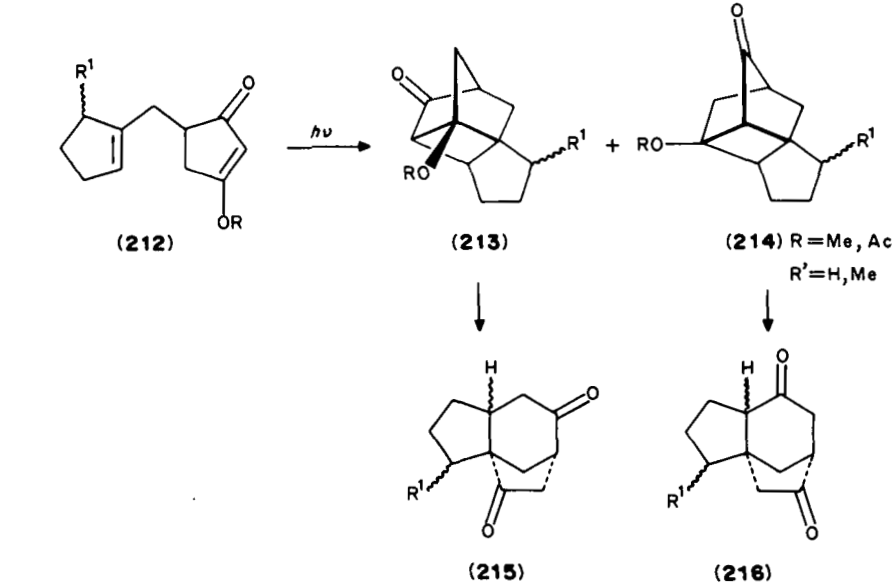
(208) **(209)** **(210)**

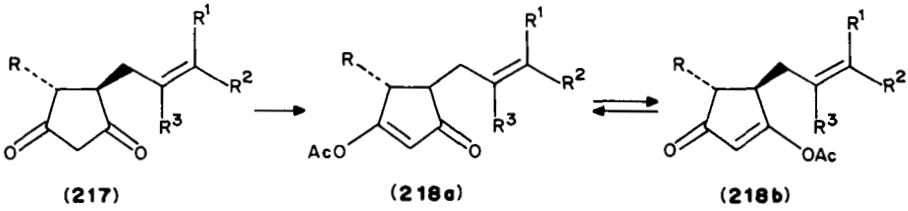


(211)

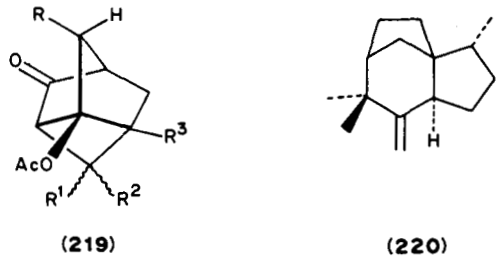
3. Photocyclization of (Z)-(3-alkenyl)enones and analogues

Irradiation of the readily accessible[198] dienone **212** furnished a mixture of regioisomeric cycloadducts **213** and **214**, which with $BF_3{\cdot}Et_2O$ fragmented to the corresponding tricyclo[6.2.1.$0^{1,5}$]undecadiones **215** and **216**[199,200]. The lack of regioselectivity observed here does not violate the 'rule of five': both processes **212** → **213** and **212** → **214** permit initial formation of a diradical intermediate possessing a five-membered ring.



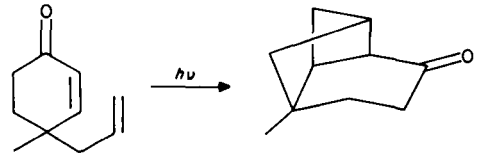


R_1, R_2, R_3 : H, Me

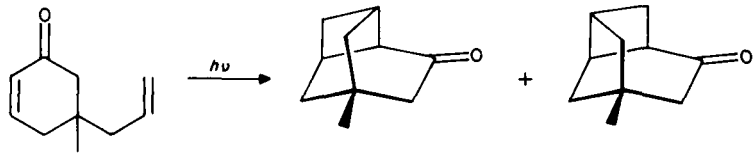


Irradiation of 1:1 mixtures of enol acetates **218a** + **218b** derived from 4-(prop-2'-enyl)cyclopentane-1,3-diones (**217**) leads to 6-acetoxytricyclo[3.2.1.$0^{3,6}$]octan-2-ones (**219**) in high yield. The adducts result from regioselective intramolecular [2 + 2] cycloadditions, suggesting that equilibration between the isomeric enol acetates **218a** ⇄ **218b** is rapid during the photolysis. Fragmentation of adducts **219** with KOH/EtOH or via the corresponding acetoxy-mesylates provides a facile route to a range of substituted bicyclo[3.2.1]octane systems[160b]. This technology has been applied by Pattenden and collaborators[160c] to the total synthesis of (±)-zizaene (**220**), the parent hydrocarbon of the zizaene family of sesquiterpenes found in vetiver oil.

The photocyclization of cyclohexenone **221** gives the tricyclic ketone **222** after 10 days irradiation in benzene. This product is exclusive and the reaction is to be compared with the photolysis of the isomeric enone **223**, which afforded the two products **224** and **225**[201].

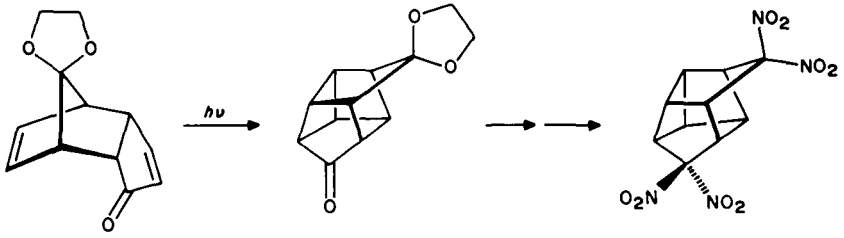


(221) (222)



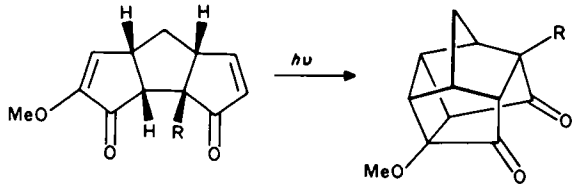
(223) (224) (225)

The use of the intramolecular [2 + 2] photocycloaddition of dienone **226**, previously reported by Vogel and Wyes[202] to afford **227**, has been employed as the key step in the synthesis of the pentacyclodecane **228**[203]. The cage compounds **230** are readily synthesized by irradiation of diene-diones **229**[164c]. Systems **230** have been proposed as candidates for solar energy storing systems[204].

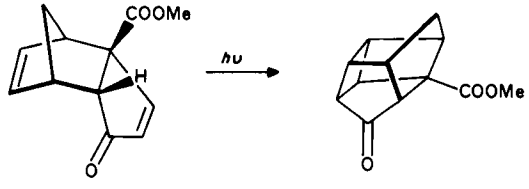


(226) (227) (228)

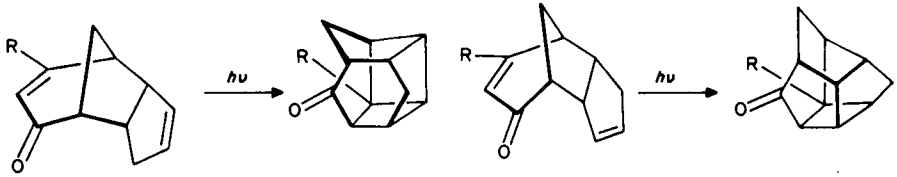
The cage compound **232** can be obtained in 84% yield by photocyclization of dienone **231**[205]. Irradiation of the isomeric dienones **233** and **235** gave the homocubanes **234** and **236**, respectively[164f].



(229) R=H, Me (230)

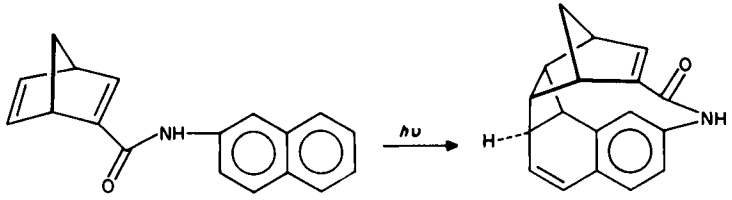


(231) (232)

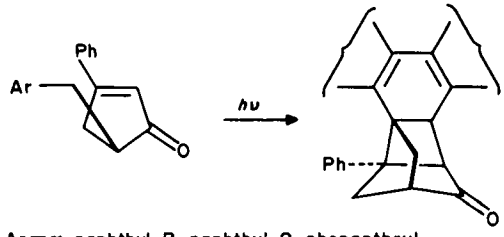


(233) R=H, Me, OMe (234) (235) (236)

Unusual olefin + arene photocycloadditions were observed in the irradiation of the enones given in equations 90[206] and 91[207].



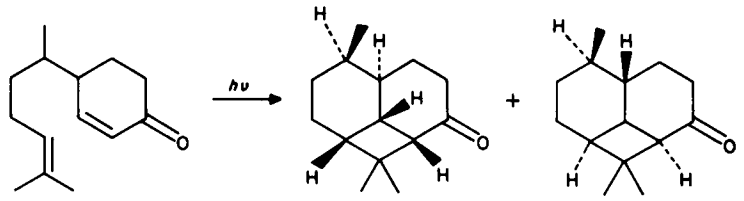
(90)



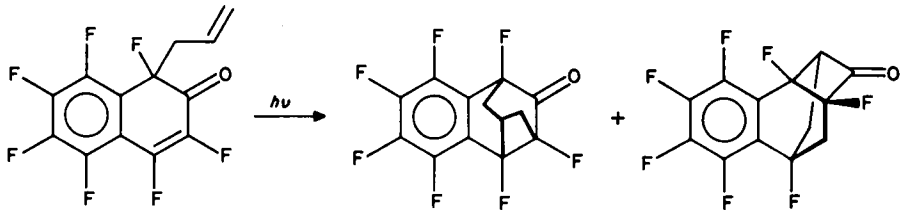
(91)

Ar = α-naphthyl, β-naphthyl, 9-phenanthryl

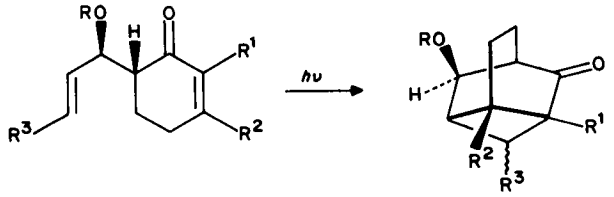
Further examples of dienone photocyclization are presented in equations 92–95.



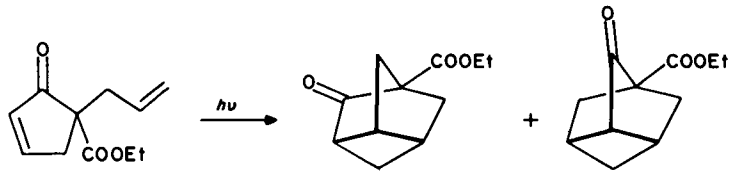
(92)[208]



(93)[209]

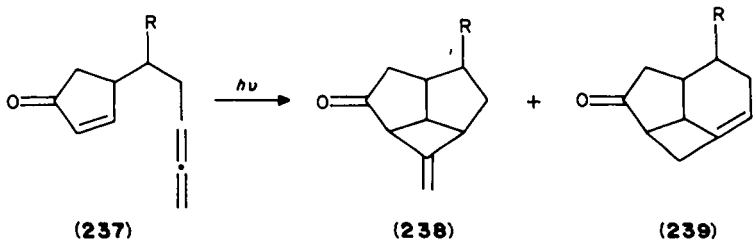


(94)[210]



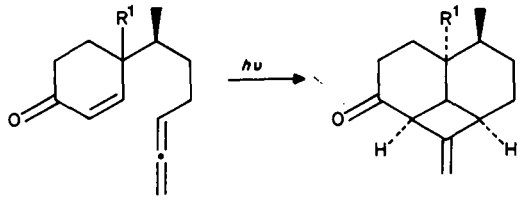
(95)[211]

The intramolecular [2 + 2] photocycloaddition of 4-(3,4-pentadienyl)cyclopent-2-en-1-ones (**237**) has been shown to yield the expected ('rule of five') *cis*-fused tricyclo[4.2.1.$0^{4,9}$]nonanones (**238**), and the unstable, bridgehead olefins **239**, resulting from a cycloaddition of the terminal double bond of the allene moiety, giving probably a diradical intermediate with a six-membered ring. Irradiation of the cyclohexenone derivative **240**, as a 3:2 mixture of *anti* and *syn* diastereomers at −70 °C, resulted in quantitative cycloaddition of the *anti* diastereomer to yield **241**. This compound is a precursor of the total synthesis of decipiene diterpenes[212]. Irradiation of derivatives **242** and **245** gave mixtures **243** + **244** and **246** + **247**, respectively. No satisfactory mechanism could be proposed for the formation of **244** and **247** concurrently with the [2 + 2] photoadducts **243** and **246**, respectively. It is possible that initial bonding at C(2) of the enone moiety is formed.

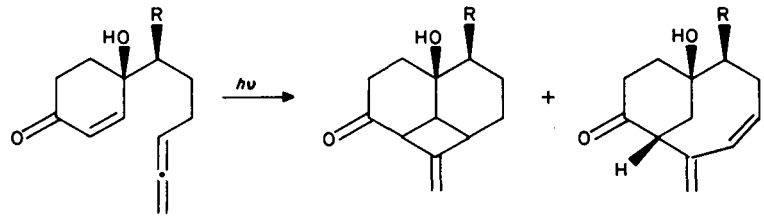


(237) (238) (239)

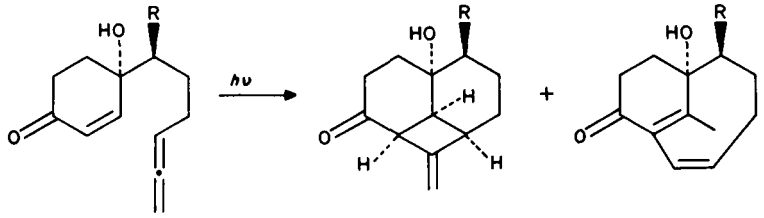
R=H, α-or β-OH, α or β-OSiMe$_2$Bu-*t*



(240) R_1=H, OH (241)



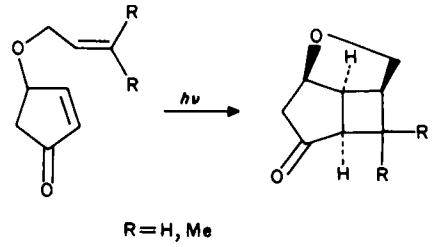
(242) R=CH_2SiMe_2Bu-*t* (243) (244)



(245) (246) (247)

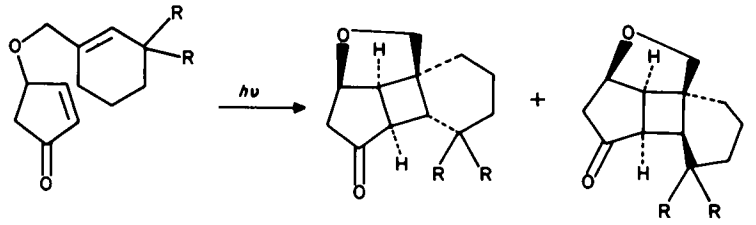
Intramolecular [2 + 2] photocycloadditions of allyl ethers of 4-hydroxycyclopent-2-en-1-ones have also been studied (equations 96 and 97)[213].

Pentaprismane (**250**) has been prepared by Eaton and coworkers[164a]. The reaction sequence involves many steps, the first of which is the photocyclization of diene-dione **248** into the cage compound **249**. Similar photocyclizations has been realized by the groups of De Mayo[164b], Mehta[164c] and Yoshino[214].

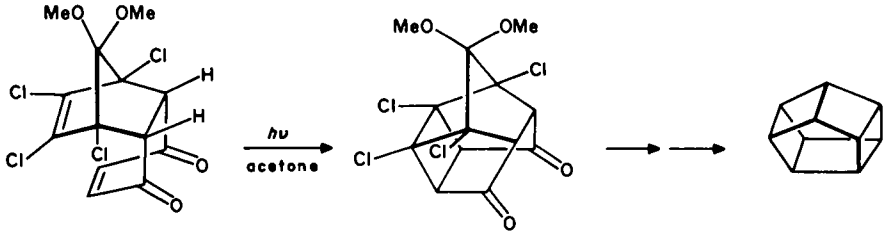


R=H, Me

(96)

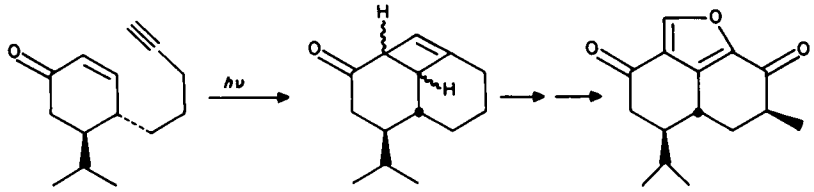


(97)



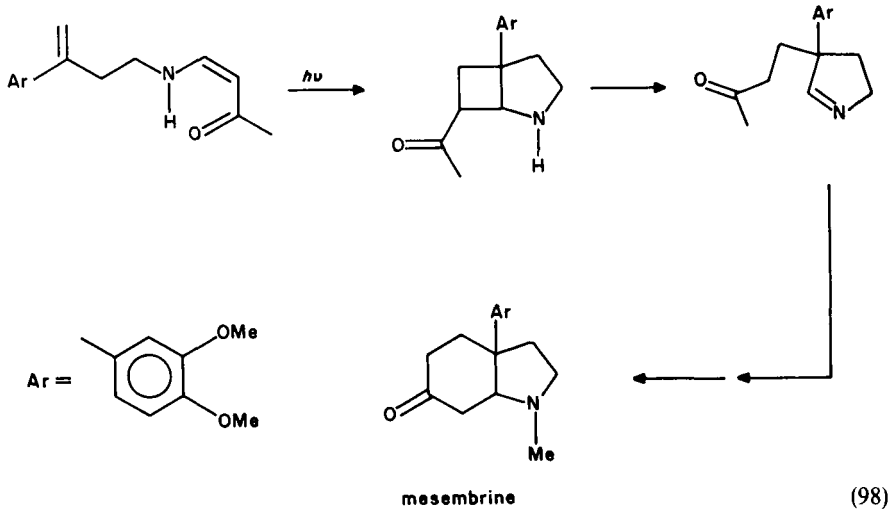
(248) (249) (250)

Koft and Smith[215] have described the total synthesis of (±)-hibiscone C (agmelofuran) (**253**) in 10 steps. Central to their synthetic strategy was the intramolecular [2 + 2] photocycloaddition of the acetylenic moiety of **251** to the conjugated enone to give the cyclobutene derivatives **252**.



(251) (252) (253)

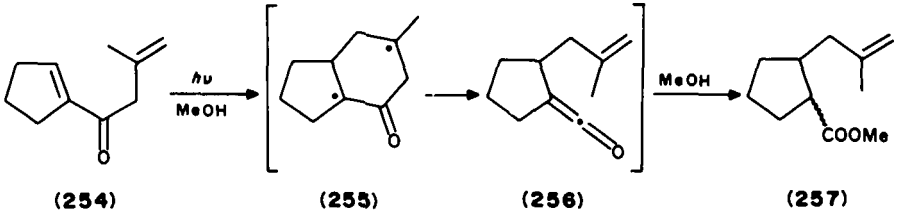
An efficient synthesis of the alkaloid mesembrine has been proposed by Winkler and coworkers[216]. It involves the photocyclization-retro-Mannich–Mannich sequence shown in equation 98.



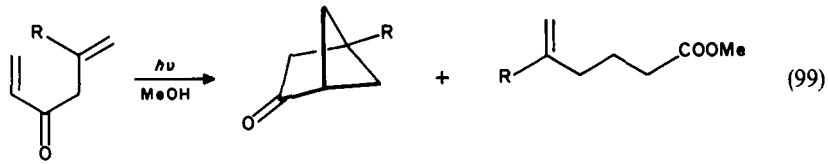
mesembrine (98)

4. Photocyclization of hexa-1,5-diene-3-ones

Contrary to predictions based on the 'rule of five', Smith and Agosta[217] noted that photolysis of dienone **254** in MeOH gave only the two isomers of ester **257**, a result requiring 1,6-closure (head-to-head) with the intermediacy of diradical **255**. Further investigation with simple acyclic analogues yielded products of both 1,5- (head-to-tail) and 1,6-closure (equation 99)[170b]. As for the photocyclization of 1-acylhexa-1,5-dienes, deviation from the 'rule of five' (equations 99–103), i.e. formation of product resulting from 1,6-closure, is observed for alkyl substitution at C(5) (stabilization of intermediate of type **255**) and incorporation of the conjugated C=C double bond in a five- or six-membered ring (equations 101 and 102)[170b].

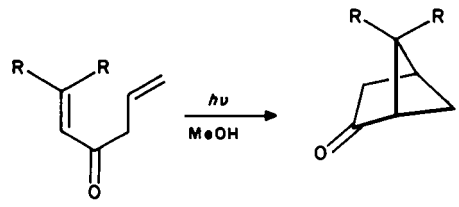


(254) **(255)** **(256)** **(257)**

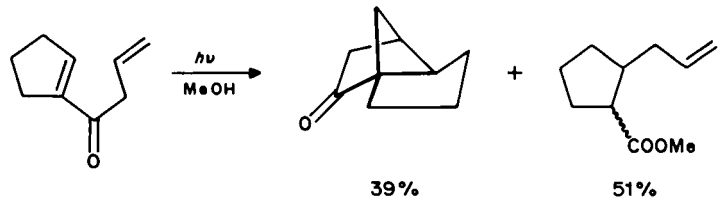


(99)

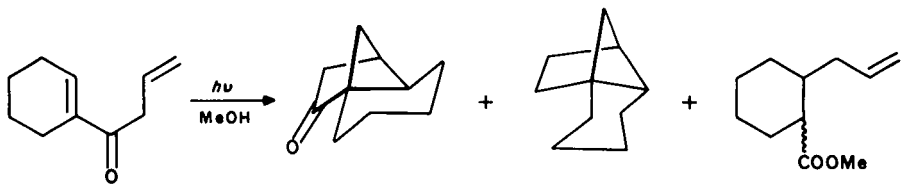
R=Me	43%	27%
R=*t*-Bu	9%	82%



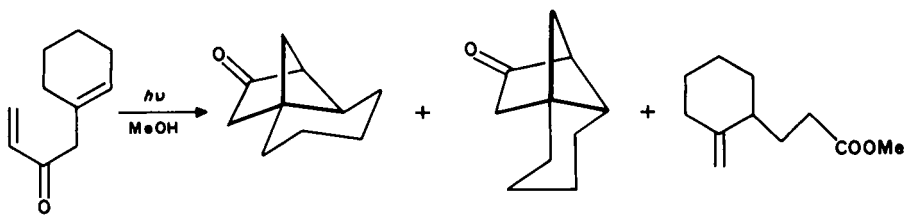
R=H, Me only 1,5-closure (100)



39% 51% (101)



40% 25% (102)

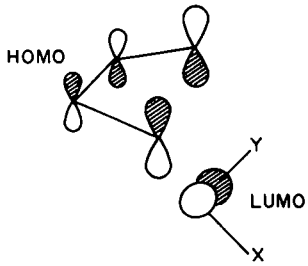


7% 41% 14% (103)

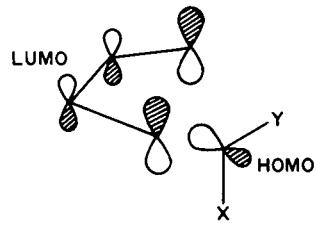
IV. [4 + 1] CYCLOADDITIONS

With 1,3-dienes, singlet carbenes usually undergo [2 + 1] cycloadditions giving vinylcyclopropanes[1,3]. The FMO theory[24] predicts, however, that a carbene, :CXY, should interact favourably with a *s-cis* butadiene moiety because of the stabilizing LUMO(:CXY)–HOMO(diene) (see e.g. **258**) and HOMO(:CXY)–LUMO(diene) interactions (see e.g. **259**) that are realized in a concerted [4 + 1] cycloaddition with the carbene approaching the diene in its mirror plane of symmetry. This prediction has been verified

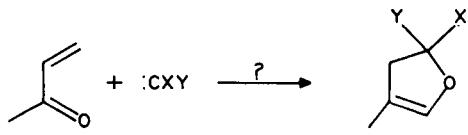
for 1,2-bis(methylene)cycloalkanes in which the 1,3-diene moiety is maintained in a s-*cis* conformation. In the presence of dihalocarbenes generated under various conditions, these systems gave mixtures of [2 + 1] and [4 + 1] cycloadducts[218,219]. No related [4 + 1] cycloadditions of carbenes with α,β-unsaturated ketones (equation 104) have been reported yet. For methylene, $:CH_2$, generated under photochemical conditions, its reaction with saturated ketones, e.g. acetone, does not yield the corresponding epoxide, but rather an unstable carbonyl ylide intermediate that undergoes a dipolar [3 + 2] cycloaddition (see e.g. equation 105)[220]. It is thus thinkable that conditions should be found for a conjugated enone to react with a carbene with formation of a vinyl carbonyl ylide intermediate of type **260** expected to undergo a facile electrocyclization (equation 104).



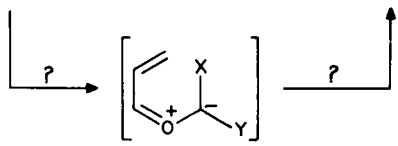
(258)



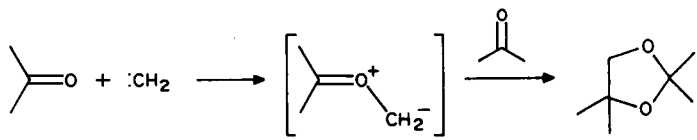
(259)



(104)



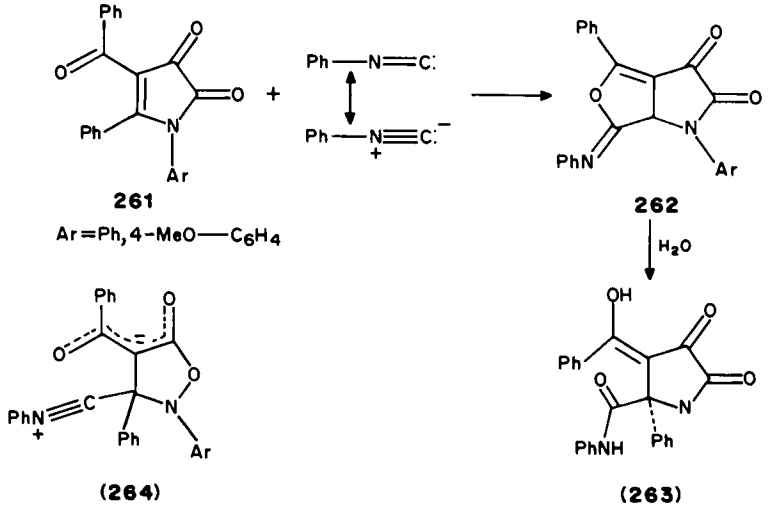
(260)



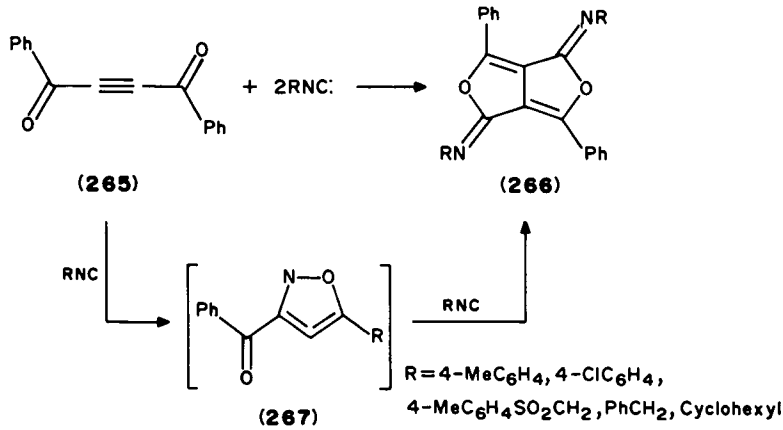
(105)

Isocyanides can be viewed as iminocarbenes. A rare example of [4 + 1] cycloaddition of conjugated enone with phenylisocyanide has been reported by Kollenz and coworkers[221]. The reaction of phenylisocyanide, a nucleophilic carbene *par excellence*, with 1,5-diaryl-4-benzoylpyrrole-2,3-diones **261** gave the corresponding [4 + 1] adducts **262**. In the presence of H_2O, the latter gave **263**. The mechanism of that reaction has not been

established. Both a concerted, one-step process, and a two-step process, involving the intermediacy of the relatively stable zwitterion **264**, can be envisioned.

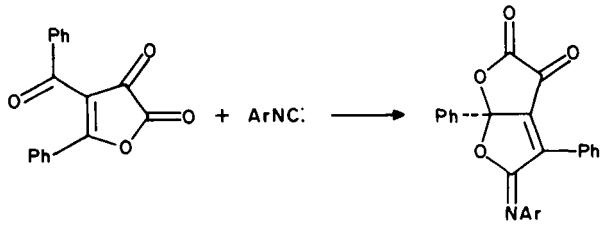


A related case of [4 + 1] cycloaddition has been reported also by Kollenz and coworkers[222]. They found that 1,4-diphenylbutyn-1,4-dione (**265**) added to a variety of isocyanides via a 'criss-cross' cycloaddition yielding the corresponding 1*H*,4*H*-furo[3,4-c]furans (**266**). The results can be interpreted in terms of two successive [4 + 1] cycloadditions with formation of the highly reactive monoadduct **267**.

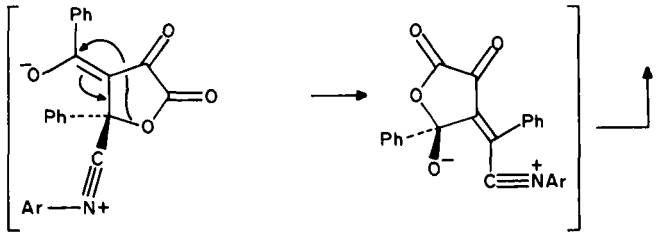


Interestingly, 4-benzoyl-5-phenylfuran-2,3-dione (**268**) (analogous with **261**) added to aryl isocyanides giving 1:1 adducts (**269**), which do not correspond to the expected products of [4 + 1] cycloaddition of the s-*cis*-conjugated enone moiety with ArNC. Products **269** are probably formed in multi-step processes involving intermediates **270** and **271**[223] (see also the reactions of isocyanides with nitroalkenes[224]).

The photolysis of diphenylcyclobutenedione (**272**) and its imine derivative **273** in the presence of 2,6-dimethylphenyl isocyanide gave ring-expanded products **276** and **277** via

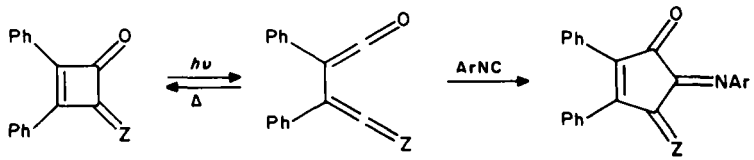


(268) (269)



(270) (271)

the conjugated bis-ketene **274** and ketene-ketenimine **275** intermediate, respectively. The latter could be observed directly by IR spectroscopy during low temperature photolysis. Reactions **274,275** + ArNC → **276,277** are [4 + 1] cycloadditions[224].



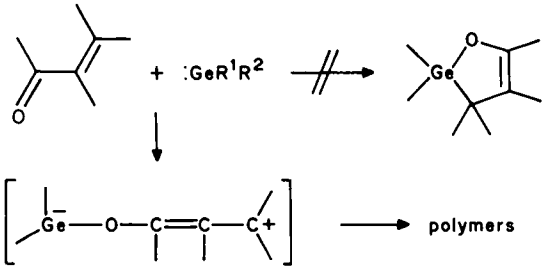
(272) Z=O (274) (276)

(273) Z=NPh (275) (277)

The silylenes $:SiR^1R^2$ [225], germylenes $:GeR^1R^2$ [226–228] and the stannylenes $:SnR^1R^2$ [229] are isoelectronic with the carbenes. These species have been reported to undergo [4 + 1]cycloadditions (or cheletropic reactions) with conjugated dienes, giving the corresponding 3-metallacyclopentenes (equation 106). There are several possible pathways for the reactions. The simplest would be a one-step, concerted [4 + 1] cycloaddition. Alternatively, the reactions could proceed via two-step processes involving unstable [2 + 1] cycloadducts (vinylmetallacyclopropanes) that rearrange to give the 3-metallacyclopentenes. The former mechanism has been shown to predominate in the case of cycloadditions with germylenes[227] and stannylenes[229], while the latter holds for silylenes[230]. There is also the possibility of the intervention of diradical intermediates[225,226]. No product of [4 + 1] cycloaddition of silylenes, germylenes and stannylenes with conjugated enones has been reported yet. With 3,5-di(tertbutyl)orthoquinone, germylenes give the corresponding 2-germa-1,3-dioxolanes[231]. Difluoro- and phenylhalogermylenes react with *α,β-unsaturated carbonyl compounds* by 1,2- and 1,4-additions after electrophilic attack of the germylenes onto the carbonyl group, as shown in equation 107[232].

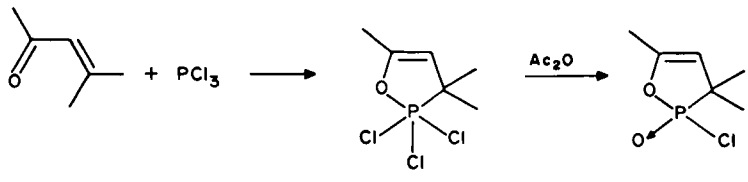
(106)

R^1, R^2 = alkyl, aryl, halide, etc.



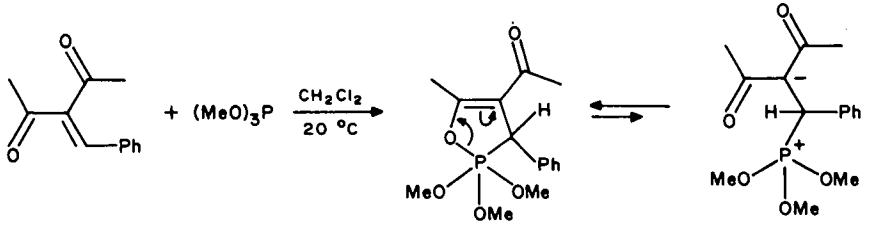
(107)

Trivalent phosphorus compounds react readily with 1,3-dienes and 1,2-diketones giving the corresponding [4 + 1] adducts[233–235]. The reactions of phosphinidenes, :PR (analogues of nitrenes), with 1,3-dienes and 1,2-diketones have been reported to give products arising probably from a [4 + 1] cycloaddition[236]. In 1920, Conant and Cook[237] proposed that the reaction of α,β-unsaturated ketones with phosphorous trichloride, PCl_3, follows a [4 + 1] cycloaddition mechanism (equation 108).



(108)

Ramirez and collaborators[238a] in 1964 reported the first authentic case of [4 + 1] cycloaddition with the reaction of trimethylphosphite and 3-benzylidene-2,4-pentanedione (equation 109). ^{31}P-NMR data were used to distinguish between the isolated, crystalline Δ^4-oxaphospholene and the corresponding zwitterionic structure.

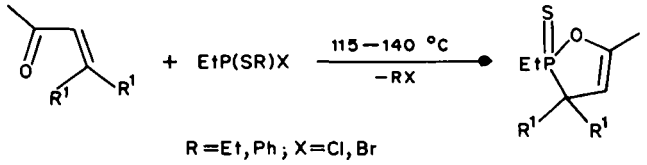


(109)

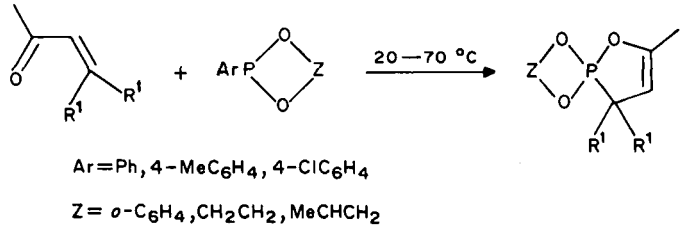
In alcoholic solvents, the reaction of trialkyl phosphites with α,β-unsaturated aldehydes and ketones gives products resulting from Michael-type addition of the phosphorus reagent, as well as addition at the carbonyl carbon atom[238b].

On heating, thiophosphinous acid halide esters (EtP(SR)X) react with conjugated enones and give the corresponding oxaphospholenes (equation 110)[239]. Similarly, the

condensation of glycolic and pyrocatechol esters of arylphosphonous acids with α,β-unsaturated ketones yields spirophosphoranes (equation 111)[240]. The mechanism of these reactions is not established yet. A concerted, one-step [4 + 1] cycloaddition cannot be excluded yet as one of the possible pathways.

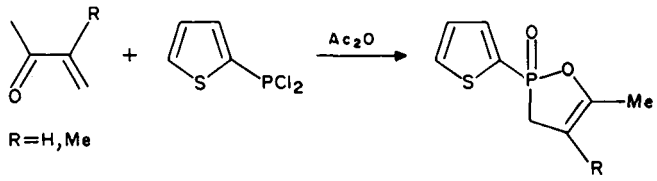


(110)



(111)

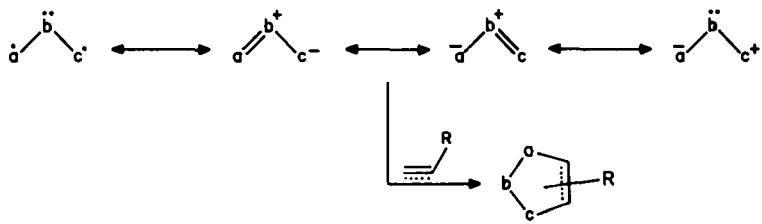
The treatment of methyl vinyl ketone and 3-methylbut-3-en-one with (α-thienyl)-dichlorophosphine in acetic anhydride afforded the corresponding oxaphosphalenes (equation 112)[241].



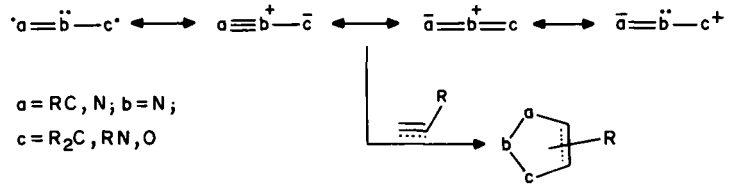
(112)

V. [3 + 2] CYCLOADDITIONS

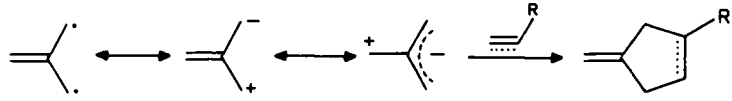
The [3 + 2] cycloaddition of 1,3-dipoles a⁻—b⁺=c or a⁻—b⁺≡c to olefinic or acetylenic moieties is a well-established methodology for the formation of five-membered heterocycles (equations 113 and 114)[242]. Five-membered carbocyclic rings can also be prepared by [3 + 2] cycloaddition, most conveniently by reaction of olefins with trimethylenemethane and its equivalents (equation 115)[243].



(113)



(114)



(115)

According to the Woodward–Hoffmann rules[4], the concerted, suprafacial, suprafacial $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition of a 1,3-dipole to an olefinic or acetylenic moiety is thermally allowed. The transition state of the reaction (see Figure 4) is isoconjugate with cyclopentadienyl anion in the same way as the transition state of the Diels–Alder addition (see Section VI) is isoconjugate with benzene[244]. Controversy still surrounds the mechanism of these cycloadditions[245–249]. For 'normal' 1,3-dipoles (equations 113 and 114), Huisgen favours a concerted, one-step mechanism[245,250–252] whereas Firestone prefers stepwise, diradical pathways[246]. Recently, Huisgen and coworkers[248,249] have reported cases of thiocarbonyl ylides, $R_2C{=}\overset{+}{S}{-}\bar{C}H_2$, whose reactions with electron-poor olefins led to zwitterionic intermediates. For reactions of nucleophilic 1,3-dipoles with α,β-unsaturated ketones, the chances for the intervention of zwitterionic intermediates are relatively large since the carbonyl group can stabilize the negatively charged moiety of these species (see Scheme 11). Depending on the nature of the 1,3-dipole, the substituents of the enone and the solvent, rotation (k_{rot}) about the σ(C—C) bond of these intermediates can be a slower or a competitive process with ring closure (k_c, k'_c). Examples maintaining the suprafacial, suprafacial stereoselectivity ($k_{rot} \ll k_c$) are numerous and will be presented below. Cases where this stereoselectivity is not respected will also be shown.

There have been several approaches to the classification of 1,3-dipoles. That of Huisgen is based on structural properties[245], while Houk[252b] considers the diradical character of

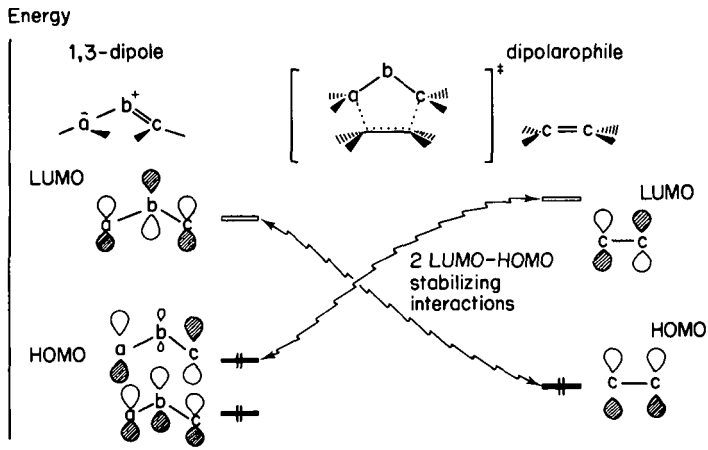
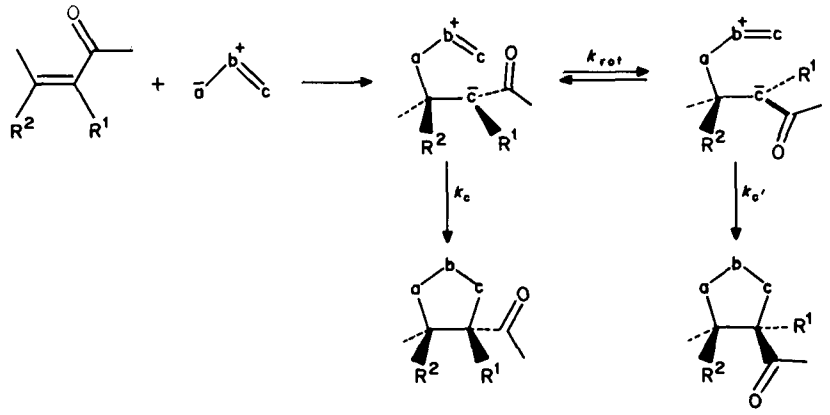


FIGURE 4. PMO diagram for [3 + 2] cycloaddition of 1,3-dipole $\bar{a}{-}\overset{+}{b}{=}c$ to an olefin[252]



SCHEME 11

the 1,3-dipole as defined by quantum mechanical calculations. A third approach advocated by Sustmann[252a] utilizes reactivity criteria. In this, the frontier orbital energies (LUMO and HOMO energies) define whether a 1,3-dipole is a nucleophilic, ambiphilic or electrophilic reagent when reacting with ethylene (reference dipolarophile, see also Section II.A). Thus, a nucleophilic 1,3-dipole would imply a HOMO(dipole)–LUMO(dipolarophile) interaction to dominate in the transition state of an hypothetical concerted reaction, whereas an electrophilic 1,3-dipole involves a dominating LUMO(dipole)–HOMO(dipolarophile) interaction. When both types of interaction intervene to a similar extent, the 1,3-dipole is classified as an ambiphilic reagent. The FMO energies of unsubstituted 1,3-dipoles are given in Figure 5 and compared with those

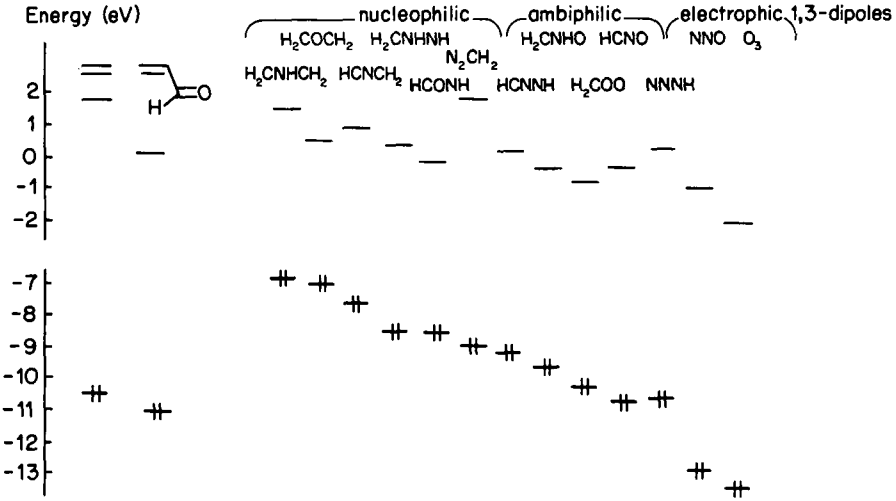
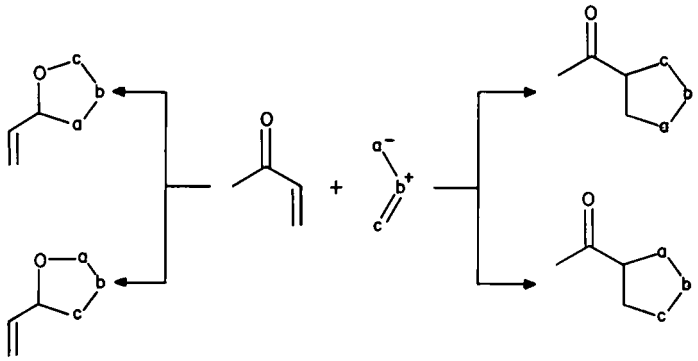


FIGURE 5. FMO energies of ethylene, acrolein and typical 1,3-dipole as given by Houk[252b]; classification of the 1,3-dipoles as proposed by Sustmann[252a] (taken from Reference 252b with permission of the editor)

of ethylene and acrolein, the prototype of a conjugated enone. According to the FMO theory[24] nucleophilic 1,3-dipoles have their [3 + 2] cycloadditions accelerated for electron-releasing substituents on the dipole and electron-withdrawing substituents on the dipolarophile. Conversely, the [3 + 2] cycloadditions of electrophilic 1,3-dipoles will be accelerated by electron-withdrawing groups on the dipole and electron-donating groups at the dipolarophile. In the case of cycloadditions of ambiphilic 1,3-dipoles, both types of substituents on the 1,3-dipole or/and the dipolarophile should accelerate the reaction.

A. Synthesis of Heterocyclic Compounds

Because of their intrinsic electrophilic character, α,β-unsaturated aldehydes and ketones are good dipolarophiles for nucleophilic 1,3-dipoles such as the azomethine ylides (e.g. $C\bar{H}_2—\overset{+}{N}H=CH_2$), carbonyl ylides (e.g. $PhC\bar{H}—\overset{+}{O}=CHPh$), nitrile ylides (e.g. $C\bar{H}_2—\overset{+}{N}\equiv CPh$), diazoalkanes (e.g. $C\bar{H}_2—\overset{+}{N}\equiv N$) (see Figure 5)[242] and trimethylenemethane[243]. *A priori*, both the C=C and C=O double bonds can undergo a [3 + 2] cycloaddition. The chemoselectivity (site selectivity) will depend on the substitution of both the 1,3-dipole and dipolarophile. Unless steric effects are dominating, the reactivity, chemo- and regioselectivity (Scheme 12) can be rationalized, in most instances, in terms of energy and shape (atomic coefficients) of the LUMO of the dipole and HOMO of the conjugated enone or enal[253].



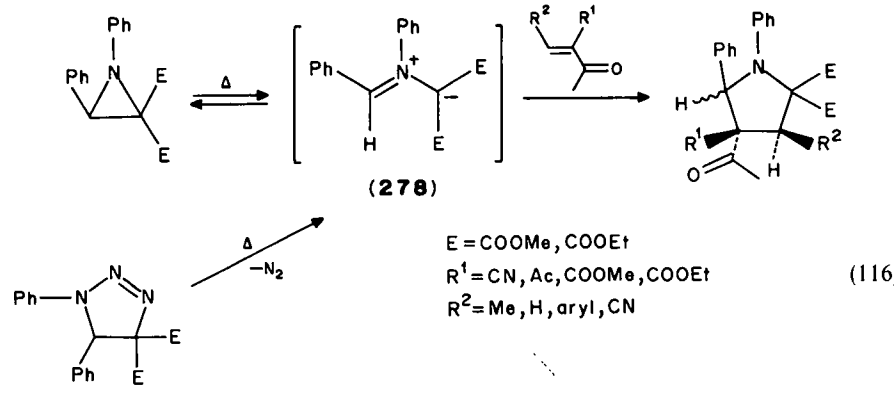
SCHEME 12

1. Cycloadditions with azomethine ylides

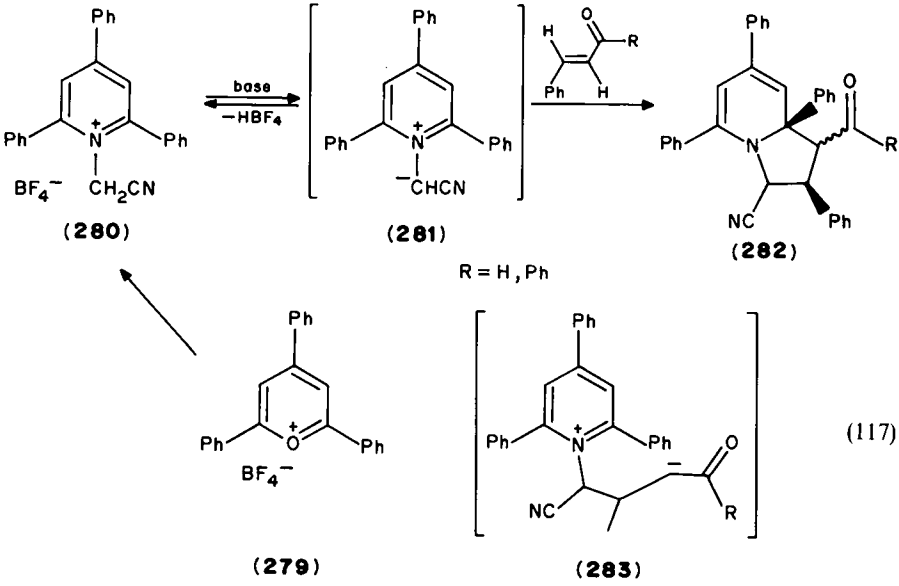
Azomethine ylides are unstable species that can be generated *in situ* by various techniques (e.g. thermolysis of aziridines, dehalogenation of immonium salts or deprotonation of imines derived from α-aminoacids) at low concentration in anhydrous solvents[254].

The monosubstituted azomethine ylide $PhC\bar{H}—\overset{+}{N}H=CH_2$ has been generated by treatment of $PhHC=NCH_2SiMe_3$ with H_2O in $(Me_2N)_3PO$[255]. The azomethine ylides react quickly with a large variety of dipolarophiles to give mono-, bi- or tricyclic heterocycles[254,255]. With α,β-unsaturated aldehydes, azomethine ylides react preferentially with the C=O double bond[256] whereas the C=C double bond is preferred with α,β-unsaturated ketones as shown in equations 116[257] and 117[258].

Pyrolysis of aziridines or of triazolines in the presence of electron-poor alkenes is a convenient methods of azacyclopentanation[259] (e.g. equation 116). Amination of the



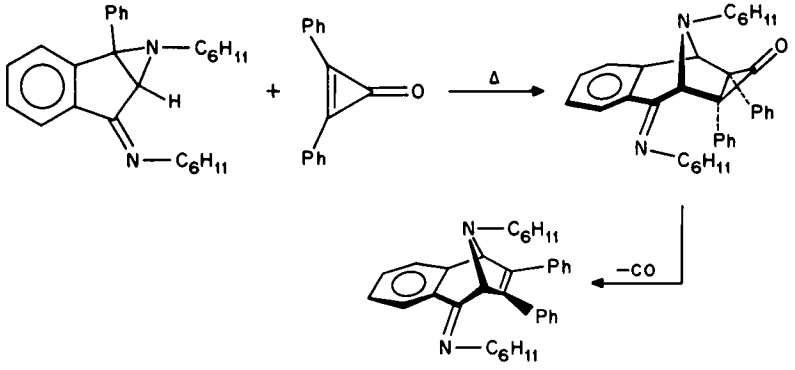
(116)



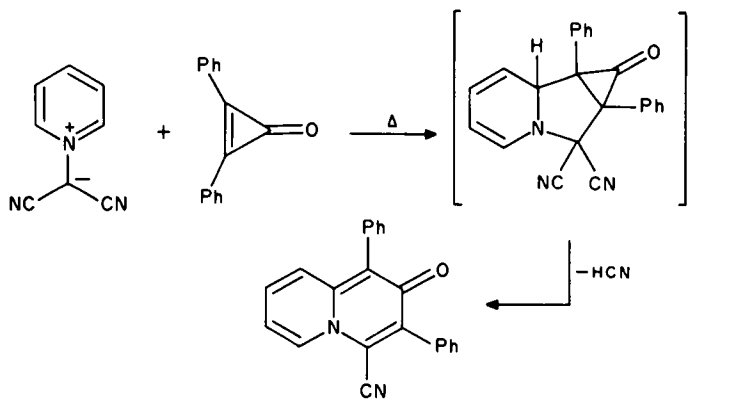
(117)

pyrylium salt **279** by H_2NCH_2CN in CH_2Cl_2 containing Et_3N gives the pyridinium salt **280** which, on treatment with conjugated enones and enals, affords the corresponding tetrahydroindolizines (**282**). Reactions of equation 117 can be interpreted in terms of the formation of the ylide intermediate (**281**), which undergoes a concerted, one-step [3 + 2] cycloaddition with the olefinic dipolarophiles (the basic media induces epimerization of the adducts, thus loosing the stereochemical information of the reaction). Alternatively, a two-step mechanism implying the zwitterionic intermediate **283** is also possible. A similar mechanism could also interpret the high regioselectivity of the [3 + 2] cycloaddition of equation 116. Pyridinium ylides have also been prepared recently by capture of phenylchlorocarbene and *tert*-butylchlorocarbene by pyridine[260].

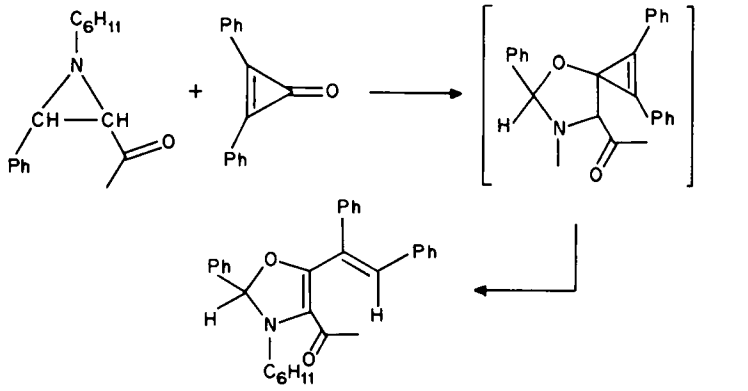
Depending on the nature of the azomethine ylide (compare equations 118, 119 and 120), diphenylcyclopropenone reacts with the C=C bond[261a] or the C=O bond[261b].



(118)



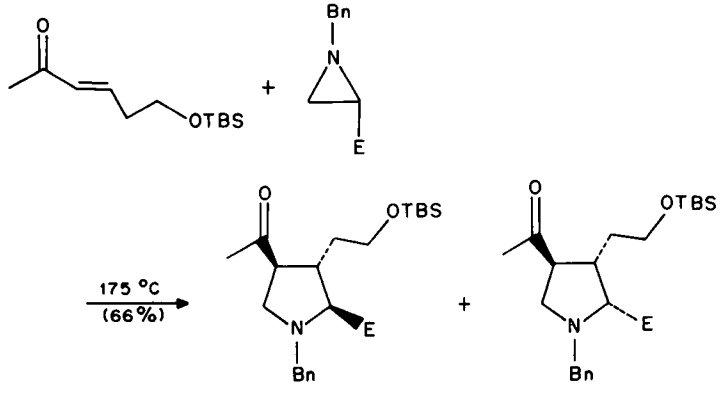
(119)



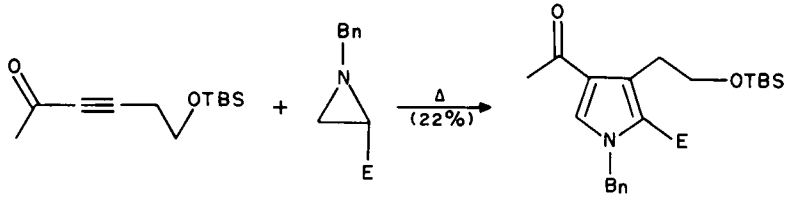
(120)

N-Alkyl- and *N*-arylaziridines carrying a single carboxy ester function undergo thermally induced electrocyclic ring opening to produce azomethine ylides that subsequently react with conjugated enones (e.g. equation 121) and enones (e.g. equation 122). (*E*)-enones lead to better yields than the corresponding (*Z*)-isomers[259]. The [3 + 2]

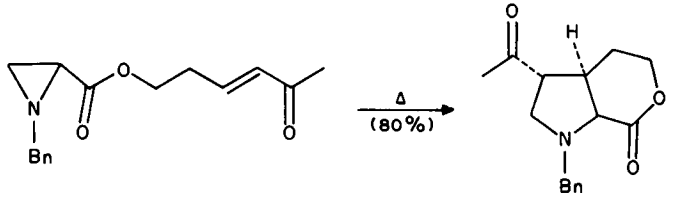
cycloaddition can also be performed in the intramolecular mode with excellent selectivity, as illustrated by equations 123 and 124[259]. A total synthesis of (±)-*allo*-kainic acid (**284**) based on the intermolecular cycloaddition of equation 121 has been presented by DeShong and Kell[262].



(121)



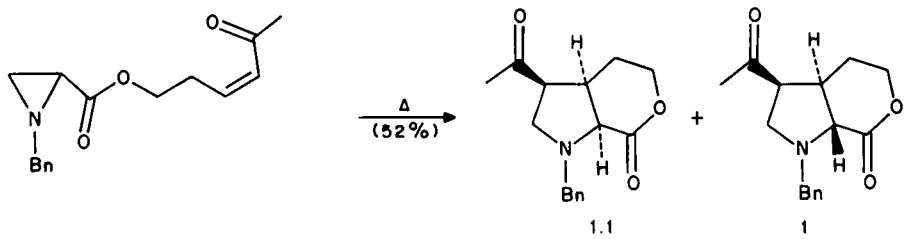
(122)



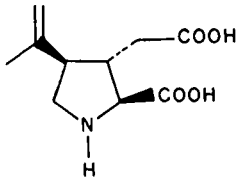
(123)

The mesoionic ring systems **285**–**289** contain the azomethine ylide moiety (1, 3-dipole). They are reactive intermediates which undergo [3 + 2] cycloadditions with electron-poor dipolarophiles[263]. For instance, the substituted 1, 3-oxazol-5-ones (münchones) react readily with dimethyl- and diphenylcyclopropenone to give unstable adducts of the C=C bond that expel an equivalent of CO_2 and afford the corresponding γ-pyridones (equation 125)[264]. Analogous reactions have been reported for the mesoionic ring systems **290** and **291**[265,266].

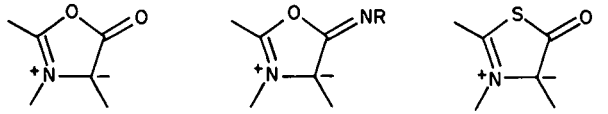
Thiazolium ylides **293**, generated by treatment of the corresponding bromides **292** with Et_3N, react with a variety of α, β-unsaturated ketones to give adducts **294**. The latter are converted into the tricyclic derivatives **295** in the presence of silica gel[267]. Products **295** can then be transformed into pyrrolidines **296** by treatment with $AgNO_3$ followed by a



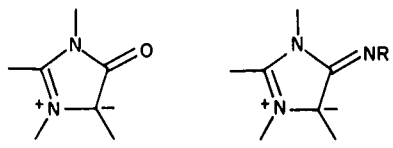
TBS = *t*-BuMe$_2$Si; E = COOCH$_3$; Bn = PhCH$_2$ (124)



(284)



1,3-oxazol-5-one (285) 1,3-oxazol-5-imine (286) 1,3-thiazol-5-one (287)

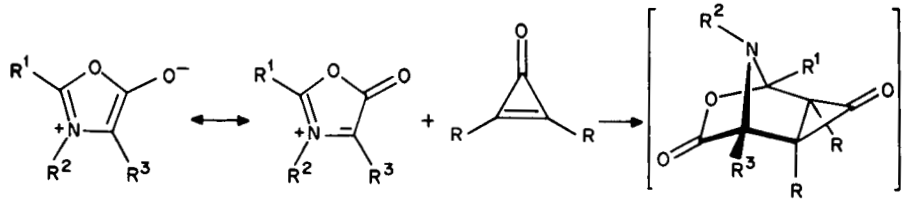


Imidazol-4(5)one (288) Imidazol-4(5)-imine (289)

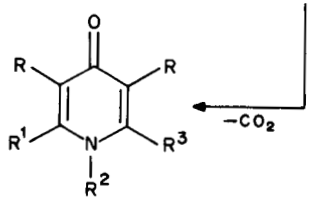
reduction with Na(CN)BH$_3$. This methodology has been applied by Kraus and Nagy[267a] in their total synthesis of (±)-α-*allo*-kainic acid (**284**).

2. *Cycloaddition with carbonyl ylides*

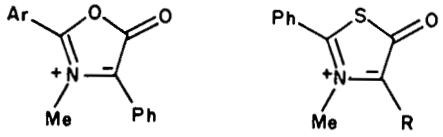
Based on the FMO theory, Houk and collaborators[268] proposed that carbonyl ylides, generated via ring opening of oxiranes, are nucleophilic 1,3-dipoles susceptible to undergo [3 + 2] cycloadditions with electron-poor alkenes. This has been confirmed experimentally for α,β-unsaturated carbocyclic systems[269–274] (see e.g. equations 126 and 127)[274]. The configuration of the dipolarophiles is retained in the cycloadducts, consistently with a concerted [3 + 2] cycloaddition. However, solvent effects, steric hindrance and also orbital overlap may affect the product distribution[271]. With non-symmetrically substituted carbonyl ylides (e.g. RCH=$\overset{+}{O}$—$\overset{-}{C}$(Ph)CN)[272] the regioselectivity of the [3 + 2] cycloadditions is high with electron-rich alkenes but is low with electron-deficient olefins.



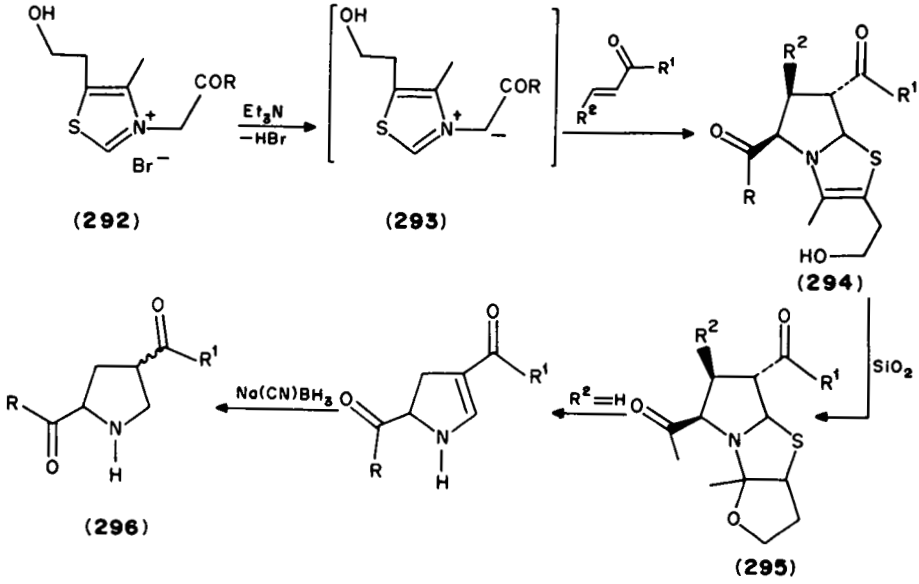
R, R¹, R², R³: Me, Ph



(125)

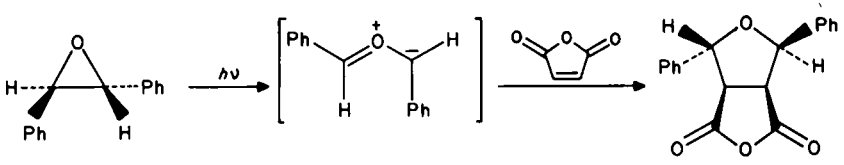


(290) Ar = Ph; 4-$NO_2C_6H_4$ (291) R = Ph, H



(292) (293) (294) (295) (296)

The addition rate is greater with electron-deficient than with electron-rich dipolarophiles in agreement with the hypothesis that HOMO(dipole)–LUMO(dipolarophile) interaction controls the reaction. The cycloadditions of dipolarophiles containing π substituents take place with high *syn* stereoselectivity due to secondary orbital interaction[273].



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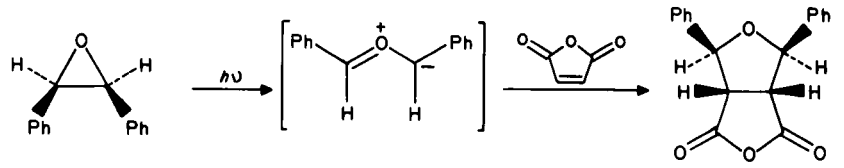

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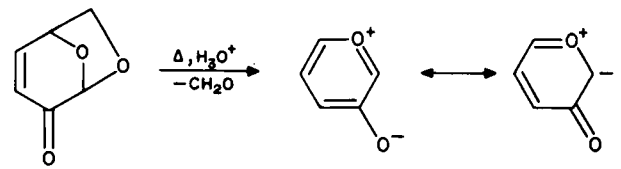
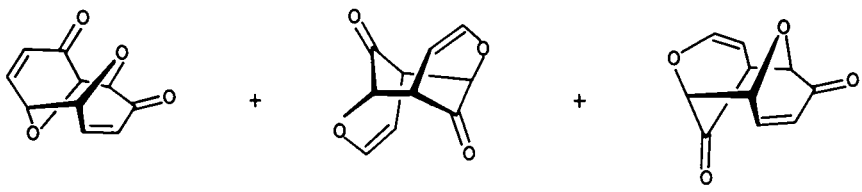
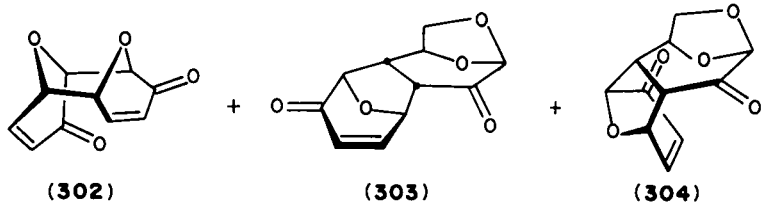


(297) (298) (298')



(299) (300) (301)

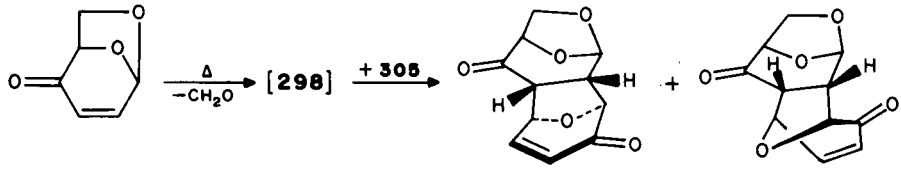


(302) (303) (304)

Rare are the cases of carbonyl ylide cycloadditions with enones. Two examples involving 3-oxidopyrylium (**298**) are shown above[275,276]. The major product from the pyrolysis of acid-doped cellulose is levoglucosenone (**297**) which undergoes under the

conditions of its formation a deformylation process **297** → **298** + CH_2O. The zwitterion **298**, a masked cyclic carbonyl ylide as shown with the limiting structure **298′**, gives the four isomeric dimers **299–302** and also adds to unreacted enone **297** to give the [3 + 2] cycloadducts **303** and **304**, both resulting from attack of the carbonyl ylide onto the less crowded face of the C=C double bond in **297**. It is interesting to note that the cycloaddition is highly regioselective, since the negatively charged centre of **298′** attacks the β-carbon atom of the conjugated enone.

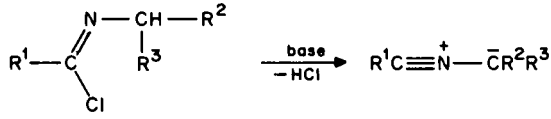
3-Oxidopyrylium **298** was also formed on heating (210–260 °C) isolevoglucosenone (**305**), with loss of formaldehyde. The ylide was efficiently trapped by enone **305** to yield the [3 + 2] cycloadducts **306** and **307**. In that case also the reaction was highly regioselective[276].



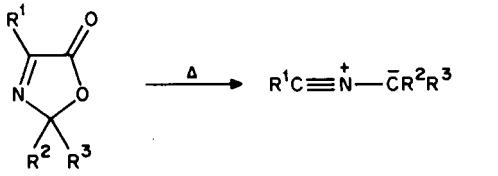
(**305**) (**306**) (**307**)

3. *Cycloadditions with nitrile ylides*

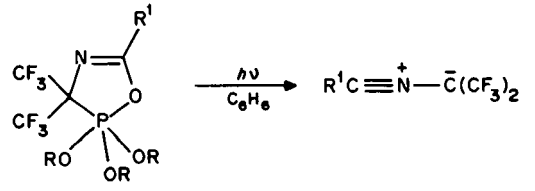
The most versatile methods for the generation of nitrile ylides[277a] include the Huisgen procedure which involves β-elimination of hydrogen chloride from imidoyl chlorides (equation 128), the thermal cycloelimination of CO_2 from oxazolin-5-ones developed by Steglich and coworkers[277b] (e.g. equation 129), the thermal extrusion of alkyl esters of phosphoric acid from 2,3-dihydro-1,4-2λ⁵-oxazaphospholes proposed by Burger and coworkers[277c] (e.g. equation 130), the extrusion of isocyanide from 3-imino-1-azetines induced photochemically (e.g. equation 131) and the photochemical ring opening of 3-aryl-2*H*-azirines (equation 133).



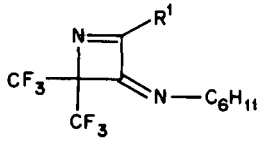
(128)



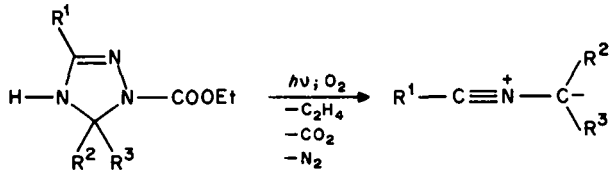
(129)



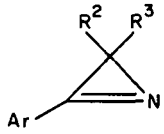
(130)



$$\xrightleftharpoons[\Delta]{h\nu} R^1C{\equiv}\overset{+}{N}{-}\bar{C}(CF_3)_2 + C_6H_{11}\overset{+}{N}{\equiv}\bar{C}: \qquad (131)$$

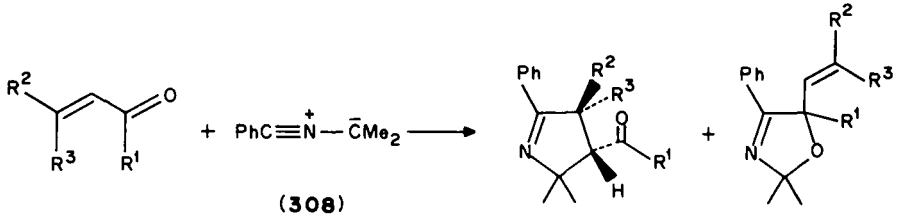


(132)



$$\xrightarrow{h\nu} ArC{\equiv}N{-}\bar{C}R^2R^3 \qquad (133)$$

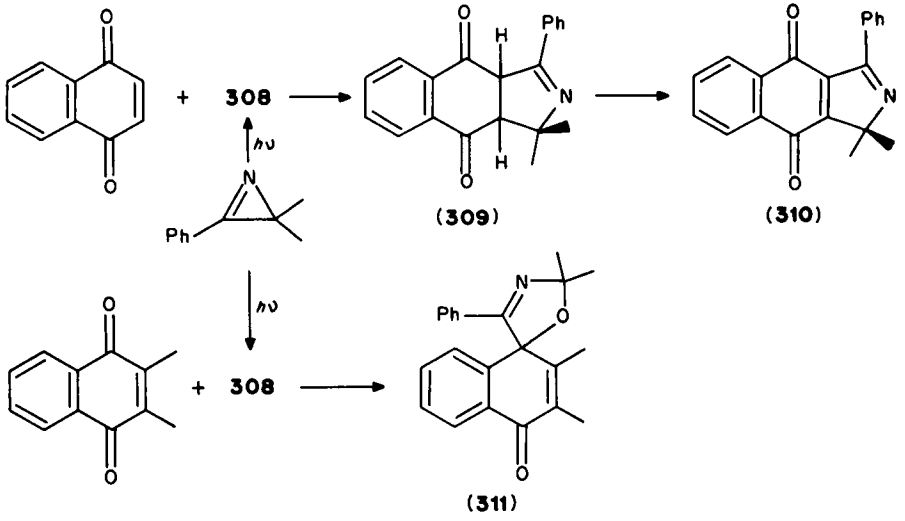
With ambident dipolarophiles such as α,β-unsaturated aldehydes and ketones, nitrile ylides undergo competitive [3 + 2] cycloadditions at C=C and C=O functions[277,278]. Examples are given below for the reactions of benzonitrilio 2-propanide (**308**)[277]. The chemoselectivity (site selectivity) strongly depends on the substitution pattern of the enone. For instance, *p*-naphthoquinone adds to **308** preferentially onto the C=C double bond to give adduct **309**, which is readily oxidized into **310**. In contrast, 2,3-dimethyl-*p*-naphthoquinone reacts preferentially with the C=O double bond to afford the corresponding 3-oxazoline **311**. With ethylene benzoquinone monoacetal, the C=O double bond was also more reactive than the two C=C bonds toward **308**[277]. Exclusive C=C [3 + 2] cycloadditions are observed, however, in the reactions of **308** with cycloalk-2-en-1-ones (equation 134)[277] and diethyl chelidonate (equation 135)[279].

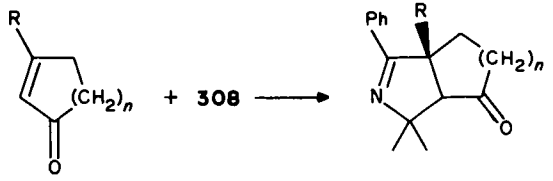


(**308**)

$R^1=R^2=R^3=H$	39%	46%
$R^1=Me, R^2=R^3=H$	74.5%	0.5%
$R^1=R^2=R^3=Me$	3%	30%
$R^1=Me, R^2=(EtO)_2PO, R^3=H$	41%	31%
$R^1=Me, R^2=OMe, R^3=H$	21%	34%

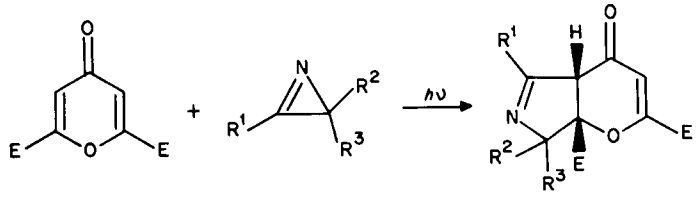
Recently, Tsuge and coworkers[280] have presented a new and general route to 1-pyrrolines **314** (Scheme 13). The *N*- or *S*-alkylation or -silylation of *N*-(silylmethyl)-amidines or -thioamides and the subsequent desilylation of the silylmethyl group (CsF in





(134)

$n = 1$, R = H: 78%; $n = 2$, R = H: 52%; $n = 2$, R = Me: 34%
$n = 3$, R = H: 52%

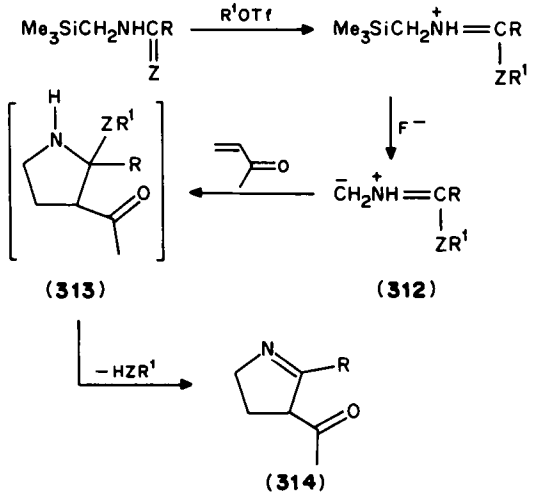


(135)

E = COOEt; R^1 = Ar, $R^2 = R^3$ = Me, $(CH_2)_5$

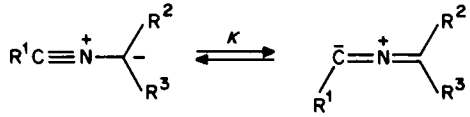
dimethoxyethane) generate N-protonated azomethine ylides (**312**) bearing a leaving group. The ylides **312** undergo [3 + 2] cycloadditions with electron-deficient alkenes such as methyl vinyl ketone, and give the expected adduct **313** with high regioselectivity. As the leaving group is eliminated under the reaction conditions, the azomethine ylides (**312**) can be seen as synthetic equivalent of non-stabilized nitrile ylides, $\bar{C}H_2$—$\overset{+}{N}$≡CR, which are otherwise difficult to obtain.

The regioselectivity of the [3 + 2] cycloadditions of substituted nitrile ylides to electron-deficient dipolarophiles can be interpreted by analyzing the shape of the HOMO of the 1,3-dipole and the LUMO of the enone. Houk and coworkers[281,282] have calculated (*ab*



SCHEME 13

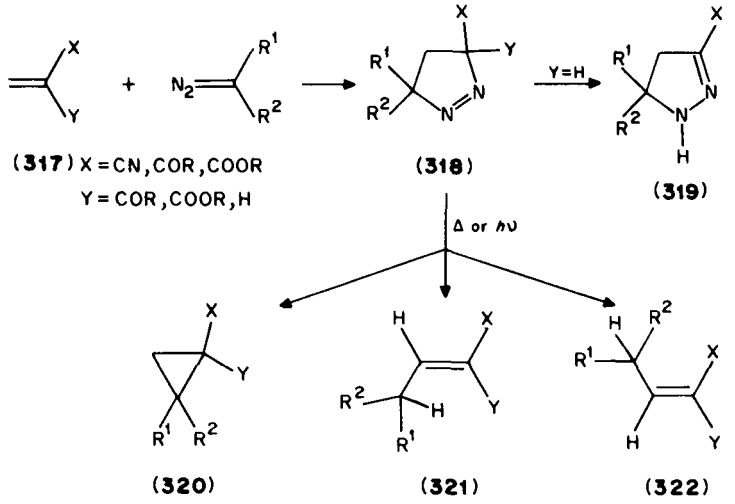
initio MO—SCF calculations) that the equilibrium constant between the 'propargylic' structure **315** and the 'allenic' structure **316** depends on the nature of the substituents R^1, R^2 and R^3 of the nitrile ylide. If R^2 and R^3 are electron-withdrawing, structure **315** is favoured, thus making the trigonal carbanion moiety of the ylide the most nucleophilic centre (with the largest coefficient in its HOMO); it is this centre that attacks the most electrophilic centre of the conjugated enone, i.e. the carbonyl carbon atom or the β-carbon atom. On the other hand, if R^2 and R^3 are electron-releasing groups (e.g. alkyl, aryl), as in **308**, the 'allenylic' structure **316** is favoured in which the digonal nitrile C atom is the most nucleophilic centre and this attacks the carbonyl carbon centre (see also reaction of **308** with a C=S double bond[283]) or the β-carbon centre of the α,β-unsaturated ketone (e.g. equation 134). In the case of diethyl chelidonate (see equation 135), the conjugation of the ester and oxy functions makes the carbon atom α to the ketone function the most electrophilic one, leading to the regioselectivity observed.



4. Cycloadditions with diazoalkanes and derivatives

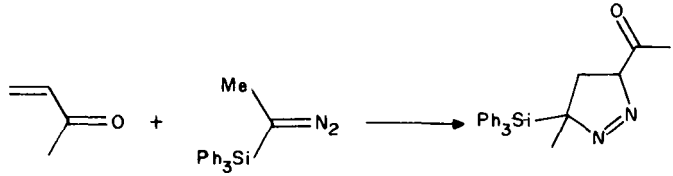
The [3 + 2] cycloadditions of diazoalkanes have been studied extensively[284]. For diazomethane, $CH_2—N\equiv N$, and its alkyl or aryl substituted derivatives, $R^1R^2C=N_2$, the reactivity with α,β-unsaturated carbonyl systems is governed mainly by the HOMO(1,3-dipole)–LUMO(dipolarophile) interaction[253]. For methyl diazoacetate, $MeOOCCH=N_2$, the ester function lowers the energies of the HOMO and LUMO of this 1,3-dipole, making it less nucleophilic and more electrophilic. The latter is in fact an ambiphilic 1,3-dipole. Others diazoalkanes such as dimethyl diazomalonate, $(MeOOC)_2CN_2$, and methyl diazo(phenylsulphonyl)acetate, $MeOOC(PhSO_2)C=N_2$,

that bear two strongly electron-withdrawing groups are electrophilic 1, 3-dipoles and thus react sluggishly with α,β-unsaturated aldehydes and ketones. The reactions of diazoalkanes with the electron-deficient olefins **317** give the corresponding Δ^1-pyrazolines **318** with good regioselectivity. The latter are usually not very stable compounds; they isomerize (Y = H) into the corresponding Δ^2-pyrazolines **319**, or lose a nitrogen molecule to afford the corresponding cyclopropane derivatives **320**. In some cases, the exclusion of N_2 is accompanied by the formation of the substituted alkenes **321** and **322** (Scheme 14). Typical examples of reactions of diazoalkanes with conjugated enals and enones are given below.

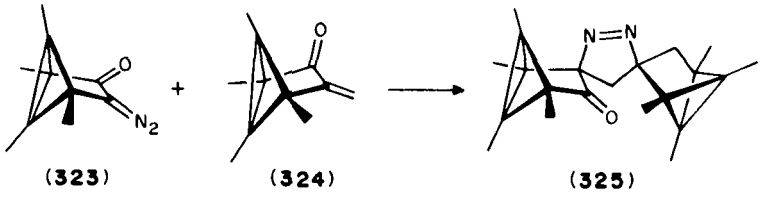


SCHEME 14

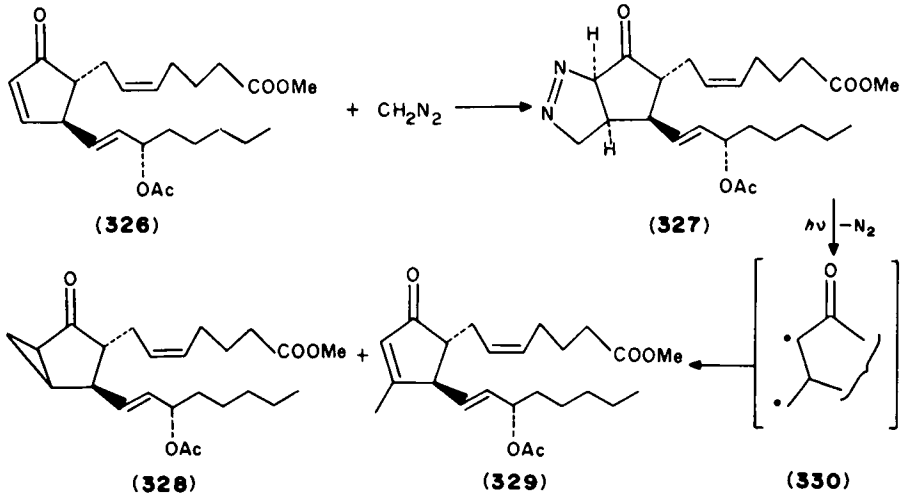
With methyl(triphenylsilyl)diazomethane, methyl vinyl ketone gives exclusively the corresponding Δ^1-pyrazoline in 90% yield (equation 136)[285]. Similarly, the diazoketone **323** adds to the α-methylene ketone **324** to afford the [3 + 2] cycloadduct **325** with high chemo-, regio- and stereoselectivity[286].



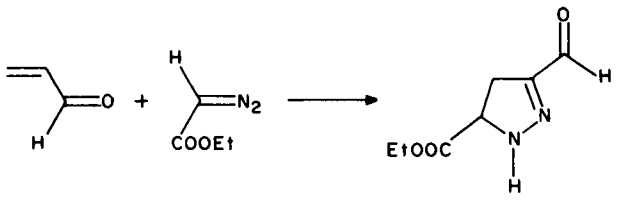
(136)



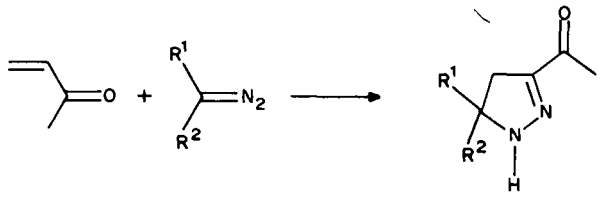
The reaction (20 °C, 16 h) of diazomethane with the PGA_2 derivative **326** gives mostly the unstable Δ^1-pyrazoline **327**. Interestingly, the carbonyl, C=O, and unconjugated C=C double bonds of that system do not react as quickly as the conjugate enone C=C double bond, in agreement with predictions based on the FMO theory[253] (LUMO of the enone is lower in energy than the LUMO of the non-conjugated olefin moieties). Irradiation ($\lambda_{irr} > 290$ nm) of the yellow Δ^1-pyrazoline (**327**) leads to a mixture of the 10,11-methylene (**328**, 22–37%) and 11-methyl (**329**, 25–33%) prostaglandine derivatives[287]. The mechanism of these reactions probably involves the intermediacy of a 1,3-diradical (**330**) which undergoes ring closure into **328** and concurrent H migration to yield **329**. (For a related study with Lumisantonin, see Reference 288).



With ethyl diazoacetate, acrolein gave the corresponding Δ^2-pyrazoline in 80% yield (equation 137)[289]. Similarly, Δ^2-pyrazolines were the main products isolated from the reactions of methyl vinyl ketone with a variety of diazoalkanes substituted with electron-withdrawing groups (equation 138)[290–294]. This was also the case for the reactions of (*E*)-benzylideneacetophenone with diazomethane, diazoethane, 2-diazopropane and diazoacetophenone (equation 139)[295]. In contrast, the reaction of (*E*)-benzylideneacetophenone with 9-diazofluorene leads exclusively to the formation of the corresponding *trans*-1,2-dibenzoylcyclopropane derivative (equation 140)[296], with the α-substituted acroleins reacting with ethyl diazoacetate; the major products isolated are also the corresponding cyclopropanes (equation 141)[289]. The reaction of ethyl diazoacetate with α-methylacrolein gives, in addition to the two isomeric cyclopropanes **332** and **333**, the α,β-unsaturated aldehyde **334** and the carbinolamine **335** which corresponds to a stereospecific dimerization of the Δ^2-pyrazoline intermediate **331**[289]. With the cyano-substituted benzylidenebenzophenone **336**, diazomethane reacted to afford exclusively the substituted enones **337** + **338**[297].

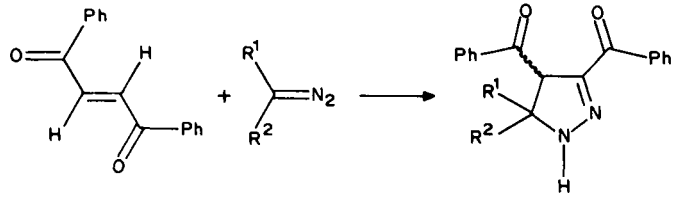


(137)



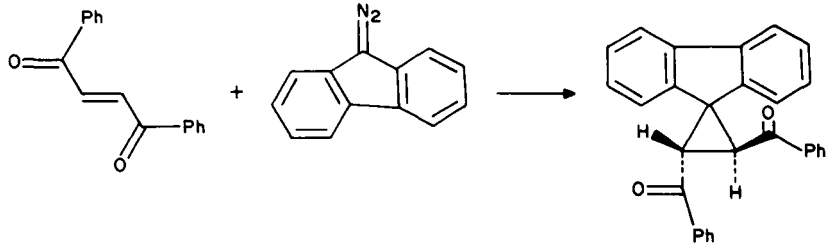
R^1=Ph, R^2=PO(OMe)$_2$	92%[290,291]
R^1=Me, R^2=PO(OMe)$_2$	90—100%
R^1=Ph, R^2=POO(Et)$_2$	55%[292]
R^1=Ph, R^2=POPh$_2$	89%[293]
R^1=R^2=SO_3K	50%[294]

(138)



R^1=R^2=H
R^1=R^2=Me
R^1=H, R^2=Me
R^1=H, R^2=PhCO

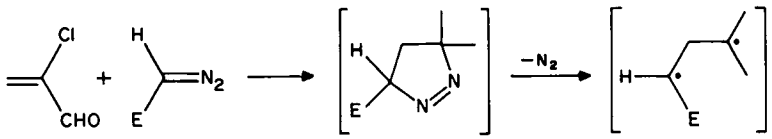
(139)



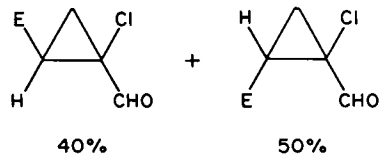
(140)

The β-chlorovinyl ketones reacted with diazomethane to give the corresponding 3-acylpyrazoles **340**[298,299]. The results were interpreted in terms of the intermediacy of the Δ^1-pyrazoline **339** that loses one equivalent of HCl under the reaction conditions, followed by 1,5-sigmatropic migration of a hydrogen atom. In contrast, the reactions of β-chlorovinyl ketones with diphenyldiazomethane led to the isolation of pyrazoles **341** whose formation implies the migration of a phenyl group. The latter reaction has been shown to be catalyzed by acids[300].

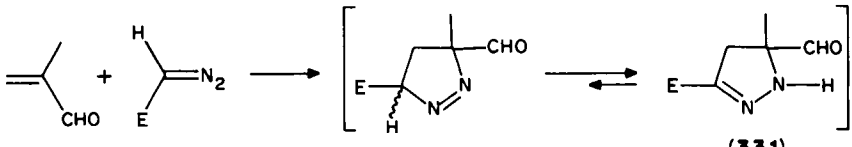
With cyclopropenone, diphenyldiazomethane gave the diazoketone **343**. Its formation was interpreted in terms of initial [3 + 2] cycloaddition of the diazoalkane onto the C=C



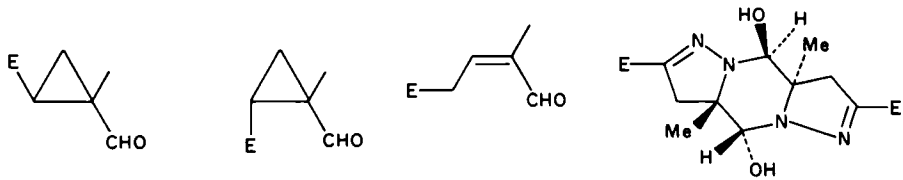
(141)



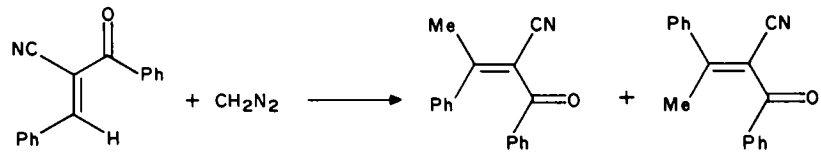
40% 50% E=HCOOEt



(331)



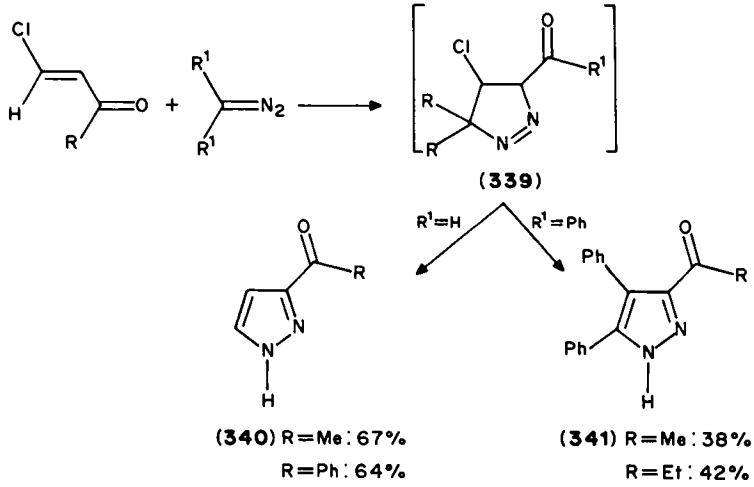
(332) 30% (333) 25% (334) 15% (335) 10%



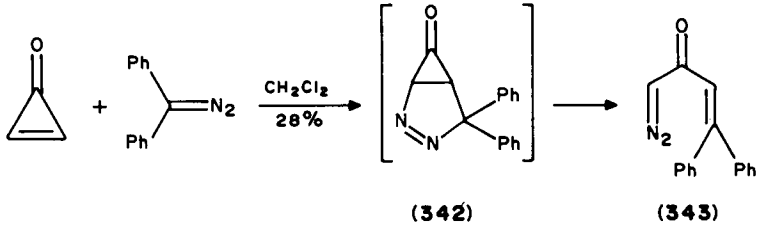
(336) (337) (338)

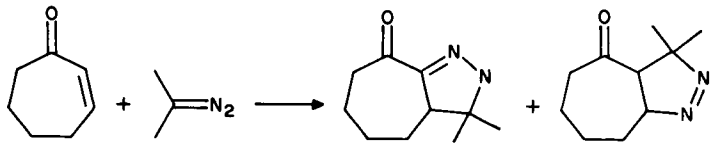
double bond giving the intermediate adduct **342**. The latter undergoes a [3 + 2] cycloreversion to give **343**[301].

As shown above, and in agreement with predictions based on the FMO theory[253,284], diazoalkanes add to α,β-unsaturated aldehydes and ketones with good regioselectivity,

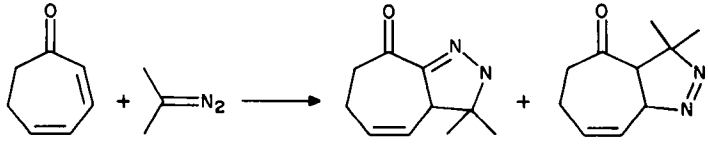


the carbon atom of the 1,3-dipole attacking preferentially the β-carbon centre of the dipolarophile. In the case of 2-diazopropane adding to cyclohept-2-en-1-one (equation 142) and cyclohept-2,4-dien-1-one (equation 143), the 'normal' adducts (isolated as Δ^2-pyrazolines) and the 'inverse' adducts (isolated as Δ^1-pyrazolines) were formed in similar proportions[302]. Tropone and 2-diazopropane gave the 'inverse' adduct (**344**), an unstable compound observable at low temperature by NMR (ether, $-35\,^{\circ}C$), that decomposed with loss of N_2 and formation (45%) of 8,8-dimethylcycloocta-2,4,6-trien-1-one (**346**). A small amount (5%) of 8,8-dimethylhomotropone (**348**) was also obtained. The results were interpreted in terms of the intermediacy of ketene (**345**) and zwitterion (**347**).



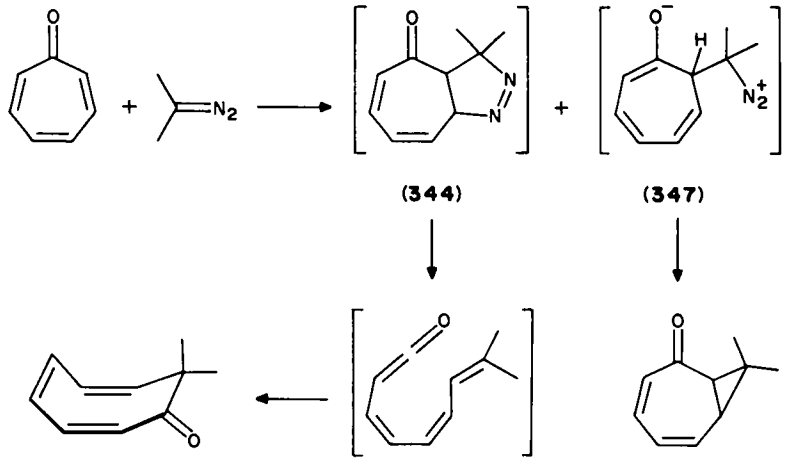


(142)

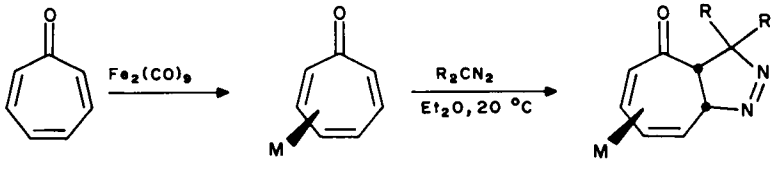


(143)

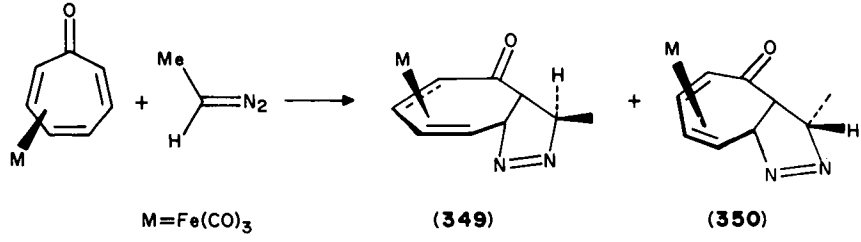
The latter explains the 'inverse' regioselectivity observed for the [3 + 2] cycloaddition of tropone with 2-diazopropane. Similar enolate formation cannot be invoked in the cases equations 142 and 143. It was thus proposed that steric effects are responsible for the observation of 'inverse' adducts[302].



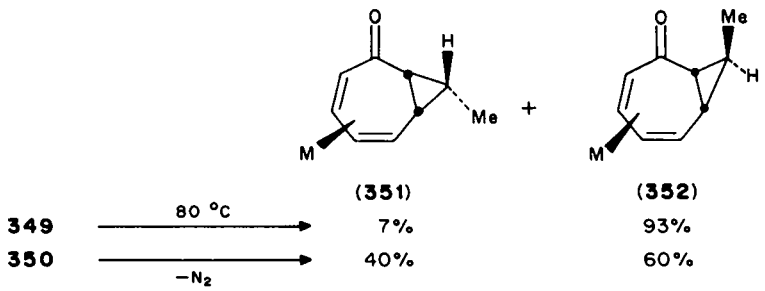
The 'inverse' regioselectivity is also observed for the reactions of diazoalkanes with the tricarbonyliron complex of tropone (equations 144 and 145). As expected from steric effect criteria, the face *anti* to the $Fe(CO)_3$ moiety is preferred by the 1,3-dipole. With diazoethane, the *exo* and *endo* adducts **349** and **350** are obtained in a 2.7:1 product ratio. Thermolysis is benzene (80 °C) of **349** and **350** gives mixtures of the corresponding 8-methylhomotropones **351** and **352**. These reactions are not stereospecific, thus indicating the intermediacy of 1,3-diradicals and their rapid epimerization[303].



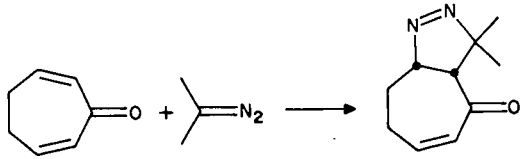
(144)



(145)

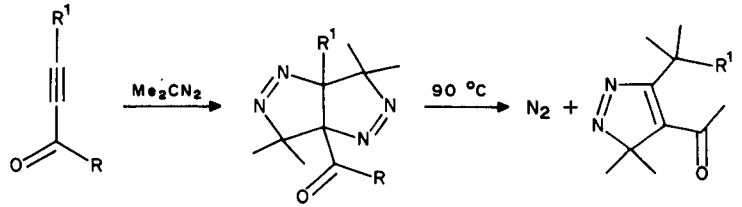


In contrast to the [3 + 2] cycloadditions of equations 142 and 143, and as for those of a complexed tropone (equations 144 and 145), the reaction of 2-diazopropane with cyclohepta-2,6-dien-1-one gave only one mono-adduct, the Δ^1-pyrazoline **353** (70%, isolated) corresponding to the 'inverse' regioselectivity (equation 146). Products of double addition of the 1,3-dipole were not reported[302].



(146)

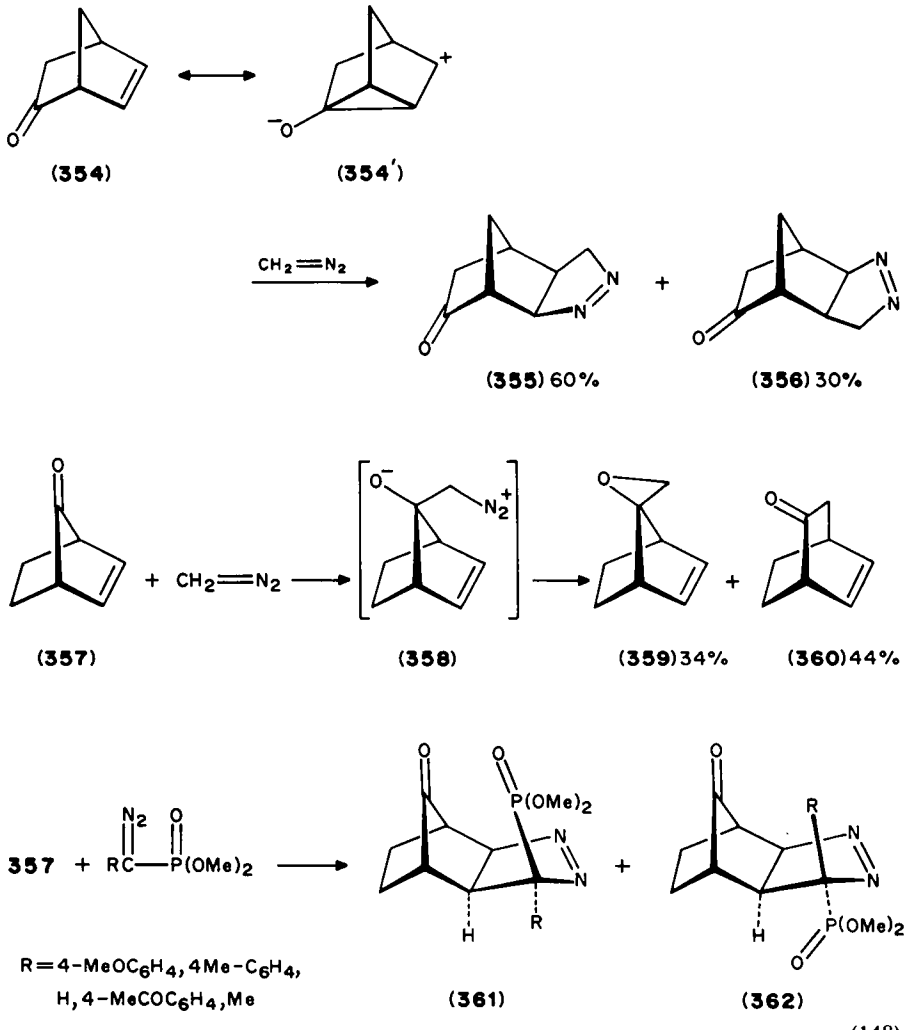
With conjugated ynones, 2-diazopropane gave bis-adducts with the 'normal' regioselectivity ($R^1 = H$). On heating, the latter lost one equivalent of N_2 and afforded the corresponding 3*H*-pyrazoles (equation 147)[304].



(147)

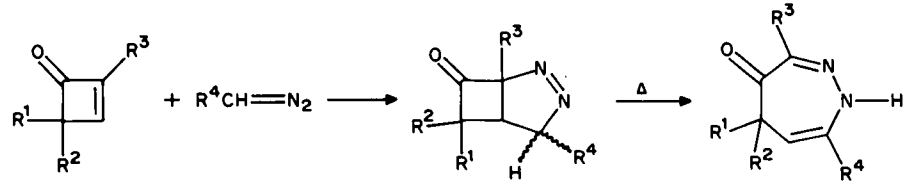
R=Me, Ph; R^1=H; COMe, COPh

Ethereal diazomethane containing 10% MeOH reacts onto the *exo* face of the C=C double bond of bicyclo[2.2.1]hept-5-en-2-one (**354**: dehydronorcamphor) to give a 2:1 mixture of the Δ^1-pyrazolines **355** and **356**[305]. The major adduct **355** corresponds to the 'normal' regioisomer expected for the cycloaddition of the β,γ-unsaturated ketone in which the homoconjugative interaction **354**↔**354'** is operative. Interestingly, the reaction of diazomethane with bicyclo[2.2.1]hept-2-en-7-one (**357**) does not lead to adducts of the C=C double bond but produces a mixture of products **359** and **360** resulting from the attack of the C=O bond, probably via the intermediacy of zwitterion **358**[305]. With the less nucleophilic dimethyl aryl- and alkyldiazomethylphosphonates, $RC(N_2)P(O)(OMe)_2$, **357** reacted preferentially onto the *exo* face of its C=C double bond giving mixtures of the *syn* and *anti* adducts **361** and **362**, respectively (equation 148)[306].



(148)

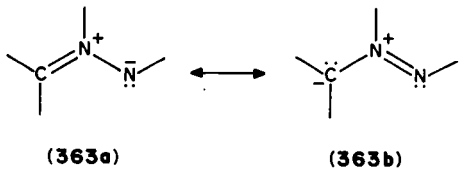
The cycloadditions of diazoalkanes and ethyl diazoacetate to cyclobutenones proved to be a useful method for the preparation of diazatropone derivatives (equation 149)[307].



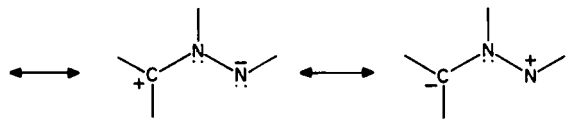
(149)

5. Cycloadditions with azomethine imines

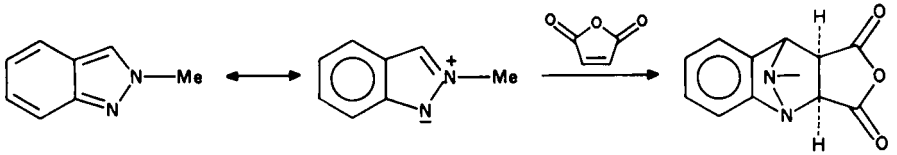
Azomethine imines **363** belong to the class of 1,3-dipoles of the allyl type with an iminium centre in the middle of the molecule. The resonance formula **363a** is expected to be more important as a result of the higher electronegativity of the nitrogen atom relative to the carbon atom. Azomethine imines are isoelectronic with the azomethine ylides (Section V.A.1). Because of the higher electronegativity of the nitrogen atom relative to the carbon atom, the former dipoles are less nucleophilic than the corresponding azomethine ylides (see Figure 5).



(363a) (363b)

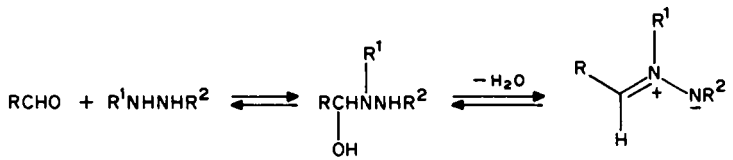


(363c) (363d)

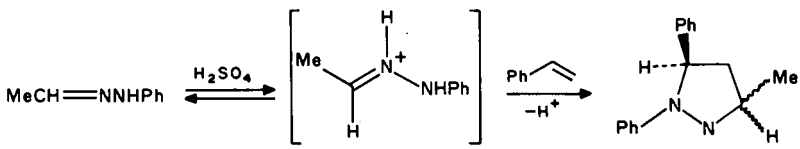


(364a) (364b) (365)

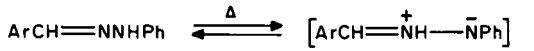
Among the earliest examples of azomethine imines, 2-methylindazol (**364**), known since 1893[308], must be cited. The reaction of **364** with maleic anhydride proceeds via the [3 + 2] cycloadduct **365**, which can also be seen as a Diels–Alder adduct. The most general methods for the generation of azomethine imines (usually as unstable intermediates) are given in equations 150–164[309].



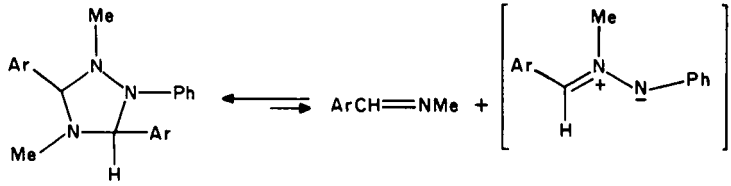
(150)



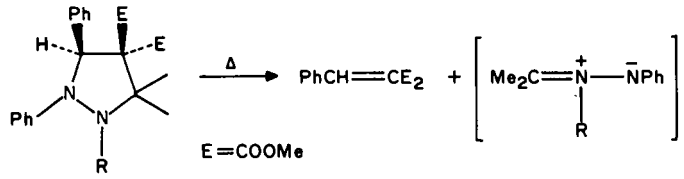
(151)



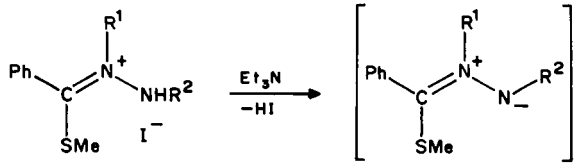
(152)



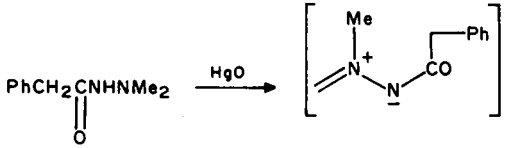
(153)



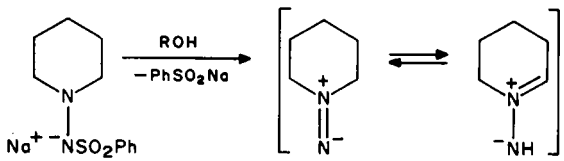
(154)



(155)

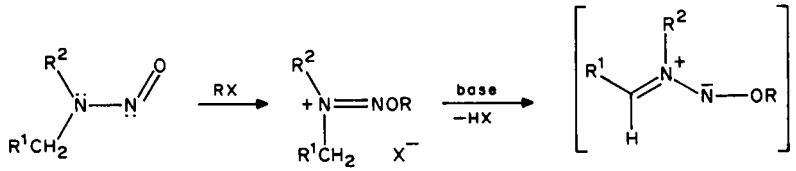


(156)

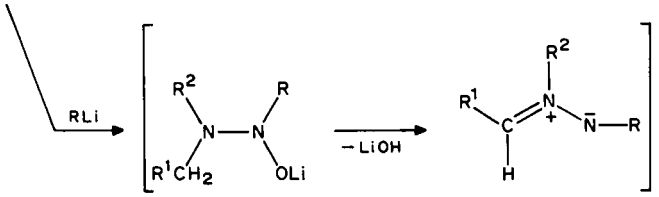


(157)

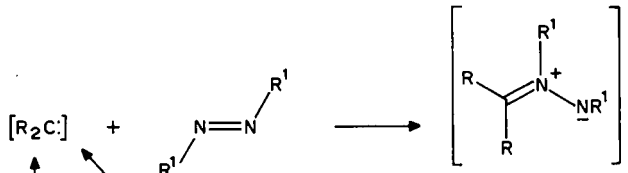
The reactions of unsubstituted azomethine imines with electron-poor dipolarophiles, such as the conjugated enones, are predicted to be controlled by the LUMO-(dipolarophile)–HOMO(1, 3-dipole) interaction[253]. Alkyl and aryl substituents, as in **366**, lead to an increase of the HOMO energy and to a decrease of the LUMO energy of the 1, 3-dipole. This makes the HOMO(dipolarophile)–LUMO(1, 3-dipole) interaction to play a non-negligable role, conferring an ambiphilic character to the azomethine imine (e.g. equation 165)[310]. Derivatives with electron-withdrawing groups, as in **367**, have their



(158)



(159)



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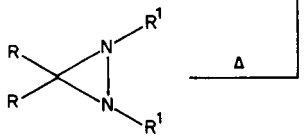
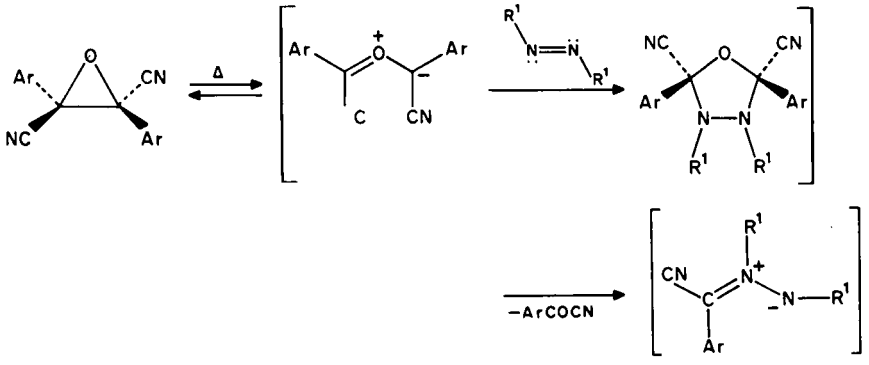
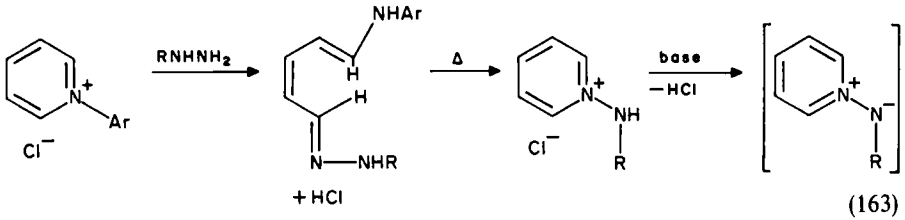


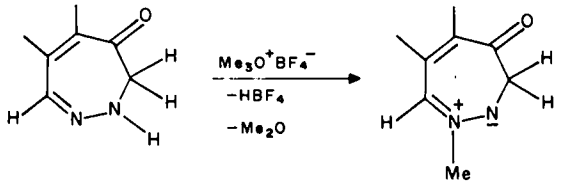
(161)



(162)

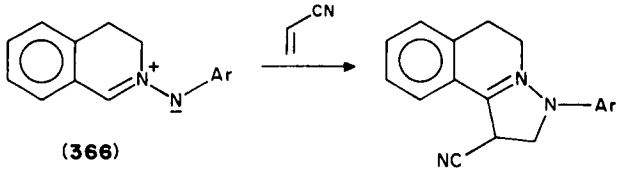


(163)

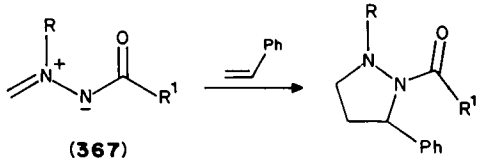


(164)

reactivity and regioselectivity dominated by the LUMO(1,3-dipole)-HOMO-(dipolarophile) interaction (e.g. equation 166)[311].

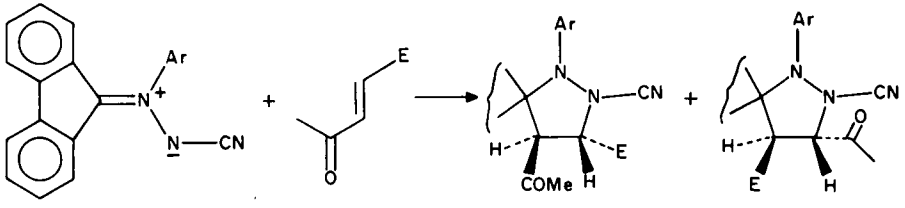


(165)



(166)

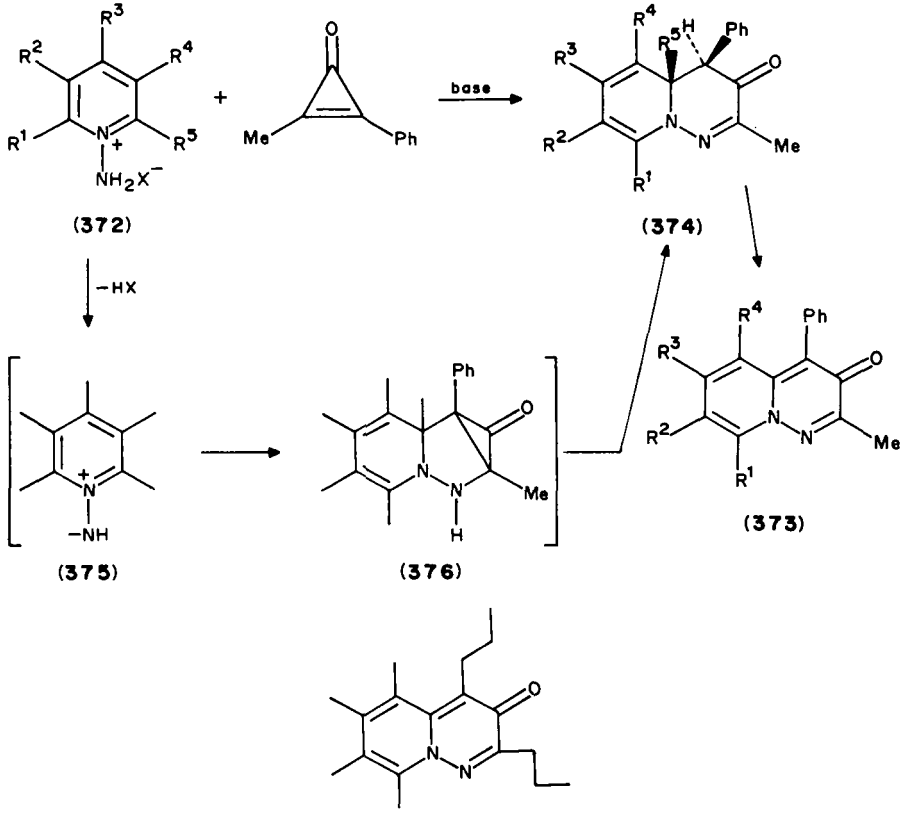
The C-(2,2'-biphenylylen-N^{α}-(4-chlorophenyl)-N^{β}-cyanoazomethine imine **368** reacts with methyl (*E*)-3-acetylacrylate **369** to give a 57:23 mixture of the [3 + 2] cycloadducts **370** and **371**. Comparison with the regioselectivities observed for the reactions of **368** with other dipolarophiles confirmed that the directional force of the acetyl group exceeds that



Ar=4-Cl-C_6H_4, E=COOMe

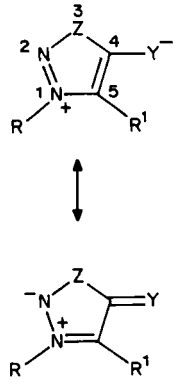
of the ester group, in agreement with reactions controlled by the LUMO(dipolarophile)–HOMO(1,3-dipole) interaction (regioselectivity given by the shape of the FMOs). Interestingly, the *trans* configuration of the disubstituted dipolarophile **369** was maintained completely in the cycloadducts **370** and **371** in agreement with a mechanism involving a concerted, one-step [3 + 2] cycloaddition[312].

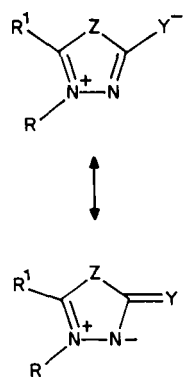
Pyridinium *N*-imine salts (**372**) reacted smoothly with methylphenylcyclopropenone in CH_2Cl_2 in the presence of Et_3N at 20 °C, to give the corresponding 2-methyl-4-phenyl-3*H*-pyrido[1,2-*b*]pyridazin-3-ones (**373**). In some cases ($R^1 = R^2 = R^3 = R^4 = R^5 = H$; $R^1 = R^5 = Me$, $R^2 = R^3 = R^4 = H$; $R^1 = H$, $R^2 = CN$, $R^3 = R^4 = R^5 = H$; $R^1 = R^2 = R^3 = H$, $R^4 = CN$, $R^5 = H$) the corresponding 4,4*a*-dihydro intermediates **374** were isolated. These reactions were interpreted in terms of formation of the reactive azomethine imine **375** that underwent [3 + 2] cycloadditions with methylphenylcyclopropenone to give the unstable cycloadducts **376** that rearranged into **374** and then into **373**[313]. Salts **372** with di(*n*-propyl)cyclopropenone did not react in the presence of Et_3N in CH_2Cl_2 at 20 °C. On heating to 40 °C, however, a reaction occurred giving the corresponding 2,4-dipropyl-3*H*-pyrido[1,2-b]pyridazin-3-ones **377**[313].



Azomethine imines are present as masked 1,3-dipoles in the mesoionic systems **378**–**384**[314]. The commonly used method for the preparation of sydnones **378** is based on the

acylation of *N*-nitrosoglycine derivatives that gives the corresponding anhydro-5-hydroxy-1,2,3-oxadiazolium hydroxides **378** (equation 167)[315]. The latter add to olefins to give [3 + 2] cycloadducts with regioselectivities lower than with simpler, acyclic azomethine imines (equation 168). This was attributed by Houk's group[253] to LUMO(sydnone)–HOMO(olefin) interactions that dominate the reactivity of these [3 + 2] cycloadditions. Since the atomic coefficients at N(1) and C(5) in **378** are nearly the same, it thus explains the low regioselectivity[253].





(**378**: sydnones) Y=Z=O

(**379**: sydnones imines) Y=NR, Z=O

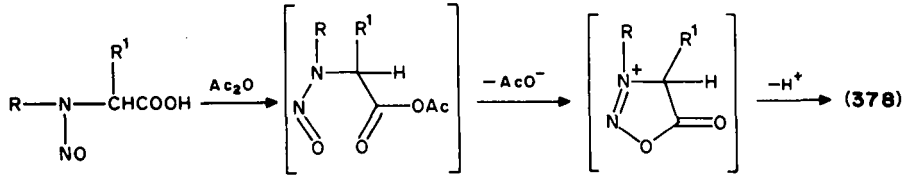
(**380**) Y=O, Z=NR

(**381** : isosydnones) Y=Z=O

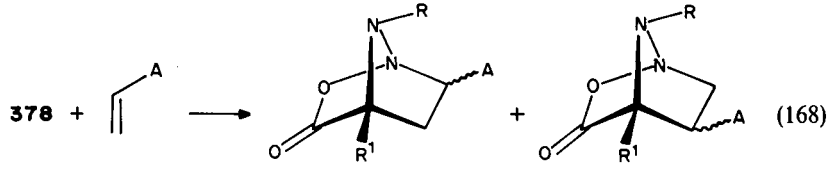
(**382**) Y=O, Z=NR

(**383**) Y=Z=S

(**384**) Y=NR, Z=S



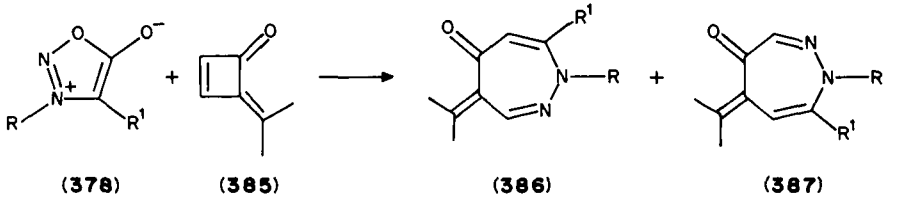
(167)



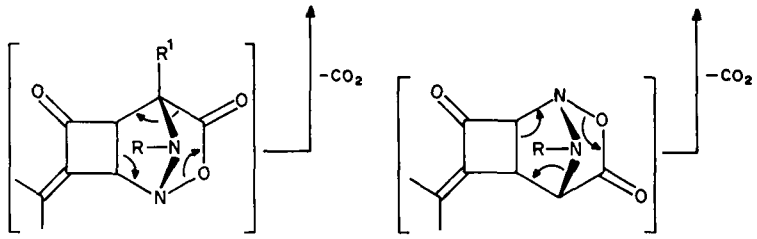
(168)

The [3 + 2] cycloadditions of sydnones **378** to isopropylidenecyclobutenone **385** gave the diazepinones **386** or/and **387**[316]. For the reactions of sydnones with R = Ph and R′ = H, Cl, Me, and with R, R′ = —$(CH_2)_3$—, —$(CH_2)_4$—, only the corresponding regioisomers **386** were isolated in good yield. With derivatives **378** having R = Me and R^1 = H, or with R = CH_2Ph and R^1 = H, the two regioisomeric products **386** and **387** were

formed. Products **386** and **387** resulted from the cycloreversion of the intermediate adducts **388** and **389**, respectively. According to Martin and coworkers[316] these results were not explained correctly by the FMOs theory. More sophisticated calculations on the encounter complexes between **378** and **385** were necessary to rationalize the observations.



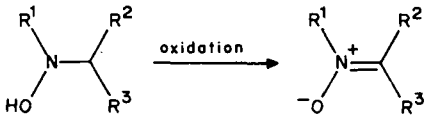
(378) (385) (386) (387)



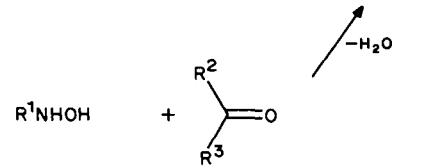
(388) (389)

6. Cycloadditions with nitrones

The two general methods used to generate nitrones are the oxidation of *N*, *N*-disubstituted hydroxylamines (equation 169) and the condensation of *N*-substituted hydroxylamines with aldehydes or ketones (equation 170). There are also more specific methods that have been proposed[317,318]. The [3 + 2] cycloadditions of nitrones have been studied extensively (for a recent review, see Reference 318) both for mechanistic reasons and for their synthetic applications[319,320].



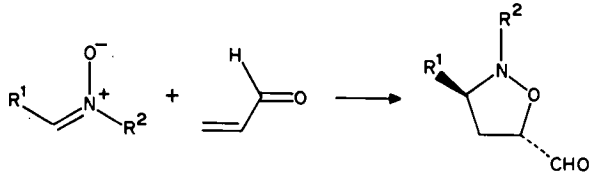
(169)



(170)

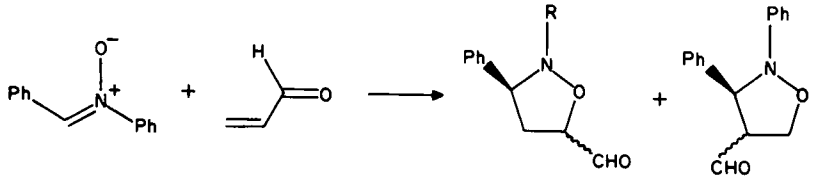
According to Sustmann[252] (see Figure 5), the nitrones are classified as ambiphilic 1,3-dipoles. The regioselectivity of their cycloadditions with conjugated enones is controlled by the LUMO(nitrene)–HOMO(enone) interaction. Typical examples of reactions are given in equations 171–180[321–329].

Depending on the substituents, the preferred regioisomeric isoxazolines derive either from attack of the oxygen centre of the nitrone at the α- (see equations 171–173, 176, 177

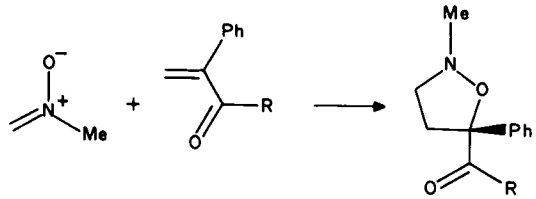


R^1=COOMe, R^2=CH_2Ph 61% 39%
R^1=COOMe, R^2=$CH(Ph)_2$ 81% 19%

(171)[321]

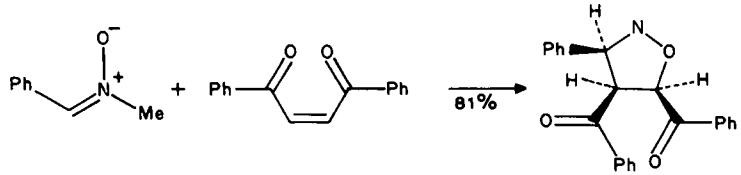


(172)[322]

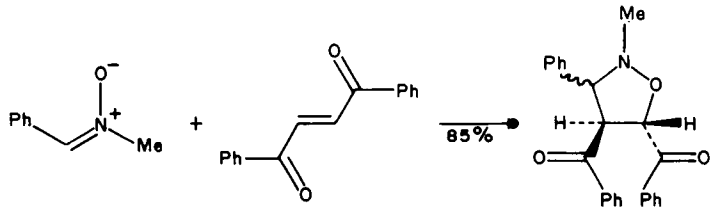


R=Me 79%
R=Et 85%
R=Ph 86%

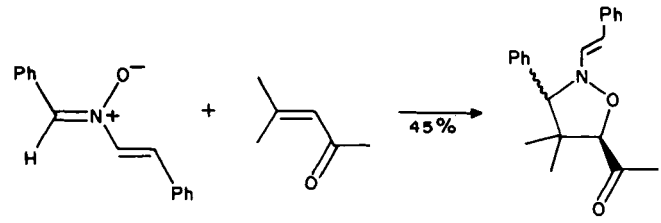
(173)[323]



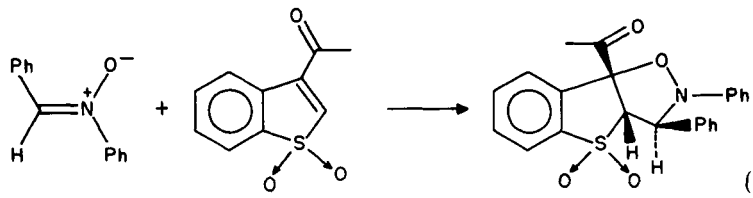
(174)[324]



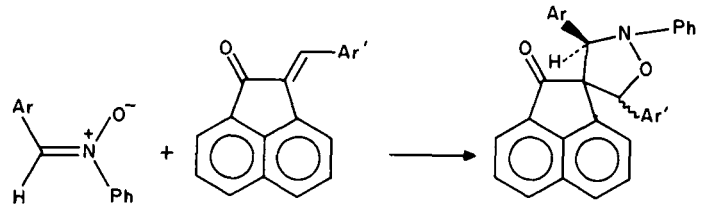
(175)[324]



(176)[325]

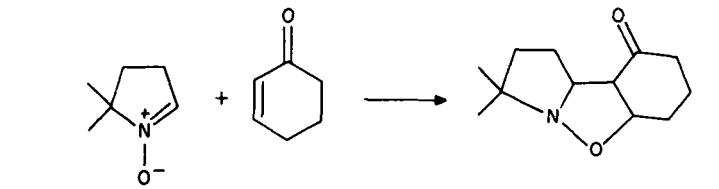


(177)[326]

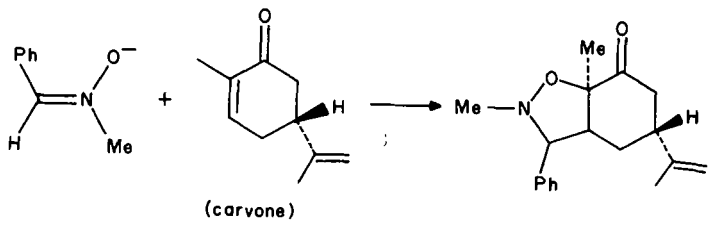


(178)[327]

Ar = Ar' = Ph	48%
Ar = Ph, Ar' = 4-Cl-C_6H_4	51%
Ar = *p*-Cl-C_6H_4, Ar' = Ph	37%
Ar = Ar' = *p*-Cl-C_6H_4	33%

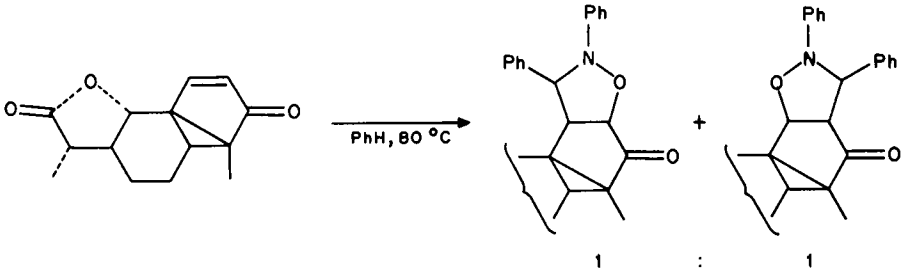


(179)[328]

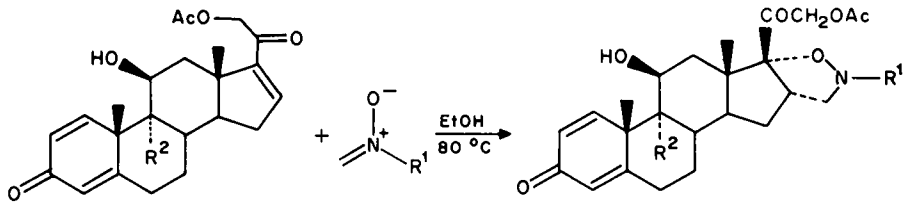


(180)[329]

and 180) or β-centre (see equations 178 and 179) of the α,β-unsaturated carbonyl system. In most instances, the observed regioselectivities are explained by the shape of the FMOs of the dipolarophiles and nitrones[318]. For the reactions of polysubstituted reactants, steric effects can also play a role in the regioselectivity[330]. [3 + 2] Cycloadditions of natural enones such as carvone (equation 180)[329] and Lumisantonin (equation 181)[288] have been reported. While the cycloaddition of *N*-methyl-*C*-phenylnitrone to carvone gave only one adduct (equation 180), the reaction of α,*N*-diphenylnitrone to Lumisantonin gave a 1:1 mixture of two regioisomeric adducts (equation181). Steroidal enones **390** reacted with nitrones **391** and, for some derivatives, gave antianflammatory compounds **392**[331]. It is interesting to note that the α,β-unsaturated ketone moiety in **390** reacted faster than the cyclohexa-2,6-dien-1-one moiety.



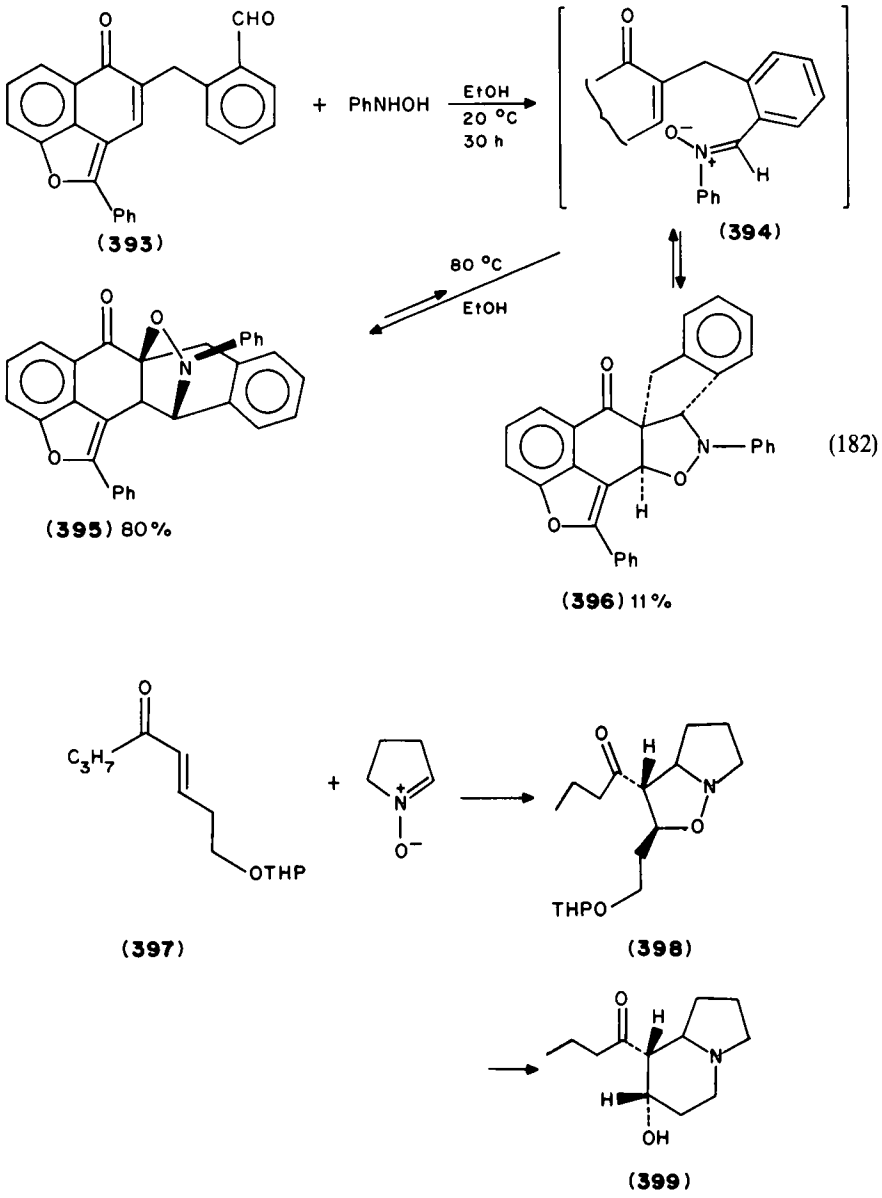
(181)



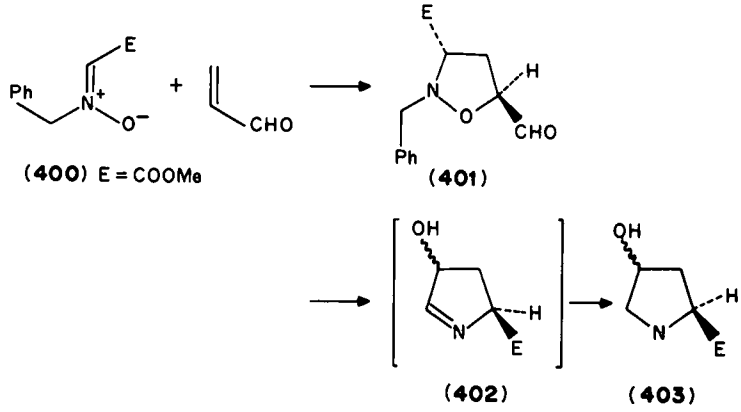
(390)	(391)	(392)
R^1 = Me, R^2 = F		30%
R^1 = Me, R^2 = H		40%
R^1 = $PhCH_2$, R^2 = F		24%
R^1 = $PhCH_2$, R^2 = H		33%

An example of intramolecular [3 + 2] cycloaddition of a nitrone to a conjugated enone is shown in equation 182[332]. Upon treatment of aldehyde **393** with phenylhydroxylamine in EtOH (20 °C, 30 h) a mixture of product **395** and **396** was obtained in 80 and 11% yield, respectively. The latter were equilibrated, probably via cycloreversion into **394**, on heating in EtOH. This cyclization procedure was successfully applied to produce tetracyclic substances of biological interest[332].

A total synthesis of elaeokanine C (**399**) based on the intermolecular [3+2] cycloaddition of pyrroline-1-oxide to the *trans* enone **397**, to give adduct **398**, has been developed[333]. A further application of [3+2] cycloaddition of nitrones to the total

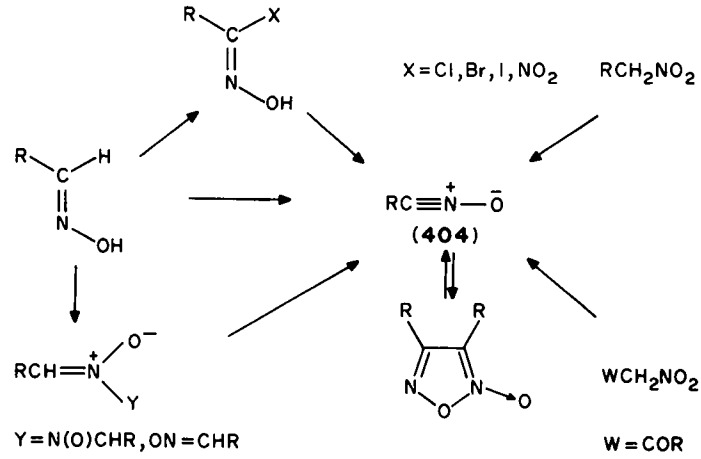


synthesis of natural product is shown with the synthesis of 4-hydroxyproline methyl esters (**403**) that involves cycloaddition of *N*-benzyl-α-methoxycarbonylmethanimine-*N*-oxide (**400**) to acrolein[334]. The cycloadduct **401** was hydrogenolyzed to yield a mixture of epimeric 4-hydroxypyroline methyl esters (**403**) via the intermediate imine **402**.



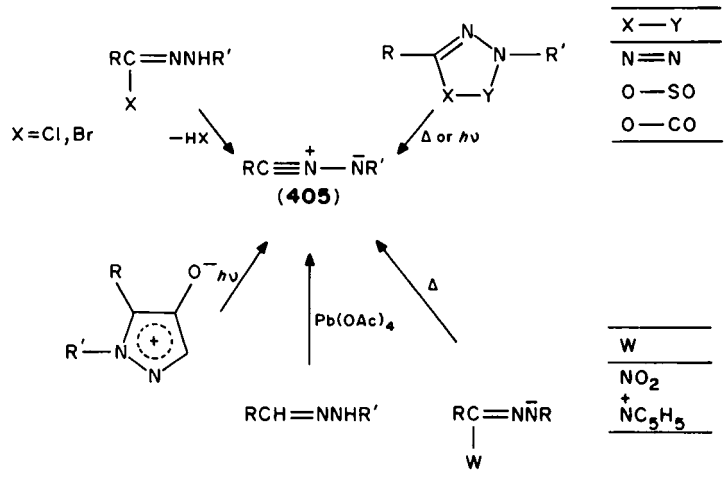
7. Cycloadditions with nitrile oxides and nitrile imines

The most useful methods for the generation of nitrile oxides (**404**) and nitrile imines (**405**) are summarized in Schemes 15 and 16, respectively[335]. These unstable species must be generated *in situ*. They behave as ambiphilic 1,3-dipoles (see Figure 5)[252].

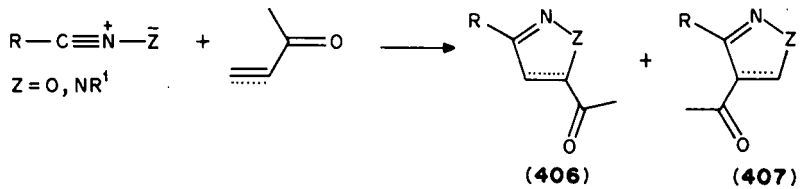


SCHEME 15

The reactions of (**404**) and (**405**) with α,β-unsaturated aldehydes and ketones are generally controlled by both the HOMO(dipolarophile)–LUMO(1,3-dipole) and HOMO(1,3-dipole)–LUMO(dipolarophile) interactions. While the former interaction favours the formation of adducts (**406**: 4-acyl derivatives), the latter interaction leads to the corresponding regioisomers (**407**: 5-acyl derivatives). This interprets[253] the general observation of mixtures of regioisomeric adducts for the [3 + 2] cycloadditions of nitrile oxides (**404**)[336–344] and nitrile imines (**405**)[339,343–344] with conjugated enones, as illustrated in Table 3. The regioselectivity is also influenced by the bulk of the substituents of the 1,3-dipoles and of the dipolarophiles, and by the solvents[336]. The product ratio **406**/**407** is generally larger for the reactions of nitrile imines than for the corresponding



SCHEME 16



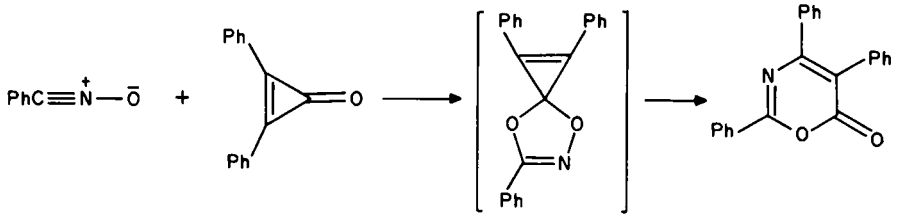
nitrile oxides. For both types of 1,3-dipoles, this regioselectivity decreases going from alkenones to alkynones (see Table 3). In a recent study, Sustmann and Sicking[345] showed evidence that the simple FMO theory applied to the [3 + 2] cycloadditions of formonitrile oxide with alkenes does not rationalize the regioselectivity in a satisfactory fashion. It was

TABLE 3. Regioselectivity of the [3 + 2] cycloadditions of benzonitrile *N*-phenylimide (BNPI) and benzonitrile oxide (BNO) with α,β-unsaturated ketones[339]

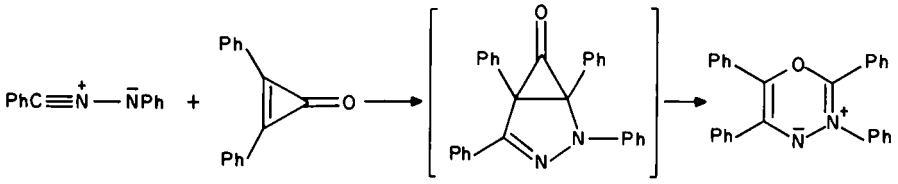
1,3-Dipole	BNPI		BNO	
Dipolarophile	Adducts: 4-acyl (%) (406)	5-acyl (%) (407)	4-acyl (%) (406)	5-acyl (%) (407)
Cyclopent-2-en-1-one	50	50	92	8
Cyclohex-2-en-1-one	39.5	60.5	75	25
Cyclohept-2-en-1-one	29.5	70.5	65	35
Cyclohepta-2,6-dien-1-one	45	55	95	5
MeCH=CHCOMe	36	64	50	50
PhCH=CHCOMe	40	60	59	41
PhCH=CHCOPh	—	100	29	71
MeCH=CHCOPh	—	100	32	68
CH_2=CHCOMe	—	100	—	100
CH_2=CHCOPh	—	100	—	100
CH≡CCOPh	6.5	93.5	14.0	86.0
PhC=CCOPh	86	14	98	2
PhC=CCOMe	89.5	10.5	100	—

thus suggested that more accurate models of the cycloaddition transition state, as well as more detailed calculations, are required to interpret the results. It was proposed that the regioselectivity can be explained better by the non-covalent repulsion between the reactants than by the FMO interactions.

With benzonitrile oxide, diphenylcyclopropenone adds preferentially with its C=O function (equation 183)[343]. In contrast, diphenylnitrilimine adds to the C=C bond of diphenylcyclopropenone and affords the mesoionic compound **408** equation 184)[344]. Nitrones also add to the C=C double bond of diphenylcyclopropenone[344].



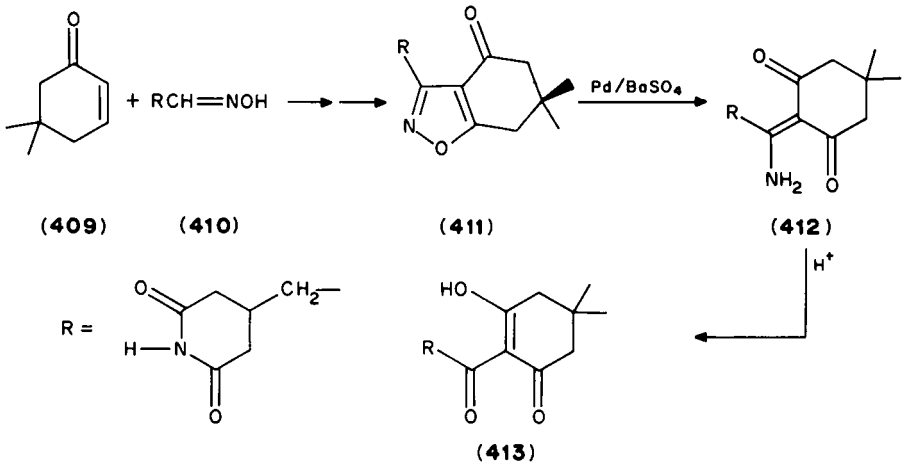
(183)



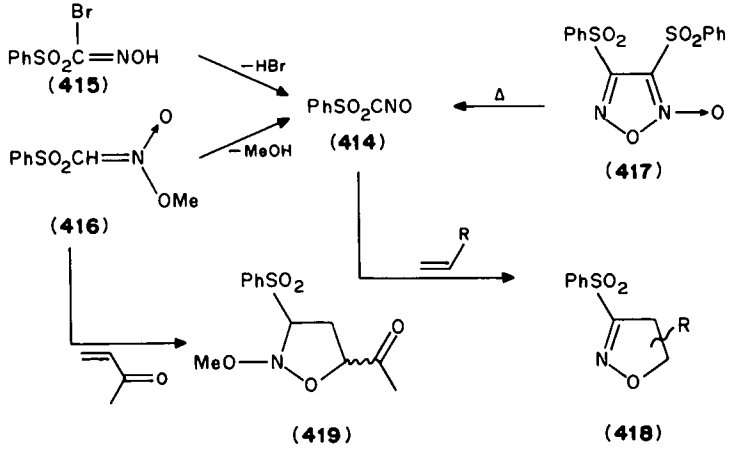
(408)

(184)

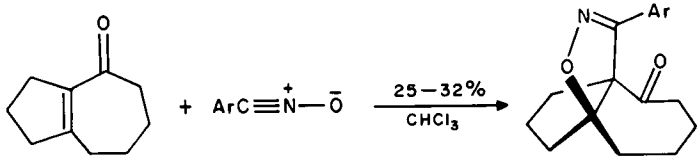
A simple preparation of an interesting intermediate (**413**) along the route to the glutarimidic antibiotic family has been reported[338,342] which utilizes the cycloadduct **411** resulting from the reaction of 5,5-dimethylcyclohex-2-en-1-one (**409**) and the nitrile oxide generated from oxime (**410**), followed by oxidation with chloranil. Reductive cleavage followed by acidic hydrolysis of the derived enamino-ketone (**412**) gave **413**.



Benzenesulfonylnitrile oxide (**414**) can be generated by HBr elimination from the corresponding hydroxamoyl bromide (**415**), by MeOH elimination from the corresponding nitronic ester (**416**) or by cycloreversion of furoxan (**417**)[340]. **414** reacted with electron-rich olefins only and gave Δ^2-isoxazolines (**418**). In contrast to the low reactivity of **414** towards conjugated enones, the nitronate (**416**) added smoothly to methyl vinyl ketone at reflux in chloroform giving the isoxazolidine **419** in 56% yield[340]. Nitronic esters are thus better nucleophilic 1,3-dipoles than the corresponding nitrile oxides[252].



Heterocyclic propellanes[341] have been obtained by [3+2] cycloadditions of bicyclo[5.3.0]dec-1(7)-en-2-one to arylnitrile oxides (see equation 185) and nitrile imines.



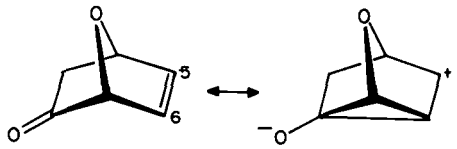
(185)

Ar = Ph, 2,4,6-$(Me)_3C_6H_2$, 2,6-$(Cl)_2$-C_6H_3

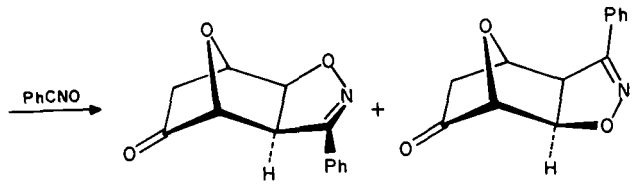
The β,γ-unsaturated ketone **420** added to benzonitrile oxide to give a 65:35 mixture of the regioisomeric cycloadducts **421** and **422**. The regioselectivity was not improved in the presence of a Lewis acid such as $AlCl_3$ or ZnI_2. The shape of the FMOs of **420** suggested that C(5) in **420** is slightly more electrophilic than C(6), as predicted for the homoconjugative interaction involving the electron-withdrawing ability of the carbonyl group and represented by the limiting structures **420**↔**420**. From the shape of the FMOs of PhCNO it was predicted that the oxygen atom of this 1,3-dipole is the most nucleophilic centre, thus favouring adduct **421**, as observed[346].

8. *Cycloadditions with azides*

According to Sustmann[252] (see Figure 5) azides, R-N_3, are ambiphilic 1,3-dipoles. With electron-rich alkenes their reactions are controlled mostly by the LUMO(azide)–HOMO(alkene) interaction giving preferentially 5-substituted Δ^2-triazolines

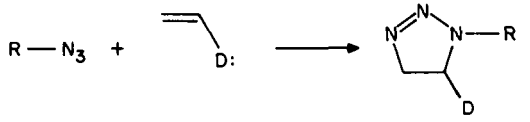


(420) (420')

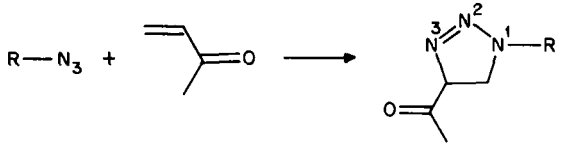


(421) (422)

(423)[347]. Electron-withdrawing groups on the azide enhance the reactivity and the regioselectivity. In contrast, with electron-poor dipolarophile such as α,β-unsaturated aldehydes and ketones, the [3+2] cycloadditions with azides are controlled by the LUMO(dipolarophile)–HOMO(azide) interaction which favours 4-substituted Δ^2-triazolines (**424**). Electron-donating substituents on the azide accelerate the cycloaddition and enhance this regioselectivity[347].



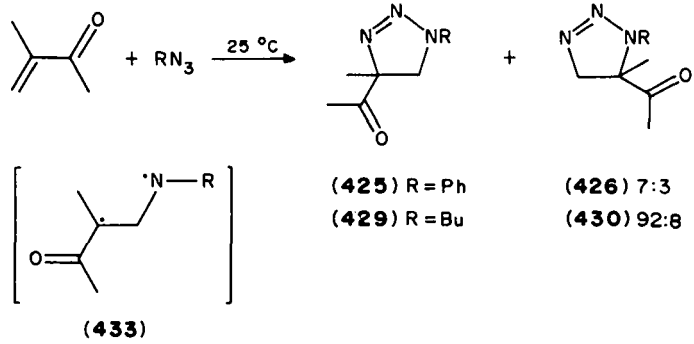
D = electron-releasing substituent (423) (major)



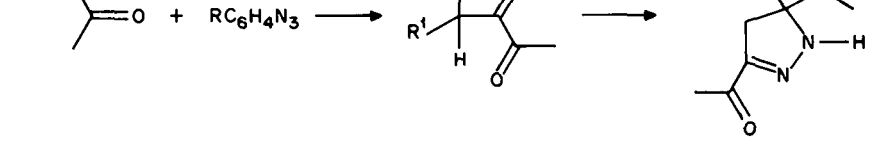
(424) (major)

The triazolines are relatively unstable heterocycles. They can undergo a number of reactions as illustrated below. If substituent R at N(1) is electron-withdrawing, the Δ^2-triazoline loses easily an equivalent of N_2 with formation of the corresponding aziridines. For instance, methyl isopropenyl ketone reacted with phenyl azide to give a 7:3 mixture of Δ^2-triazolines **425** and **426**. Product **425**, observable at 0 °C, was not stable at 25 °C and gave aziridine (**427**) nearly quantitatively. Isomer **426** decomposed only above 100 °C to give a mixture of **427** and the β-ketoenamine **428**. With butylazide, methyl isopropenyl ketone gave at 25 °C the cycloadducts **429** and **430** in a 92:8 product ratio. The Δ^2-triazoline **429** was more stable than **425**. It was decomposed at 90–130 °C into a 3:2 mixture of aziridine (**431**) and enamine (**432**)[348]. The facile thermal decompositions of the Δ^2-triazolines **425** and **429** occur probably via diradical intermediates **433**. Thus, a 1-

phenyl substituent, in comparison with a butyl substituent, lowers the decomposition temperature of the triazoline because of its radical stabilizing effect. The hypothesis of diradical pathway was supported by kinetic measurements on related reactions[349]. The decomposition of **426** into **427** and **428** can be interpreted in terms of the intermediacy of diradical **434**, a species less stable than **433**, thus conferring higher stability to **426** compared with that of **425**. The diradical intermediate **434** undergoes ring closure to **427** and concurrent acyl group migration to afford **428**.

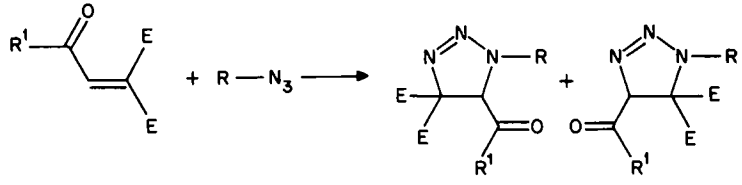


Huisgen and coworkers[350] have studied the reactions of methyl vinyl ketone and ethylidene acetone with various arylazides. The expected Δ^2-triazolines were not isolated. The latter were rearranged into the more stable, yellow diazoketones **435–437**. With an excess of methyl vinyl ketone, *p*-nitrophenyl azide and *p*-methoxyphenyl azide gave the 1:2 adducts **438** and **439**, respectively, which arose from the [3 + 2] cycloadditions of **436** and **437** onto the C=C double bond of the dipolarophile[350].

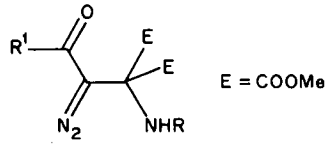


The cycloadditions of methyl azide to enones **440** and **441** gave mostly adducts **442** and **443**, respectively. The regioisomeric adducts **444** and **445** were present in trace amounts

only. With phenyl azide, however, the regioselectivity was not as good, **440** giving a 76:24 mixture of **446** and **447** and **441** a 81:19 mixture of **448** and **449**[351]. The minor adducts **447** and **449** were not stable and isomerized into the corresponding diazoketones **450**. The regioselectivity of these [3+2] cycloadditions appears to be controlled by the two ester groups in **440** and **441**[351].



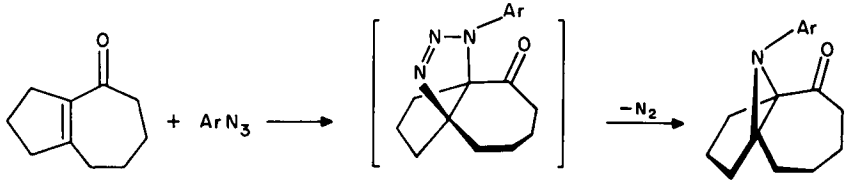
(**440**) R^1 = Ph (**442**) R = Me, R^1 = Ph (**444**) >20:1
(**441**) R^1 = Me (**443**) R = Me, R^1 = Me (**445**) >20:1
(**446**) R = Ph, R^1 = Ph (**447**) 76:24
(**448**) R = Ph, R^1 = Me (**449**) 81:19



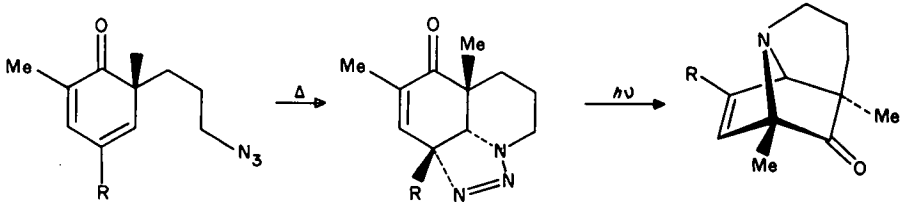
E = COOMe

(**450**)

Heteropropellanes have been prepared by [3+2] cycloadditions of acyl azides to bicyclo[5.3.0]dec-1(7)-en-2-one, followed by loss of nitrogen (equation 186); cf. also equation 185)[341].



(186)

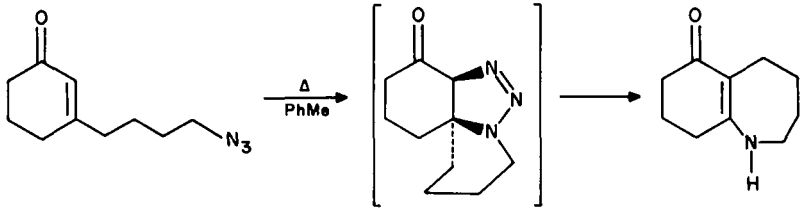


R = Me 43% 79%
R = *t*-Bu 91% 86%

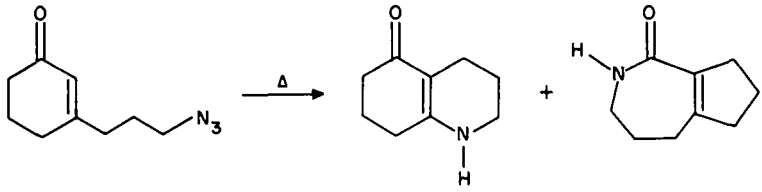
(187)

Schultz and coworkers[352] have studied the intermolecular [3+2] cycloadditions of azide onto cyclohexa-2,4-dien-1-ones. The reactions are highly regio- and stereoselective giving stable Δ^2-triazolines, which could be converted into the corresponding tricyclic systems containing the 7-azanorborn-5-en-2-one moiety by irradiation (equation 187).

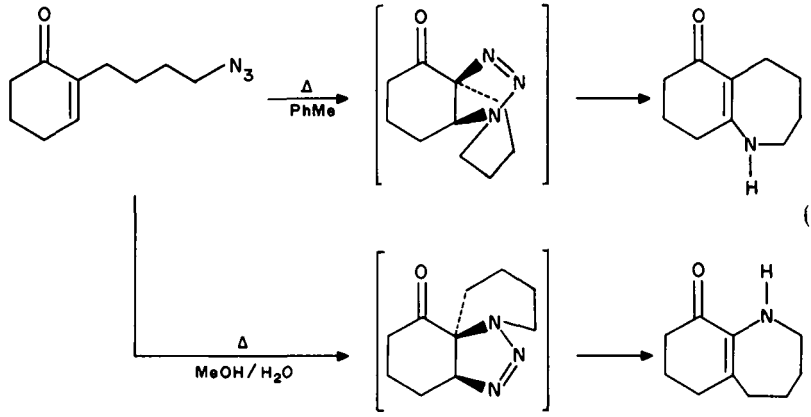
Sha and coworkers[353] have reported the intramolecular [3+2] cycloadditions of a series of azidocyclohex-2-en-1-ones. Depending on the substitution, thermal decomposition of the triazolines gave either products of annelation (equation 188–191) or the corresponding aziridines (equations 192 and 193). Reduction of aziridine (**451**) with $CrCl_2$ gave spiro amino ketone **452**, a synthetic precursor of (±)-desamylperhydrohistrionicotoxin. The reversal of regioselectivity of the cycloadditions of equations 190 and 191 changing the solvent from toluene to aqueous MeOH is remarkable, and not readily explained.



(188)

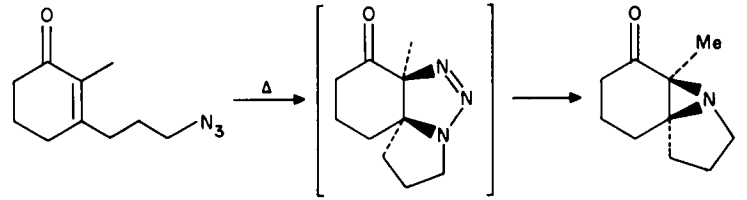


(189)

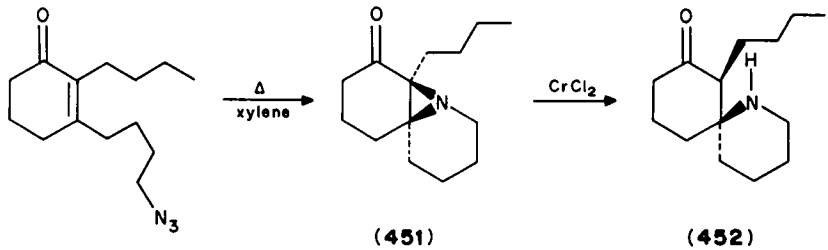


(190)

(191)



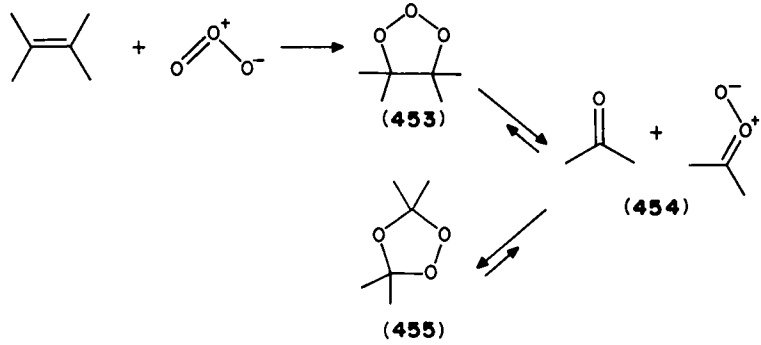
(192)



(193)

9. Miscellaneous

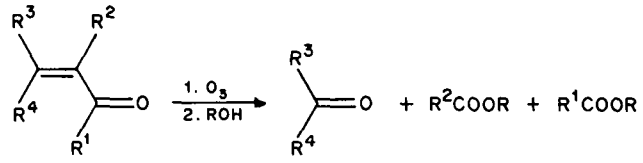
Ozone is probably the most reactive and most electrophilic 1,3-dipole known (Figure 5)[252]. Its reactivity with olefins is controlled by the LUMO(O_3)–HOMO(olefin) interaction. According to the Criegee mechanism (Scheme 17)[354,355], the ozonolysis of alkenes is a three-step process involving first a [3+2] cycloaddition to give the unstable, primary ozonide **453**. Through a rapid [3+2] cycloreversion, the latter fragments into a carbonyl compound and a carbonyl oxide **454** that are capable of undergoing a facile [3+2] cycloaddition to afford a more stable, secondary ozonide **455**.



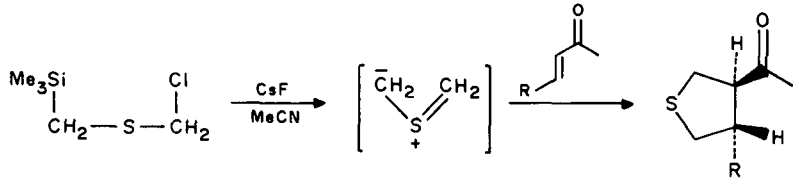
SCHEME 17

Though less reactive than alkyl substituted alkenes, α,β-unsaturated aldehydes and ketones react smoothly with ozone at low temperature[355,356]. On solvolysis the ozonides are decomposed into a variety of products (equation 194)[355].

On heating conjugated enones with α-chloro,α'-(trimethylsilyl)dimethyl sulphide in CH_3CN in the presence of CsF, the corresponding tetrahydrothiophenes are obtained (equation 195)[357].

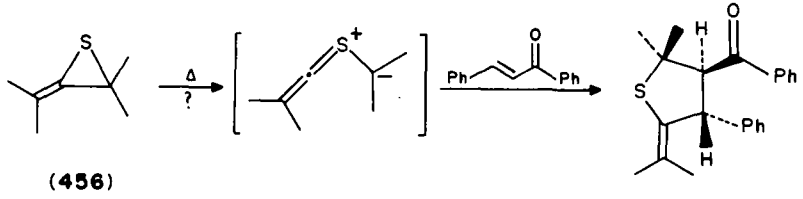


(194)



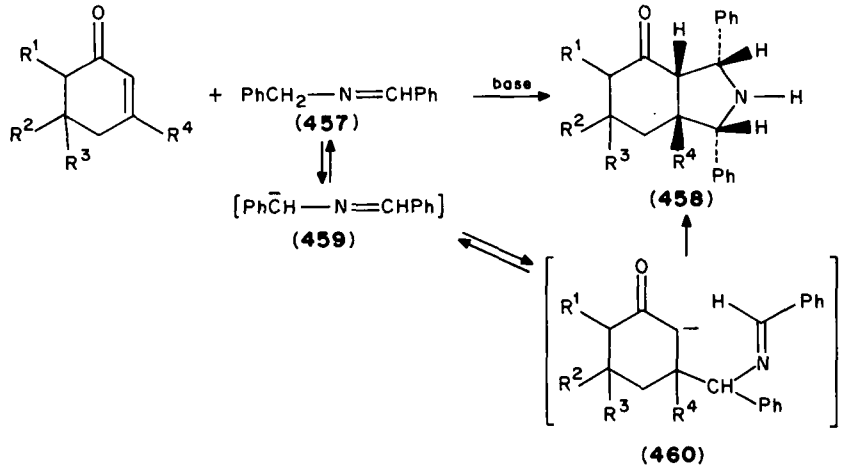
(195)

A similar reaction involves heating of the thiirane derivative **456** with conjugated enones to give the corresponding tetrahydrothiophenes (equation 196)[358]. The same thiacyclopentanation can be induced by $BF_3 \cdot Et_2O$. The mechanisms of reactions 195 and 196 are not elucidated yet; they may imply the generation of nucleophilic thiocarbonyl ylide intermediates. Alternatively, a multistep process involving a Michael addition is also possible.



(456)

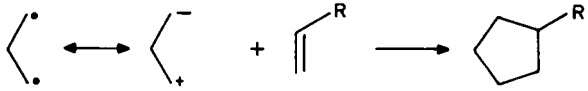
(196)



Heterocyclopentanation does not have to go through a [3 + 2] cycloaddition of a 1,3-dipole reagent. For instance, hexahydro-4-oxoisoindolines (**458**) were prepared by addition of *N*-benzylidenebenzylamine (**457**) to cyclohex-2-en-1-ones in DMSO in the presence of aq. NaOH at 20 °C[359]. The results were interpreted in terms of formation of an anionic reagent (**459**) that undergoes Michael addition onto the enones giving enolates (**460**). The latter cyclizes onto the imide moiety and gives finally products **458**. Anionic cycloaddition of anion **459** generated by deprotonation of **457** with lithium diisopropylamide at −70 °C have been described by Kauffmann[360].

B. Cyclopentanations

The direct formation of five-membered carbocycles through [3 + 2] cycloaddition of an all-carbon alkane-1,3-dipole **461** to an olefin (equation 197) is a relatively new technique of cyclopentanation[361,362].

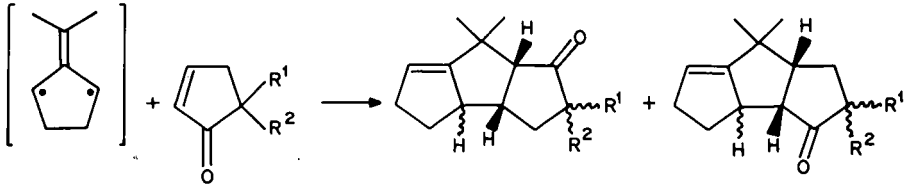


(197)

For the intermolecular reaction to occur, the ring closure of **461** or its disproportionation reactions must be slowed down. This is possible by stabilizing this species by π conjugation or/and substitution by highly polarizable groups such as transition metal moieties. The examples of reactions given below illustrate this point.

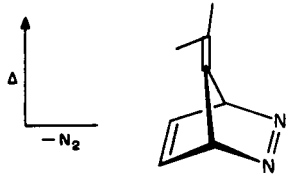
1. Cycloaddition of trimethylenemethanes (2-methylenepropane-1,3-diyls)

Whereas capture of trimethylenemethane itself (generated by thermal isomerization of methylenecyclopropane) by olefins proceeds in poor yields, the cyclic analogue **462** leads to cycloaddition products in good yields[363]. Even though cyclopent-2-en-1-one (**463**) is a poor dienophile, it reacts smoothly with **462**, generated by thermolysis (70 °C, CH_3CN) of **464**, and gives a 43:57 mixture of adducts **465** and **466**. In contrast, the substituted cyclopentenone **467** reacts with excellent regioselectivity affording adduct **468** (50% yield)[364].



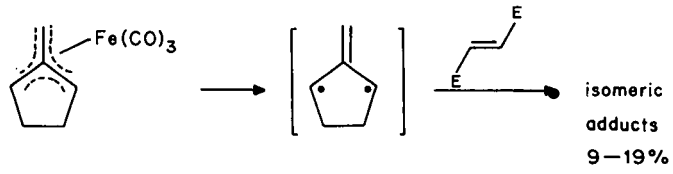
(462) **(463)** $R^1 = R^2 = H$ **(465)** **(466)**

(467) $R^1 = Me$, $R^2 = COOEt$ **(468)**



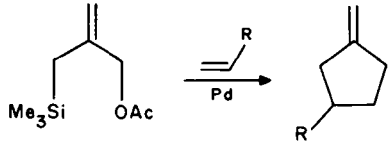
(464)

This cyclopentane annulation technique has been applied to the synthesis of numerous natural products[362]. The 2-methylenecyclopentane-1,3-diyl generated by oxidation (Me_3NO, PhH, 60 °C) of the corresponding tricarbonyliron complex added in only poor yields to electron-deficient olefins such as ethyl fumarate[365].

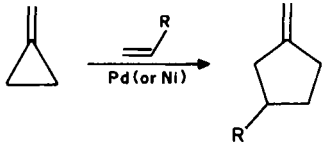


2. Palladium catalyzed methylenecyclopentenations

The cyclopentane annulations of alkenes with trimethylenemethane itself are greatly facilitated when using transition metal complexes of these 4-π-electron ligands. These complexes can be generated through reaction (equation 198) of (2-acetoxymethyl)-3-allyl)trimethylsilane (**469**) with a Pd complex (e.g. $(Ph_3P)_4Pd$ + bis(diphenylphosphino)ethane) or by thermal isomerization of methylenecyclopropane in the presence of a Ni or Pd complex (equation 199). The first approach (equation 198), developed by

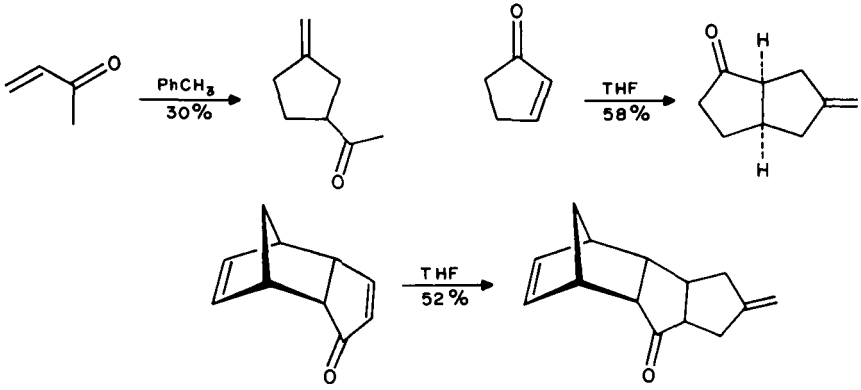


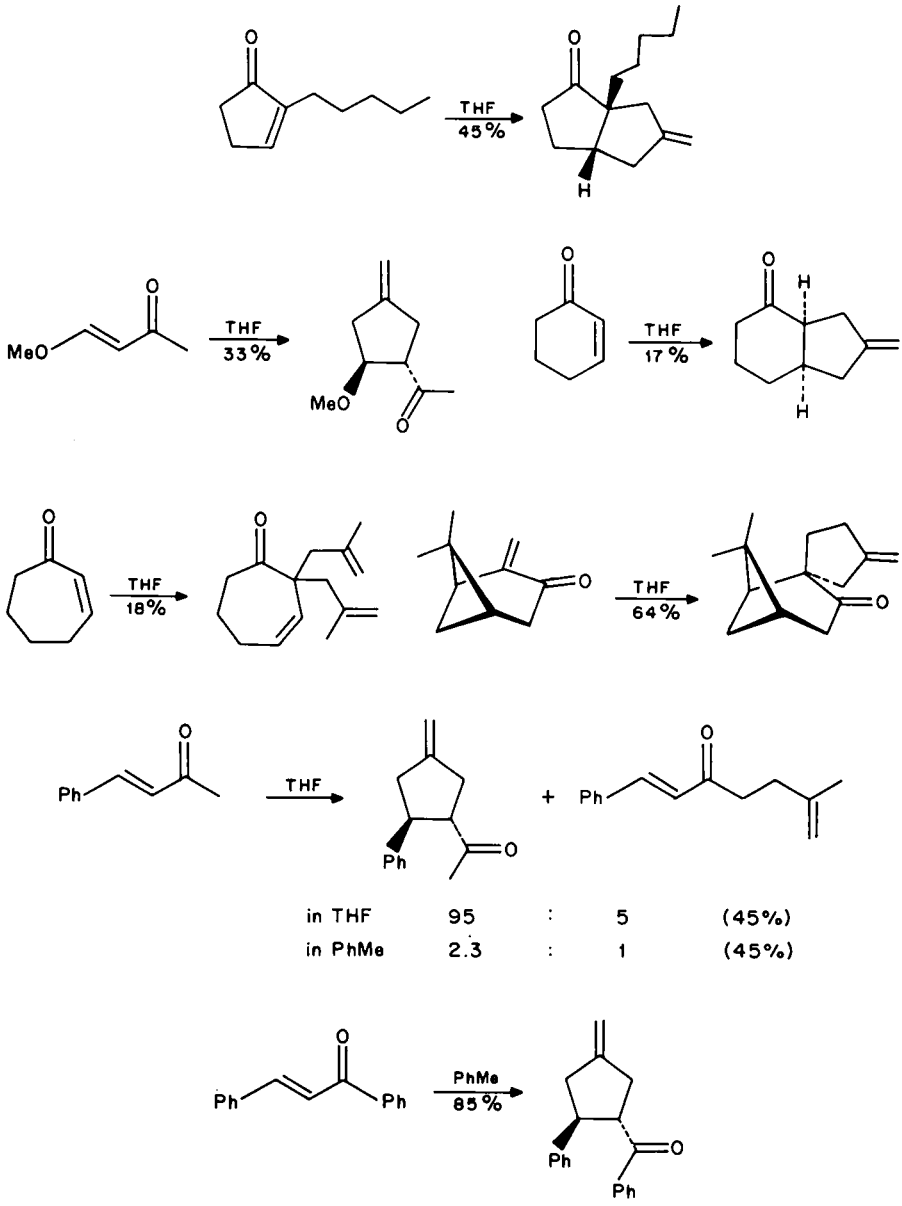
(469) (198)



(199)

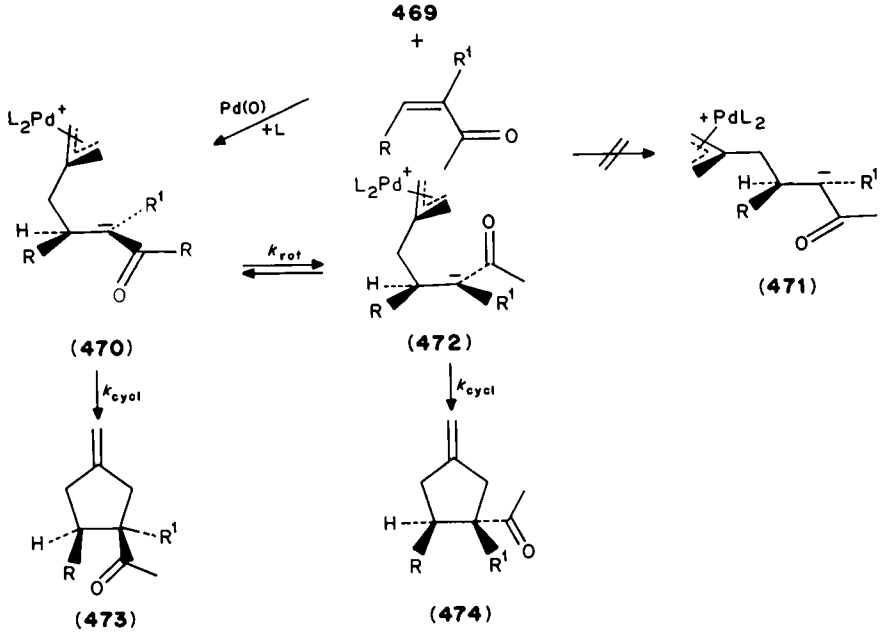
Trost and coworkers[362,366], has been applied widely to α,β-unsaturated ketones; selected examples are shown below[362,366,367].





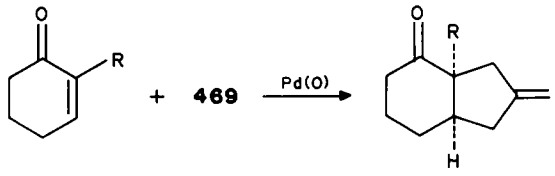
The mechanism proposed by Trost and Miller[368] (Scheme 18) implies a highly ordered non-concerted, multistep process. The stereoselectivity of the reaction suggests formation of the cisoid zwitterion **470**, which minimizes charge separation rather than the transoid one (**471**). A related cisoid intermediate has been proposed by Huisgen and coworkers[72,73,369] to account for the stereochemical observations of some thermal [2+2] cycloadditions (see Section III). Depending on substituents R and R^1, rotation of **470** into

conformer **472** is a slow or competitive process with cyclizations into the adducts **473** and **474**.



SCHEME 18

Paquette and coworkers[370] have studied the effect of α-substitution on the cyclopentenation of cyclohex-2-en-1-one and cyclohept-2-en-1-one. An α-methyl group reduced the yield of the reaction (equation 200) whereas an α-electron-withdrawing substituent such as an ester function led to better yields.

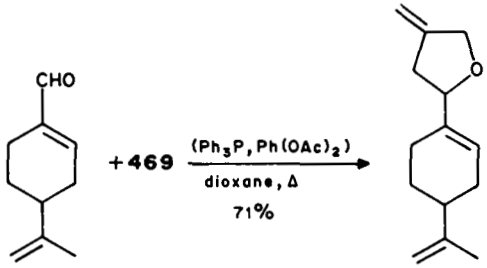


(200)

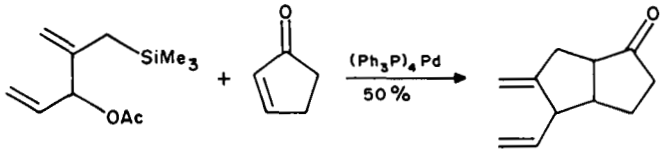
R = Me 6%
R = COOMe 46%
R = H 17%

α,β-Unsaturated aldehydes can add on their C=C or on their C=O double bond, as illustrated in equation 201[371]. Trialkyltin acetate was found to be a co-catalyst in the cycloaddition of **469** to aldehydes[371].

Substituted trimethylenemethane intermediates can also be generated under catalytical conditions with Pd and allow one to prepare complex cyclopentane derivatives through cycloaddition with olefins. An example using an enone is given in equation 202[362].

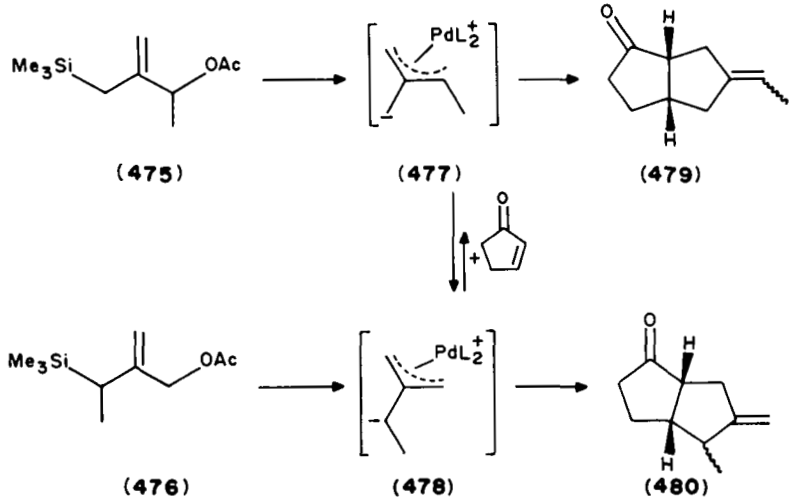


(201)



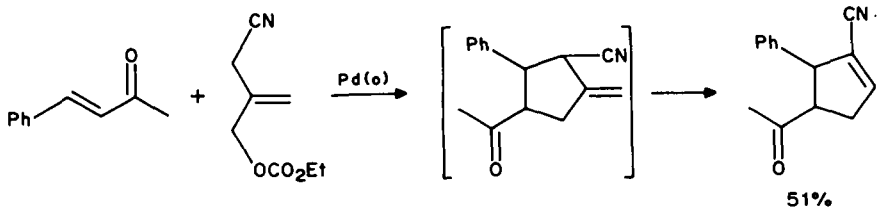
(202)

The isomeric methyltrimethylenemethane precursors **475** and **476** allowed for a test of equilibrating allylpalladium complex intermediates **477** and **478**. In the presence of cyclopent-2-en-1-one, both precursors **475** and **476** gave identical product mixtures in which adduct **480** predominates over adduct **479** (>20:1)[372]. On the other hand, a more reactive trap, such as benzylidenemalonate, gave different mixtures of adducts with **475** and **476**[362].



Further examples of enone cyclopentenations by [3+2] cycloadditions of substituted trimethylenemethanes are given in equations 203, 204[362] and 205[373].

A novel approach to substitutive cyclopentenation has been proposed by Trost and colloborators[374]. On heating a 1:1 ratio of 2-[(trimethylsilyl)methyl]-3-(trimethyl)prop-2-en-1-yl methyl carbonate (**481**) and a conjugated enone, with 2 mol% $(Ph_3P)_4Pd$ in toluene at 80 °C, the acids (mixture of stereoisomers) **482** were obtained in good yield with high regioselectivity.



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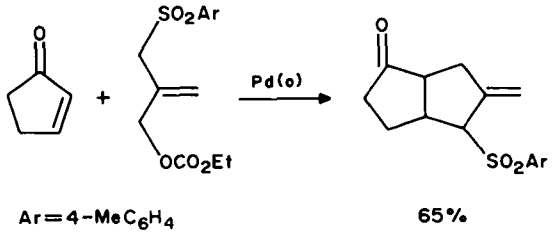
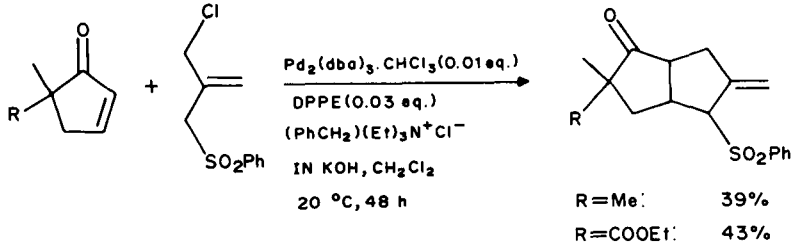
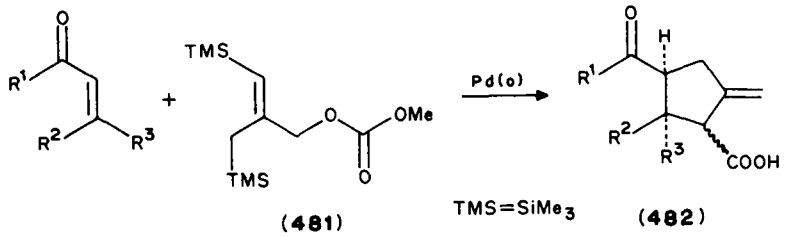


(204)



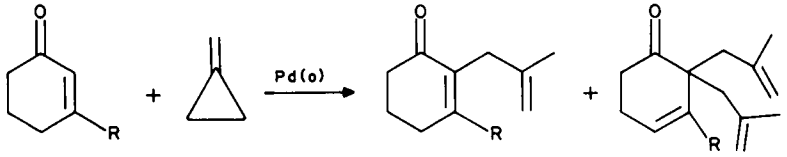
(205)

The methylenecyclopropane strategy (equation 199) leads in general to low yields of reaction. With cyclohex-2-en-1-ones, products of addition rather than cycloadducts were isolated (equation 206)[375]. In contrast, diphenylmethylenecyclopropane (**489**) reacts with cycloalk-2-en-1-one give regioisomerically pure cycloadducts (equation 207)[376].

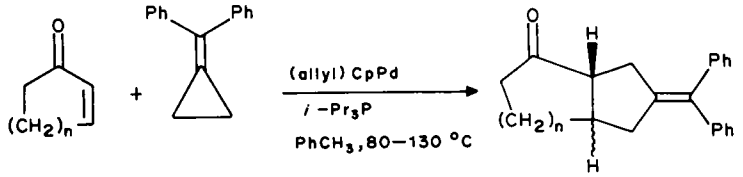


3. Cyclopentenation with cyclopropane derivatives

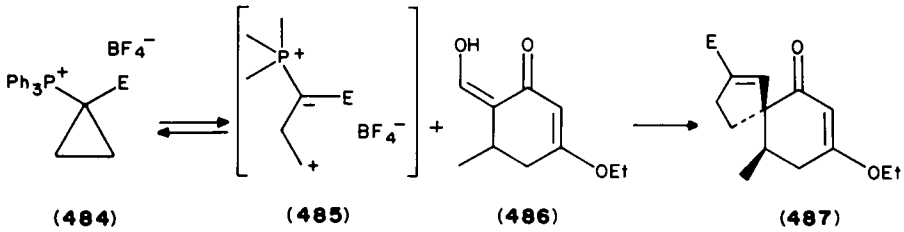
The cyclopropylphosphonium salt **484** adds (20 °C, NaH, HMPT) to enols such as **486** to give the spiro derivative **487** in 25–38% yield. This reaction represents formally a [3 + 2] cycloaddition of the stabilized 1,3-dipole **485**[377].



(206)



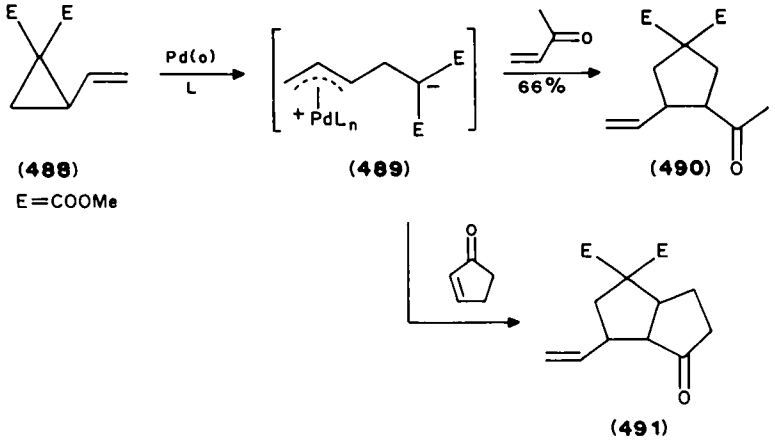
(207)



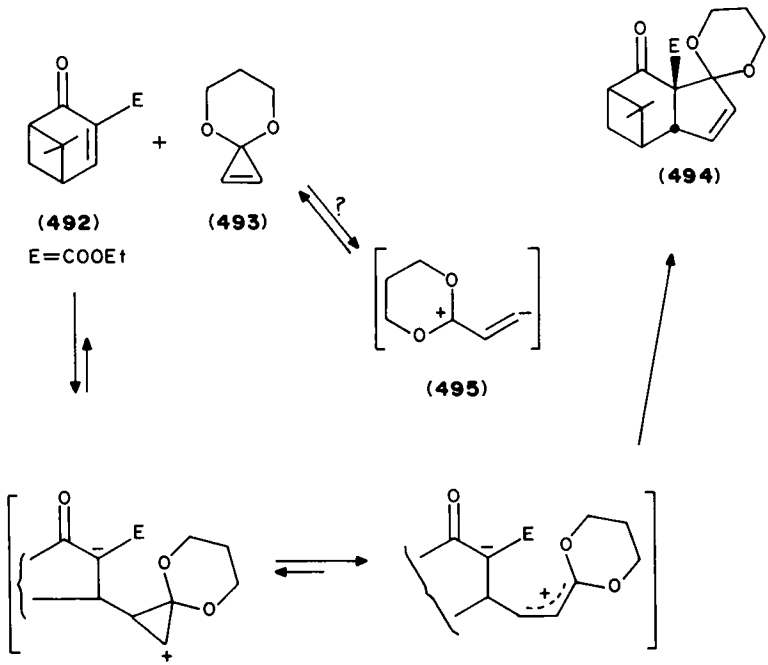
Tsuji and coworkers[378] reported that vinylcyclopropane with two ester substituents (**488**) reacts with α,β-unsaturated esters and ketones in the presence of Pd(dibenzalacetone)$_3$·$CHCl_3$ and tributylphosphine catalyst in DMSO to give the corresponding vinylcyclopentanes (e.g. **490**, **491**) in good yields. The results were interpreted in terms of formation of the relatively stable zwitterionic π-allylpalladium complex (**489**) that undergoes [3+2] cycloadditions with electron-deficient alkenes. The reaction can be a concerted, one-step process or, alternatively, a two-step process (via Michael addition, the negatively changed centre of **489** attacking the C(β) centre of the enone).

4. *Cyclopentenations*

Boger and Brotherton[379] reported a formal dipolar [3+2] cycloaddition of cyclopropenone ketals to electron-deficient olefins. For instance, heating enone **492** with **493** in PhH (75 °C) afforded the product of cyclopentenation **494** in 45% yield. Ketal **493** can be



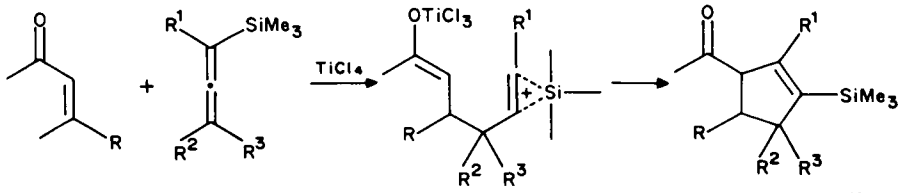
considered as an equivalent of the stabilized 1,3-dipole **495** capable of direct [3+2] cycloaddition to the conjugated enone. However, the multistep mechanism shown in Scheme 19 is believed to be more probable[379].



SCHEME 19

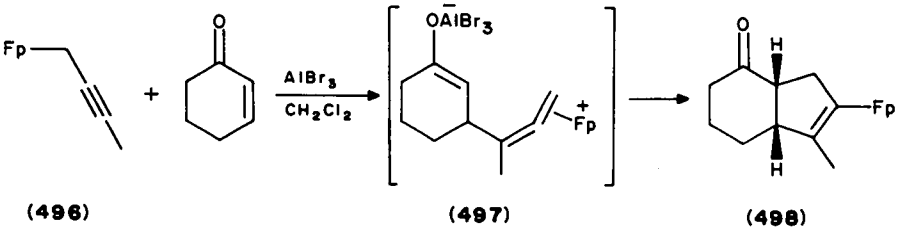
A regioselective approach to the synthesis of five-membered rings using (trimethylsilyl)allenes and conjugated enones has been proposed by Danheiser and

coworkers[380] (equation 208). The reaction involves initial complexation of the enone with $TiCl_4$ to generate an alkoxy allylic carbocation. Regioselective electrophilic substitution of this cation at C(3) of the (trimethylsilyl)allene generates a vinyl cation intermediate stabilized by interaction with the adjacent C—Si bond. A 1,2-shift of the Me_3Si group then affords an isomeric vinyl cation, which is intercepted by the titanium enolate to produce the corresponding cyclopentene derivative.



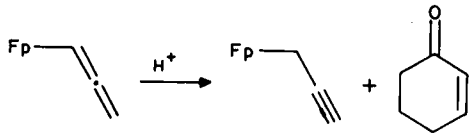
(208)

A related [3+2] cyclopentene annulation was reported by Rosenblum and coworkers[381]. In the presence of catalytic amounts of $AlBr_3$, cyclohexenone and (η^1-2-butynyl)(η^5-cyclopentadienyl)(dicarbonyl)iron (**496**) yield cycloadduct **498** (20%). This reaction (equation 209) was interpreted in terms of a multistep mechanism involving the zwitterionic intermediate **497**. The reaction of the allenyl complex (**499**) with cyclohexenone, in the presence of $AlBr_3$, takes an entirely different route and gives the [2 + 2] cycloadduct **502**.



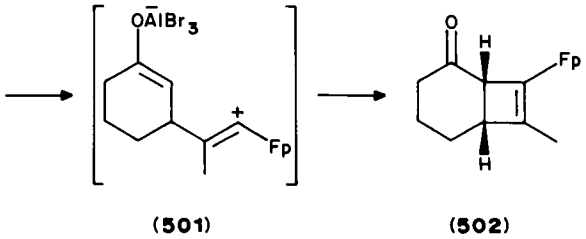
(496) (497) (498)

(209)



(499) (500)

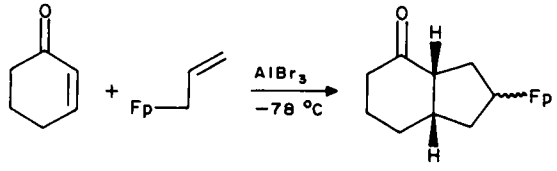
Fp = $(C_5H_5)(CO)_2Fe$



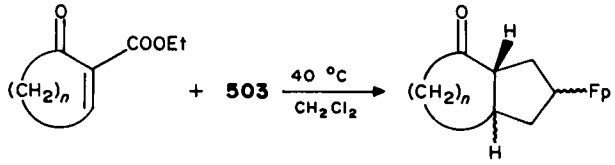
(501) (502)

The same product (**502**) was obtained in better yield when (η^1-1-propynyl)Fp (**500**) was used instead of **499**. It thus appears that **499** is initially isomerized by traces of acid to **500** and this latter complex is the effective reactant in both reactions. The formation of **502** may be explained by invoking the intermediacy of zwitterion **501**.

Similar to equation 209, a method for the cyclopentanation of α,β-unsaturated ketones with (η^1-allyl)Fp complex **503** has also been developed (see e.g. equation 210 and 211)[381,382]. Cyclohexenone itself failed to react with **503** even at elevated temperatures. However, activation of the enone with $AlBr_3$ made the formal [3 + 2] cycloaddition possible at −78 °C in CH_2Cl_2 and led to the *cis* hindranes **504**.



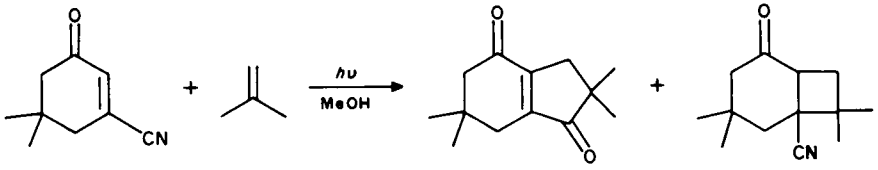
503 **504** (210)



$n = 2,3,4$ $Fp = (C_5H_5)(CO)_2Fe$ (211)

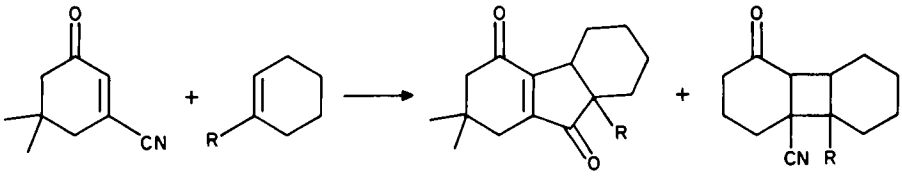
5. Photochemical cyclopentenation

Saito and coworkers[383] reported that irradiation of 3-cyano-5,5-dimethyl-cyclohex-2-en-1-one in the presence of olefins (MeOH, pyrex filter, Hg lamp) yields mixtures of [2 + 2] and [3 + 2] cycloadducts (see e.g. equations 212 and 213). The results were interpreted in terms of formation of diradical intermediates (e.g. **505**) that can cyclize into the corresponding cyclobutane derivatives or undergo rearrangements into nitrenes (e.g. **506**) which finally give the observed cyclopentenones (equations 212 and 213).



38% 46% (212)

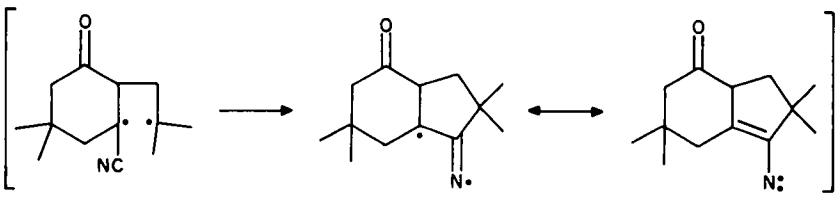
Margaretha and collaborators[384] reported recently that irradiation of 3-alkynylcyclohexenones **507** with tetramethylethylene in *t*-BuOH leads to mixtures of [3 + 2] cycloadducts **508** and **509**. This reaction can be explained in terms of formation of diradical intermediates **510** that can rearrange to form the corresponding vinylcarbene **511**. Insertion into the O—H— bond of solvent then gives **508**, while 1,4-transfer of hydrogen



R=Me 35% 30%

R=H >1% 80%

(213)



(505) (506)

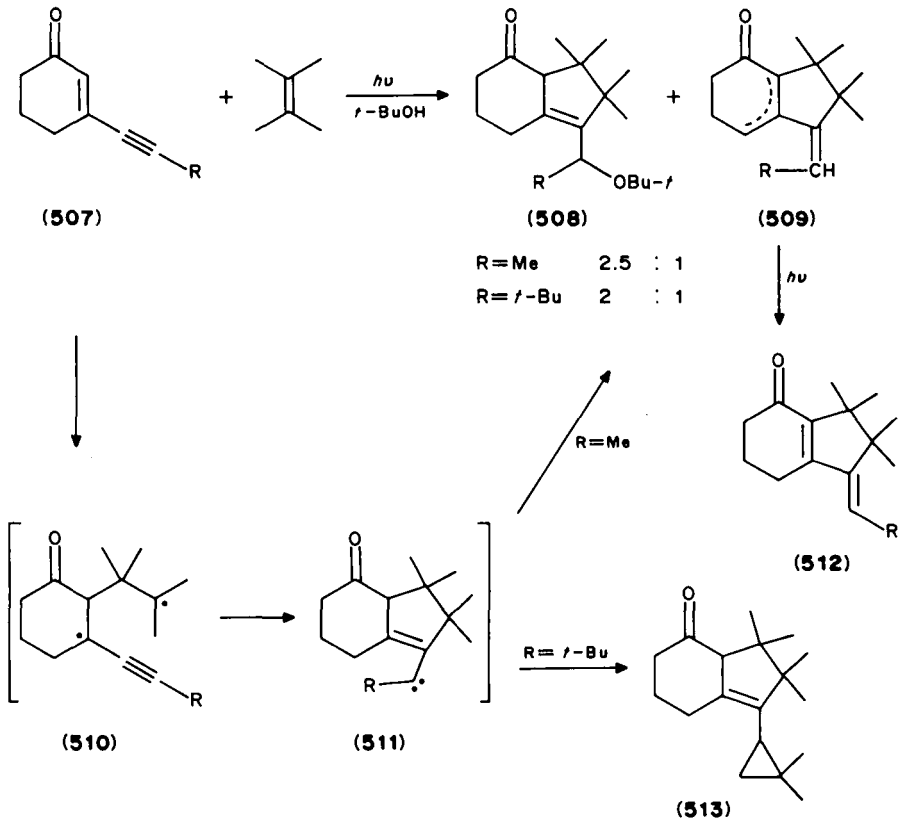
furnishes **509**, R = Me. Irradiation of the derivative with R = *t*-Bu gave a mixture of **512** and **513**. The cyclopropane derivative **513** results probably from C—H insertion of the carbene intermediate (**511**, R = *t*-Bu). Double bond migration **509** → **512** was observed under the conditions of the photoadditions ($\lambda_{irr} > 340$ nm).

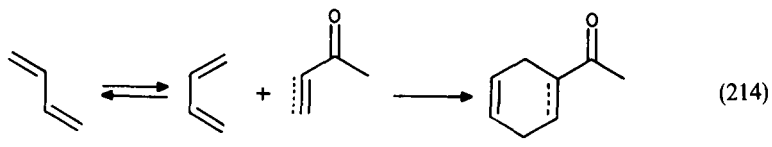
VI. DIELS–ALDER ADDITIONS OF ENONES

For sixty years, the Diels–Alder addition[385–388] has been one of the best methods for the preparation of six-membered carbocycles. The typical [4 + 2] cycloaddition condenses a diene moiety onto an alkene or alkyne system (dienophile) to afford a cyclohexene or cyclohexa-1,4-diene derivative (equation 214). As we shall see, α,β-unsaturated aldehydes and ketones are good dienophiles. Since the report that the thermal dimerizations of acrolein and methyl vinyl ketone were shown to be highly regioselective and to give six-membered heterocycles[389,390], the Diels–Alder addition of conjugated enals and enones as 1-oxabutadienes to olefinic dienophiles (equation 215: hetero-Diels–Alder addition) has become a powerful method for the synthesis of 3,4-dihydro-2*H*-pyrans[391,392]. Because of the recent and complete review by Boger and Weinberg[393] of reaction 215, our survey will describe mostly examples of reactions 214. Six-membered heterocycles can also be generated via the Diels–Alder additions of α,β-unsaturated aldehydes and ketones to thiabutadienes[393b] and 1-aza and 2-azabutadienes[393c,394,395]. Examples will be given in this section.

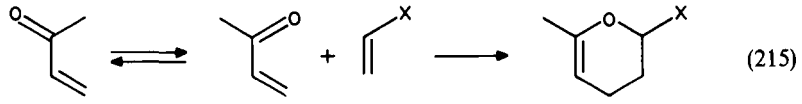
A. Diels–Alder Reactivity

According to the Woodward–Hoffman rules[4], the concerted suprafacial, suprafacial[$_{\pi}4_s + {}_{\pi}2_s$] cycloaddition (C_s transition state) of a diene and dienophile is thermally allowed. This is also true for the reverse reaction, the [$_{\pi}2_s + {}_{\sigma}2_s + {}_{\sigma}2_s$] cycloreversion called retro-Diels–Alder reaction, which fragments a cyclohexene or cyclohexa-1,4-diene systems into diene + olefin or acetylene moieties. The frontier





(214)



(215)

molecular orbital (FMO) theory[24,396–406] applied to these reactions predicts that with α,β-unsaturated aldehydes and ketones as dienophiles, the rate and regioselectivity of the [4 + 2] cycloadditions will be controlled mostly by the LUMO(dienophile)–HOMO(diene) interaction (Diels–Alder additions with 'normal' electronic demand[406]) as illustrated in Figure 6a. This implies that electron-donating substituents on the dienes and/or electron-withdrawing groups on the dienophile will accelerate the cycloaddition. In the case of α,β-unsaturated aldehydes and ketones adding as oxabutadienes, the FMO

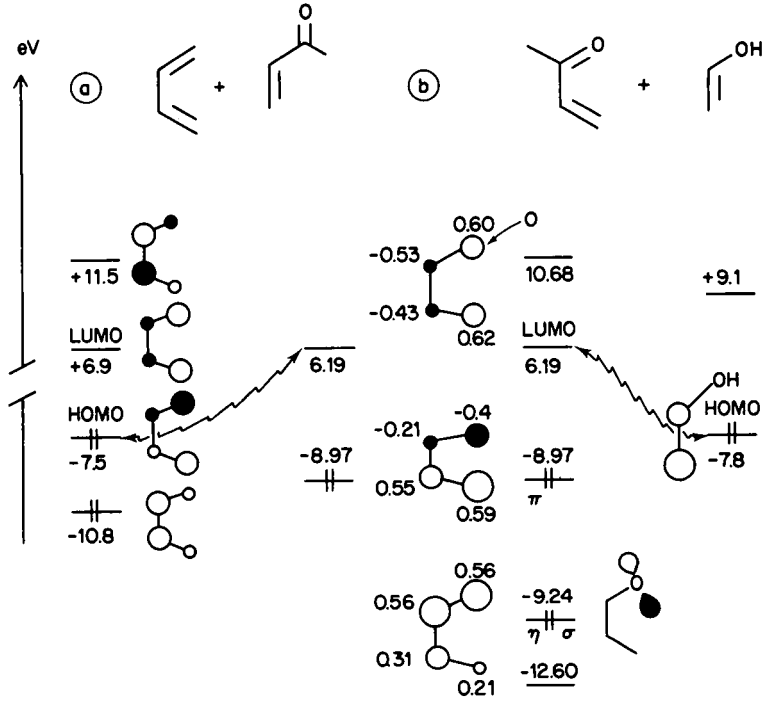


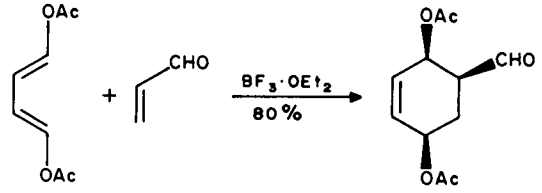
FIGURE 6. PMO diagrams illustrating the interactions between FMOs of (a) s-*cis* butadiene and acrolein (dienophile) and of (b) acrolein (oxabutadiene) and hydroxyethylene (dienophile). The energies and 2p atomic coefficients were obtained[407] by the *ab initio* STO 3G technique[408] for geometries optimized by the MNDO method[409]

theory predicts that the rate and regioselectivity of cycloadditions will be controlled mostly by the LUMO(oxabutadiene)–HOMO(dienophile) interaction (hetero-Diels–Alder reaction with inverse electronic demand[406]) as shown in Figure 6b. Thus one predicts that electron-releasing substituents on the dienophiles and/or electron-withdrawing substituents at the oxabutadienes will favour the cycloadditions.

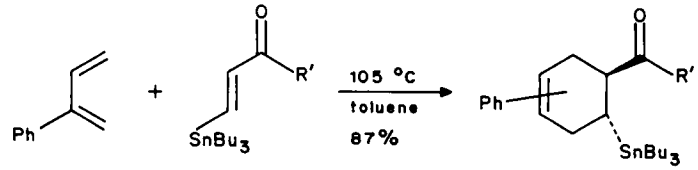
1. *Stereoselectivity*

The '*cis* principle' states that Diels–Alder additions require a cisoid conformation for the diene and suprafacial, suprafacial mode of reaction, i.e. both ends of the diene attack from the same face the two ends of the dienophile in a *syn* fashion. As a consequence, the relative configuration of centres C(1) and C(4) of the diene and C(α) and C(β) of the α, β-unsaturated aldehyde or ketone are maintained in the transition state of the [4 + 2] cycloaddition and in the cycloadducts. Illustrations of that principle are given with the particular examples shown in equations 216[410] and 217[411].

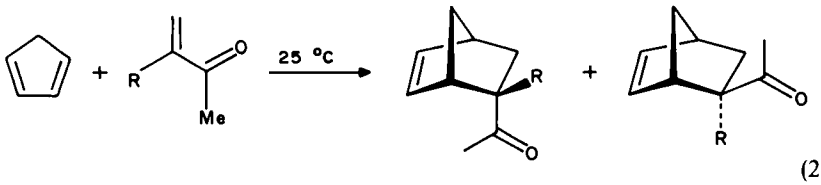
Under conditions of kinetic control, the Diels–Alder additions of conjugated enals and enones to cyclic 1, 3-dienes quite often give the *endo* adducts that are less stable than their *exo* isomers. This is the '*endo* rule'[388], first proposed by Alder and Stein[412] and illustrated by the examples given in equations 218[413,414], 219[413], 220[415] and 221[416].



(216)

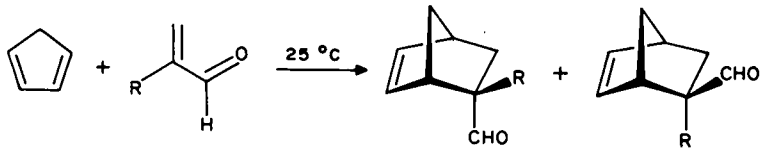


(217)



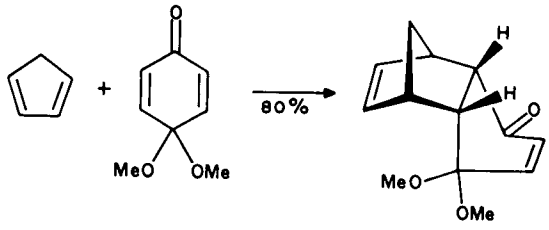
(218)

R=H	80	:	20[413]
R=Me	47	:	53[413]
R=EtO	34	:	66[414]
R=Me_3SiO	32	:	68
R=CH_3CO	53	:	47
R=PhCO	39	:	61
R=2,4-$(NO_2)_2C_6H_3CO$	42	:	58

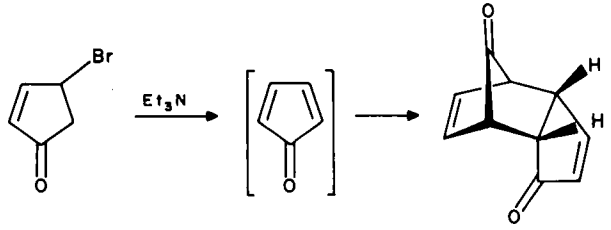


R=H	75	:	25
R=Me	17	:	83

(219)

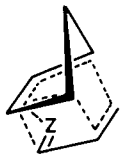


(220)

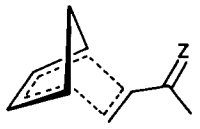


(221)

The '*endo* rule' is usually rationalized as a result of the principle of 'maximum accumulation of unsaturation'. The polarizability of the diene and dienophile creates dispersive forces making the *endo* transition state **514** more stable than the *exo* transition state **515**. According to Woodward and Katz[417], secondary overlaps are possible in **514**

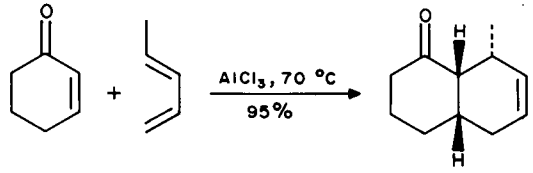


(514)

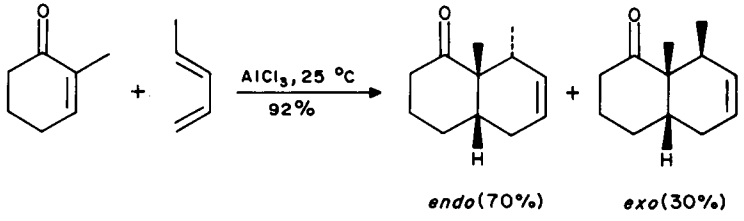


(515)

leading to secondary binding forces that stabilize this transition state. Confirmation of that hypothesis has been found by high-pressure kinetics[418]. The relative *endo* selectivities of methyl substituted dienophiles adding to cyclopentadiene were found to decrease in the order *cis*-β-*Me* > *H* > *trans*-β-Me > α-Me, indicating that the methyl group itself (and other alkyl groups) possesses an appreciable *endo*-orienting ability[413]. For instance, while the *endo* adducts are favoured for the Diels–Alder additions of cyclopentadiene to acrolein and methyl vinyl ketone, the *exo* adducts are the major adducts with the α-methyl substituted dienophile, methylacrolein and methyl propenyl ketone (see equations 218 and 219)[413]. A similar α-methyl effect was noticed for the Lewis-acid catalyzed additions (see Section VI.B.1) of cycloalk-2-en-1-ones to acyclic 1,3-dienes[419–422]. For instance, while unsubstituted cyclohex-2-en-1-one added to (*E*)-piperylene to give the corresponding *endo* adduct in 85% yield (equation 222), 2-methyl-cyclohex-2-en-1-one gave with (*E*)-piperylene a 7:3 mixture of the corresponding *endo* and *exo* adducts (equation 223)[419,423]. The effect

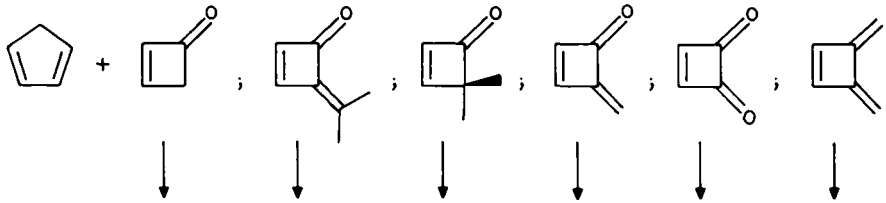


(222)

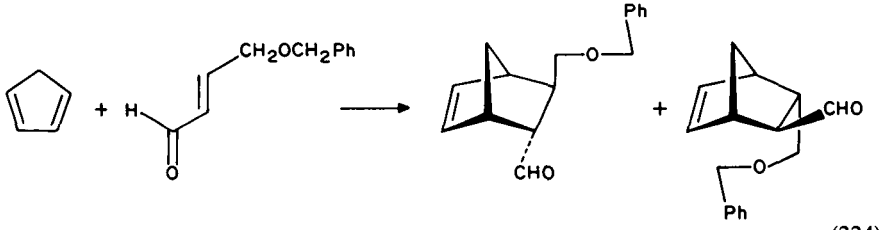


(223)

of the α-methyl group has been attributed to non-bonded interactions with the π system of the diene in the *exo* transition state (**515**)[413]. Repulsive steric effects and dipole–dipole effects between the substituents of the two cycloadducts can also play a role on the *endo/exo* stereoselectivity[414,418,424] as illustrated in equation 219[414] and also below for the cycloadditions of cyclopentadiene to various cyclobutenones[425].



Solvents different from water (see Table 4 below) have little effect on the *endo* selectivity[426,427]. However, the temperature or/and the presence of a Lewis-acid catalyst can dramatically affect it, as illustrated in equation 224[428]. Coordination with a Lewis acid can modify the equilibrium constant between the cisoid and transoid dienophile[429] as well as their intrinsic relative reactivity.



(224)

0 °C/240 h	66	:	34
200 °C/6 h	34	:	66
$+BF_3 \cdot Et_2O$/−15 °C	90	:	10

The *endo* vs *exo* product ratio of the Diels–Alder addition of cyclopentadiene to methyl vinyl ketone (equation 218, R = H) was not affected by the solvent, except for H_2O (see Table 4). Thus, water-like solvents such as ethylene glycol or dimethylformamide (DMF) do not share some of the most stricking characteristics of H_2O itself[427,430]. The special

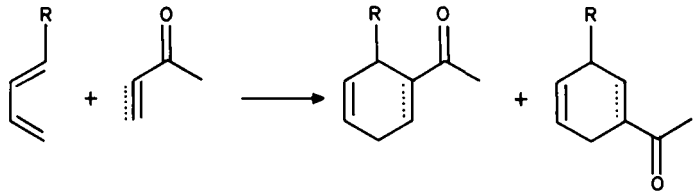
TABLE 4. Second-order rate constant and *endo* vs *exo* product ratio of the cycloaddition of cyclopentadiene to methyl vinyl ketone in various solvents[427]

Solvent	$k^{II} \times 10^5$ [$M^{-1}s^{-1}$, 20 °C]	*endo* vs *exo*
isooctane	5.9 ± 0.3	8.5
MeOH	75.5	8.5
DMF	318 ± 4	8.9
ethylene glycol	480	10.4
H_2O	4400 ± 70	25

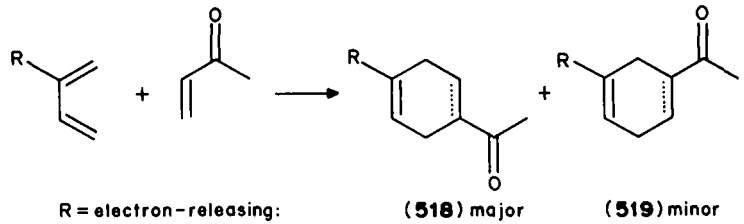
effect of H_2O on the rate and *endo* vs *exo* product ratio has also been noted for the Diels–Alder addition of 6,6-dimethylfulvene to benzoquinone[430]. Moreover, the *endo* vs *exo* product ratio could be controlled from 9:1 to 1:9 depending on the formal concentration in H_2O[430].

2. Regioselectivity

For the cycloadditions of α,β-unsaturated aldehydes and ketones (dienophiles) to 1-substituted dienes (equation 225) the '*ortho* orientation rule' states that the major adduct formed under conditions of kinetic control is the regioisomer '*ortho*' **516**. In the case of [4 + 2] cycloadditions of 2-substituted dienes (equation 226), the corresponding '*para*' adducts **518** are generally the major products ('*para* orientation rule') for substituents R = alkyl, aryl, electron-donating groups. For electron-withdrawing substituents a C(2), the '*meta*' adducts **519**, can be favoured.



(225)



(226)

These orientation rules have been rationalized by the FMO theory[24,396–406], which states that the regioselectivity of the Diels–Alder additions (and other cycloadditions) is given by the shape of the FMOs of the cycloaddends. This theory assumes the cycloadditions to be one-step concerted processes in which the two new σ bonds are formed synchronously. Furthermore, it supposes that the properties of the cycloaddends, more than those of the adducts, are reproduced in the transition state (early transition state hypothesis).

3. The diradicaloid model of the Diels–Alder transition state

Since activation volumes, $\Delta V^{\ddagger}$, and reaction volumes, ΔV_r, of Diels–Alder additions have similar values (see Section VI.B.2), the early transition state hypothesis might not be correct in all cases. Woodward and Katz[417] (and also Firestone[246]) have visualized the Diels–Alder addition transition state as diradicals, arising from the formation of one σ(C—C) bond between the diene and dienophile (see **521** in Figure 7). Since the activation enthalpies of most [4 + 2] cycloadditions are lower than those required for mechanisms involving true diradical intermediates (see e.g. **520** in Figure 7), a stabilization interaction intervenes causing these species to be diradicaloids, as advocated by Epiotis[431] and Dewar

and coworkers[432]. This concept is now presented for Diels–Alder addition of equation 225.

The early stage of the Diels–Alder reaction involves the compression of two reactants and follows the energy profile a in Figure 7. If one assumes the less substituted centres of the reactants to be involved in the formation of the first single bond, the reaction reaches the stage of a disubstituted allyl-alkyl diradical intermediate (**520**). Such species are true intermediates in cycloaddition involving halogenated cycloaddends[433]. The energy profile a can encounter the descending energy profile of the charge-transfer configuration b, which is assumed to have the same reaction coordinates as process a. The transition state of the cycloaddition is lower in energy than the crossing point of these two configuration energy profiles and can be represented by the diradicaloid **521**↔**521′** shown in Figure 7.

This model allows us to predict the effects of substituents A of the dienophile (A = $COCH_3$ for equation 225 and Figure 7) and R of the diene on the reactivity (rate) and the regioselectivity of the reaction. The more the diene substituent R is electron-donating, the lower is the ionization energy (IE) of the diene and the more it stabilizes the charge-transfer configuration (zwitterionic in character) of the diradicaloid representing the transition state of the Diels–Alder addition (**521**↔**521′**). Furthermore, the more the dienophile substituent A is electron-withdrawing, the stronger is the electron affinity of the dienophile and, once again, the more the 'zwitterionic' configuration of the transition state will be stabilized. In reaction 225, the '*ortho*' regioisomer is the favoured product. This is explained by the fact that the diradicaloid (**521**↔**521′**) representing the transition state of this reaction is better stabilized by the substituents A and R than those (see **522** and **523**) leading to the '*meta*' cycloadduct (**517**).

Whichever is the first σ bond formed during the reaction giving **517**, the charge-transfer configuration of the transition state does not couple donor and acceptor fragments in the

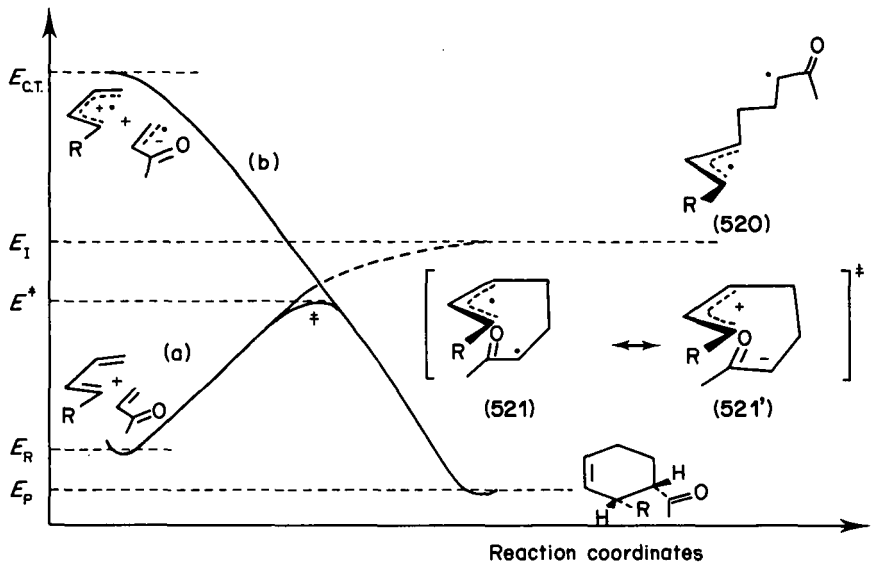
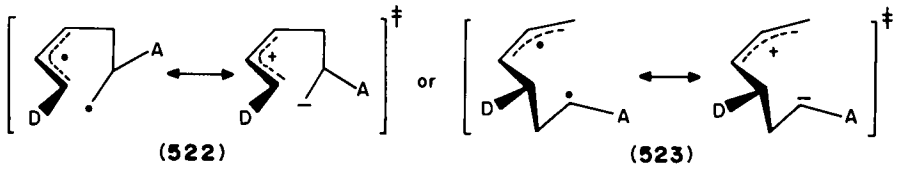
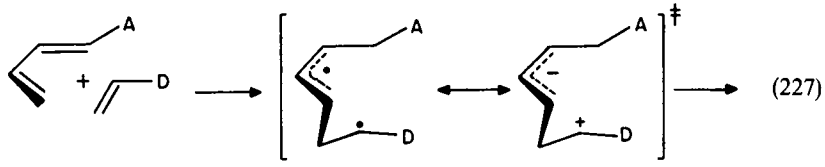


FIGURE 7. Model for the Diels-Alder addition 225. (a) Energy profile of the ground state configuration transforming the reactants into a true diradical intermediate (**520**). (b) Energy profile of the charge-transfer configuration. $E_{C.T.}$ = ionization energy of diene + electron affinity of dienophile



(522) (523)

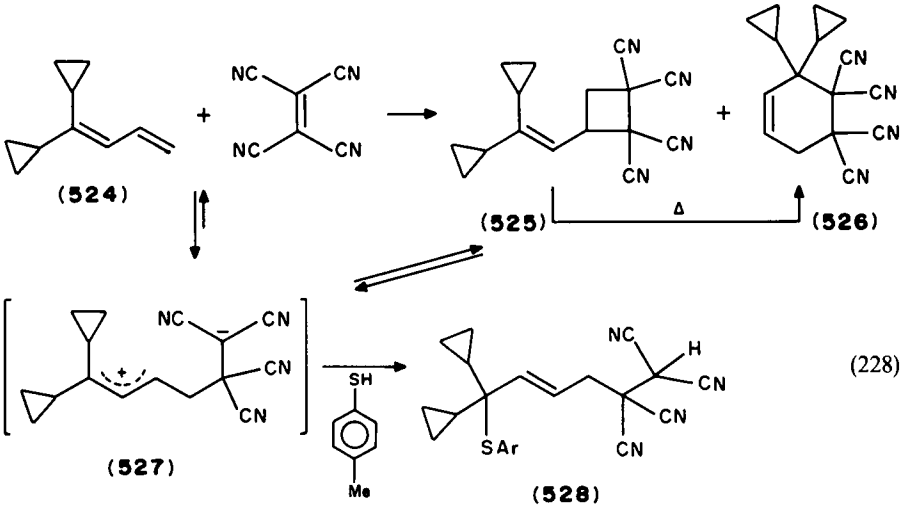
best possible way. The same model can be applied to a Diels–Alder addition with 'inverse electronic demand', i.e. for reaction 227 between an electron-poor diene and an electron-rich dienophile.



(227)

4. Solvent effects

We have commented thus far on one-step concerted Diels–Alder additions where the two σ bonds are not formed synchronously, a reasonable hypothesis (Woodward–Katz model[417]) for reactions involving non-symmetrically substituted dienes and dienophiles. For some special cases where the substituent stabilization effects on the charge-transfer configuration are very strong, a zwitterionic intermediate may be formed. The rate of such a reaction will thus be strongly solvent-dependent[434], i.e. the more polar is the solvent, the faster is the cycloaddition (see Table 4). Furthermore, the zwitterionic intermediate may cyclize into [4 + 2] and [2 + 2] cycloadducts competitively[435]. In some cases, it can be trapped by a nucleophile or the solvent. This is illustrated by reaction 228[436].

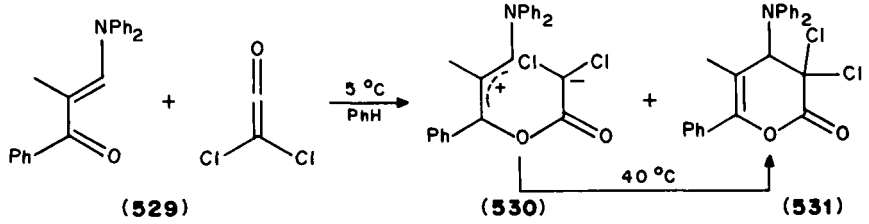


(524) (525) (526) (527) (528)

(228)

Tetracyanoethylene (TCE) adds to 1,1-dicyclopropylbutadiene (**524**) giving rise to the [2 + 2] adduct **525** and the [2 + 4] adduct **526**. When heated to 100 °C in CH_2Cl_2, **525** is

rearranged into the more stable isomer **526**. The same rearrangement occurs already at 25 °C in a more ionizing solvent such as acetonitrile. In the presence of a good nucleophile such as *p*-toluenethiol, quenching of the zwitterionic intermediate **527** generates adduct **528**. In some extreme cases, the zwitterion is extremely stable and becomes a product of reaction. Such an example is shown in reaction 229[437].



(529) **(530)** **(531)**

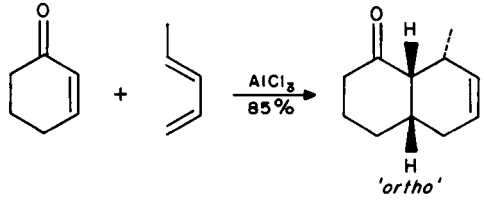
(229)

Under kinetic control (benzene, 0–5 °C), dichloroketene adds to the electron-rich enone **529** giving rise to a 55:45 mixture of the stable zwitterion **530** and lactone **531**. At higher temperature (40 °C), the zwitterion **530** cyclizes into the more stable adduct **531**.

The Diels–Alder addition of cyclopentadiene to methyl vinyl ketone (equation 218, R = H) is faster in dimethylformamide (DMF) or in ethylene glycol than in other organic solvents, but not as fast as in water solution[427] (see Table 4). The reaction is also accelerated by β-cyclodextrin. The effect of water cannot be explained only in terms of solvation of diradicaloid transition state of type **521**↔**521′** (Figure 7). The kinetic results (Table 4) indicate that there is solvophobic binding of the reactants to each other in water or into the cyclodextrin cavity.

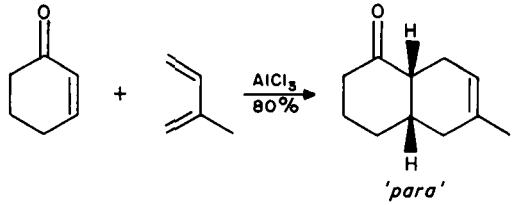
B. Examples of Intermolecular [4 + 2] Cycloadditions

Wenkert and coworkers[423,438] have recently reported their extensive work on the $AlCl_3$-catalyzed addition of alkylated dienes such as (*E*)-piperylene (equation 230) and isoprene (equations 231 and 232) to cyclopent-2-en-1-ones, cyclohex-2-en-1-ones and cyclohept-2-en-1-ones. They have shown that the '*ortho*' and '*para*' rules of addition are followed in all cases except for the reaction of 4,4-dimethylcyclohex-2-en-1-one to isoprene, where the reaction is not regioselective. This exception can be explained by a *methyl–methyl repulsion in the transition state*[439].



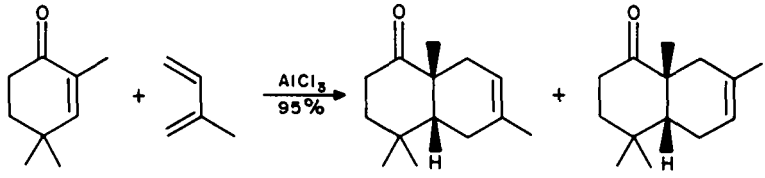
'*ortho*'

(230)



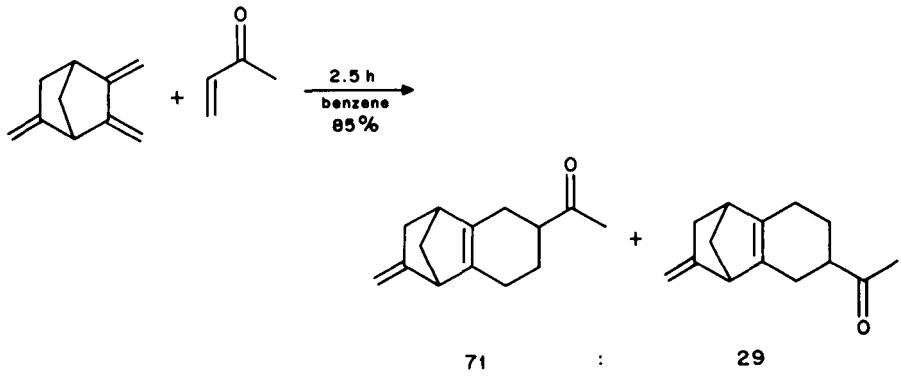
'*para*'

(231)

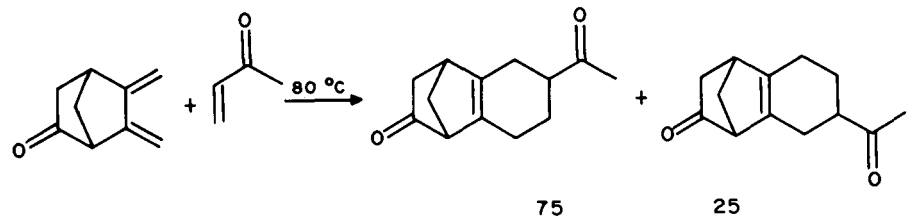


(232)

The Diels–Alder regioselectivity of an exocyclic diene moiety grafted onto bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane skeletons can be controlled by a homoconjugated group at C(5), such as a methylene[440] (equation 233) or a carbonyl group[441] (equation 234). These groups induce '*para*' regioselectivity as predicted by the FMO theory. In the case of the carbonyl group, this group acts as an electron-donating substituent. The hyperconjugative $n(CO)/\sigma[C(1),C(2)]/\pi[C(5),C(6)]$ interaction overrides the normal electron-withdrawing effect ($\pi^*(CO)/\pi[C(5),C(6)]$) interactions of this function (compare with the Diels–Alder addition of 7-oxabicyclo[2.2.1]hept-5-en-2-one, Section VI.B.5).



(233)

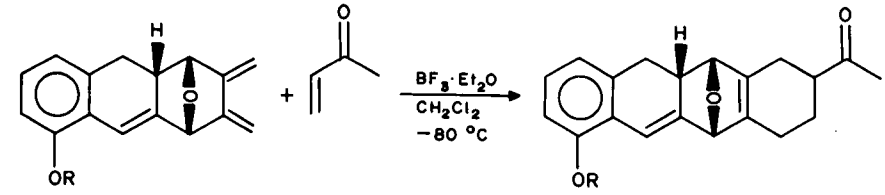


(234)

The regioselectivity was exploited in the regioselective syntheses of anthracyclines (equation 235)[442].

In accordance with the FMO theory, reaction of conjugated enones with heterosubstituted diene shows a good regioselectivity. Cyclic and acyclic 1-acyloxy-1-3-dienes add regioselectivity to enones[443,444]. The formation of the A–B ring system of verrucarol is

obtained by regioselective addition of 1-acyloxy-1, 3-butadiene to a functionalized enone (equation 236)[444].



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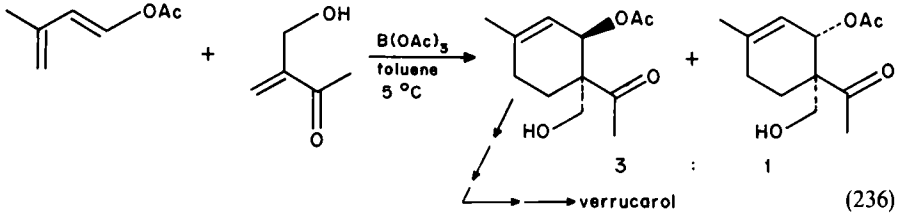
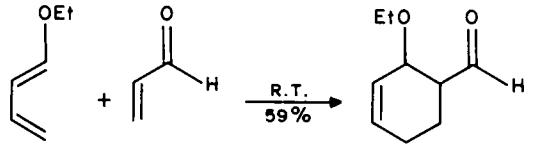
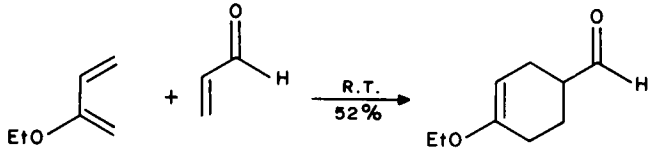


(236)

The high regioselectivity of addition of alkoxy-1, 3-dienes to enones (equations 237 and 238)[445,446] has been used in the synthesis of coronafacic acid (equation 239)[447].



(237)



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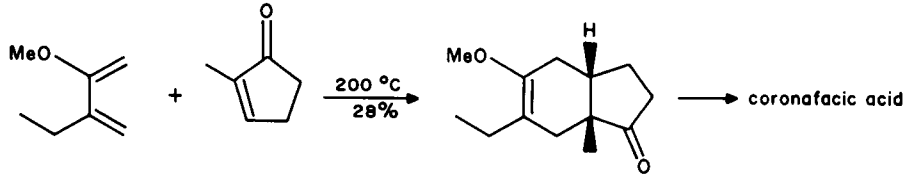
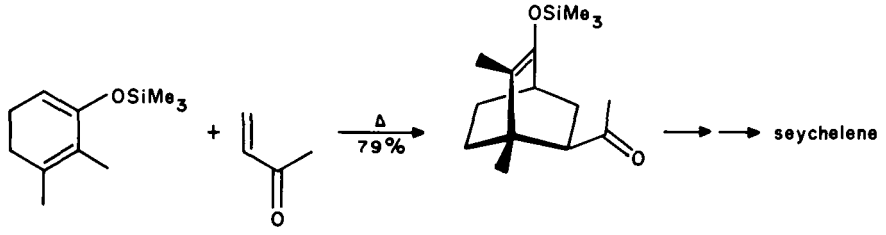


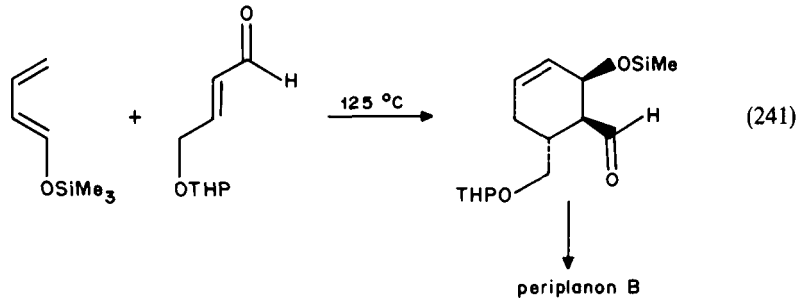
(239)

Regioselective addition of silyloxydienes[448] to conjugated enones has been noted and applied to the synthesis of seychellene (equation 240)[449] and periplanon B (equation

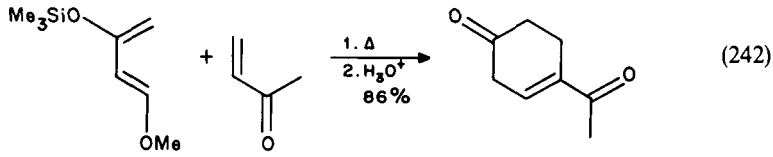
241)[450]. The use of 1-methoxy-3-trimethylsilyloxybutadiene (e.g. equation 242)[451a,b] (or 1,1-dimethoxy-3-trimethylsilyloxybutadiene[451c]) confers a high orientational effect when it reacts with α,β-unsaturated ketones and aldehydes.



(240)

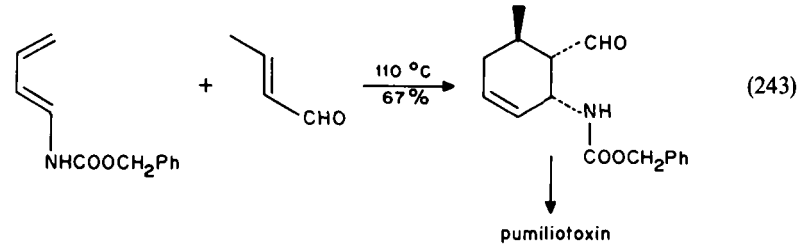


(241)



(242)

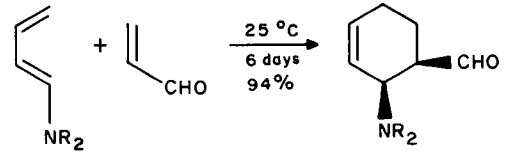
A straightforward synthesis of pumiliotoxin (equation 243) based on the highly regioselective cycloaddition of benzyl 1,3-butadiene-1-carbamate to crotonaldehyde has been reported[452].



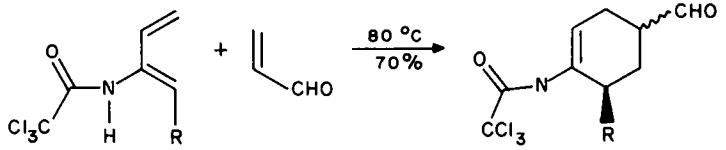
(243)

The reaction of α,β-unsaturated aldehydes and ketones with 1-(dialkylamino)-1,3-dienes (equation 244)[453], *N*-[1,3-dienyl]carbamoyl chloride (equation 245)[454], sulphur

substituted 1,3-dienes[455,456] and 2-methoxy-3-phenylthio-1,3-butadiene (equation 247)[457-459] showed very high regioselectivity. When other substituents compete in the control of the orientation of the cycloaddition with a sulphur substituent, the latter dominates the control as shown by equations 247 and 248[457-460]. This can be attributed to the better ability of sulphur than oxygen to donate electrons (polarizability), in accord with the Woodward–Katz–Dewar model (Figure 7).



(244)



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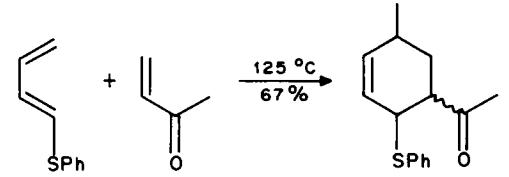
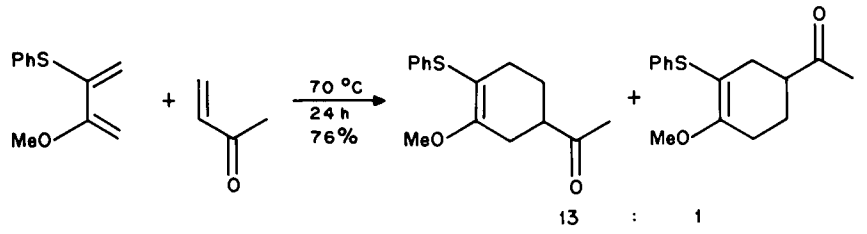
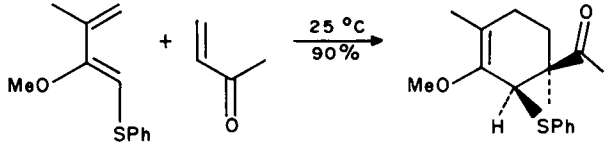


(246)



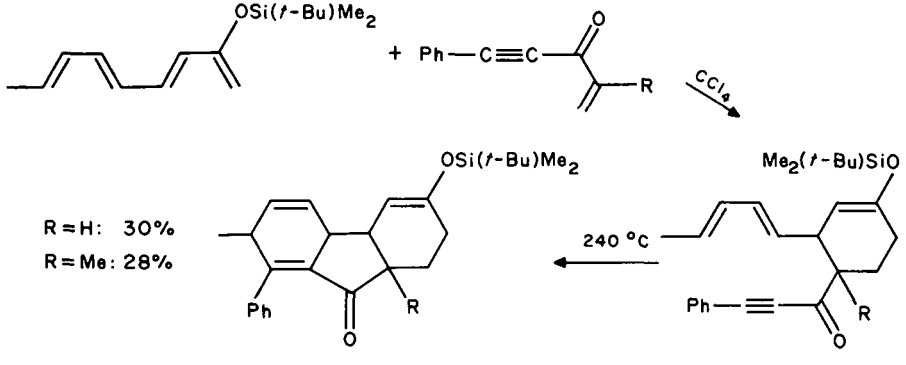
(247)



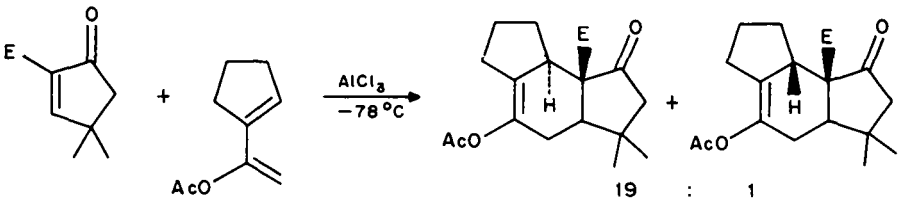
(248)

When alkyl and alkoxy substituents are both present on the diene, the latter controls, in general, the reactivity and regioselectivity of the Diels–Alder additions (see equations 239 and 240). This property (alkoxy is a better electron-releasing substituent than an alkyl

group) is further illustrated by the 'timed Diels–Alder additions' shown in equation 249[461], and by the cycloaddition of the cyclic reagents of equation 250[462].

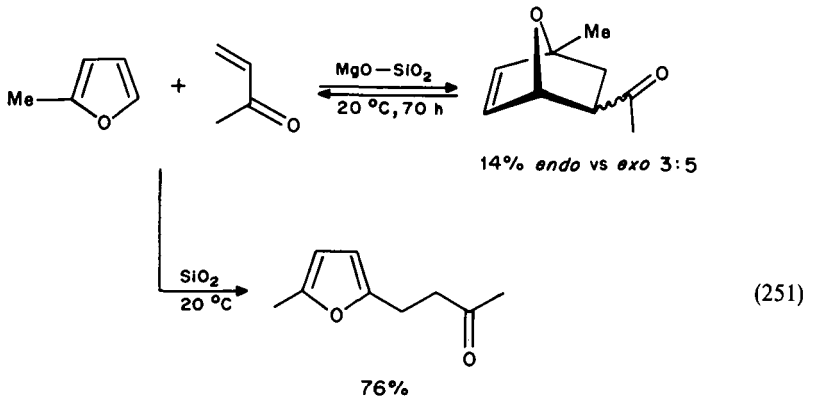


(249)



(250)

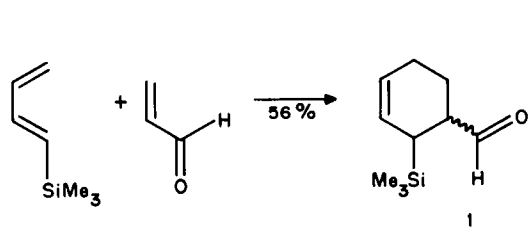
As already mentioned for the Lewis-acid catalyzed Diels–Alder additions of cycloenones (equations 230–232), the '*ortho* orientation rule' is not always followed. In the case of the silica-gel + MgO catalyzed cycloaddition of methyl vinyl ketone to 2-methylfuran (equation 251)[463], the major adduct formed corresponds to the '*meta*' adduct. This result can be explained by the fact that at 20 °C and in the presence of a catalyst, the 7-oxabicyclo[2.2.1]heptene adducts equilibrate with the cycloaddends



(251)

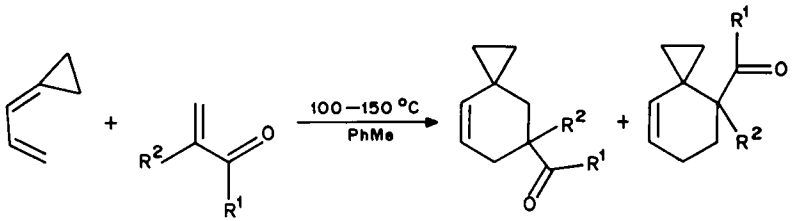
(aromaticity of furan). Under these conditions the most stable regioisomeric adduct is expected to be formed (the '*ortho*' adduct suffers from steric repulsions between the methyl and acyl substituents). In the absence of MgO, SiO_2 catalyzed the Michael addition of 2-methylfuran to methyl vinyl ketone more efficiently than the Diels–Alder addition[463].

Deviation from the '*ortho* orientation rule' was also observed in the case of the Diels–Alder addition of 1-trimethylsilylbutadiene to acrolein (equation 252)[464]. Although the trimethylsilyl group is a good electron-releasing substituent which, according to the FMO theory and the Woodward–Katz–Epiotis–Dewar model (Figure 7), should favour the '*ortho*' adducts, a 1:1 mixture of '*ortho*' and '*meta*' adducts was obtained. This result can be interpreted in terms of competitive steric effect (orienting '*meta*') and electronic effect (orienting '*ortho*') that intervene with the bulky trimethylsilyl group at C(1) of the diene.



(252)

Another apparent deviation from the '*ortho* orientation rule' is given by the cycloadditions of allylidenecyclopropane to various electron-poor alkenes, including α,β-unsaturated aldehydes and ketones (see e.g. equation 253)[465]. These results are in fact most simply interpreted with the diradicaloid model of the transition states of reactions 253. For the cycloadditions leading to the major '*meta*' adducts, transition states of type **532** can be invoked in which the high electron-releasing ability of the cyclopropyl substituent can intervene[466]. In the case of the reactions giving the minor '*ortho*' adducts, the diradicaloid **533** representing their transition states cannot make use of the stabilizing ability of the cyclopropyl group.

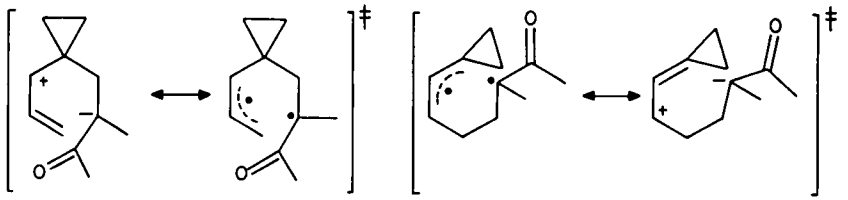


R^1=COMe, R^2=H	80%	<1%
R^1=CHO, R^2=H	51%	21%
R^1=CHO, R^2=Me	39%	?

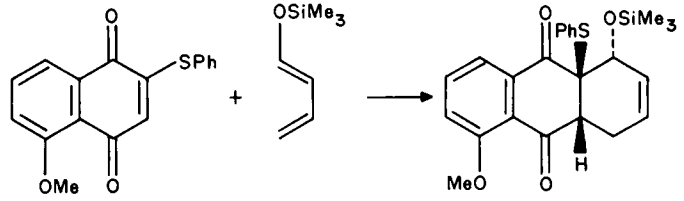
(253)

The diradicaloid model of the Diels–Alder transition state also rationalizes the regioselectivity observed for the cycloaddition of 2-phenylthiojuglone to 1-(trimethylsilyloxy)-butadiene (equation 254)[467]. In this case the sulphur substituent plays the role of the α-carbanion stabilizing group due to its inductive effect and its polarizability.

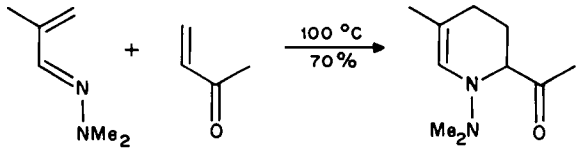
Heterodienes such as 2-aza-1,3-dienes (equation 255)[468] or α,β-unsaturated hydrazones (equation 256)[469] add to α,β-unsaturated aldehydes and ketones with high regioselectivity, in accord with the '*ortho* orientation rule'.



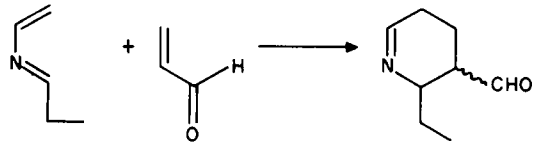
(532) (533)



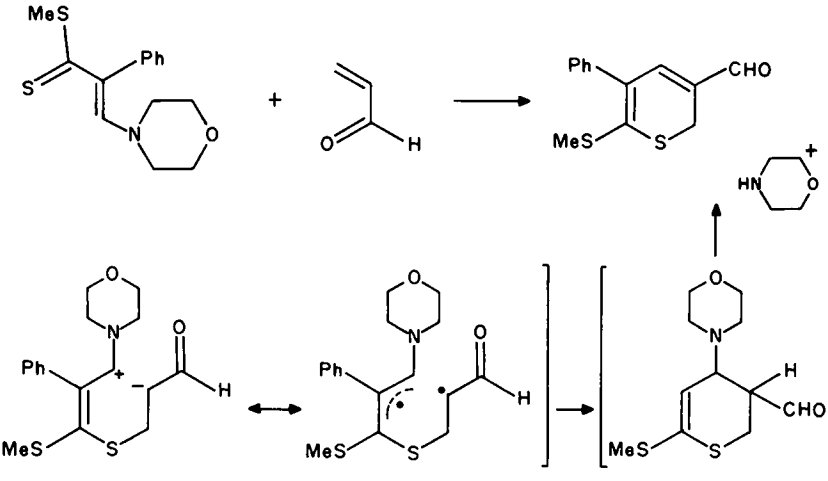
(254)



(255)



(256)

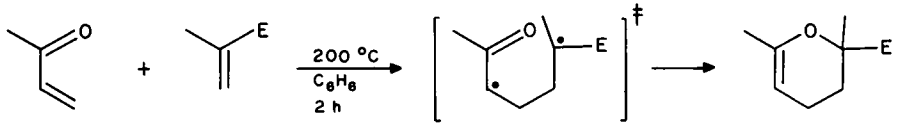


(534)

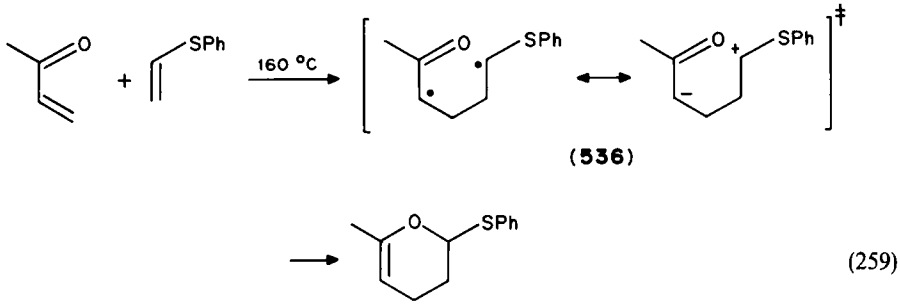
(257)

Thiopyrans are obtained by hetero-Diels–Alder addition of acrolein (dienophile) to vinyldithiocarbamate (e.g. equation 257)[470]. The high regioselectivity of that cycloaddition can be rationalized with the diradicaloid (**534**) model of the transition state.

When conjugated enones react as oxabutadiene with electron-poor (e.g. equation 258)[471] or electron-rich dienophiles (e.g. equation 259)[472], the same regioselectivity is observed for both types of reaction. FMO theory and the diradicaloid model can interpret the results. In the case of reaction 258, the acyl substituent cannot be invoked to stabilize a positively charged centre in the zwitterionic form of the diradicaloid. However, this substituent is expected to stabilize the diradical form, e.g. **535**. In the case of reaction 259 the transition state can be represented by the diradicaloid **536**, which is stabilized through its zwitterionic form by both the carbonyl and phenylthio moieties.



(**535**) (258)



(**536**)

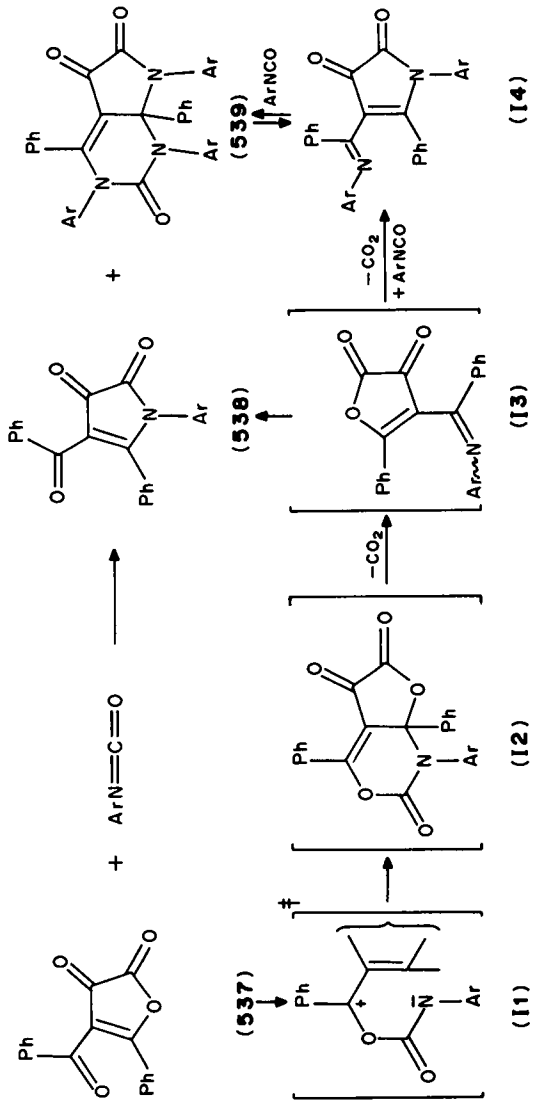
(259)

Unusual examples of hetero-Diels–Alder additions are given by the reactions of 4-benzoyl-5-phenylfuran-1,3-dione (**537**) with acyl isocyanates (equation 260)[473] and with diaryl or arylalkylcarbodiimides (equation 261)[474]. Reaction 260 yields the pyrrole-2,3-diones (**538**) and the pyrrolo[2,3-*d*]pyrimidines (**539**). It implies the formation of the adduct intermediate **I2** whose regioselectivity can be explained by the diradicaloid↔zwitterion model of transition state **I1**.

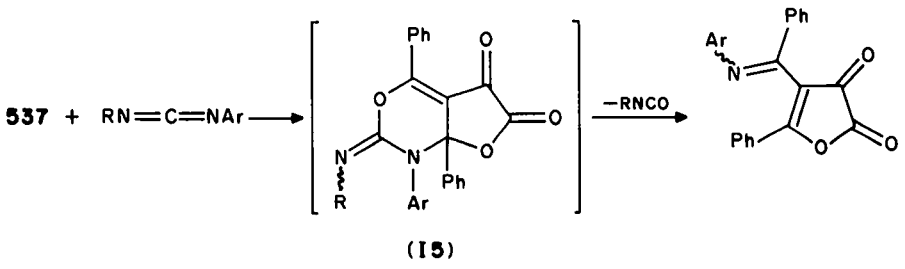
The unstable adduct **I2** eliminates CO_2 and rearranges into **I3**, which can cyclize into **538** or exchange a CO_2 moiety with a ArNCO moiety to yield **I4**, which equilibrates with ArNCO to afford **539**. Reaction 261 is analogous to reaction **537** → **I3**, the isocyanate being replaced by the carbodiimide dienophile. It takes place probably through the adduct intermediate **I5** that eliminates an equivalent of isocyanate RNCO to afford the observed 4[(α-arylimino)benzyl]furan-2,3-diones (equation 261).

1. Lewis acid catalysts

As we have already seen (equations 216, 222–224, 230–232, 235, 236, 250, 251) many Diels–Alder additions necessitate the presence of a Lewis acid. It has been known since 1942 that protic acids can influence the rate of the cycloadditions[475]. In 1960, Yates and Eaton[476] reported on the remarkable acceleration of the Diels–Alder additions of dienophiles, such as maleic anhydride, *p*-benzoquinone and dimethyl fumarate, to

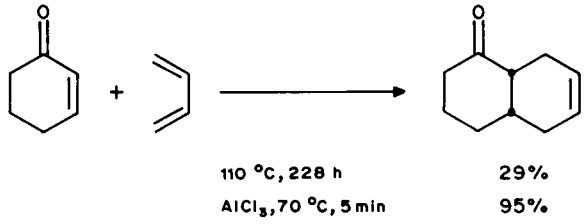


(260)



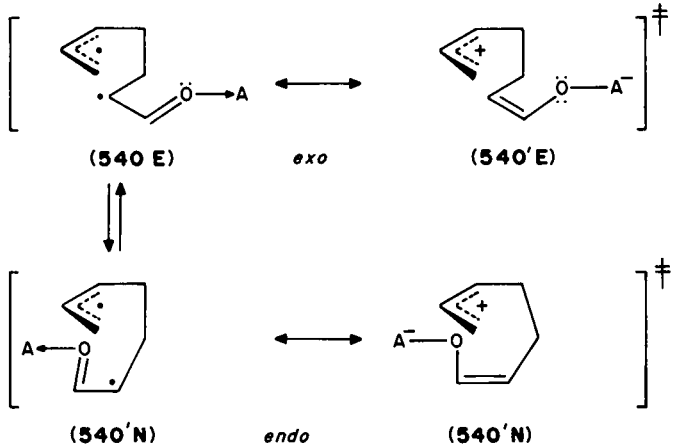
(261)

anthracene in the presence of $AlCl_3$. This important discovery then made possible the use of conjugated cycloalkenones[477] that are much less reactive than acyclic α,β-unsaturated aldehydes and ketones[478] in Diels–Alder additions. For instance, while cyclohex-2-en-1-one reacts with butadiene (equation 262) only sluggishly at 110 °C, the cycloaddition is complete after 5 min at 70 °C in the presence of $AlCl_3$[423].



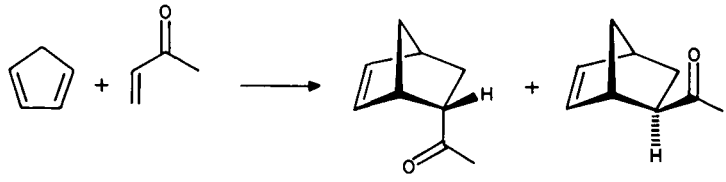
(262)

The accelerating effect of protic and Lewis acids on the Diels–Alder reactions involving enones is readily explained by coordination of the carbonyl group of the dienophile to the acid, giving a species with a lower LUMO energy or a higher electron affinity (see Figure 7). In other words, coordination by the acid strongly stabilizes the zwitterionic form of the diradicaloid model (e.g. **540**) of the transition state.



Lewis acids such as $ZnCl_2$[479], $ZnBr_2$[480], ZnI_2[481], $AlCl_3$[482], $B(OAc)_3$[484], $BF_3 \cdot OEt_2$[483], $SnCl_4$[484], $EtAlCl_2$[485] and Et_2AlCl[486], $TiCl_4$[487] and $Yb(fod)_3$[488] have been found to

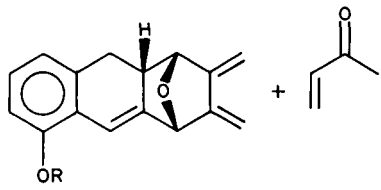
enhance the rate of the Diels–Alder additions of conjugated enones to 1,3-dienes. Clay doped with $FeCl_3$[489] (K-10-Fe^{3+}) or with $AlCl_3$[490], zeolite containing CuI_2[491], silica gel[463,492], $Et_3O^+BF_4^-$[484e] and $(Me_3P)W(NO)(CO)_3^+SbF_6^-$[493] are very good catalysts for these reactions. In general, the steroselectivity[494] ('*endo*' vs '*exo*'; see equations 224 and 263)[489] and regioselectivity[449,458,495] (see equation 264)[442] of the cycloadditions are improved in the presence of Lewis acid. The better '*endo*' selectivity can be interpreted in terms of the diradicaloid transition state **540N** which enables a better electrostatic stabilizing interaction in its zwitterionic form **540'N** than for diradicaloid **540E↔540'E** representing the transition state of the '*exo*' mode of addition.



(263)

20 °C, EtOH 8.5 : 1

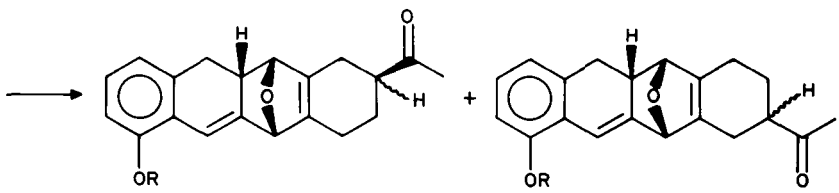
20 °C, EtOH + K-10-Fe^{3+} 14 : 1



toluene, 90 °C

$BF_3 \cdot Et_2O/CH_2Cl_2$, −85 °C

R = α-naphthoyl



β(61%), α(7%)

β(86%), α(<2%)

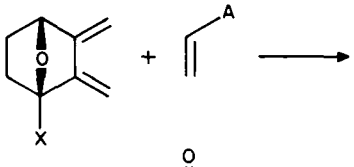
β(19%), α(13%)

β(14%), α(<1%)

(264)

Under thermal conditions (80–100 °C, without solvent or in PhH), the Diels–Alder addition of 1-(dimethoxymethyl)-2,3-dimethylidene-7-oxabicyclo[2.2.1]heptane to methyl vinyl ketone was not regioselective. However, when the dienophile was precomplexed first with $BF_3 \cdot Et_2O$ or $EtAlCl_2$ in CH_2Cl_2, the cycloaddition was highly regio- and stereoselective (equation 265 below)[495b]. Most interestingly, for the $EtAlCl_2$-catalyzed

cycloaddition the regioselectivity could be reversed by a small solvent modification, as shown below. The results were interpreted in terms of co-coordination $EtAlCl_2$ with the acetal group of the diene and the carbonyl group of the enone which favours the '*meta*-β' adduct. This is possible in an uncoordinating solvent such as hexane. In the presence of a coordinating solvent such as CH_2Cl_2, the latter competes with the acetal-diene for the coordination to $EtAlCl_2$–dienophile complex, and consequently '*para*' attack is preferred for steric reasons.



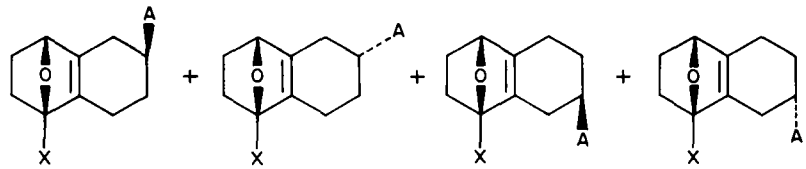
X=CH(OMe)$_2$, A=$\overset{O}{\overset{\|}{C}}CH_3$

PhH, 100 °C

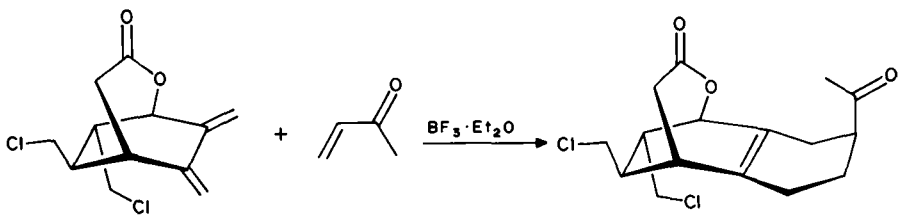
$BF_3 \cdot Et_2O$ in CH_2Cl_2, −85 °C

$EtAlCl_2$ in 5:1 CH_2Cl_2/hexane, −90 °C

$EtAlCl_2$ in 1.5:1 CH_2Cl_2/hexane, −90 °C



'para-β'		*'para*-α'		*'para*-β'		*'para*-α'
2.3	:	1	:	2.3	:	1 (90%)
13.5	:	1	:	2.5	:	1.2 (94%)
28.5	:	1	:	3	:	2 (95%)
10	:	1	:	24	:	1 (68%)



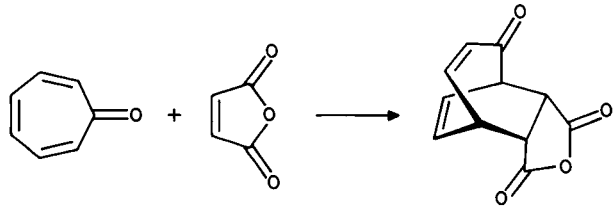
(541)

Another interesting remote substituent effect on the Lewis-acid catalyzed Diels–Alder addition of methyl vinyl ketone to an exocyclic diene system is shown above. While the

thermal addition of **541** to methyl vinyl ketone was not regioselective, only one adduct was obtained in the presence of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at $-78\,°C$[495c].

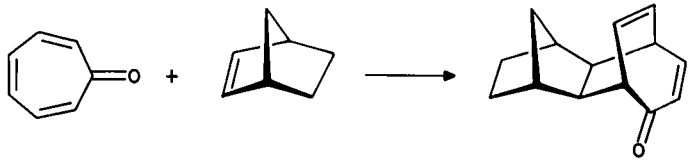
2. Effect of high pressure

Enhanced reactivity of the Diels–Alder additions has been observed under microwave thermolysis[496] and under high pressure[418,497]. This is due to the fact that most Diels–Alder reactions have negative volumes of activation, $\Delta V^{\ddagger}$[498], as illustrated in equations 265 and 266[499].



(265)

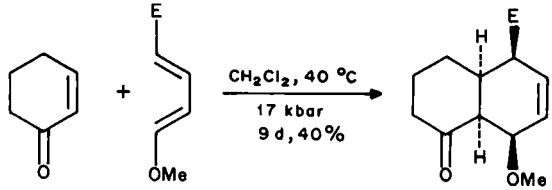
$\Delta V^{\ddagger}(i\text{-PrC}_6H_5) = -21.4\,cm^3\,mol^{-1}$
$\Delta V^{\ddagger}(DMF) = -16.8\,cm^3\,mol^{-1}$



(266)

$\Delta V^{\ddagger}(i\text{-PrC}_6H_5) = -30.0\,cm^3\,mol^{-1}$
$\Delta V^{\ddagger}(DMF) = -27.8\,cm^3\,mol^{-1}$

Quite often, application of high pressure improves the regio- and stereoselectivity of the cycloadditions as shown in reactions 267[500] and 268[501].



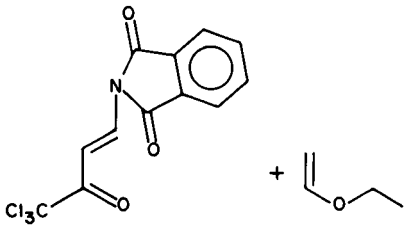
(267)

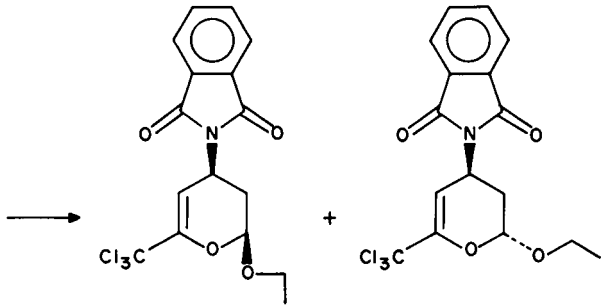
E=COOR

A synthesis of (+)-Jatropholones A and B based on the high-pressure-induced Diels–Alder addition of a furan and a cycloalkenone has been proposed by Smith and coworkers (equation 269)[502].

3. Effect of structural strain of the enones

With butadiene, cyclopropenone gives only a polymeric material. In the presence of methanol, however, a quantitative yield of the hemiacetal of the expected Diels–Alder

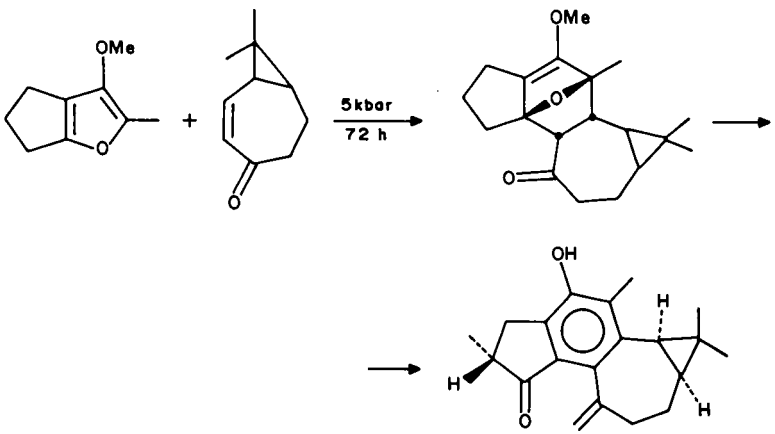




(268)

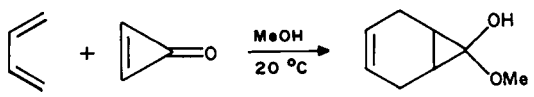
1 bar, 90 °C 1.6 : 1; $-\Delta\Delta V^{\ddagger} = 5.8 \pm 0.5\ cm^3\ mol^{-1}$

6 kbar, 0.5 °C 13.6 : 1

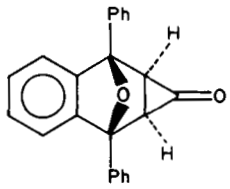


(269)

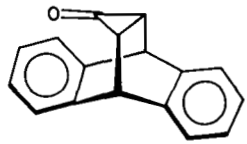
adduct is obtained (equation 270)[503]. Cyclopropenone reacts also with 2,5-diphenylisobenzofuran and 9,10-dimethylanthracene at 20 °C to give the cyclopropanone derivatives **542** and **543**, respectively[504].



(270)

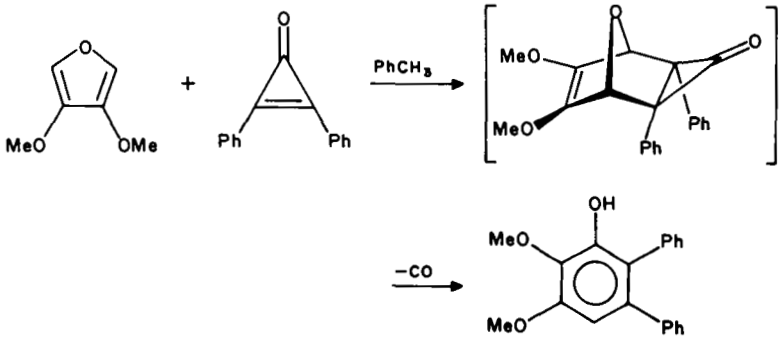


(542)



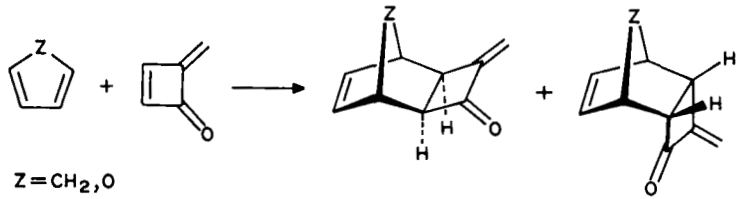
(543)

Diphenylcyclopropenone is unreactive with furan[505]. However, with 3,4-dimethoxyfuran, a more electron-rich diene than furan itself, diphenylcyclopropenone gives the expected [4 + 2] adduct which eliminates quickly a mole of CO to afford finally a substituted phenol derivative (equation 271)[506].



(271)

The ease of the Diels–Alder addition of cyclopropenone and its derivatives can be attributed to the strain of these dienophiles. Methylenecyclobutenone is also a highly reactive dienophile for the same reason; it adds readily at 20 °C to cyclopentadiene and furan (equation 272)[425].

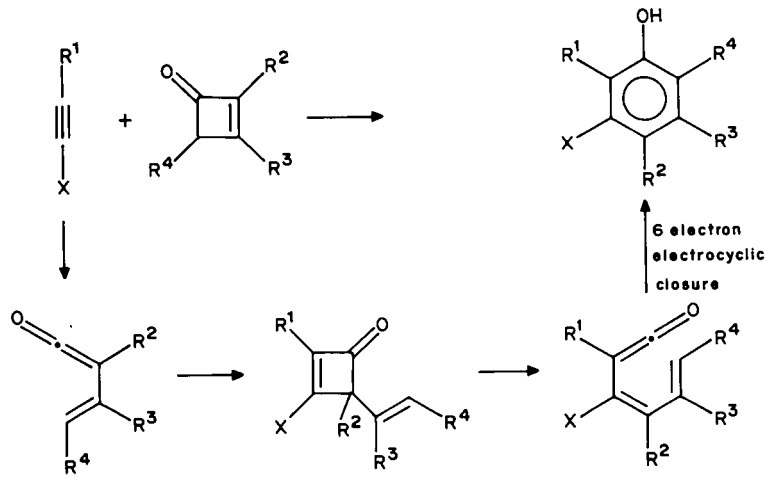


(272)

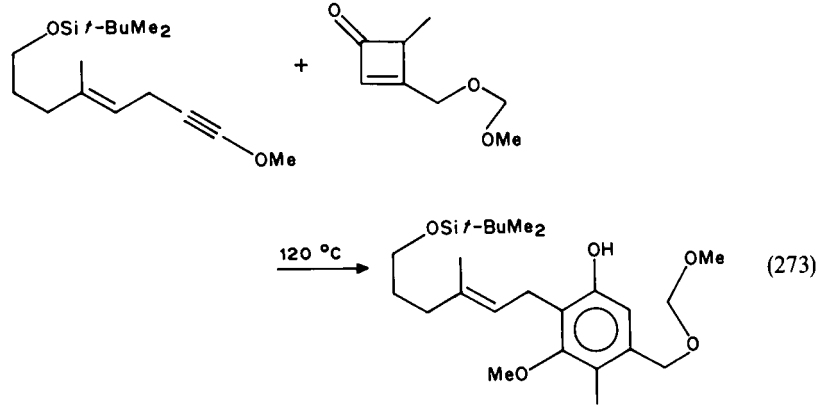
Thermolysis of cyclobutenone derivatives in the presence of alkynyl ethers allows the construction of pentasubstituted resorcinol derivatives via a cascade of four pericyclic reactions (Scheme 20)[507]. This annelation strategy has been applied to an efficient total synthesis of the antitumor antibiotic mycophenolic acid (equation 273)[508].

As a result of their strain, bridgehead enones are extremely unstable. Their alkene moieties are twisted from planarity and this enhances the inherent dienophilicity of the enone moieties[509].

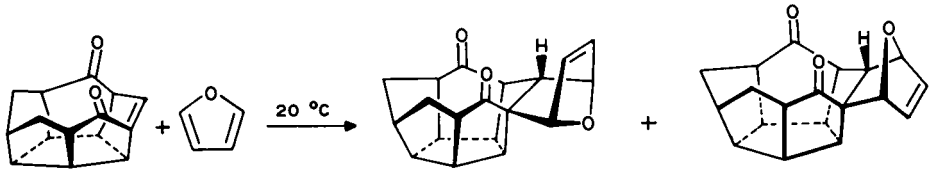
Peristylenones, norperistylenones (equation 274)[510], bicyclo[3.3.1]non-1-en-3-one (equation 275)[511] are known to be exceptionally reactive compounds, forming Diels–Alder adducts with furan at room temperature.



SCHEME 20

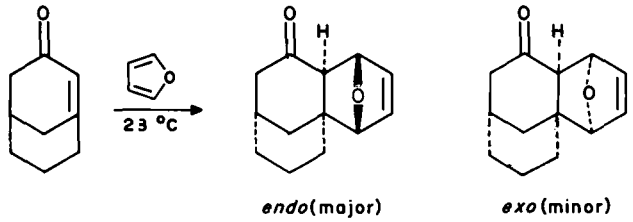


(273)



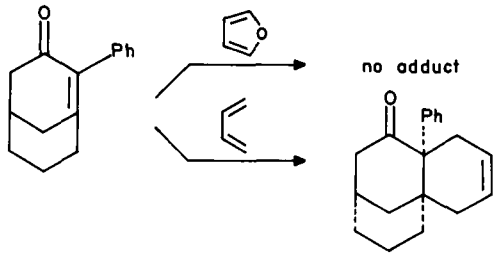
(274)

On the other hand, 2-phenylbicyclo[3.3.1]non-1-en-3-one[509] and strained α,β-unsaturated ketones failed to react with furan, indicating that these enones are

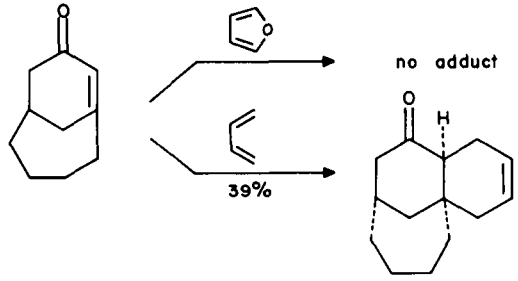


(275)

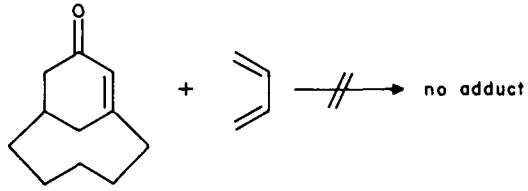
significantly less reactive than bicyclo[3.3.1]non-1-en-3-one. Nevertheless, the 2-phenylbicyclo[3.3.1]nonenone (equation 276) and the bicyclo[4.3.1]dec-6-en-8-one (equation 277) are converted to the corresponding Diels–Alder adducts in the presence of butadiene. The next higher homologue, bicyclo[5.3.1]undec-7-en-8-one, failed to react with butadiene (equation 278)[512].



(276)



(277)

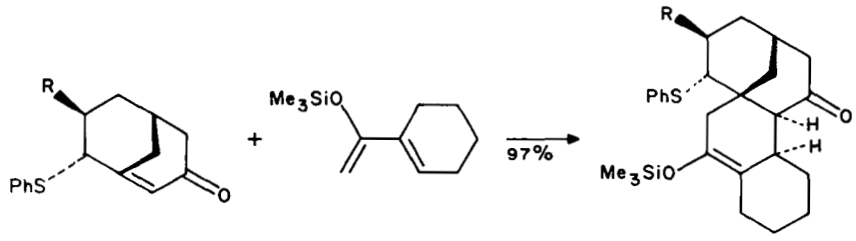


(278)

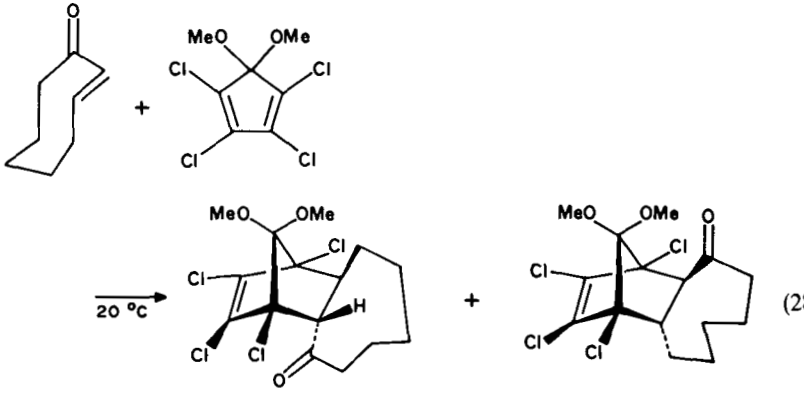
In the particular case of a bridgehead enone reacting with a diene bearing electron-donating groups, high yield of cycloadduct was obtained, with high *exo* stereoselectivity (e.g. equation 279). The latter has been interpreted in terms of a stepwise mechanism involving ionic intermediates[513].

The highly strained (*E*)-cyclooct-2-en-1-one is locked into a rigid conformation, in

which the π-orbital planes of the carbonyl and ethylenic groups are orthogonal. This compound reacts vigorously at room temperature with 1,3-dienes (equation 280)[514].



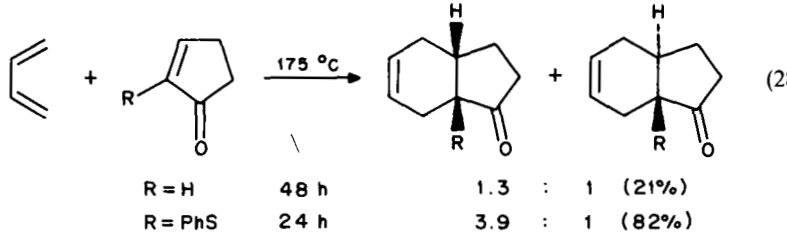
(279)



(280)

4. Substituent effects on the enone dienophilicity

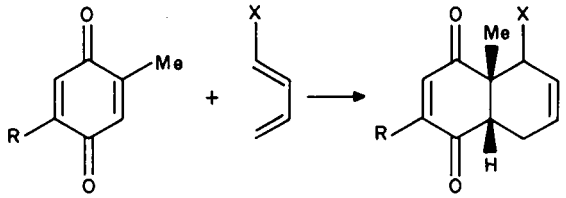
The introduction of an amide[515], formyl[516], alkoxycarbonyl[517], phenylthio[518] or phenylseleno[519] substituent at the C(α) centre of α,β-unsaturated aldehydes and ketones enhances their Diels–Alder reactivity toward electron-rich dienes. For instance, while butadiene adds to cyclopent-2-en-1-one only sluggishly at 175 °C (equation 281), its reaction with 2-phenylthiocyclopent-2-en-1-one gives 82% yield of the expected adducts.



(281)

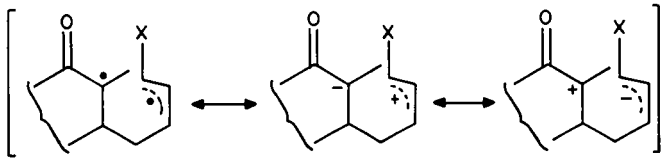
Bohlmann and coworkers[520] reported that several Diels–Alder additions of substituted benzoquinones (equation 282) show regioselectivities that are not those predicted by the shape of the frontier orbitals (FMO) of dienes and dienophiles. The high '*ortho*'

regioselectivity observed suggested that the methyl group behaves like an electron-withdrawing substituent rather than an electron-releasing group. The apparently anomalous substituent effect ('shizophrenic' substituents[521]) is easily interpreted by the diradicaloid model for transition state **544**↔**544'** which implies the stabilizing effect of the methyl substituent on radicals. The methyl substituent can also stabilize the charge-transfer configurations (zwitterionic forms) **544'** and **544"** because of its polarizability[522].



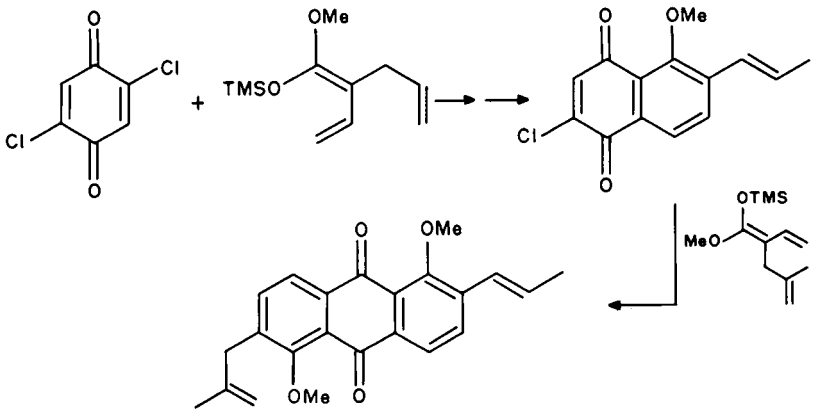
(282)

R = Me, MeO; X = Me, CH_2OAc, COOMe



(544) **(544')** **(544")**

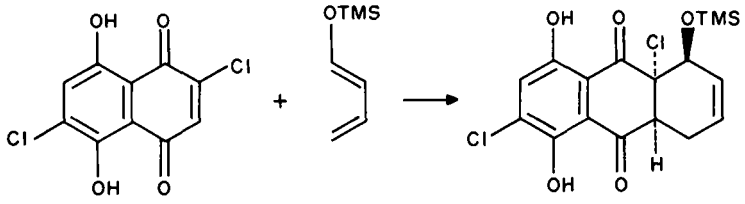
A similar '*ortho* orienting effect' has been observed for the chloro substituent in the Diels–Alder addition of dichloroquinones (equation 283)[523] and dichloronaphthoquinones (equation 284)[524].



(283)

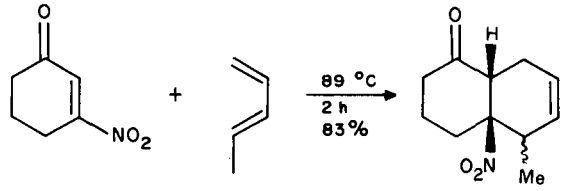
Substitution at the C(β) centre by electron-withdrawing groups[525] such as carbonyl[526], ester[527], benzenesulphonyl[528] or nitro[529] functions is also a possibility for enhancing the dienophilicity of α,β-unsaturated aldehydes and ketones. In the case of a β-nitro conjugated enone, is Diels–Alder regioselectivity is controlled by the NO_2 group rather

than by the carbonyl moiety (equation 285). In the example shown in equation 286, the *ortho* orienting effect of the ester and phenylthio substituents of the enone overwhelms that of the carbonyl group.

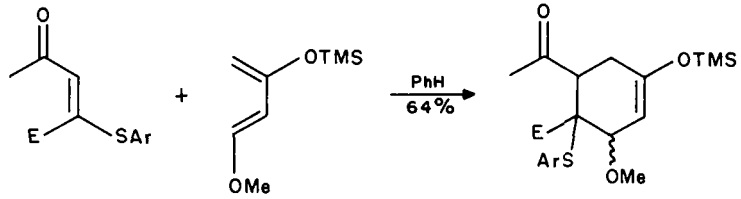


(284)

TMS = Me_3Si



(285)



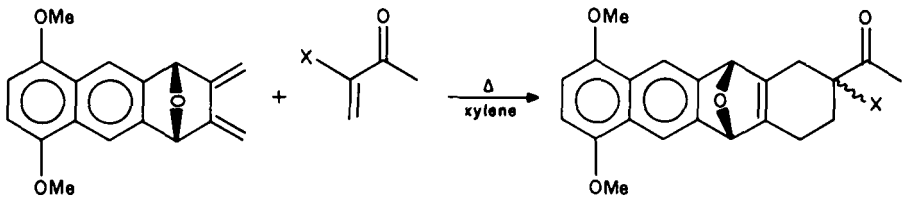
(286)

E = COOEt, Ar = 4Cl−C_6H_4, TMS = $SiMe_3$

But-3-en-2-one derivatives substituted at C(3) with oxy groups are less reactive than methyl vinyl ketone itself toward 1,3-dienes[530–532]. However, the Diels–Alder reactivity of α-oxy-substituted α,β-unsaturated ketones could be enhanced by protecting the enol function with electron-withdrawing groups such as acetyl[414,533] or arenecarbonyl[414], as illustrated by the reactions of equation 287. Kinetic measurements on the cycloadditions of cyclopentadiene to 1-acetylvinyl arenecarboxylates showed that the 2,4-dinitrobenzoate derivative is as reactive as methyl vinyl ketone under thermal conditions[414].

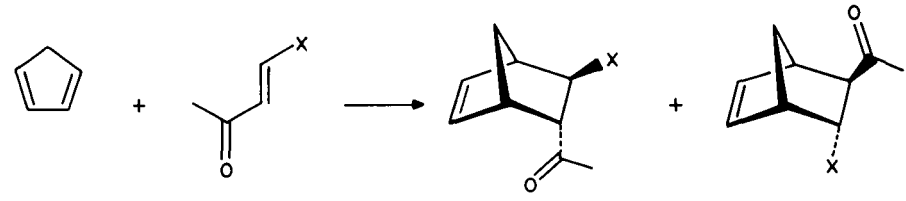
4-Methoxybut-3-en-2-one does not add to cyclopentadiene. However, 4-acetyloxybut-3-en-2-one does react and gives a 2.6:1 mixture of the *endo* and *exo* cycloadducts (equation 288)[534]. This result confirms the better electron-withdrawing ability of the acetyloxy group compared with that of the methoxy substituent.

Remote substituents can affect the dienophilicity of an enone and eventually control the regioselectivity of its Diels–Alder additions. This fact is illustrated below by examples of cycloadditions of substituted naphthoquinones. The reaction of 5-acetoxynaphthoquinone to 1-acetoxybutadiene (equation 289) yields a 1:3 mixture of the corresponding '*ortho*' and '*para*' cycloadducts. This regioselectivity was explained in terms of the electron-



$X = Me_3SiO$	160 °C; 12 h; 30% yield	α/β	(50:50)
$X = EtO$	160 °C; 5 h; 21%		(50:50)
$X = CH_3COO$	160 °C; 4 h; 68%		(65:35)
$X = PhCOO$	160 °C; 3 h; 70%		(60:40)
$X = 4\text{-}NO_2C_6H_4COO$	140 °C; 5 h; 50%		(40:60)
$X = 2,4\text{-}(NO_2)_2C_6H_3COO$	140 °C; 3 h; 66%		(40:60)

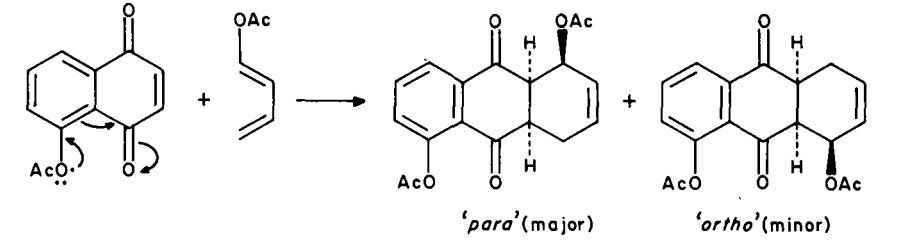
(287)



X = OMe
X = OAc

yield 0%
58%

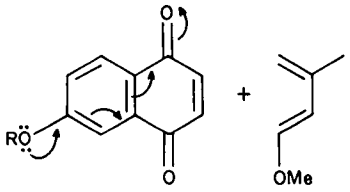
(288)

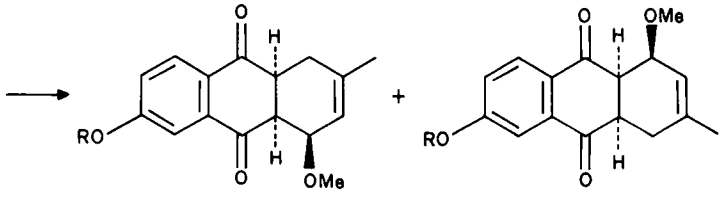


'*para*' (major) '*ortho*' (minor)

(289)

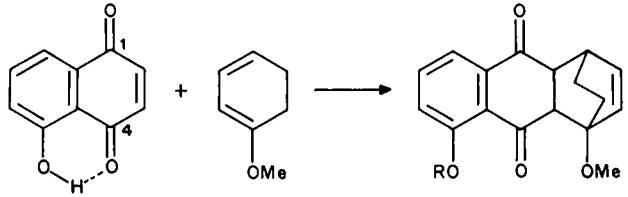
donating effect of the oxy function at C(5) which makes the carbonyl group at C(4) less electron-attracting than the CO group at C(1)[535]. This interpretation could also be applied to explain the regioselectivities observed for the Diels–Alder additions (equation 290) of 6-oxy substituted naphthoquinones[536]. Interestingly, juglone (**545**: 5-hydroxybenzoquinone) added to 1-methoxycyclohexa-1,3-diene to give a quantitative yield of the '*ortho*' adduct **546**[537]. This result was interpreted in terms of chelation of the carbonyl group at C(4) by the peri hydroxy group, which makes this function more electron-poor (internal acid catalysis) than the carbonyl group at C(1). The same interpretation can be retained to explain the high regioselectivity of the cycloaddition of borate (**547**) derived from juglone and an optically pure binaphthol derivative. The adduct was transformed into the methoxy derivative **548** with an enantiomeric excess better than 98%[538].



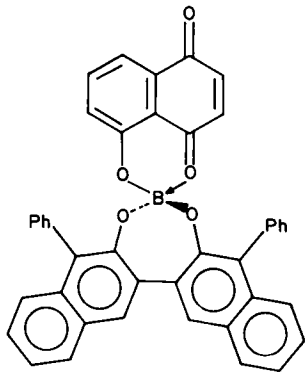


R = H	75	:	25
R = Me	75	:	25
R = Ac	60	:	40

(290)



(545) (546) R=H (548) R=Me



(547)

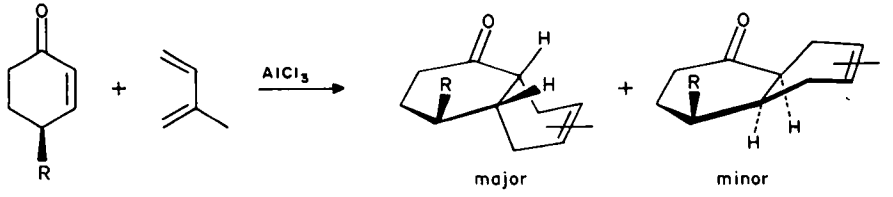
The simple interpretations given above for the regioselectivity of the Diels–Alder addition of juglone and its derivatives cannot be retained in all cases, as it was shown that

the selectivity depends strongly on the nature of the diene and of the reaction conditions[539-541].

5. *Facial selectivity*

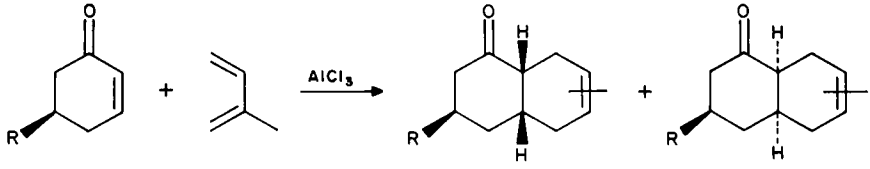
The diastereofacial selectivity of Diels–Alder reactions has been the subject of two recent reviews[542]. Rules have been proposed to account for the observed diastereoselectivity, but they are all of limited use[543-545]. The spacial orientation of the diene and of the dienophile toward each other determines the stereochemistry of the product of Diels–Alder reactions. For a diene adding to a dienophile whose π plane is not a symmetry plane, because of the substitution, apart from the *endo* and *exo* mode of additions, the diene can attack the dienophile on one or other face of the π system leading to *syn* vs *anti* selectivity. Examples of Diels–Alder reactions of asymmetric conjugated enones are given below.

The addition of 4-alkylcyclohex-2-en-1-ones (equation 291)[422,546] and of 5-alkylcyclohex-2-en-1-ones (equation 292)[547] to isoprene are *anti* selective, most probably for steric reasons. This hypothesis is confirmed by the observation of the highest facial selectivities for the reactions involving the *t*-Bu substituted enones. It contrast, the cycloadditions of 6-methylcyclohex-2-en-1-one to isoprene and to (*E*)-piperylene were found to prefer the *syn* face of the dienophile (see e.g. equation 293)[548].



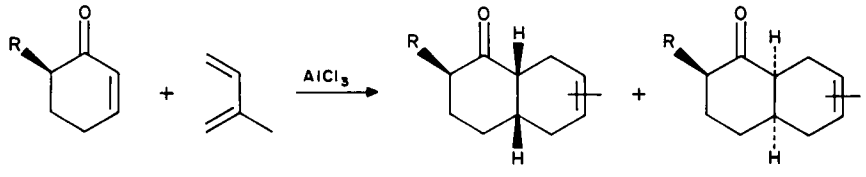
	major	:	minor
R=Me	90	:	10
R=*i*-Pr	91	:	9
R=*t*-Bu	100	:	0

(291)



		:	
R=Me	97	:	3
R=*i*-Pr	92	:	8
R=*t*-Bu	91	:	9

(292)

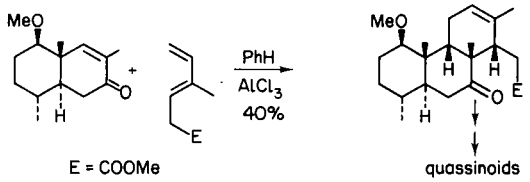


minor	:	major
35	:	65

(293)

This can be explained on the basis of the following considerations: (1) the reaction rate depends on the reactivity of both the cyclohexenone conformers present and on their concentration[422]; (2) in the absence of strong steric hindrance, the diene–dienophile interaction prefers an axial approach of the diene antiparallel to the pseudo-axial substituent at the cyclohexenone at C(6), creating a *cis*-fused cyclohexanone with a chair conformation in the transition state.

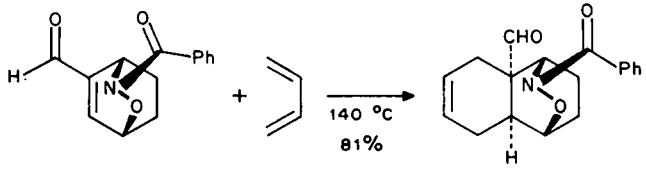
The *syn* vs *anti* facial selectivity has been used in the synthesis of cadinenes[549], quassinoids (equation 294)[550], morphine-related compounds[551] and (±)-luciduline[552].



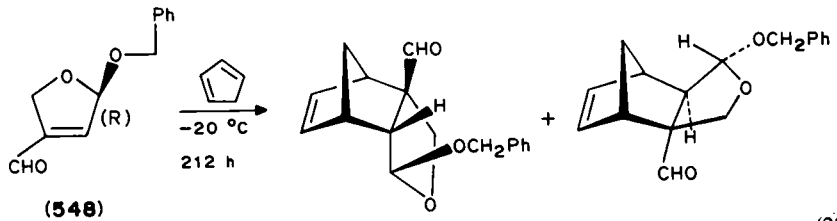
(294)

When the α or β position of a conjugated enone is substituted by a chiral group containing heteroatom, the approach of the diene can be *anti* or *syn* with respect to the heteroatom (Figure 8).

The reaction of *N*-benzoyl-3-aza-2-oxabicyclo[2.2.2]oct-5-en-6-one with a diene proceeds stereoselectively *syn* with respect to the N—O bridge (equation 295)[553]. In contrast, the Diels–Alder addition of cyclopentadiene to **548** (chiral γ-centre) was *anti* selective (equation 296) with respect to the alkoxy group of the enone[554,555]. The benzyloxy group causes the attack of cyclopentadiene to occur preferentially from the least hindered face of the dienophile.



(295)



(296)

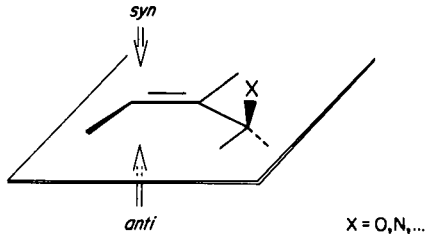
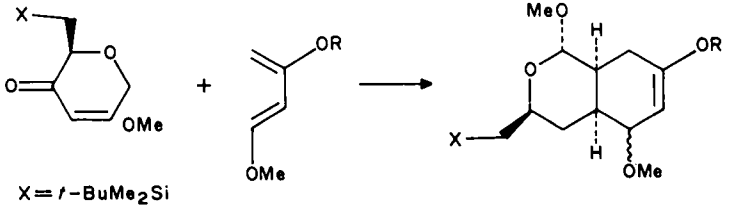


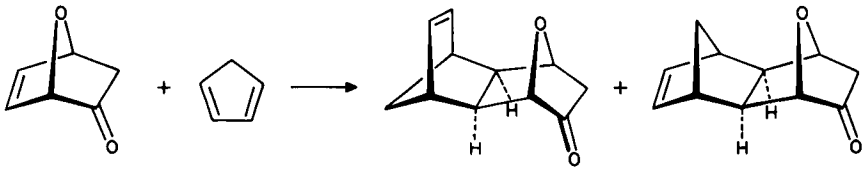
FIGURE 8

In the same way, enones derived from carbohydrates add to dienes with β-face selectivity, i.e. *anti* facial selectivity with respect to the alkoxy group at the γ-position[515,556] (see e.g. equation 297).



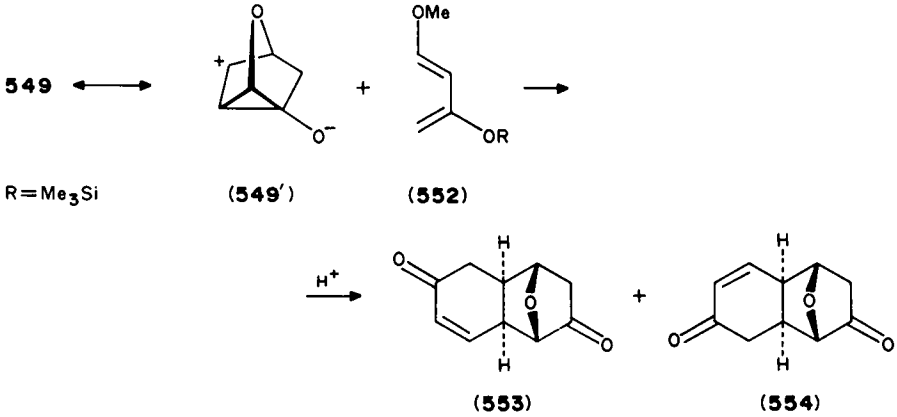
(297)

The homoconjugated ketone **549** adds to cyclopentadiene to give a 9:1 mixture of adducts **550** and **551** resulting from the *exo* face attack of the C(5)=C(6) double bond of 7-oxabicyclo[2.2.1]hept-5-en-2-one. In this case, the facial selectivity is *syn* with respect to the heteroatom, probably because the *endo* face of the bicyclic enone is more sterically hindered.



(549) **(550)** **(551)**

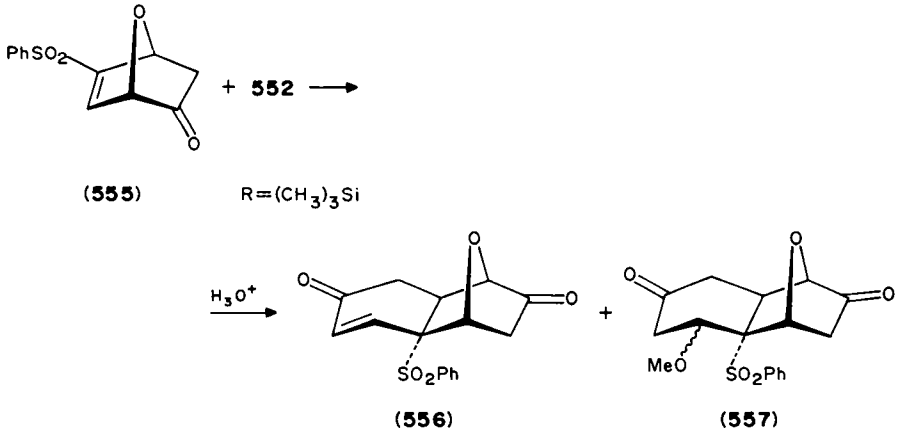
The Diels–Alder addition of the Danishefsky diene **552** to **549** (80–120 °C) was a sluggish reaction giving a mixture of adducts, from which a 3:1 mixture of enediones **553** and **554** was isolated after acidic work-up. In this reaction, the carbonyl group acts, as expected, as a homoconjugated electron-withdrawing group, as illustrated by the limiting structure **549'**.



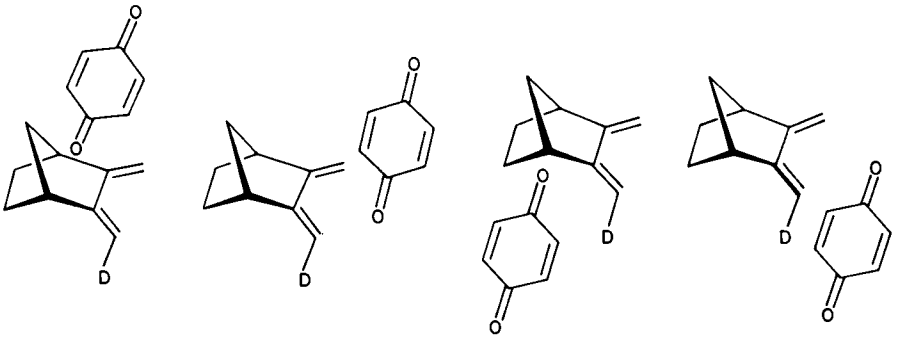
(553) **(554)**

The Diels–Alder regioselectivity of **549** was dramatically improved on substituting C(5) of this enone by a benzenesulphonyl groups as in **555**. The latter added to non-symmetrical dienes such as **552** with high facial selectivity, because of the bicyclic structure of the

dienophile, and with high regioselectivity because of the $PhSO_2$ substituent, giving products **556** (10%) and **557** (90%), after acidic work-up[557].

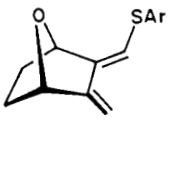


Good facial selectivities have also been observed for the Diels–Alder additions of various dienophiles to 1, 3-diene moieties grafted onto bicyclo[2.2.1]heptane skeletons[558]. For instance, the thermal cycloadditions of *p*-benzoquinone to 2-(D)-methylidene-3-methylidenebicyclo[2.2.1]heptane was found to prefer the *endo* face of the bicyclic diene and the *anti*-Alder rule orientation as shown in Scheme 21. The preferred *endo* face attack has been attributed to a stereoelectronic factor[559], the same factor being responsible for the non-planarity of the bicyclo[2.2.1]hept-2-ene double bond[560]. The Diels–Alder additions of the S-substituted dienes **558** and **559**, and the tetraene **560**, to electron-poor dienophiles are highly '*ortho*' regioselective. Their face selectivity depends on the nature of the dienophile. It is *exo* face selective with bulky dienophiles such as TCNE and 2-nitro-1-butene, and *endo* face selective with methyl vinyl ketone, methyl acrylate and but-3-yn-2-one. In the presence of Lewis acids, the facial selectivity can be reversed[561].

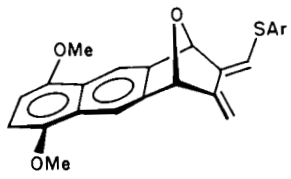


exo-face	*exo*-face	*endo*-face	*endo*-face
Alder Rule	*anti* Alder	Alder Rule	*anti* Alder
5 ± 1%	6 ± 1%	6 ± 1%	83 ± 4%

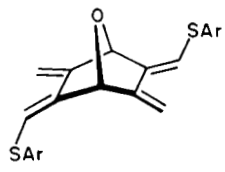
SCHEME 21



(558)



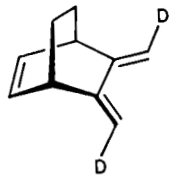
(559)



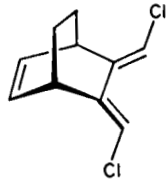
(560)

Ar = 2-$(NO_2)C_6H_4$; C_6H_5

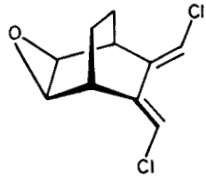
The Diels–Alder additions of strong dienophiles to dienes **561–563** prefer, in general, the face *syn* to the endocyclic double bond or of the epoxide of the bicyclo[2.2.2]octane system[562], perhaps owing to steric reasons or polarizability of the homoconjugated functions.



(561)

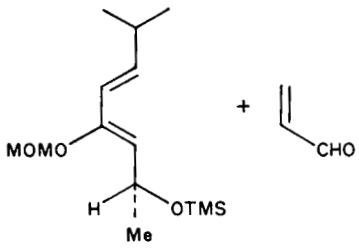


(562)

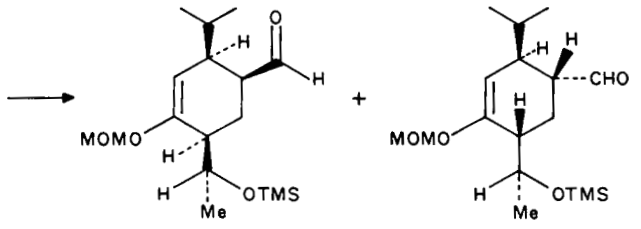


(563)

Acyclic dienes with a stereogenic allylic carbon show a face selectivity in the Diels–Alder reaction with α,β-unsaturated aldehydes and ketones. The enone is adding *syn* to the directing oxy group of the diene (see e.g. equation 298)[563]. Stereoelectronic factors as well as steric repulsive effects may play a role in making these reactions face-selective.



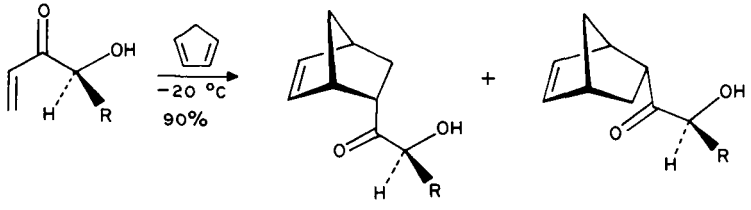
MOM = $MeOCH_2$



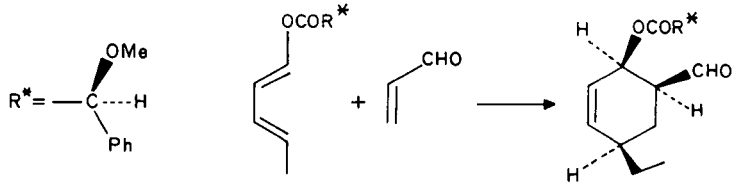
(298)

93 7

High diastereofacial selectivity is observed with chiral ketol such as **564**, which adds to cyclopentadiene to give a 100:1 mixture of the *endo* adducts **565** and **566**. No *exo* adduct is detected. The high selectivity observed is attributed to the strong hydrogen bonding between the hydroxyl and ketone functions in **564**. This reduces the flexibility of the dienophile and renders one of its faces more accessible than the other. Attachment of a chiral auxiliary at the diene can also lead to facial selectivity as illustrated by equation 299[565].

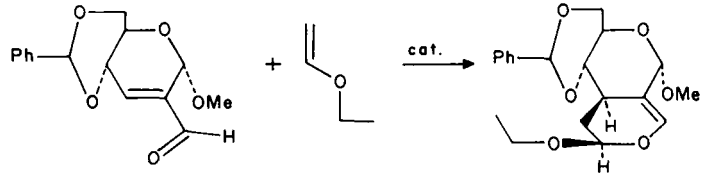


(564) **(565)** **(566)**

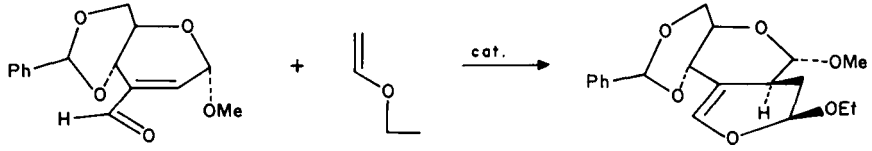


(299)

Chiral oxadienes **567** and **569**, derived from D-glucose, add to ethyl vinyl ether with high setereoselectivity, in the presence of $Eu(fod)_3$ (fod = 1, 1, 1, 2, 2, 3, 3-heptafluoro-7, 7-dimethyloctane-4, 6-dionato) as catalyst, giving adducts **568** and **570**, respectively[566a] (for an example of facial-selective hetero-Diels–Alder addition of a chiral oxy-substituted olefin to oxabutadienes, see Reference 566b).

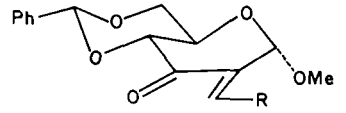


(567) **(568)**



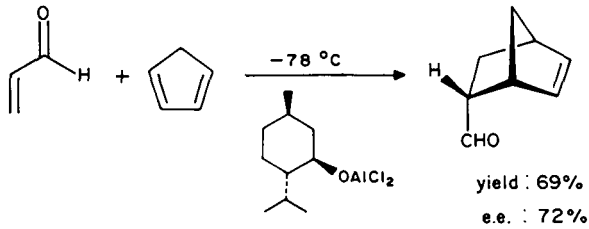
(569) **(570)**

Hetero-Diels–Alder additions of the α,β-unsaturated ketones **571** derived from carbohydrates with enol ethers were also studied and shown to be completely stereospecific[567].



(571) R=Me, Et

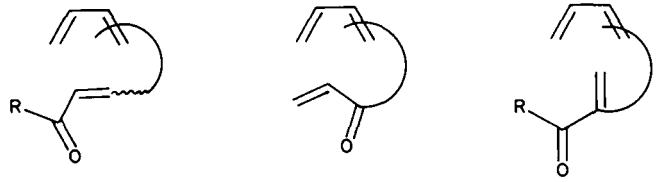
Finally, asymmetric induction in the Diels–Alder addition of conjugated enals and enones is possible by using optically pure, chiral Lewis-acid catalysts. An example is shown in equation 300[568].



(300)

C. Examples of Intramolecular [4 + 2] Cycloadditions

Intramolecular Diels–Alder Additions (IMDA) are important, so several reviews on the topic have appeared[569–572]. The most attractive feature in IMDA stems from its potential for regio- and stereospecific construction of complex polycyclic systems. The IMDA of enones with dienes is a valuable and often employed strategy in building natural product skeletons. There are several types of trienones according to the way the diene and enone moieties are joined together, as shown below (see also Schemes 22 and 24).



1. Enones attached at C(1) of the (E)-diene moiety

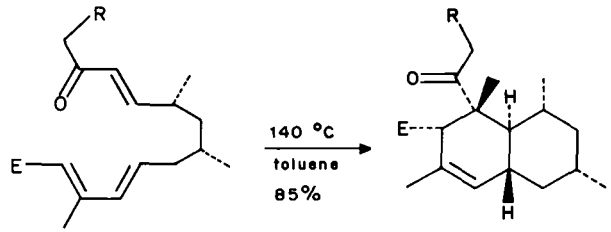
When the enone is joined at the C(1) centre of the diene moiety in a *trans* fashion, relatively strain-free products are formed. There are four possible modes for which the IMDA occur[569–573], as depicted below.

Mode I Mode II Mode III Mode IV

When the bridge between the diene and the enone units comprises four atoms or less, mode II is prohibitively strained and the (*E*)-diene will cyclize through mode I. With longer

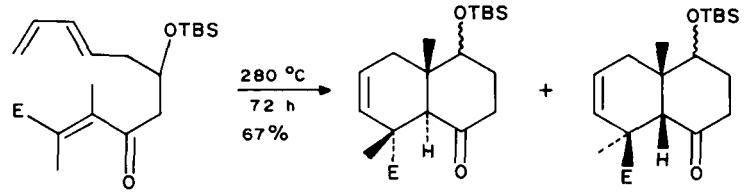
bridges mode II becomes available[574]. With (*Z*)-dienes, modes III and IV occur with similar chances. The stereochemistry of the cyclization is established by the spacial orientation of the enone moiety as it approaches the diene unit, so that the cyclization may proceed in a suprafacial, suprafacial manner. With (*E*)-dienes, and independently of the type of trienone, two transition states are accessible (Scheme 22). The energy difference between the two transition states depends on the bonding and non-bonding interactions between the substituents, and on conformational effects.

Under thermal conditions, the Alder *endo* rule is followed in many IMDA. Depending on the type of trienone, an *endo* transition state can lead to a *cis*-fused or *trans*-fused bicyclic product (Scheme 22). In the case of a trienone of type T1′, an *endo* transition state is responsible for the *trans*-fused bicyclic product[569]. Such systems have been used to build the skeleton of diplodiatoxin (equation 301)[575].



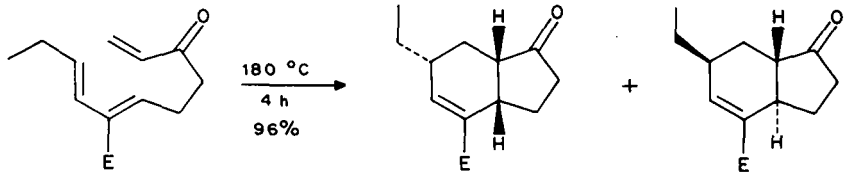
(301)

The thermolysis of trienone **572** (type T2) gave a 3:1 mixture of cycloadducts **573** and **574**. The major product **573** corresponds to an *exo* transition state[576].



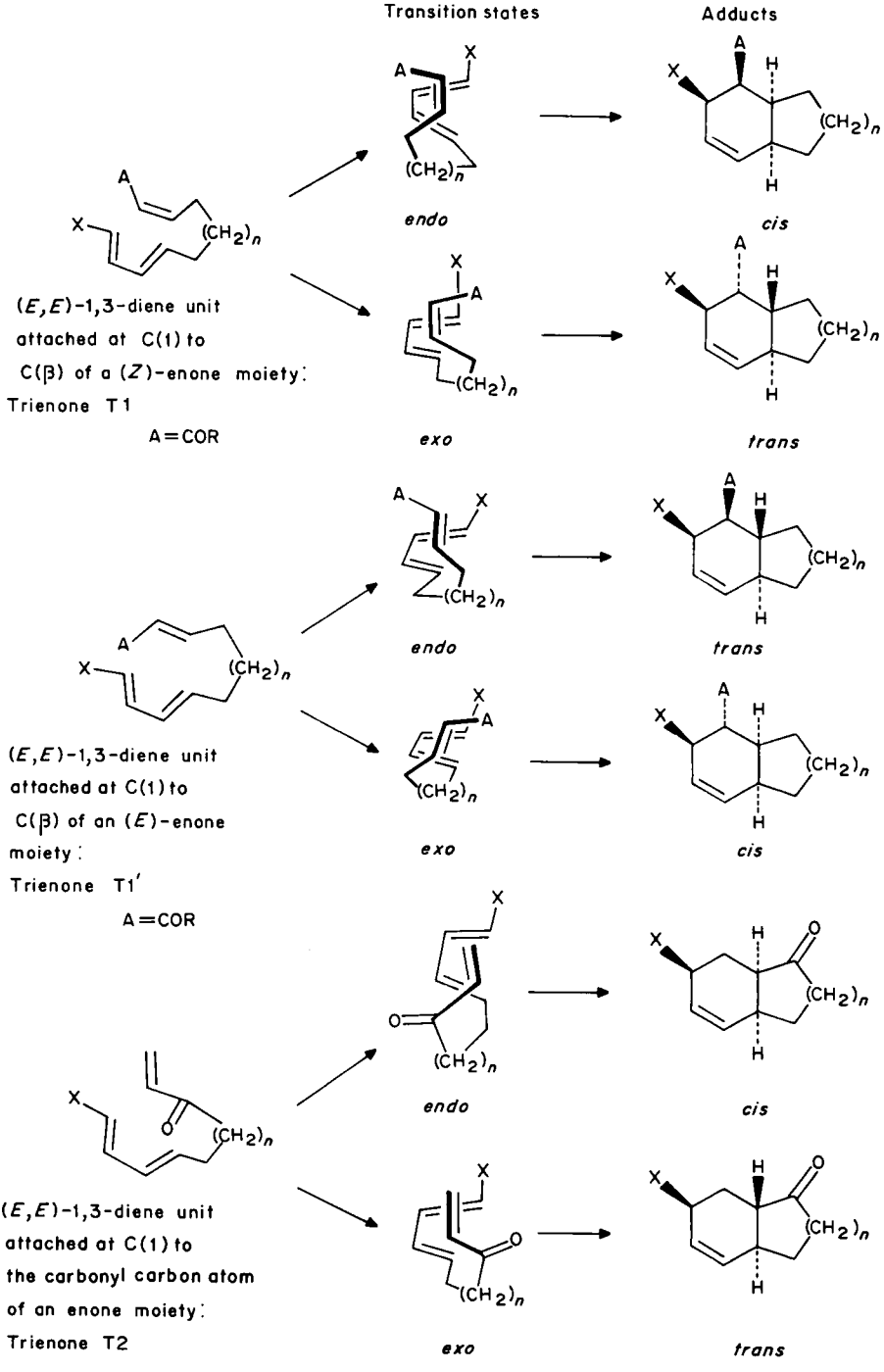
(572) TBS = *t*-BuMe$_2$Si **(573)** **(574)**

Depending on the substituent at position C(3) of the diene moiety, either the *exo* or *endo* transition state can be favoured. This has been illustrated during the synthesis of the framework of the (±)-coronafacic acid. The *endo* transition state is preferred when the C(3) position of the diene moiety is substituted by an ester group (equation 302)[577]. When the C(3) position is substituted by an acetal group, the *exo* transition state is then preferred (equation 303)[578].

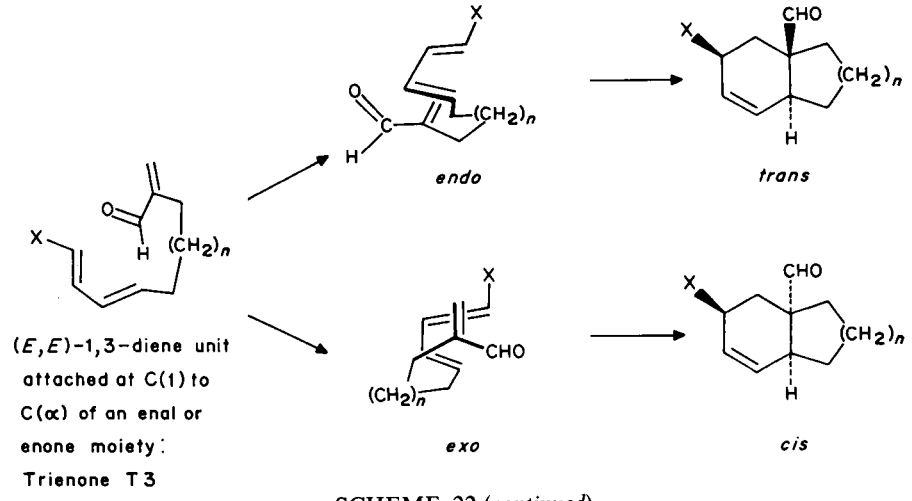


E=COOEt 60 40

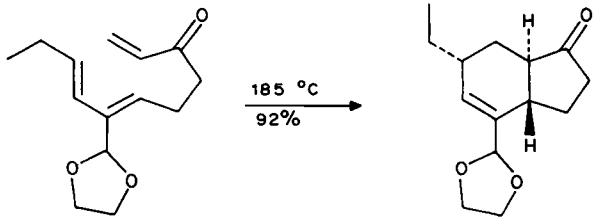
(302)


Transition states
Adducts
endo
exo
cis
trans
(E,E)-1,3-diene unit attached at C(1) to C(β) of a (Z)-enone moiety: Trienone T1
A=COR
(E,E)-1,3-diene unit attached at C(1) to C(β) of an (E)-enone moiety: Trienone T1'
A=COR
(E,E)-1,3-diene unit attached at C(1) to the carbonyl carbon atom of an enone moiety: Trienone T2

SCHEME 22



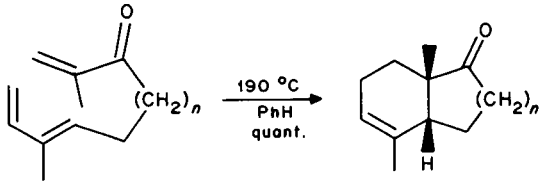
SCHEME 22 (*continued*)



(303)

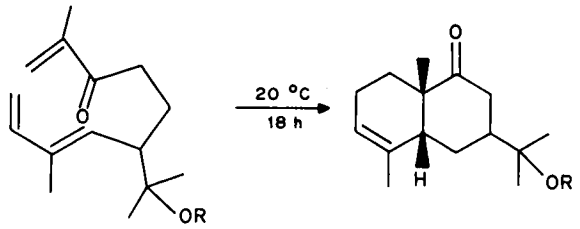
In the *endo* transition state (equation 303), the acetal group generates severe non-bonding interactions involving the hydrogen atoms at the α position of the enone moiety. In the case of the ester substituted system (equation 302), the repulsive steric interaction is presumably weaker owing to the smaller size of ethyl ester vs acetal group.

Further examples of IMDA of dienones of type T2 are given in equations 304 and 305[571,579,580]. In general, the IMDA generating bicyclo[4.4.0]decenone derivatives are more facile than those forming bicyclo[4.3.0]nonenone systems. *Endo* transition states are usually preferred and they lead to *cis*-fused bicyclic compounds. Deviations from this rule are observed when the substituents of the trienones introduce specific steric repulsions or conformational changes.



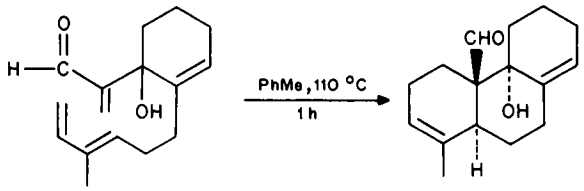
(575)

(304)

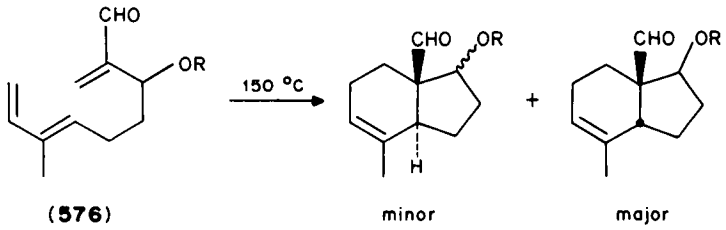


(305)

Examples of IMDA of trienones of type T3 are given in equations 306 and 307[579,581]. Under thermal conditions trienones **576** give *cis*-fused cycloadducts, following an IMDA with an *exo* transition state[579,581]. It has been argued that, in this case, the two new σ bonds are not formed in a synchronous fashion, the outer carbon termini of the diene and enone moieties interacting first to give a nine-membered ring diradical intermediate in which non-bonding interactions are minimized.

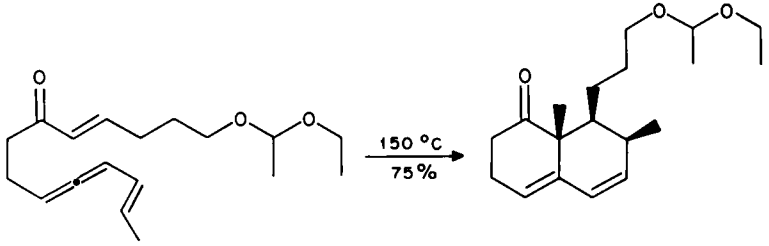


(306)



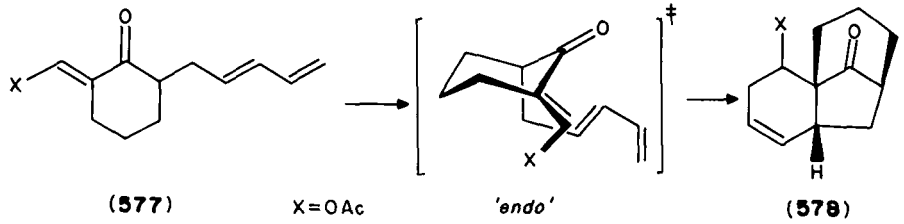
(307)

Many natural product syntheses have applied the IMDA approach. In the case of the synthesis of the hexahydronaphthalene moiety of compactin, a vinylallene acts as the diene moiety (equation 308)[582]. Owing to the rigidity of the allene function, the *exo* orientation is favoured in the transition state.

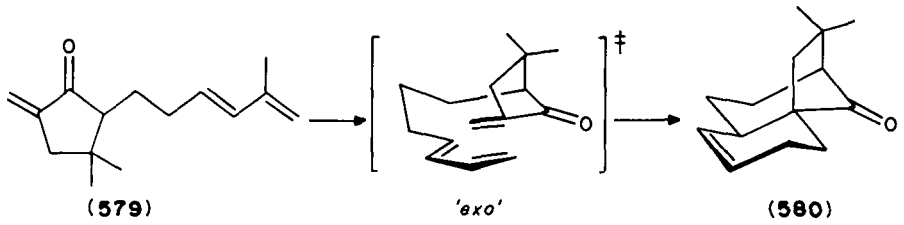


(308)

As the bridge between the diene and the enones is shortened from four to three atoms, the stereoselectivity of the cyclization changes as shown in the accompanying examples[571,579,583–586].



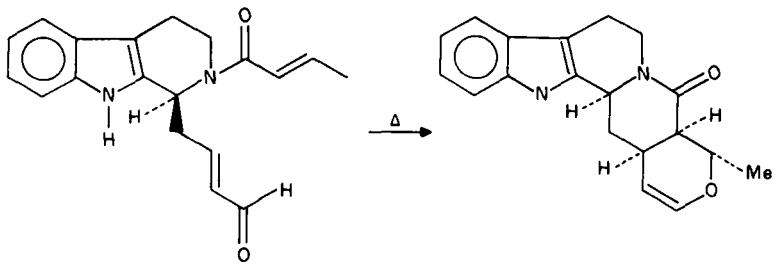
(577) (578)



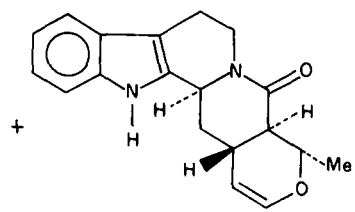
(579) (580)

In the case of the cyclohexanone derivative **577**, an *endo* transition state leads to the formation of the tricyclic compound **578**[585]. In the case of the cyclopentanone derivative **579**, an *exo*-selective IMDA is observed[584,586]. The *endo* transition state is ruled out, since its geometry requires the developing of a cyclohexanone ring system to adopt a boat conformation, thereby creating serious non-bonding interactions. The IMDA of the cyclohexanone derivative **577** was used to build the skeletons of cedrane, stemodane and perhydroazulene[585]. Cyclopentanone derivative **579** was used to prepare the skeletons of quadrone[586] and quassimarin[584].

A concise strategy for the syntheses of indole alkaloids of the heteroyohimboid and corynantheioid families has been presented recently by Martin and coworkers[587]. It is based on the intramolecular hetero-Diels–Alder addition of trienone (**581**). Thermolysis of



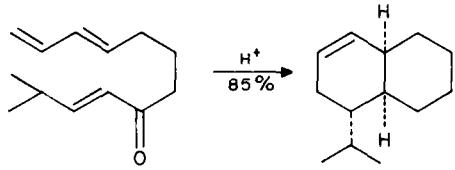
(581) (582)



(583)

581 in mesitylene (40 h) produced a readily separable 9:1 mixture of the two pentacyclic cycloadducts **582** and **583** in 89% total yield.

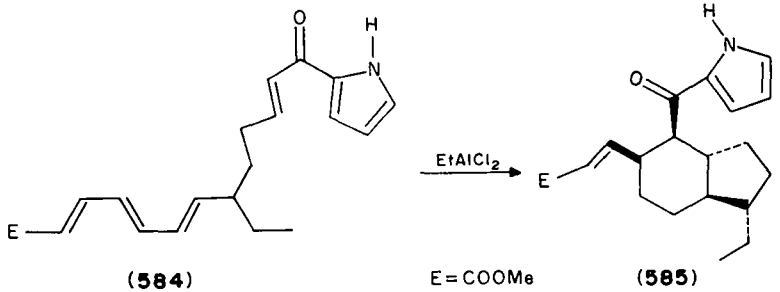
IMDA can also be catalyzed by protic or Lewis acids as the intermolecular Diels–Alder additions[588]. An example is given in equation 309 for a triene of type T2 for which a high *cis* stereoselectivity was obtained. Acid catalyzed IMDA have been applied to the total syntheses of (±)-torreyol[589], compactin precursors[590], diterpenes[591], sclerosporin[592] and candinane[593].

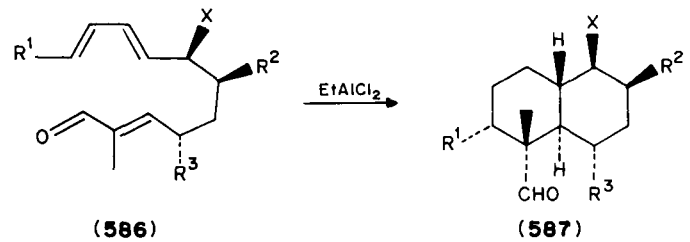


(309)

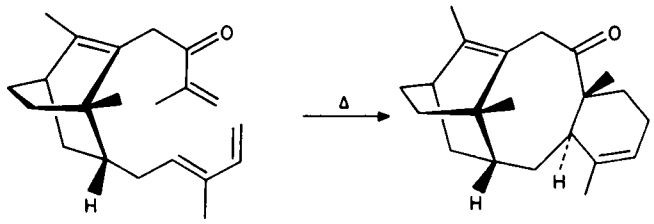
When the chain connecting the diene and enone moieties contains one (or more) asymmetric centre, diastereoselectivity can be expected for the IMDA[594,595]. For instance, in their synthesis of antibiotic X-14574 A, Roush and Myers[596] found that the $EtAlCl_2$ catalyzed IMDA of **584** gave only one (i.e. **585**) of the two possible diastereoisomeric adducts arising from an *endo* transition state due to the ethyl substituent at the connecting chain.

Similarly, in the synthesis of the hydronaphthalene substructure of kijamicin, the substituents of trienones **586** forced a high diastereoselectivity in the IMDA, giving only one type of *trans*-fused adduct **587**[597].



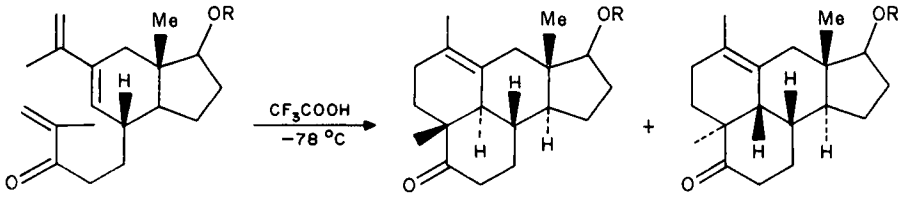


A high diastereoselectivity can be expected for the IMDA if the connecting chain between the diene and enone moieties is part of a rigid system, such as a bicyclic hydrocarbon, as shown in equation 310 for the construction of a taxane model system[598].



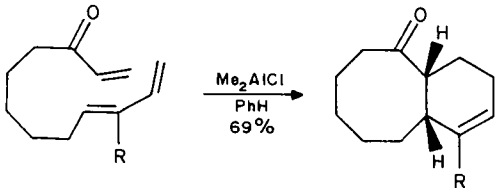
(310)

Firm control of the stereoselectivity of a IMDA can be achieved by including the diene moiety in a cyclic system, as illustrated in the reaction of equation 311 used by Stork and collaborators[599a] to prepare 11-oxygenated steroids, and by Heathcock and collaborators to prepare merilonin[599b].

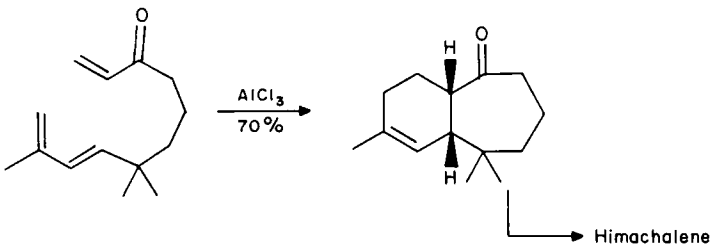


R = *t*-BuMe$_2$Si 94 : 1 (311)

We have presented above numerous examples of IMDA leading to bicyclo[4.3.0]nonene (6/5-membered ring systems) and to bicyclo[4.4.0]decene derivatives (6/6-membered ring systems). Larger ring systems can be generated by the IMDA as shown already in equation 310 (8/6-membered ring system) and further illustrated in equations 312[600] and 313[601] that generate 8/6-membered and 7/6-membered ring systems, respectively.



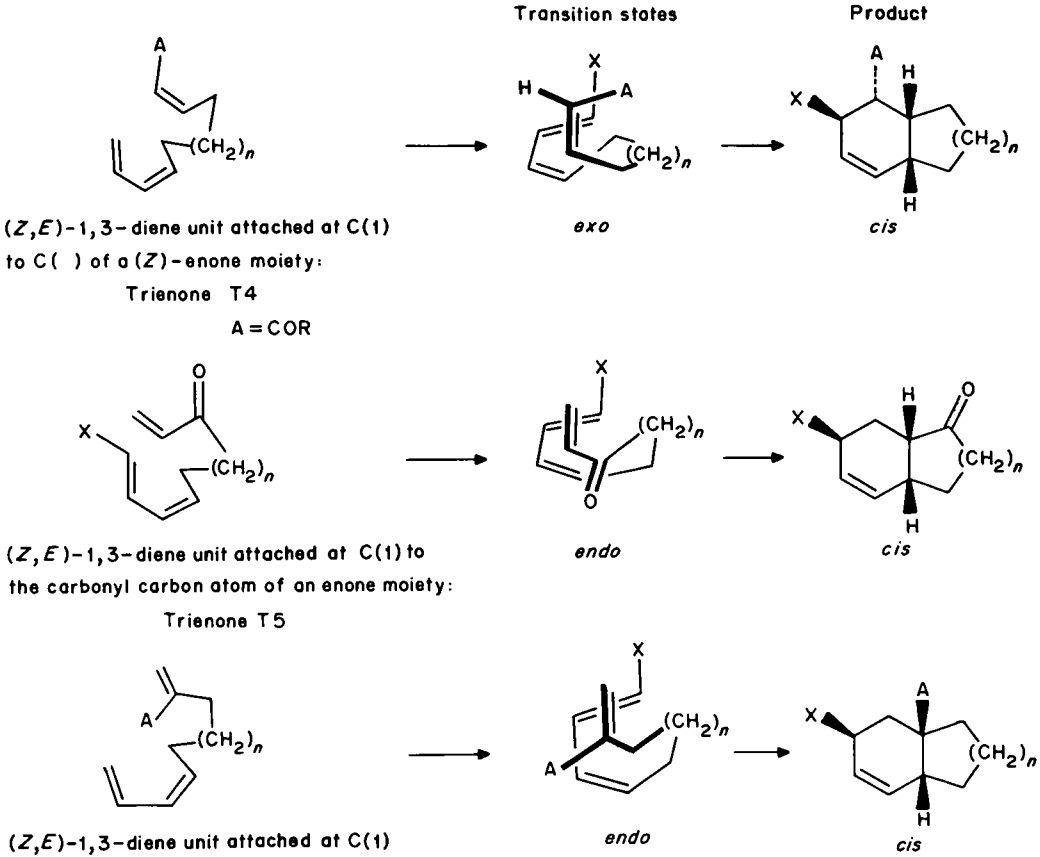
(312)



(313)

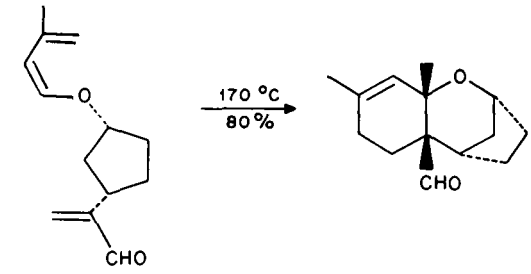
2. Enones attached at C(1) of the (Z)-diene moiety

When the diene moiety of a trienone is attached to the enone moiety in a way that makes the diene of (*Z*) configuration, only a limited number of conformations are possible in the

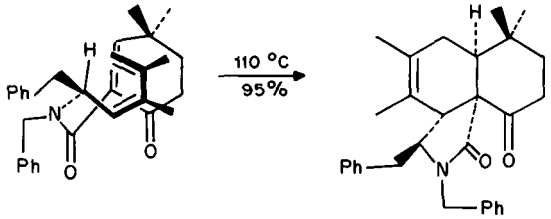

Transition states
Product
A
X
H
A
(CH2)n
exo
cis
(Z,E)-1,3-diene unit attached at C(1) to C( ) of a (Z)-enone moiety:
Trienone T4
A = COR
O
X
(CH2)n
endo
cis
(Z,E)-1,3-diene unit attached at C(1) to the carbonyl carbon atom of an enone moiety:
Trienone T5
A
(CH2)n
endo
cis
(Z,E)-1,3-diene unit attached at C(1) to C(α) of an enone moiety:
Trienone T6
A = COR

SCHEME 23

transition state of the IMDA as depicted in Scheme 23. In all cases, *cis*-fused adducts are expected. An example is given in equation 314 used in the synthesis of the verrucarol skeleton[602]. Complete stereo- and enantioselectivity has been attained in the IMDA of equation 315[603], which uses a trienone of type T6 with a chiral connecting chain between the diene and enone units.

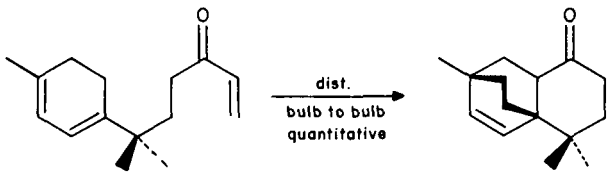


(314)

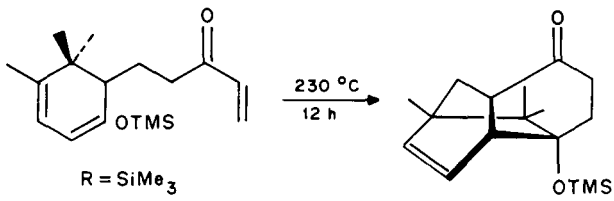


(315)

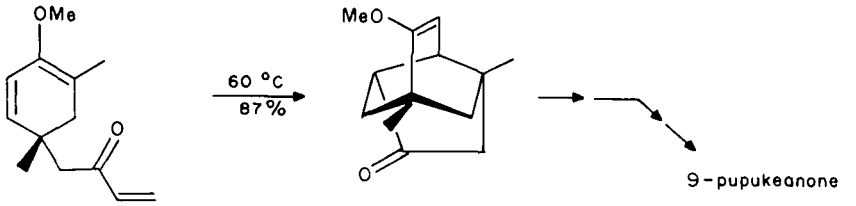
In the following examples (equations 316[604], 317[605] and 318[606]) the diene moiety is part of a six-membered ring. Depending on the size of the substituents, the IMDA is more or less facile. There is competition between the accelerating effect due to maintaining the diene unit in its s-*cis* conformation and repulsive steric effects between the substituents that retard the cycloaddition.



(316)

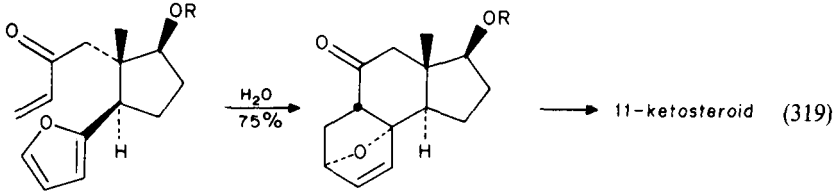


(317)



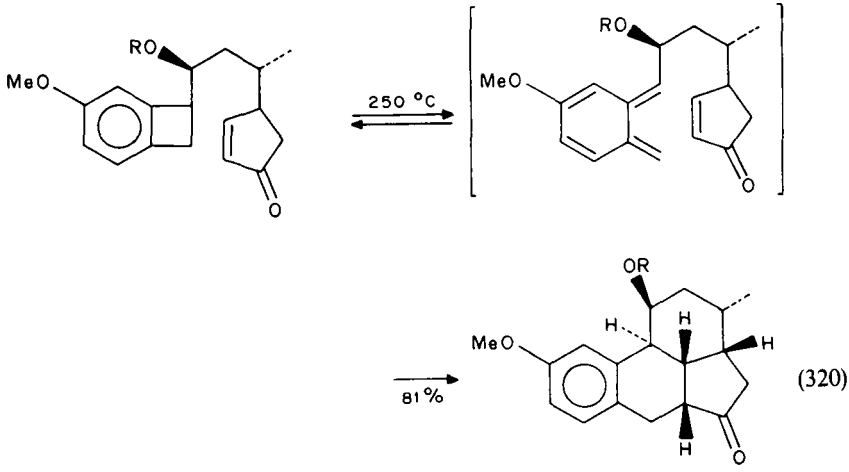
(318)

Intramolecular Diels–Alder additions of trienones whose diene moiety is part of an heterocyclic are also possible[607]. For instance, the reaction of equation 319 run in water has been applied by DeClerq and coworkers[608] in their synthesis of 11-ketosteroids. It features the IMDA of a furan to an enone.



(319)

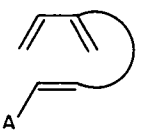
On heating, benzocyclobutenes equilibrate with the corresponding *ortho*-quinodimethanes that are highly reactive intermediates in Diels–Alder addition. The intramolecular version of this principle has been extremely useful in the synthesis of a great number of natural products such as isoatisirene[609], bruceantin[610] and klaineanone[611]. An example of such a IMDA is shown in equation 320. The high stereoselectivity obtained is attributed to conformational and steric factors[569–572].



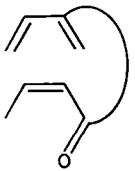
(320)

3. *Enones attached at C(2) of the diene moiety*

For trienones whose enone moiety is attached at C(2) of the diene unit, their IMDA leads to bridgehead olefins of the type bicyclo[n.3.1]alkenone, as shown in Scheme 24 for



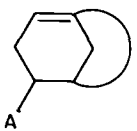
1,3-Diene unit attached at C(2) to C(β) of an enone moiety:
Trienone T7

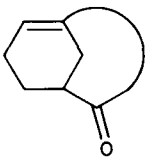


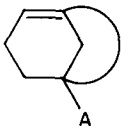
1,3-Diene unit attached at C(2) to the carbonyl carbon atom of an enone moiety:
Trienone T8

1,3-Diene unit attached at C(2) to C(α) of an enone moiety:
Trienone T9

A = COR

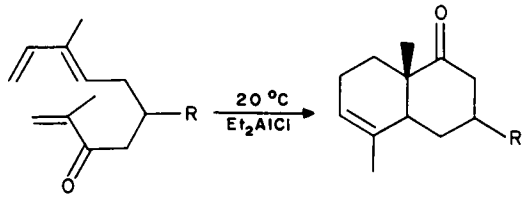




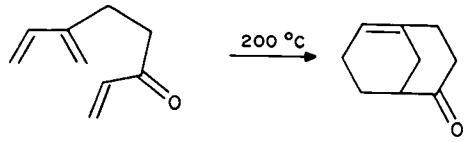


SCHEME 24

trienones of type T7, T8 and T9. Unlike the facile thermal IMDA of trienones of type T2 (e.g. equation 321) that generate usually strain-free cycloadducts (connecting chain containing two or three atoms), the IMDA of trienones of type T8, for instance (equation 322), requires high temperatures to occur[612]. These reactions can be accelerated, however, by the use of Lewis acid. For instance, while reaction 322 occurs at 200 °C in the absence of a catalyst, in the presence of Et_2AlCl it occurs at 20 °C[613].

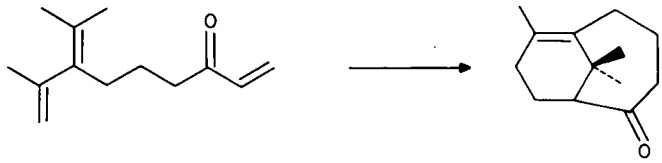


(321)



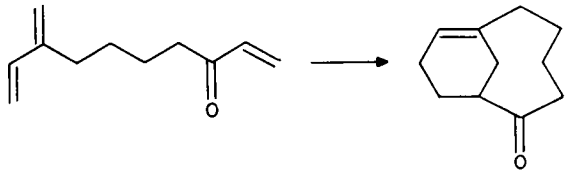
(322)

Interestingly, it was found that the methylated trienone **588** was considerably more reactive than the non-methylated analogue **590** under Lewis-acid catalyzed conditions. This pattern of reactivity contrasts with the thermal behaviour where **590** was found to be significantly more reactive than **588**. The crossover in diene reactivity may reflect a greater responsiveness of the alkylated diene to an electron-deficient dienophile in the Lewis-acid catalyzed reaction[613] (see the diradicaloid model for Diels–Alder addition transition state).



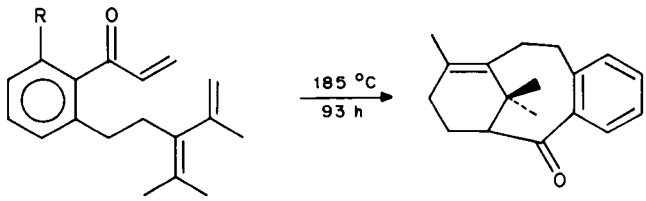
(588) **(589)**

conditions:	yield
Et_2AlCl, 20 °C, 5 min	71%
185 °C, 72 h	10%



(590) **(591)**

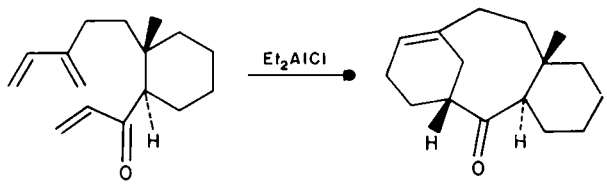
conditions:	yield
Et_2AlCl, 21 °C, 2 h	75%
155 °C, 13 h	0%



(592) (593) 70%

IMDA of trienone of type T8 has been used in the elaboration of the taxane skeleton **593**[614]. The benzannulated derivative **592** is *ca* 10^6 times more reactive than the non-benzannulated compound **590**.

Another alternative for the construction of the taxane skeleton **595** employed the IMDA of trienone **594**[615]. One simple isomer was isolated in 72% yield. The remarkable stereochemical control observed arises from the preference for a chair-boat conformation of the eight-membered ring created in the transition state.



(594) (595)

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