Organic Synthesis with α-Diazocarbonyl Compounds

Tao Ye and M. Anthony McKervey*

School of Chemistry, The Queen's University, Belfast BT9 5AG, Northern Ireland, U.K.

Received September 7, 1993 (Revised Manuscript Received March 14, 1994)

Contents

I. Introduction

α-Diazocarbonyl compounds have a long history of useful applications in organic chemistry. They are easily prepared from readily accessible precursors and can be induced to undergo a wide variety of chemical transformations under very mild conditions. Although our primary purpose in writing this review is to demonstrate the ongoing utility of α-diazocarbonyl compounds in modern organic synthesis, it is appropriate by way of introduction to summarize briefly the more important methods of preparation, drawing attention to recent improvements in experimental procedures.[1]

II. Synthesis of α-Diazocarbonyl Compounds

The first recorded synthesis of an α-diazocarbonyl compound dates back to the work of Curtius[2] on diazotization of natural α-amino acids (ethyl diazoacetate was first synthesized in 1883 from glycine) and although Wolff discovered in 1912 the diazocarbonyl rearrangement which now bears his name, simple diazocarbonyl compounds only became readily available in the late 1920s with the discovery by Arndt and Eistert[3-5] and by Bradley and Robinson[6] that the key to successful acylation of diazomethane with an acid chloride, a reaction previously believed capable of furnishing chloromethyl ketone only, lies in the use of diazomethane in sufficient excess to sequester the hydrogen chloride liberated and thereby prevents its addition to the diazo ketone. Acylation of diazomethane remains the single most important route to acyclic terminal α-diazo ketones. The diazo group transfer technique, which is now available for both terminal and nonterminal systems, also occupies an important place in diazocarbonyl methodology.

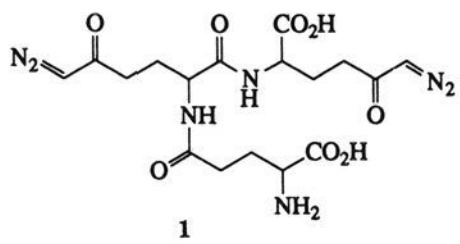
0009-2665/94/0794-1091$14.00/0

Tao Ye was born in Huang Shan city (P. R. China) in 1963. He received his B.Sc. (1983) and M.Sc. degrees (1986) from East China University of Chemical Technology, the latter with the late Professor Gong Wong. In 1986 he joined the faculty at East China University of Chemical Technology for teaching/research work and was promoted to the rank of lecturer in 1988. In 1989 he resigned the lecturership and went to Ireland to join Professor M. A. McKervey's research group, initially at University College Cork and later at the Queen's University of Belfast. He obtained his Ph.D. (1993) in organic chemistry from Queen's University with a thesis entited "Catalytic Asymmetric Synthesis Using Diazocarbonyl Intermediates". His current research interests include the development of new synthetic methods particularly related to enantioselectivity and synthesis of biologically significant compounds. He is currently a postdoctoral fellow with Professor M. A. McKervey and will join Professor G. Pattenden's research group (University of Nottingham) in June 1994.

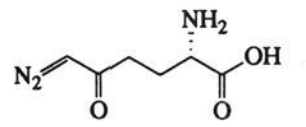
Professor M. A. McKervey was born in Co. Fermanagh, N. Ireland, in 1938. He received his B.Sc. (1961) and Ph.D. degrees (1964) from Queen's University, Belfast, where his research supervisor was Professor H. B. Henbest. Following a period at M.I.T. where he was postdoctoral fellow with the late Professor A. C. Cope and assistant professor, he returned to Queen's to a lecturership and, in 1973, a readership. In 1976 Professor M. A. McKervey was appointed to the Chair of Organic Chemistry in University College Cork, Republic of Ireland. He returned to Queen's in 1990 as professor of Organic Chemistry and Head of the Research Division of the School of Chemistry. He has authored or coauthored over 200 research publications and current research interests includes the synthetic chemistry of diazocarbonyl compounds, amino acids and furans, and the construction of novel ionophores using chemically modified calixarenes.

A. Acylation of Diazoalkanes

The Arndt–Eistert synthesis of diazo ketones involves addition of an acyl chloride to ethereal diazomethane (at least 1–2 equiv excess) at or below 0 °C; extensive purification of the product is usually unnecessary. Pettit and Nelson[7] have designed an apparatus for diazo ketone preparation in which the carboxylic acid in ether in one compartment is first treated with oxalyl chloride, triethylamine, and a catalytic amount of dimethylformamide to furnish the acyl chloride. The resulting solution is then filtered into ethereal diazomethane at −78 °C. This technique was developed for the synthesis of the anticancer bis diazoketone, azotomycin (**1**).[7] The antibiotic 6-diazo-5-oxo-L-norleucine (**2**), commonly known as DON, has been synthesized several times[8,9] from the N-protected acyl chloride and diazomethane, albeit in very low (0.5–1.0%) overall yields. Much of the inefficiency appears to be associated with the formation of the acyl chloride for which the most useful method is the reaction of the dicyclohexyl ammonium salt of *N*-(trifluoroacetyl)glutamic acid with oxalyl chloride.[10]



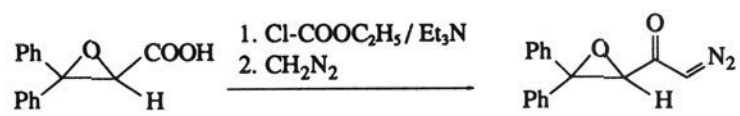
1



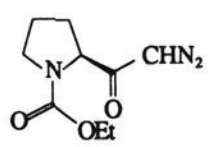
2

Anhydrides are also suitable acylating agents for diazomethane.[11,12] A convenient procedure involves treatment of the carboxylic acid with dicyclohexylcarbodiimide to form the anhydride which is then allowed to react with ethereal diazomethane.[13] A convenient *in situ* procedure to form mixed anhydrides is now available involving anhydride formation between the carboxylic acid and a chloroformate, followed by treatment with diazomethane. For example, 3-(diazoacetyl)-2,2-diphenyloxirane has been synthesized by this route (Scheme 1).[14,15] This route has also been

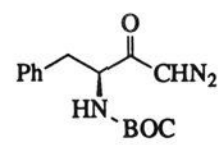
Scheme 1



applied to the production of homochiral α-diazo ketones from N-protected amino-acids, proline, and phenylalanine furnishing diazo ketone **3** and **4**, respectively.[16]



3



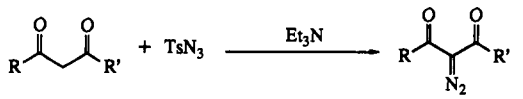
4

Acylation of higher diazoalkanes with acyl chlorides and anhydrides is also possible, although less efficiently than with diazomethane. Numerous synthetic intermediates containing the diazoethyl group have been obtained in this way.[17]

B. Diazo-Transfer Reactions

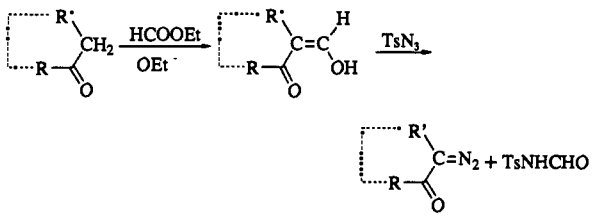
An obvious limitation of diazoalkane acylation is that it is not applicable to cyclic α-diazo ketones. Although many routes to cyclic diazo ketones have been developed, none competes in usefulness with the diazo-transfer technique introduced by Regitz and his collaborators[18,19] in 1967. Diazo transfer is now the standard route, not only to cyclic α-diazo ketones, but to many acyclic systems not accessible by acyl-transfer processes. In the broadest sense, diazo transfer refers to the transfer of a complete diazo group from a donor

Scheme 2



R , R' = Alkoxy; R, R' = Alkyl; R = Alkyl, R' = Alkoxy

Scheme 3



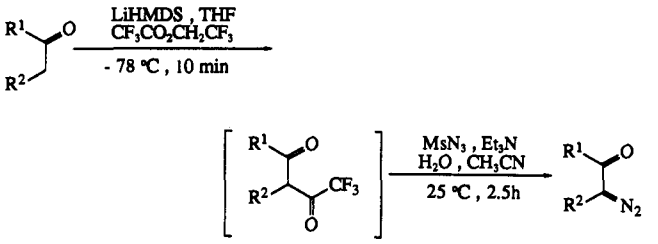
to an acceptor, which for α-diazocarbonyl products must therefore be an acid or ketone derivative. The diazo donor is invariably a sulfonyl azide.[19]

Diazo transfer to the α-methylene position of a carbonyl compound requires the presence of a base of sufficient strength to deprotonate the substrate. Prior activation of the substrate may be necessary. Substrates can therefore be divided into two broad categories on the basis of their acidity: those in which the α-methylene position is already sufficiently reactive toward diazo transfer, and those which require prior activation to ensure smooth transfer in the presence of a mild base.[20,21] Of greatest importance in the former groups are malonic esters, β-keto esters, and β-diketones which are readily converted into 2-diazo-1,3-dicarbonyl products by the standard Regitz procedure of exposure to tosyl azide in dry chloroform or ethanol using triethylamine as the base (Scheme 2).

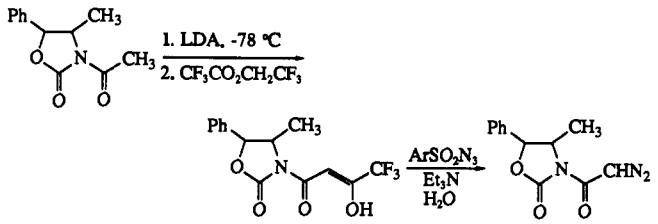
Almost all of the β-lactam intermediates bearing diazocarbonyl side chains to be discussed in a later section of this review were obtained in this way. While the diazo-transfer reaction works extremely well for cases in which the reaction site is activated by two flanking carbonyl functions, the standard Regitz procedure usually fails in cases where the methylene group is activated by a single carbonyl group only. Although satisfactory results can sometimes be achieved with single carbonyl compounds by optimizing the system of base and diazo-transfer reagent (*vide infra*), in general, however, best results are usually obtained by activation in the form of acyl aldehydes prior to diazo transfer. This technique, often referred to as deformylating diazo transfer, has found widespread application since its introduction in 1967.[18,19] It involves Claisen condensation of the ketone with ethyl formate in order to introduce the strongly activating formyl group which is subsequently released as the sulfonamide in the course of the actual diazo transfer; either the metal salt or the neutral formyl compound can be employed as the activated intermediate (Scheme 3).

Variations in the groups R and R′ allow most types of acyclic and cyclic α-diazo ketones to be synthesized in this way.[18-22] Recently, Danheiser and co-workers[23] found that deformylating diazo transfer in a number of crucial cases produced the desired α-diazo ketones in relatively low yield. Particularly problematic were reactions involving base-sensitive substrates such as α,β-enones where the difficulties were attributable in part to the harsh conditions typically required for the Claisen condensation step. By substituting the trifluoroacetylation of kinetically generated lithium enolates for the usual Claisen formylation step, Danheiser found that the efficiency of the diazo-transfer reaction can be improved, in some cases quite dramatically. A key feature of the new protocol (Scheme 4) is the activation of the ketone precursor as the corresponding α-trifluoroacetyl derivative, the reaction of the ketone enolate with trifluoroethyl trifluoroacetate taking place essentially instantaneously at −78 °C. Doyle[24] has employed a similar strategy (Scheme 5) to achieve diazo transfer to a base sensitive *N*-acyloxazolidinone derivative.

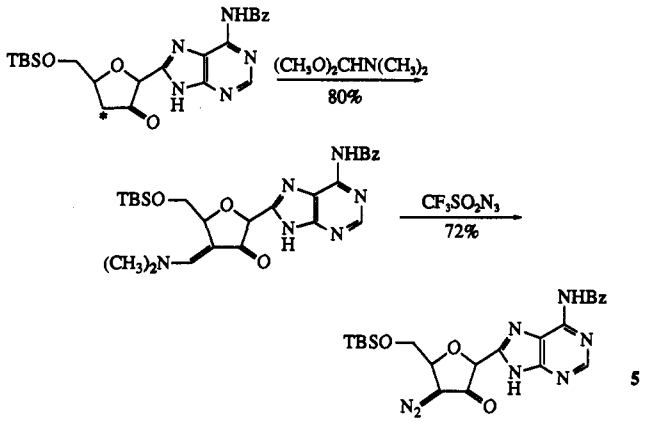
Scheme 4



Scheme 5



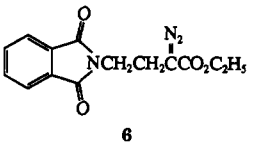
Scheme 6



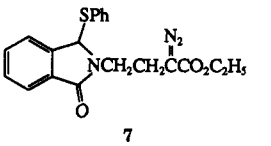
5

Norbeck and Kramer,[25] seeking to employ diazo ketone **5** in their synthesis of (−)-oxetanocin, activated the appropriate starred (*) carbon to give the enamino ketone and then used triflyl azide as diazo-transfer reagent (Scheme 6).

Diazo ester compounds can be synthesized by treating the ester anion with ethyl formate so as to produce the doubly activated species. Reaction of this formyl compound with the appropriate diazo-transfer reagent then occurs, proceeding to the diazo ester by a subsequent cleavage of the formyl group. For example, compounds **6**[26] and **7**[27] were prepared by this method.

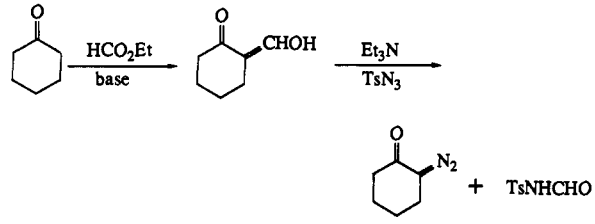


6

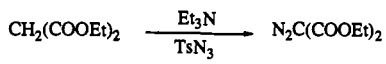


7

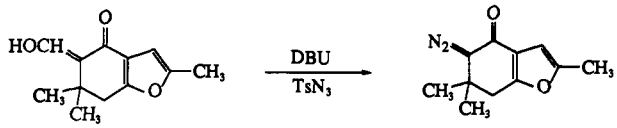
Scheme 7



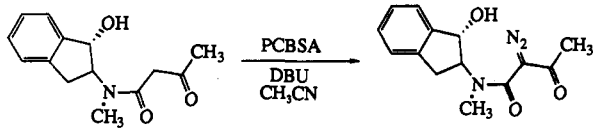
Scheme 8



Scheme 9

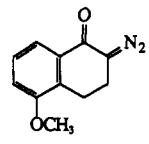


Scheme 10

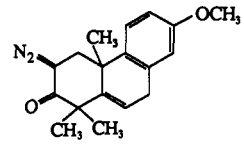


Two examples, representative of cyclic and acyclic diazo transfer, in which tosyl azide was the transfer agent and triethylamine the base are shown in Schemes 7[28] and 8.[29] In cases where triethylamine is insufficiently basic to cause complete deprotonation of β-dicarbonyl compounds, Koskinen and Muñoz[30] have advocated the use of potassium carbonate in acetonitrile under which conditions practically quantitative diazo transfer from tosyl azide to a range of β-keto esters was complete in 1 h at room temperature, the workup simply consisting of filtration of the inorganic salts and the sulfonamide byproduct after addition of diethyl ether. Problems associated with hydrolysis of base-sensitive methyl acetoacetate were not encountered.[31] Benalloum and Villemin[32] have reported a convenient synthesis of diazocarbonyl compounds from tosyl azide and carbonyl compounds with Al_2O_3–KF as a solid base and Nikolaev and co-workers[33] have used a potassium fluoride–crown ether combination as the base system in the diazo-transfer reaction of cyclic and acyclic diketone compounds. The successful use of potassium fluoride in this reaction is apparently due to the facile deprotonation of diketones by the "naked" anion of fluorine, even in the case of sterically hindered compounds. Rao and Nagarajan have successfully used 1,8-diazobicyclo-[5.4.0]undec-7-ene (DBU)[34] for smooth diazo transfer, notably in the case of hindered compounds where the standard diazo-transfer conditions were inefficient, e.g. as in Scheme 9. Actually, for acetoacetamide precursors, diazo transfer with *p*-carboxybenzenesulfonyl azide (PCBSA) and triethylamine in acetonitrile proved unsuccessful. However, when DBU was used, the reaction was complete in a few hours (Scheme 10).[35]

An application of phase-transfer catalysis to the diazo-transfer process using an aqueous base has been devised by Ledon.[36] When diazo transfer is complete, the organic layer contains only the diazo compound and traces of the ammonium salt. The latter is eliminated during distillation or by rapid filtration through a silica gel column. Mander and Lombardo[37] have found that when 2,4,6-triisopropylbenzenesulfonyl azide is substituted for tosyl azide some unactivated cyclic ketones can be converted into α-diazo derivatives under phase-transfer conditions employing potassium hydroxide, 18-crown-6, and tetrabutylammonium bromide. Two compounds prepared via this modification are shown below in **8** and **9**. The limitation of this method is that it is not suitable for substrates sensitive to aqueous basic hydrolysis, e.g. methyl esters.

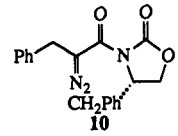


8

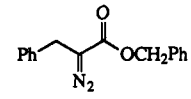


9

By employing a stronger base as deprotonation reagent, direct diazo transfer to *N*-acyloxazolidinones and esters is also successful. The competing azidation reaction in these direct diazo-transfer reaction systems can be reduced by choosing appropriate sulfonyl azides.[38] Thus highly electron deficient *p*-nitrobenzenesulfonyl azide (PNBSA) resulted in predominant formation of the diazo-transfer product, whereas the sterically demanding 2,4,6-triisopropylbenzenesulfonyl azide affords maximum yields of the azide-transfer product. These observations contrast with Mander and Lombardo's precedent.[37] The mechanism of direct diazo transfer was also studied by Evans and co-workers.[38] Two examples of products obtained via the direct diazo transfer to acyloxazolidinones and ester are shown in **10** and **11**:



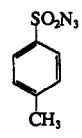
10



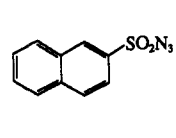
11

Some benzyl ketones can be converted to α-diazo ketones directly by this technique provided that a potassium alkoxide is employed as the base.[39,40] However, when DBU is employed as base, this type of transformation is also successful.[41]

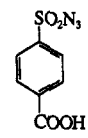
Although tosyl azide is by far the most frequently employed diazo donor and was first used in this capacity by Doering and DePuy in 1953 in their synthesis of diazocyclopentadiene,[42] workers in the Merck Laboratories[43] have raised doubts regarding safety aspects of this reagent. In the first place, the *Organic Syntheses*[44] preparation of tosyl azide calls for the use of ethanol as the reaction solvent. But as Curphey[45] has pointed out, ethanol is an inappropriate solvent for the reaction of tosyl chloride with sodium azide; replacement with acetone gives a cleaner product not requiring recrystallization. The Merck chemists,[43] faced with the need to develop a large scale diazo transfer in their synthesis of thienamycin (*vide infra*), examined the five reagents **12**–**16** from the standpoint of utility,



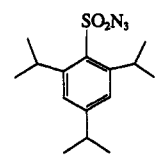
12



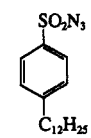
13



14



15



16

thermal stability, ease of handling, safety, and cost. In addition to desired performance, the specific heat of decomposition, thermal decomposition temperature, relative rates of decomposition, and impact sensitivity of all five compounds were measured. Tosyl azide 12 was found to be the most hazardous, combining the highest impact sensitivity with the lowest initiation temperature and the largest heat of decomposition. In fact, pure tosyl azide is classified officially as an explosive under German law. Some serious accidents with tosyl azide have been reported.[46,47] Although *p*-carboxylbenzenesulfonyl azide (14) had the highest initiation temperature, this reagent is expensive and its use necessitates 2 mol of base per mole of substrate which is not ideal for base sensitive substrates; the carboxyl group, however, does offer a chemical handle for removal from neutral products. *p*-Dodecylbenzenesulfonyl azide (16), which was actually an isomeric mixture within the alkyl side chain, exhibited the lowest specific heat of decomposition and no impact sensitivity at the highest test level, making it the safest reagent of the group. Moreover, byproduct dodecylbenzenesulfonamides are noncrystalline, facilitating isolation of crystalline diazo ketones. If, on the other hand, the diazo product is a liquid, naphthalene-2-sulfonyl azide (13) can be employed to take advantage of the fact that the sulfonamide byproduct is sparingly soluble. Hazen et al.[43] successfully employed this diazo-transfer reagent in the synthesis of ethyl 2-diazo-3-oxobutanoate.

Polymer-bound sulfonyl azide[48] has also been employed as diazo-transfer agent to a variety of 1,3-dicarbonyl compounds. Advantages of its use include better safety in handling plus the convenience of a cleaner workup, the sulfonamide byproduct remaining attached to the insoluble polymer.

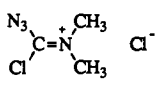
Recently, Taber and his collaborators[49] claimed that methanesulfonyl (mesyl) azide is a generally superior reagent to tosyl azide for diazo transfer; its main advantage being the greater ease with which the sulfonamide byproduct is removed from the reaction mixture by washing with 10% aqueous NaOH solution. However, stability data for mesyl azide have not been reported and great caution should attend its use. Davies and his collaborators[50] claimed that *p*-acetamidobenzenesulfonyl azide is a practical and cost-effective reagent for use in diazo-transfer reactions. They also give the stability data and the general applicability of this reagent. By using this diazo-transfer regent in the synthesis of α,β-unsaturated diazo esters, the resulting yields are generally good.[50-52] Nikolaev and co-workers[33] have reported the use of *p*-nitrobenzenesulfonyl azide instead of tosyl azide. The low solubility of both the starting azide and the *p*-nitrobenzenesulfonyl amide produced, and the significantly higher absorption ability of these compounds on silica gel simplifies the purification of the corresponding diazo ketone.

More recently McGuiness and Shechter[53] have reported that azidotris(diethylamino)phosphonium bromide is an exceptionally safe diazo-transfer reagent, which is stable to shock, friction, and rapid heating. Also the diazo-transfer reaction generates a neutral leaving group, hexaethylphosphoramidic triamide, which is easily removed as its hydrobromide salt.

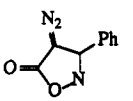
Although we have briefly reviewed several reagents for diazo transfer reactions, it should be noted that other azide reagents are available which in some applications have advantages with respect to safety, economy, and the facility of product separation.[54]

The preparative scope of the diazo group transfer reaction is considerably widened by using azidinium salts as diazo group donors. Balli and collaborators[55-57] described the use of stable heterocyclic azidinium salts 17 as the diazo-transfer reagent in a pH 0–8 range. This procedure was fairly successful with a variety of active methylene compounds. Kokel and Viehe[58] showed that the iminium salt 18 was also an effective diazo-transfer reagent in acidic medium. Since the reaction proceeds only in the neutral and acid ranges in which sulfonyl azides are unreactive, it is particularly suitable for diazo compounds that undergo coupling. Two compounds prepared by this method are shown: 19 and 20.[56] The applicability of diazo group transfer using azidinium salts is limited by the fact that the reaction must be carried out in acidic to neutral medium. The procedure is no longer applicable when the active methylene component does not form an anion under the above conditions, or when the diazo compound is unstable to acid.[18,19]

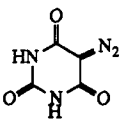
17



18



19

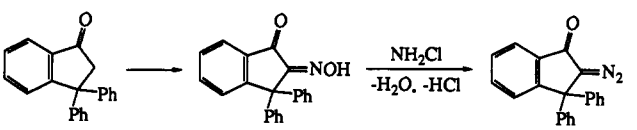


20

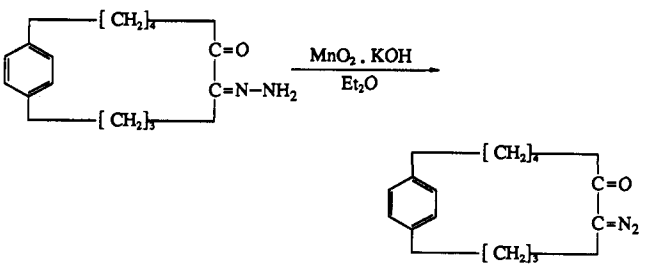
C. Other Routes to α-Diazocarbonyl Compounds

Among other routes to α-diazo ketones that have diminished somewhat in usefulness since the introduction of the diazo-transfer process, are the Forster reaction in which oxime formation at the α-methylene position of a ketone is followed by reaction with chloramine as, for example, in Scheme 11;[59] dehydrogenation of hydrazones, e.g. as in Scheme 12;[60] and the Bamford-Stevens tosylhydrazone decomposition in Scheme 13.[61] These reactions have been reviewed in detail by Regitz.[1a]

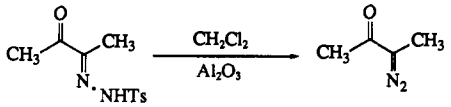
Scheme 11



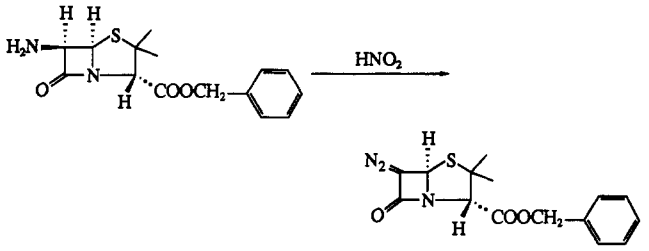
Scheme 12



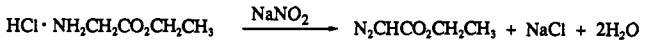
Scheme 13



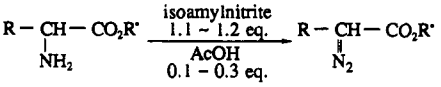
Scheme 14



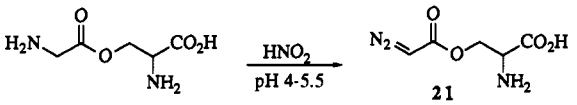
Scheme 15



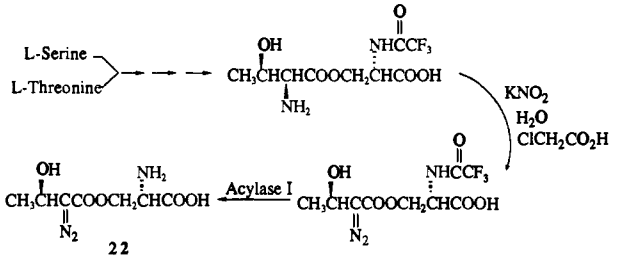
Scheme 16



Scheme 17



Scheme 18

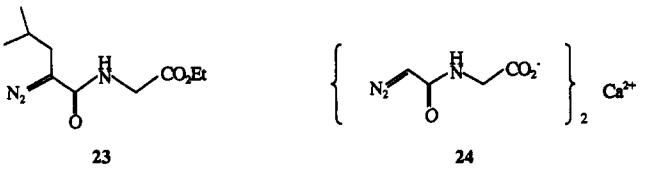


Diazotization remains the method of choice for production of the synthetically versatile 6-diazopenicillanates[62] from 6-aminopenicillanic acid esters (Scheme 14) and of ethyl diazoacetate from glycine ethyl ester (Scheme 15).[63] Extension of the diazotization process to the higher amino acids such as alanine, phenylalanine, isoleucine, and methionine is also possible (Scheme 16);[64] isoamyl nitrite is the preferred diazotization agent. The antibiotic azaserine **21**, active against certain tumours, was isolated from a broth-culture of a streptomyces[65] and shown to be *O*-(diazoacetyl)-L-serine[66] and could be prepared by diazotizing the corresponding *O*-glycylserine (Scheme 17).[67]

Recently Nishimura and his collaborators[68] synthesized a new antitumour antibiotic, FR900840 (**22**), which was isolated from a culture broth of a strain of streptomyces, by diazotizing the corresponding amino acid (Scheme 18).

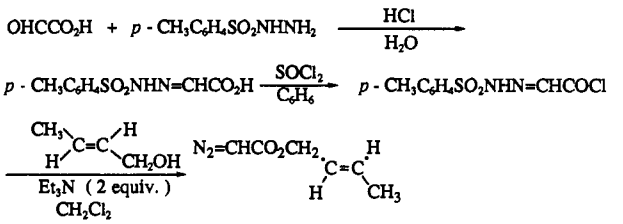
Challis and Latif[69] reported the synthesis of diazopeptides by aprotic diazotization with N_2O_4 at −40 °C. For example, **23** and **24** were synthesized by this method.

House[70,71] has devised a very useful scheme for the preparation of diazo esters not readily accessible by diazotization (Scheme 19). Glyoxylic acid is first

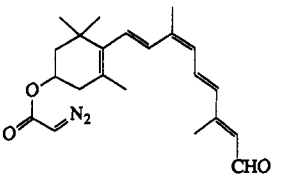


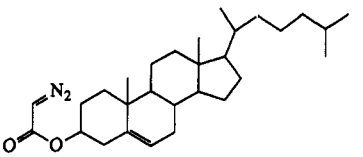
converted into its tosylhydrazone which is then treated with thionyl chloride to form the acyl chloride. The

Scheme 19



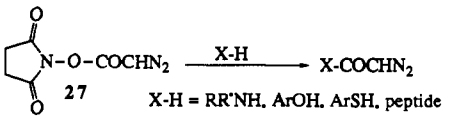
acyl chloride is combined with the appropriate alcohol to produce the ester hydrazone and the process is completed by decomposition of the hydrazone with triethylamine. This method has been used for the synthesis of the photoaffinity diazo esters **25**[72,73] and **26**.[74] Diazoamides have also been synthesized via





House's method. An improved method for the preparation of diazoacetamides includes the cyclohexylcarbodiimide-mediated coupling of an amine with glyoxylic acid tosylhydrazone.[75,76] A very recent improvement in the House's diazoacetylation by Badet and co-workers[77] involves the use of succinimidyl diazoacetate **27** which can be easily obtained and stored at room temperature for long periods. Succinimidyl diazoacetate **27** can be used for direct diazoacetylation of aromatic or aliphatic amines, phenols, thiophenol and peptides under mild conditions (Scheme 20).

Scheme 20



D. Chemical Modification of α-Diazocarbonyl Compounds

Another aspect of diazocarbonyl synthesis that is receiving increasing attention, mainly through the work of Regitz's group,[78] is the chemical modification of the α-position with retention of the diazo function. Numerous examples of substitution reactions at the

Table 1. Substitution Reaction of α-Diazocarbonyl Compounds

reaction	substrate	conditions	product	yield, %	ref(s)
metalation	$PhCOCHN_2$	HgO, 20 °C	$Hg(CN_2COPh)_2$	97	79
	$N_2HCCOOEt$	*n*-BuLi, -100 °C	$LiCN_2COOEt$		80
	$N_2HCCOOEt$	Ag_2O, ≤0 °C	$AgCN_2COOEt$		81
halogenation	$Hg(CN_2COOEt)_2$	SO_2Cl_2, -30 °C	$ClCN_2CO_2Et$	30	82
	$Hg(CN_2COOEt)_2$	Br_2, ether–THF, -100 °C	$BrCN_2CO_2Et$	80–90	82
	$Hg(CN_2COOEt)_2$	I_2, 0 °C	ICN_2CO_2Et	70–90	82, 83
nitration	$N_2HCCOOEt$	N_2O_5, CCl_4, -30 °C	$O_2NCN_2CO_2Et$		84
alkylation	$AgCN_2CO_2Et$	$H_2C{=}CHCH_2I$ ether, 0 °C	$H_2C{=}CHCH_2CO(N_2)O_2Et$	66	81

diazocarbonyl carbon atom in terminal, acyclic substrates bear witness to the stability of the diazo group, even under quite drastic conditions. In general, the hydrogen atom can be substituted by electrophilic reagents. In addition to halogenation, metalation, nitration, and alkylation processes are possible, leading to new substituted diazocarbonyl compounds. Regitz reviewed these reactions in detail in 1985;[1a] just a few representative examples are summarized in Table 1. Some uses of the metalated derivatives are discussed in a later section.

III. Diazocarbonyl Reactions in Synthesis

α-Diazocarbonyl compounds constitute a class of organics of quite exceptional flexibility in synthesis. Their most significant reactions are those that proceed with loss of nitrogen which can be brought about thermally, photochemically, or catalytically. Diazocarbonyls react stoichiometrically with many Brönsted acids and electrophiles and catalytically with numerous transition metals and their salts. Reactive intermediates include free carbenes, carbenoids (complexed carbenes), carbonyl ylides, and diazonium cations. We have chosen to group diazocarbonyl reactions not on the basis of common intermediates or mechanisms, but rather according to product type since the latter arrangement makes it much easier to appreciate their versatility in synthesis. α,α-Substitution, for example, the process whereby the diazo group is replaced by two new substituents, may, depending on reaction conditions, span the entire spectrum of reactive intermediates.

The most serviceable of diazocarbonyl reactions are cyclopropanation, Wolff rearrangement, insertion into unactivated C–H bonds, aromatic cycloaddition, α,α-substitution, dipolar addition, acid-catalyzed cyclization of unsaturated substrates, dimerization, electrophilic aromatic substitution, oxidation and ylide formation followed by sigmatropic rearrangement. Without exception, each intermolecular process has its intramolecular counterpart. Indeed it is the success of intramolecular processes that has maintained the high level of interest in diazocarbonyl compounds as synthetic intermediates. Undoubtedly the single most significant contribution to the recent surge of interest in diazocarbonyls which has greatly extended their usefulness in synthesis was the discovery by the Belgian group of Teyssié, Hubert, and Noels and their coworkers of rhodium carboxylate catalysis.[85-93] Although copper catalysts also have important uses in this area, particularly in cyclopropanation, they do not have the broad spectrum of reactivity associated with rhodium(II) carboxylates which are catalytically active, not just in cyclopropanation, but in C–H, O–H, S–H, and N–H insertion and in aromatic cycloaddition. The Belgian group first introduced rhodium(II) acetate and later were able to modulate catalytic activity using the trifluoroacetate, pivalate, and octanoate.[85-93] Many Rh(II) carboxylates are now readily available. Another feature of the catalyzed reactions that has emerged over the past year or so is the scope for use of chiral catalysts for asymmetric synthesis (*vide infra*).

A. α,α-Substitution Reactions

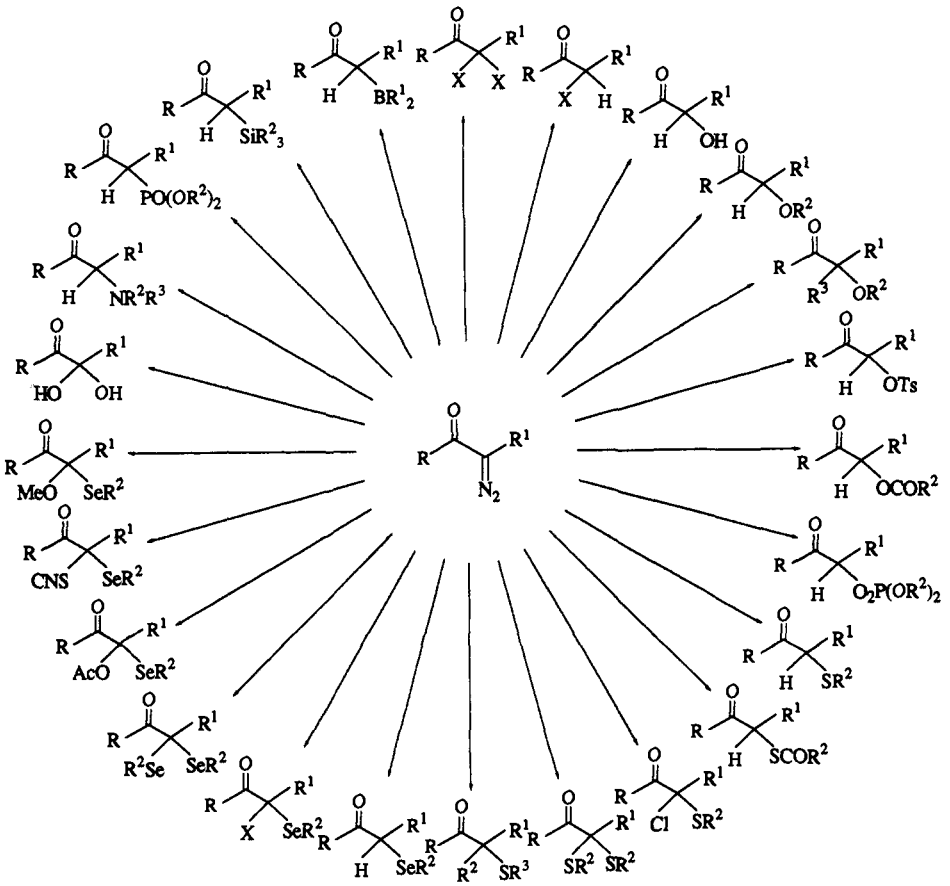
1. Introduction

α-Diazocarbonyls undergo an impressive array of α,α-substitution reactions of the type summarized in Scheme 21 in which the diazo group is replaced by two new substituents.

Scheme 21

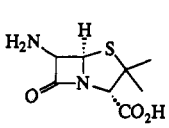
Most diazocarbonyl reactions are in fact α,α-substitutions, but we here restrict this category to processes where X and/or Y are heteroatoms. Although the adduct is formally the product of insertion into the X–Y bond, mechanistically there probably exists a broad spectrum of processes ranging from uncatalyzed electrophilic attack on the diazocarbonyl group to carbene, carbenoid, or ylide formation in situations where thermolysis, photolysis, or metal ion catalysis is employed. Scheme 22 gives some idea of the scope for variation in the reagent with much information now available for reactions in which X–Y is molecular halogen, or where X is a hydrogen atom and Y a halogen or an oxygen, nitrogen, phosphorus, sulfur, selenium, or silicon-based group. The process thus represents a quite general approach to the regiospecific mono- or difunctionalization of a ketone, in many cases under essentially neutral conditions. Furthermore, since many acyclic diazo ketones can be obtained from acyl chlorides, α,α-substitution represents a method of regiospecific functionalization which does not depend on the availability of the parent ketone. It is unnecessary to review here all the reactions in Scheme 22 individually. For convenience in the following discussion they have been collected into groups.

Scheme 22

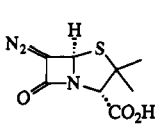


2. X–Y = F_2, Cl_2, Br_2, I_2

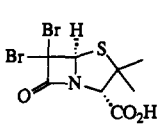
It has been known for many years that chlorine, bromine, and iodine displace nitrogen from α-diazocarbonyls, furnishing α,α-dihalogenated products.[94] Although these reactions have not been employed extensively in simple systems as routes to halogenated ketones, they are central to several syntheses of novel β-lactam antibacterials and β-lactamase inhibitors such as penams and sulbactam from 6-aminopenicillanic acid (6-APA) **28** via its 6-diazo derivative **29**. In fact, in a much wider context, diazocarbonyl compounds have acquired a major role in bicyclic β-lactam chemistry, not just through extensive use of **29** for functional group interconversion in 6-APA, but as intermediates for vital ring closure via N–H insertion reactions in penem total synthesis (*vide infra*). Although the diazo derivative **29** of 6-APA can be isolated and is stable, it is frequently generated and used *in situ*.



28



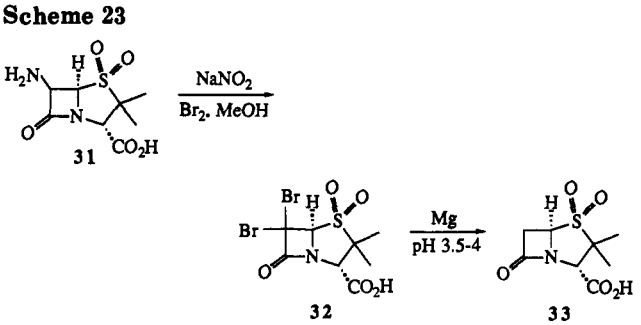
29



30

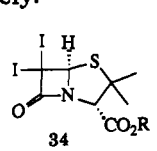
Clayton[95] was among the first to observe the formation of dibromide **30** from 6-APA under diazotization conditions. Volkmann and his co-workers[96] obtained **30** in 60% yield by adding 6-APA **28** to a cold dichloromethane–sulfuric acid mixture containing sodium nitrite and bromine. Diazotization/bromination of 6-aminopenicillanic acid *S,S*-dioxide (**31**) can be significantly influenced by carrying out the reaction in

Scheme 23

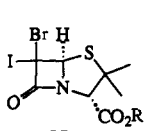


the presence of an alcohol. Kapur and Fasel[97] reported that nearly 90% yield of dibromide **32** can be obtained by replacing sulfuric acid with hydrobromic acid in the presence of methanol. Oxidation of **30** to sulfone **32** followed by reductive removal of both halogen atoms furnishes the antibiotic sulbactam **33** (Scheme 23). Dibromide **30** is also a key intermediate in the synthesis of cephalosporin and carbapenam classes of β-lactam antibiotics.[98] Furthermore, with a chain reaction mediated by tributyltin radical, the ester derivative of **30** can be converted stereoselectively to the 6β-alkylpenicillanate.[99]

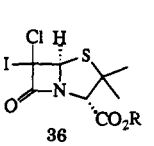
The 6-diiodo derivative **34**[95] can also be produced by a diazotization procedure and mixed halides are also accessible, IBr and ICl furnishing **35** and **36**, respectively.[96,100]



34

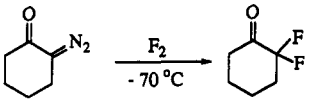


35

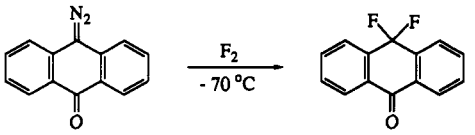


36

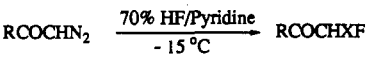
Scheme 24



Scheme 25

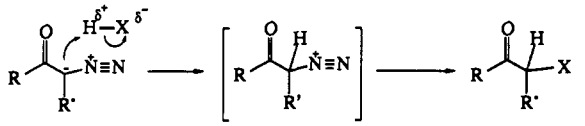


Scheme 26



R = Ph, C_6H_{11}, C_2H_5. C_2H_5O; X = Cl, Br, I

Scheme 27



The reaction of fluorine with diazocarbonyl compounds is destructively exothermic and it was not until Leroy and Wackselman[101] introduced the moderating device of diluting this halogen with an inert gas at low temperatures that α,α-difluoro adducts could be isolated. Patrick and co-workers[102] used Freon 11 as the inert diluent to convert 2-diazocyclohexanone into 2,2-difluorocyclohexanone in 65% yield (Scheme 24). A somewhat similar set of conditions was used to prepare the difluoroanthrone in Scheme 25.

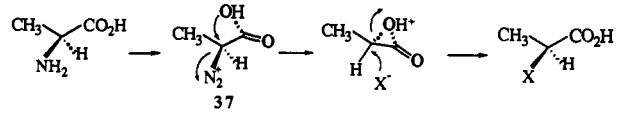
Mixed α-fluoro-α-halo ketones are formed from α-diazo ketones on reaction with either halide ion or *N*-halosuccinimide in 70% polyhydrogen fluoride at 0 °C.[103] Scheme 26 provides illustrative examples. Recently, Mascaretti[104] reported the stereoselective synthesis of 6-fluoro-6-halopenicillanates.

3. X–Y = Hydrogen Halide

The hydrogen halides, with the exception of hydrogen iodide, react rapidly with diazo ketones to furnish α-halo ketones.[105,106] The mechanisms of these reactions are probably very similar to that of halogen substitution, initial electrophilic attack on the diazocarbonyl group furnishing a diazonium ion (Scheme 27) from which nitrogen is displaced by halide ion in an S_N2 process.

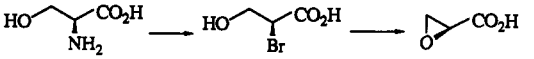
Of course Scheme 27 does not represent the only route to carbonyl-substituted diazonium ions, an important alternative being dehydration of a protonated diazotic acid generated by nitrozation of a typical amino acid such as L-alanine as shown in Scheme 28. It is appropriate to refer briefly here to the latter process for although the stereochemical outcome of the reaction precludes the intervention of a *neutral* α-diazocarbonyl intermediate, it does involve diazotization and the stereochemistry of the substitution is sufficiently well defined to make the reaction a very useful route to optically active α-halogen and α-hydroxy acids from natural amino acids. As Ingold[107] made clear in the 1950s, the neighboring carboxylic acid group of **37** (Scheme 28) plays a crucial role in the latter stages of the reaction, participating in the expulsion of nitrogen

Scheme 28

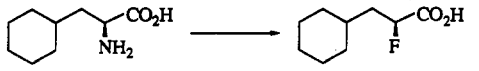


37

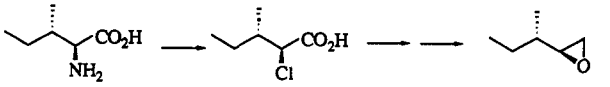
Scheme 29



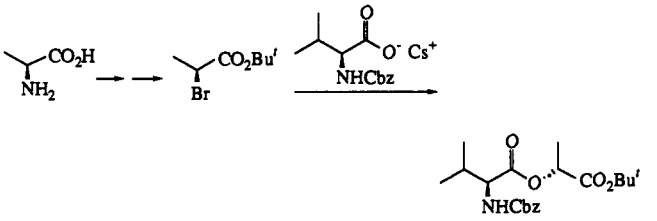
Scheme 30



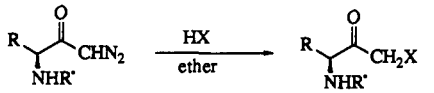
Scheme 31



Scheme 32



Scheme 33



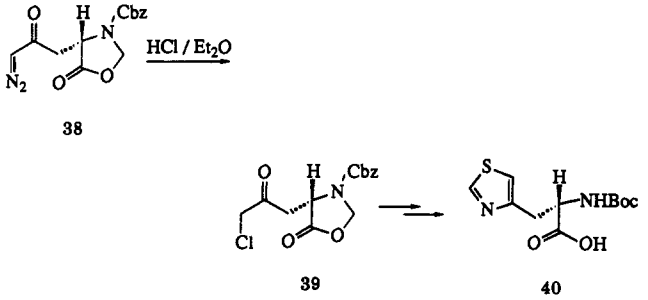
R* = protecting group; X = Cl, Br

and thereby ensuring that the attacking halide ion, X^-, enters the α-position with retention of configuration. Schemes 29–32[108–113] illustrate some applications of this methodology to the production of optically active α-substituted carboxylic acids.

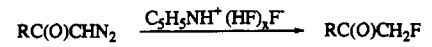
The hydrohalogenation–diazotization process has been used extensively with 6-APA. Cignarella, Pifferi, and Testa[114] originally found that diazotization of 6-APA with sodium nitrite in dilute hydrochloric acid produced the 6-chloropenicillanic acid. The stereochemistry of the product was later established by McMillan and Stoodley[115] who also confirmed that the 6-diazo derivative **29** was an intermediate in the reaction. The 6-bromopenicillanic acid derived from 6-APA has been extensively used as the key intermediate in the synthesis of penam antibiotics.[116–118]

Hydrohalogenation of diazo ketones derived from amino acids offers an attractive route to optically active N-protected α-amino-α′-bromo and chloro ketones of the type shown in Scheme 33.[119] The diazo ketone can be titrated with ethereal hydrogen chloride or hydrogen bromide without detectable amounts of racemization. This methodology has been extensively applied in the formation of chloromethyl ketone from peptides. The functionalized cyclic tetrapeptide HC-toxin analogue, *cyclo*[L-2-amino-8-oxo-9-chlorononanoyl-D-prolyl-L-alanyl-D-alanyl], was prepared via the above method.[120] The products of hydrohalogenation of diazo ketones are useful reaction intermediates, e.g. for keto azides.[119] The chloromethyl ketone **38**, prepared from the doubly protected L-aspartic acid-derived diazo ketone **39**,

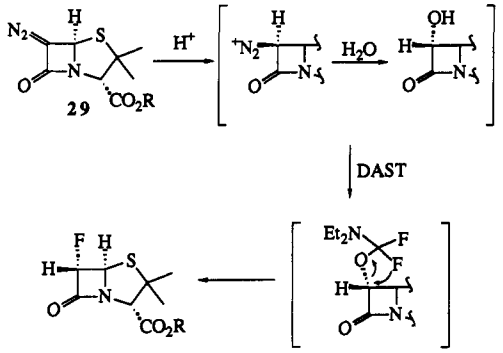
Scheme 34



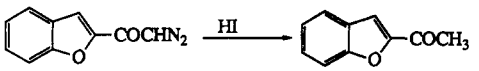
Scheme 35



Scheme 36



Scheme 37



served as a key intermediate in the synthesis of *N*-(*tert*-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine **40** (Scheme 34).[121]

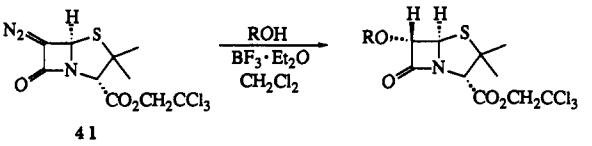
α-Fluoro ketones can be prepared by reaction of α-diazo ketones with 70% polyhydrogen fluoride–pyridine (Scheme 35).[122] Similarly, diazo ketones derived from *N*-phthaloyl amino acids can be converted into the corresponding fluoro ketones.[123] More recent work with **29** indicates that this kind of transformation can also be accomplished with DAST where the α-hydroxy ketone is believed to be an intermediate (Scheme 36).[104]

Unlike the other hydrogen halides, hydrogen iodide does not normally produce α-iodo ketones from α-diazo ketones. Rather, its reducing power results in the formation of methyl ketones.[124] The process can be very efficient; it has been recommended as a particularly mild two-step procedure for converting an acid chloride into a methyl ketone, an example of which is shown in Scheme 37.

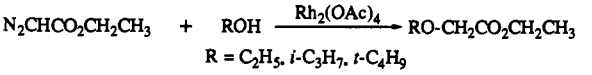
4. X–Y = H–OH, H–OR, H–OCOR, H–OSO$_2$R, H–OP(O)(OR)$_2$

There have been several imaginative uses of α,α-substitution of water and of alcohols to α-diazocarbonyl compounds in contemporary organic synthesis. Although such additions can be brought about by Brönsted and Lewis acids, notably dilute sulfuric acid and boron trifluoride, addition of alcohols to 6-diazopenicillanate **41**[125] in Scheme 38 representing an example of the latter, it has been suggested that metal salts offer greater advantages in terms of selectivity and efficiency.

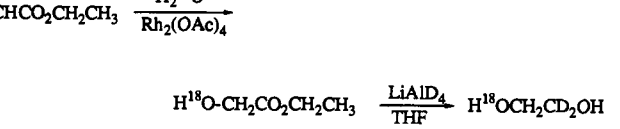
Scheme 38



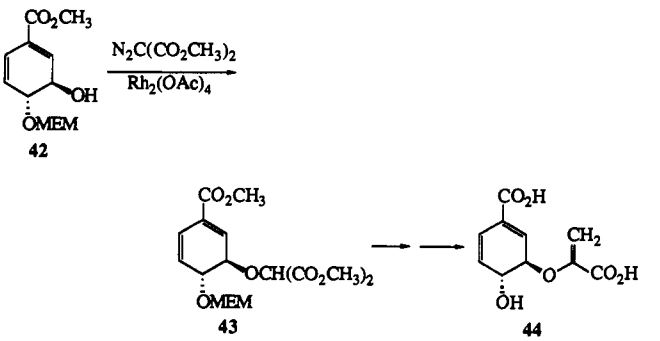
Scheme 39



Scheme 40



Scheme 41



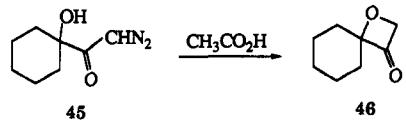
The Wolff rearrangement of diazocarbonyls in the presence of water, alcohols, and carboxylic acids can be virtually eliminated in favor of α,α-substitution in the presence of copper, nickel, palladium, and rhodium catalysts. Of these, rhodium(II) carboxylates appear to be the catalysts of choice, promoting insertion into the O–H bond at very low catalyst concentrations at room temperature as, for example, in Scheme 39.[85,93]

In a mechanistic study of the structure and stability of $C_2H_4O^+$ gas-phase isomers, Baumann and McLeod[126] synthesized a doubly labeled ethylene glycol (Scheme 40) from ethyl diazoacetate and H_2O^{18} with catalysis by rhodium(II) acetate, this route having been chosen so as to produce the maximum incorporation of the ^{18}O label.

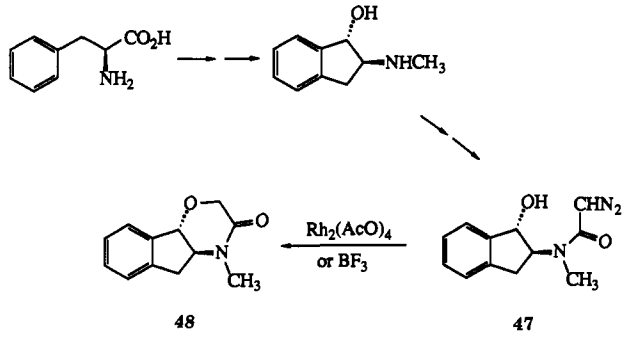
Ganem and co-workers,[127,128] faced with the difficult task of attaching an enol pyruvate side chain to an already unstable diol in their synthesis of chorismic acid (Scheme 41), found that treatment of hydroxy ester **42** with diazomalonate in the presence of rhodium(II) acetate furnished the O–H insertion product **43** suitable for further elaboration into the natural product **44**.

Berchtold[129] and Bartlett[130] and their respective collaborators have also used this approach to the introduction of the enol pyruvate side chain of shikimate-derived metabolites. Furthermore, the phosphonate analogues of chorismic acid have also been synthesized via an approach which involves the rhodium acetate-catalyzed insertion of diazo phosphonoacetate with 2-cyclohexenol.[131,132] Cholesterol diazoacetate **26**

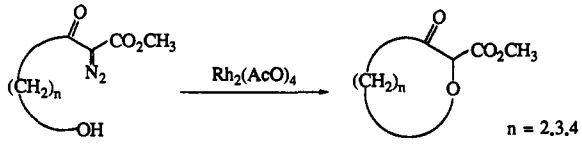
Scheme 42



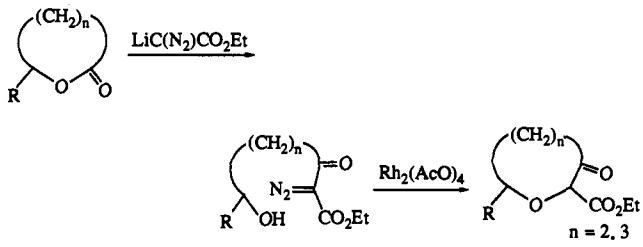
Scheme 43



Scheme 44



Scheme 45



has been synthesized for evaluation as a photolabeling agent for use in biological systems; photolysis in methanol leads to O–H insertion.[73]

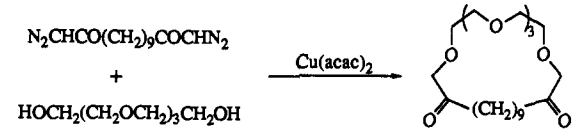
Several aspects of the intramolecular version of O–H insertion of alcohols into diazocarbonyl substrates have been studied, the earliest example being that of Marshall and Walker[133] who observed that diazo ketone **45** cyclizes in glacial acetic acid to form the oxetane derivative **46** (Scheme 42).

McClure et al.[35] found that L-phenylalanine could be transformed into the tetrahydroindeno[1.2-*b*]-1,4-oxazin-3(2*H*)-one (**48**) in Scheme 43 without racemization, cyclization of the intermediate vicinal amino alcohol having been accomplished by O–H insertion of β-hydroxy diazoacetamide **47**; rhodium acetate and boron trifluoride were both catalytically active in the key step, although in this case the Lewis acid gave the better yield.

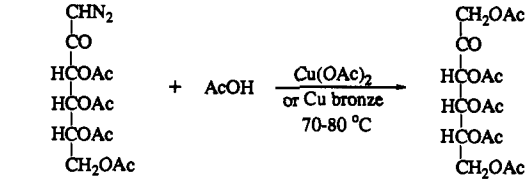
Rapoport[134] and Moody[135–141] and their respective coworkers have made extensive use of rhodium-catalyzed O–H intramolecular insertion of alcohols in the construction of five-, six-, and seven-membered cyclic ethers. Some examples are shown in Schemes 44 and 45. In Scheme 45 the acyclic diazocarbonyl precursor was conveniently constructed by a ring-opening reaction of the appropriate lactone with lithio diazoacetate.

A final example of the O–H insertion reaction of alcohols is the combined intermolecular–intramolecular

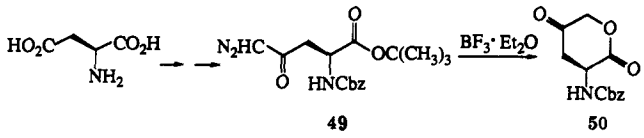
Scheme 46



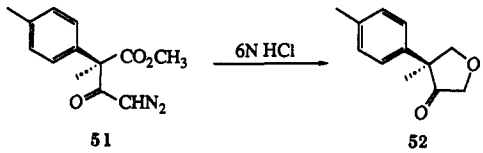
Scheme 47



Scheme 48



Scheme 49



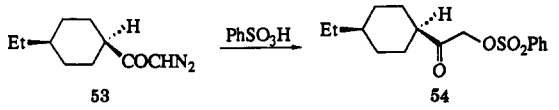
process in Scheme 46 whereby an α,ω-bifunctional diazo ketone combines with an ethylene glycol to produce a macrocyclic diketo crown ether. In this instance the catalyst employed was Cu(acac)$_2$.[142]

Carboxylic acids react with α-diazo ketones on warming to form α-keto esters. Although catalysts are usually unnecessary, copper(II)[143,144] or rhodium(II)[85] compounds or boron trifluoride[125] are often added under which conditions Wolff rearrangement as a competing reaction is suppressed. Wolfrom[144] incorporated this reaction into an homologation sequence in carbohydrate chemistry, converting, for example, a hexose carboxylic acid into the heptose diazo ketone in Scheme 47 and thence to the acetoxy ketone upon addition of acetic acid.

A recent example of intramolecular carboxylate participation occurs in the sequence shown in Scheme 48[145] in which (*S*)-aspartic acid was transformed into diazo ketone **49**. Exposure of the latter to boron trifluoride etherate in nitromethane furnished the aminoketone lactone **50**. In a similar fashion exposure of diazo ketone **51** to 6 N HCl in diethyl ether brought about cyclization to the butyrolactone system (**52**) shown in Scheme 49.[146]

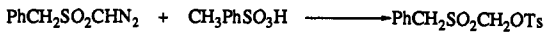
The reaction of diazo ketones with sulfonic acids constitutes a convenient, rapid route to α-keto sulfonates. Methane- and ethanesulfonic acid, trifluoromethanesulfonic acid, camphorsulfonic acid, and a variety of substituted benzenesulfonic acids have all been employed in reactions which generally proceed rapidly at room temperature without external catalysis.[147–153] The transformation of cyclohexyl diazo ketone **53** into the arenesulfonate **54** in Scheme 50 on treatment with benzenesulfonic acid represents a recent application.[147] A variation on this theme is the α,α-substitution of *p*-toluenesulfonic acid with the diazo sulfone in Scheme 51[148] in a novel synthesis of sulfone

Scheme 50

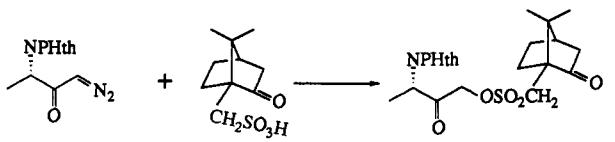


53 54

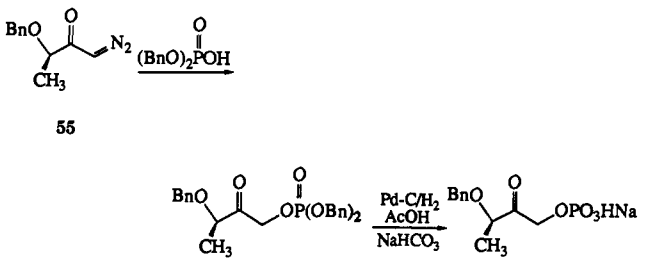
Scheme 51



Scheme 52

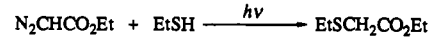


Scheme 53



55 56 57

Scheme 54



α-tosylates, mixing the reactants at room temperature in dichloromethane being sufficient to bring about reaction.

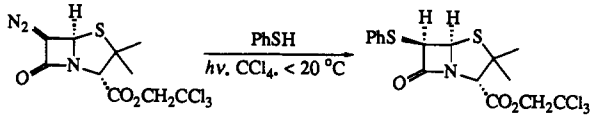
The diazo ketone–*p*-toluenesulfonic acid reaction has been used to generate tosylates suitable for photochemical production of α-keto carbonium ions.[149] The reaction of chiral diazo ketones with (+)-camphorsulfonic acid has been used to assess enantiomeric purity; the reaction of the alanine derived diazo ketone in Scheme 52 provides an illustrative example.[150]

α-Hydroxy ketone phosphates can be synthesized by reaction of diazo ketones with dibenzyl phosphate. This transformation was the key step in Whitesides's[154] synthesis of analogues of dihydroxyacetone phosphate **57**. Treatment of the optically active diazo ketone **55** with dibenzyl phosphate afforded the protected phosphate **56**. Deprotection *via* hydrogenation over palladium gave **57** (Scheme 53).

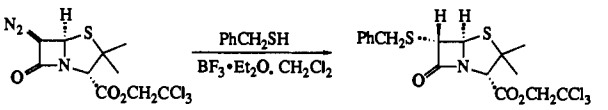
5. X–Y = H–SR, Cl–SR, RS–SR

α,α-Substitution reactions of diazocarbonyls offer versatile ways of placing sulfur-containing substituents adjacent to carbonyl groups in ketones and esters. Photolysis of ethyl diazoacetate in ethanolic ethanethiol leads to carbene insertion into the S–H bond producing moderate yields of ethyl (ethylthio)acetate. The same process can be brought about thermally using AIBN as a radical initiator under which conditions the sulfenylated product is obtained in very high yield (Scheme 54).[155] The photochemical route was used by Sheehan and co-workers[156] to produce the 6β-(phenylthio) adduct as a major product shown in Scheme 55

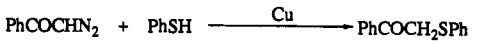
Scheme 55



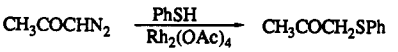
Scheme 56



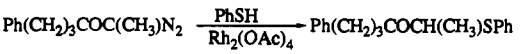
Scheme 57



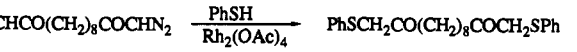
Scheme 58



Scheme 59



Scheme 60

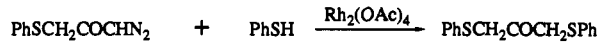


from 6-diazopenicillanate and thiophenol. A short time later Thomas et al.[125] made the contrasting observation that boron trifluoride-catalyzed addition of benzyl thiol to the same substrate produced the 6α-adduct exclusively (Scheme 56).

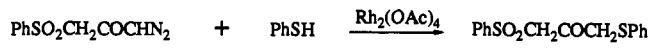
Metal-catalyzed addition of thiols to diazocarbonyls was first investigated by Yates[157] who used copper to catalyze the addition of thiophenol to diazoacetophenone (Scheme 57); in this study thiophenol was employed as the reaction solvent or was present in considerable excess. Very little subsequent work was done in this area until the Belgian group discovered the high catalytic activity of rhodium(II) acetate toward thiophenol addition to ethyl diazoacetate in nonpolar solvents.[86] This discovery, coinciding with the more general realization of the versatility of α-sulfenylated carbonyl compounds in synthesis, prompted a systematic study of the reactions of both acyclic and cyclic diazo ketones with thiophenol.[158] Simple terminal α-diazo ketones, e.g. diazo ketone in Scheme 58, and thiophenol combine rapidly at room temperature in benzene under rhodium(II) acetate catalysis to furnish α-phenylthio ketones in excellent yield. The nonterminal α-diazo ketone in Scheme 59, prepared from the appropriate acyl chloride and diazomethane, produces the adduct shown when similarly treated, thus demonstrating the regiochemical potential of this route to unsymmetrically sulfenylated ketones which would be difficult to obtain by conventional enol or enolate chemistry with the parent ketone. Acyclic bis diazo ketones also react readily to form bis α-phenylthio diones, e.g. as in Scheme 60.

Diazoketones bearing additional sulfur-containing substituents are also amenable to α,α-substitution with thiophenol, sulfenyl, and sulfonyl precursors affording the products shown in Schemes 61 and 62.[159] α-Diazocycloalkanones as, for example, in Scheme 63 also undergo smooth S–H insertion.[158] Very recently this reaction has been used to elaborate the carboxylic acid

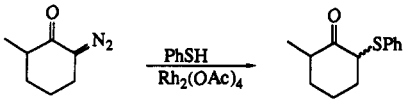
Scheme 61



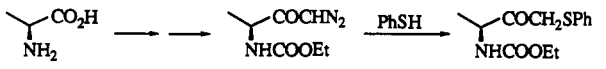
Scheme 62



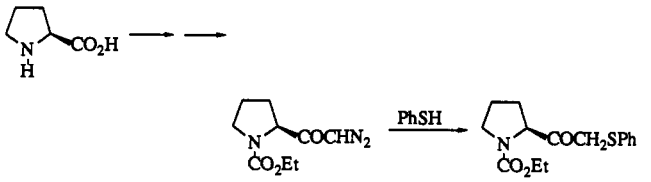
Scheme 63



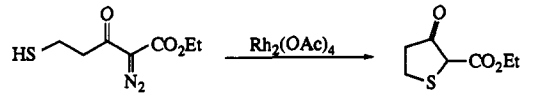
Scheme 64



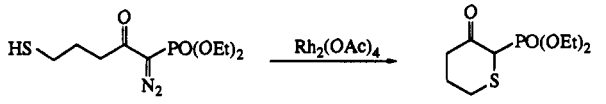
Scheme 65



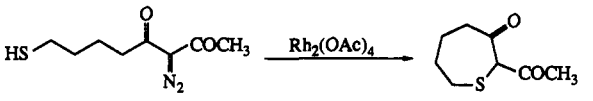
Scheme 66



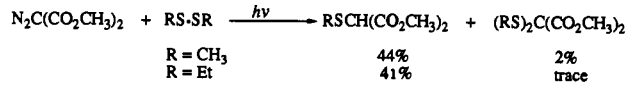
Scheme 67



Scheme 68



Scheme 69

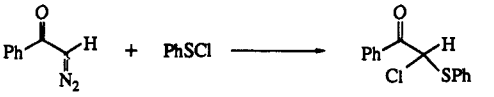


function of N-protected amino acids such as alanine and proline each of which can be transformed, via their respective diazo ketones, into sulfenyl adducts of the type shown in Schemes 64 and 65.[160]

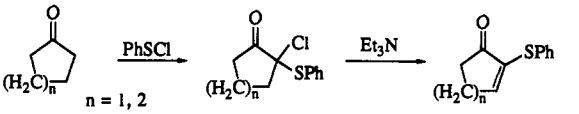
The intramolecular version of the rhodium-catalyzed S–H insertion of diazocarbonyls has been reported by Rapoport[134] and Moody[136,161] and their respective co-workers. Five-, six-, and seven-membered cyclic adducts derived from carbenoid S–H insertion are shown in Schemes 66–68. Reactions of carbenoids with disulfides have received very little attention as potential routes to acyl thioacetals. The photochemical route has been explored by Ando et al.[162] who found that monosulfenation tended to predominate over disulfenation. Typically, methyl diazomalonate and dimethyl disulfide gave the product distribution shown in Scheme 69 on benzophenone sensitized photolysis.

Of the various other reactions of diazocarbonyl compounds with sulfur-based reagents that have received attention, those involving benzenesulfenyl chloride show potential in synthesis. The original observation that benzenesulfenyl chloride and diazo ketones, e.g. Scheme 70, combine to form α-chloro-α-(phenylthio) adducts was made in 1955 by Weygand and Bestmann.[163] The reaction occurs spontaneously at or below room temperature. The implications of this double substitution, which places two reactive substituents adjacent to a carbonyl group, have been explored in several ways. In the first place, addition of PhSCl followed by hydrogen chloride elimination in diazo ketones with β-hydrogen atoms offers a route to α-sulfenylated α,β-enones. In practice, mixing the reactants at 0 °C followed by addition of triethylamine is all that is necessary to bring about such transformations, examples of which are shown in Scheme 71.[164] Secondly, the α-chloro-α-(phenylthio) adducts are powerful electrophiles for intermolecular and intramolecular aromatic alkylation. For example, sequential treatment of diazoacetone (Scheme 72) with PhSCl, and benzene with stannic chloride catalysis affords the sulfenyl benzyl ketone. The intramolecular reaction leading to a sulfenylated β-tetralone is illustrated in Scheme 73.[164] Yet another outlet for these α,α-adducts of PhSCl and diazo ketones is their ready conversion to (phenylthio)acetals and ketals on exposure to thiophenol with zinc chloride catalysis; Scheme 74 is a representative example.[165]

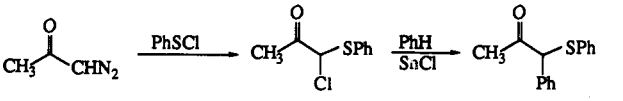
Scheme 70



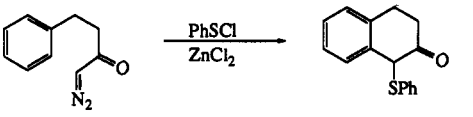
Scheme 71



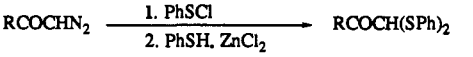
Scheme 72



Scheme 73



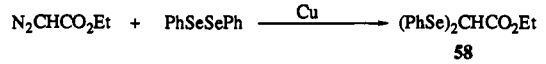
Scheme 74



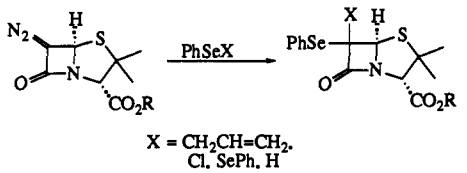
6. X–Y = H–SeR, Cl–SeR, Br–SeR, I–SeR, F–SeR, RSe–SeR

There are close similarities between the reactions of diazocarbonyls with organosulfur reagents and those of their organoselenium counterparts, although the latter are rather less well developed. Pellicciari and his co-workers[166] reported that ethyl diazoacetate and diphenyl diselenide produced the α,α-diphenylseleno adduct 58 (Scheme 75). Thomas and his co-workers[167]

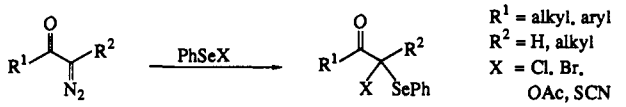
Scheme 75



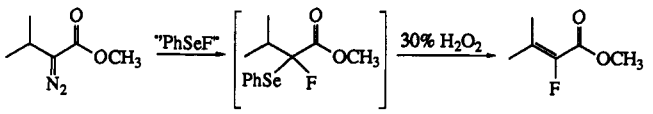
Scheme 76



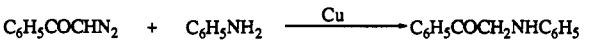
Scheme 77



Scheme 78



Scheme 79



reported the reactions of 6-diazopenicillanates with allyl phenyl selenide, phenylselenenyl chloride, diphenyl diselenide, and benzeneselenol to yield the corresponding 6,6-disubstituted penicillanates; all but reaction with phenylselenenyl chloride required catalysis (Scheme 76). McKervey and co-workers[168,169] reported that phenylselenenyl derivatives, PhSe–X (X = Cl, Br, OAc, SCN), react readily with α-diazo ketones with loss of nitrogen, to furnish α-phenylselenenyl-α-X ketone adducts in very good yields (Scheme 77). Only reaction with phenylselenenyl thiocyanate required catalysis. Similarly, reactions of PhSeSeCN with diazo ketones have also been reported.[170]

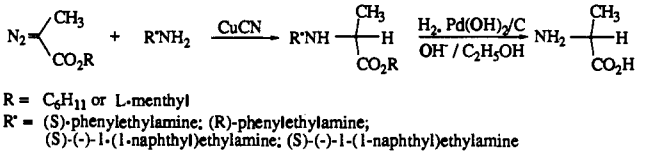
α-Fluoro-α,β-unsaturated carbonyl compound **60** can be prepared via a sequence involving the reaction of a diazocarbonyl such as **59** with a phenylselenenyl fluoride equivalent (Scheme 78). The phenylselenenyl fluoride equivalent can be prepared *in situ* by the reaction of silver(I) fluoride with phenylselenenyl bromide in dichloromethane under ultrasound irradiation. The corresponding α-fluoro-α-phenylseleno carbonyl adduct was oxidized to α-fluoro-α,β-unsaturated ester **60**.[171]

7. X–Y = H–NR¹R²

The insertion of α-keto carbenes or carbenoids into N–H bonds attracted little attention as a synthetic route to α-amino ketones or esters until 1978 when the first example of its use in bicyclic β-lactam synthesis was published from Merck laboratories.[172] Since then there have been numerous demonstrations of the power of this reaction, especially the intramolecular version leading to nitrogen heterocycles. The history of the N–H insertion reaction parallels closely that of its O–H and S–H counterparts, with early evidence that α-diazo acetophenone and aniline under copper catalysis yield the α-anilino ester in Scheme 79.[157] Cuprous cyanide

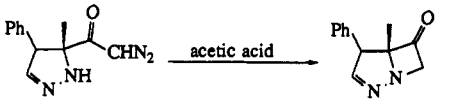
Scheme 80

Scheme 81

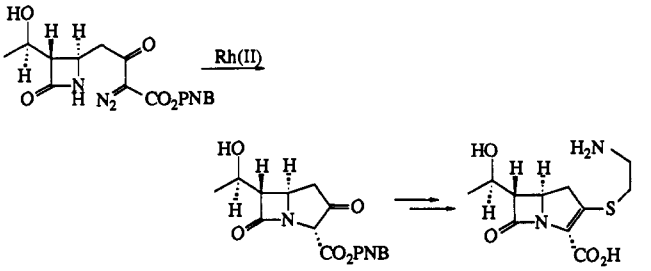


R = C_6H_{11} or L-menthyl
R' = (S)-phenylethylamine; (R)-phenylethylamine; (S)-(-)-1-(1-naphthyl)ethylamine; (S)-(-)-1-(1-naphthyl)ethylamine

Scheme 82



Scheme 83

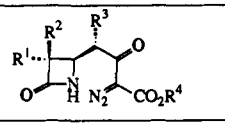
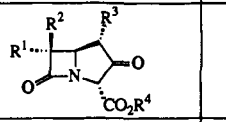
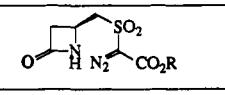
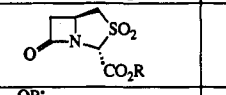
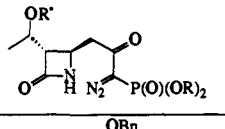
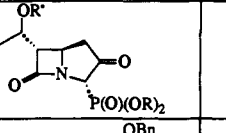
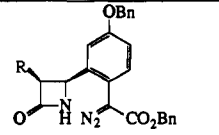
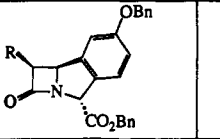
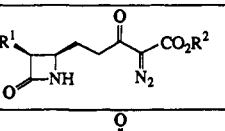
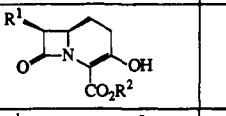
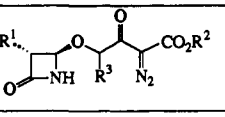
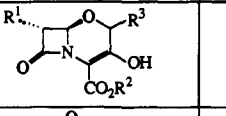
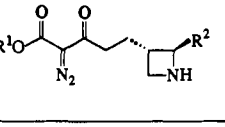
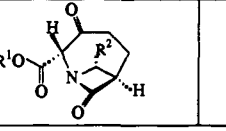


or chloride were later used as catalysts for the insertion of ethyl diazoacetate into the N–H bond of piperidine, morpholine, and *n*-butylamine.[173] Almost inevitably now, introduction of rhodium catalysts led to major improvements, the reaction in Scheme 80 furnishing 70% of the insertion product in the presence of rhodium(II) acetate.[86] Nicoud and Kagan[174] used cuprous cyanide as catalyst in the sequence shown in Scheme 81, the objective being to bring about N–H insertion of diazopropionates with chiral benzylamines and thereby effect an asymmetric synthesis of alanine after debenzylation and hydrolysis. In the event, although the insertion reaction was successful, the enantioselection accompanying the creation of the new stereogenic center was disappointingly low (15–26% ee).

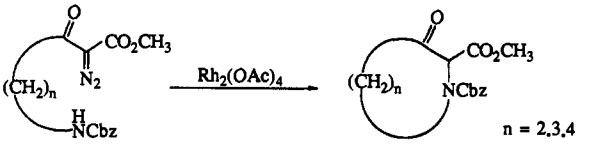
By far the most successful N–H insertions have been in intramolecular reactions leading to small-ring bicyclic heterocycles. Although Moore and Medeiros[175] in 1959 reported the formation of an azacyclobutane derivative from the reaction of the diazo ketone in Scheme 82 with acetic acid, the potential of N–H insertion was not appreciated until Cama and Christensen[172] at Merck reported the conversion of a penicillin analogue into the carbapenem nucleus via rhodium-catalyzed insertion of a keto carbenoid into the N–H bond of the β-lactam, a process which was later to become the key step in the Merck synthesis of the antibiotic thienamycin (Scheme 83).[176,177] The N–H insertion proceeds in yields far exceeding 90% on a production scale.

This and many subsequent applications, a few of which are summarized in Table 2,[1b] suggest that the N–H carbenoid insertion reaction is probably the most efficient method yet devised for synthesizing highly strained β-lactam bicyclic systems. This transformation is also among the most practicable carbenoid reactions in organic synthesis.

Table 2. Synthesis of β-Lactam Bicyclic Systems

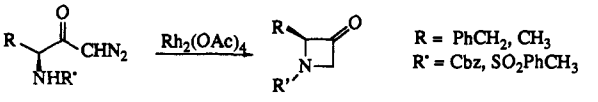
Diazocarbonyl	Product	Reference
		176-202
		203
		204
		205, 206
		207-209
		210-212
		213

Scheme 84



n = 2,3,4

Scheme 85

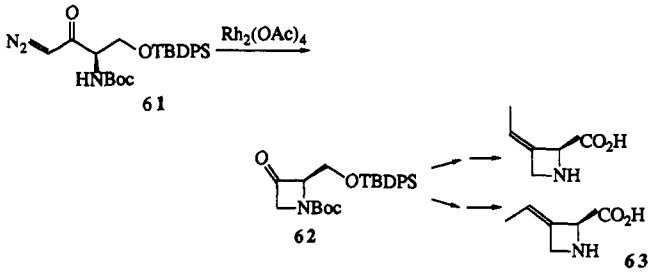


R = $PhCH_2$, CH_3
R' = Cbz, SO_2PhCH_3

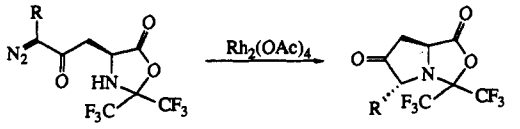
Intramolecular carbenoid N–H insertion has been demonstrated to be a mild, efficient, and regiospecific method for the construction of various-sized aza rings (Scheme 84).[134] The formation of the 3-oxoazetidine-2-carboxylate (Scheme 84, $n = 1$) via rhodium-catalyzed N–H insertion has received considerable attention. Boc-protected 3-oxoazetidine-2-carboxylate, obtained via this protocol, was further transformed to the racemic polyoximic acid which is a constituent of the nucleoside tripeptide antibiotic polyoxins.[214] Diazo ketones derived from N-protected α-amino acids undergo intramolecular N–H insertion under rhodium(II) catalysis to form optically active substituted 3-azetidinones (Scheme 85).[215] The substituted 3-azetidinone **62**, obtained from the N- and O-protected D-serine-derived diazo ketone **61**, can be transformed into optically active *cis*- and *trans*-polyoximic acid **63** (Scheme 86).[216]

Other examples of intramolecular N–H insertion leading to five- and six-membered nitrogen-containing heterocycles include those in Schemes 87[217] and 88,[218] the catalyst being rhodium acetate in both cases.

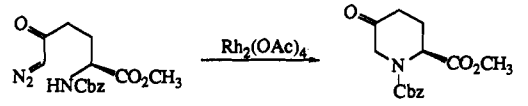
Scheme 86



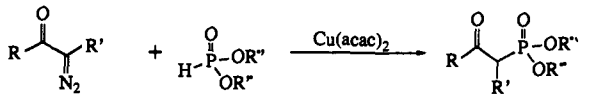
Scheme 87



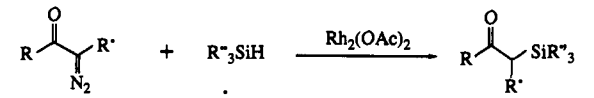
Scheme 88



Scheme 89



Scheme 90



R = OC_2H_5, R' = H, R" = Ph; R = Ph, R' = CH_3, R" = C_2H_5

8. X–Y = H–P(O)(OR)₂

Carbenoid insertions into the P–H bond of phosphites are rather less well developed. Polozov and co-workers[219] have reported a carbenoid P–H insertion which is illustrated in Scheme 89. The diazo compounds studied included α-diazo ketones, α-diazo esters, and 2-diazo 1,3-diketones.

An analogous reaction with a diazo ketone derived from phthaloyl-protected L-alanine proceeds via P–H insertion with diethyl hydrogen phosphite. However, extension of this reaction to other types of protected (for example, Cbz, Boc) amino acid-derived diazo ketones was unsuccessful.[220]

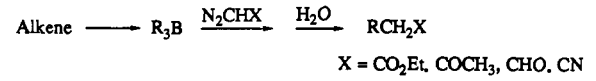
9. X–Y = H–SiR₃

Carbenoid insertion into Si–H bonds has been used to give the corresponding α-silyl carbonyl adducts. However, this type reaction has only been employed by Doyle's group using simple diazocarbonyl precursors as shown in Scheme 90.[221]

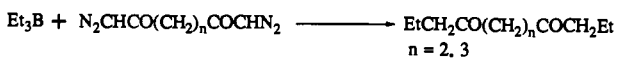
10. X–Y = R–BR₂

Trialkylboranes, generated from alkenes via hydroboration, react with α-diazocarbonyl compounds with expulsion of nitrogen to form intermediates which on hydrolysis furnish α-alkylated carbonyl compounds. Hooz and his co-workers have reported such alkylations with ethyl diazoacetate, diazoacetone, diazoaceto-

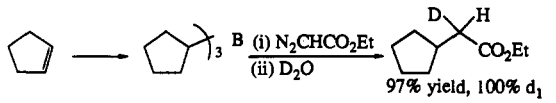
Scheme 91



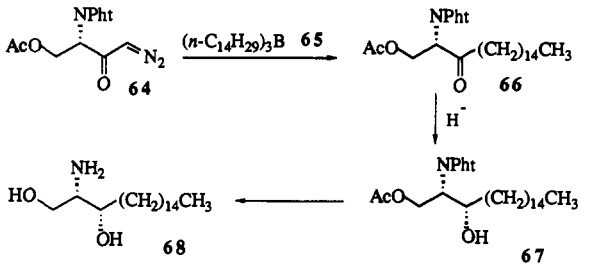
Scheme 92



Scheme 93



Scheme 94



phenone, diazoacetaldehyde, diazoacetonitrile.[222-225] The process, overall, summarized in Scheme 91, represents the homologation of an alkene to a carbonyl compound or a nitrile.

Alkylation of bis diazo ketones is also possible, triethylborane furnishing symmetrical diketones of the type shown in Scheme 92 in high yield.[226] Alkylation with boranes derived from terminal alkenes and cyclopentene proceed rapidly and in very good yields at low temperatures while sterically hindered boranes react sluggishly with lower yields of products.[223]

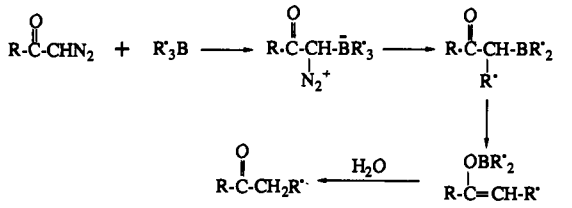
When D_2O is used instead of H_2O in the hydrolytic stage of the process, high yields of site-specific monodeuterated esters and ketones can be produced. Alkylation of ethyl diazoacetate with cyclopentene (Scheme 93) provides an illustrative example.[227]

Newman[228,229] has applied this methodology to the synthesis of D-*threo*-sphinganine **68**. Thus, treatment of the diazo ketone **64** derived from the doubly protected L-serine with a trialkylborane **65** gave ketone **66**. A stereoselective reduction of the keto group of **66** with tri-*tert*-butoxyaluminum hydride produced the desired threo configuration in alcohol **67**. Acidic methanolysis of the acetoxy group, followed by hydrazinolysis of the phthaloyl moiety, gave D-*threo*-sphinganine **68** (Scheme 94).

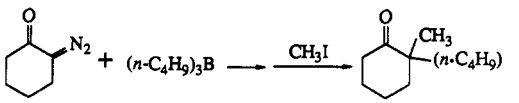
The intermediates responsible for this type of behavior are believed to be enol borinates formed in a sequence commencing with coordination of the diazocarbonyl compound to the acidic trialkylborane and followed by a rapid 1,2-alkyl shift from boron to carbon with loss of nitrogen. Migration of boron to oxygen forms the enol borinate which is rapidly hydrolyzed by water (Scheme 95).

Both Hooz and Pasto recognized that under anhydrous conditions these enol borinates could be intercepted in a variety of synthetically useful processes. Various ways were devised of producing both internal and terminal enol borinates in a regiospecific fashion

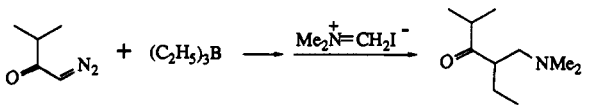
Scheme 95



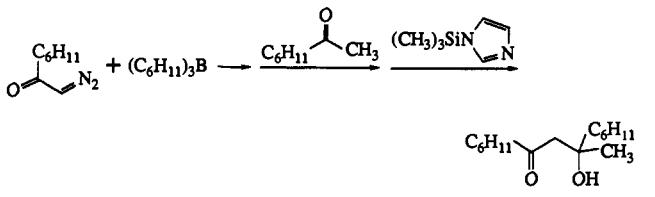
Scheme 96



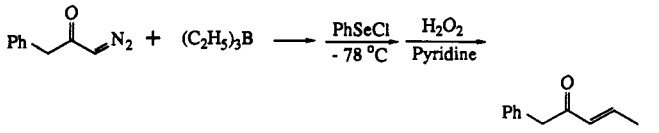
Scheme 97



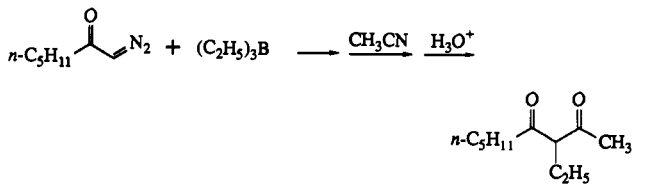
Scheme 98



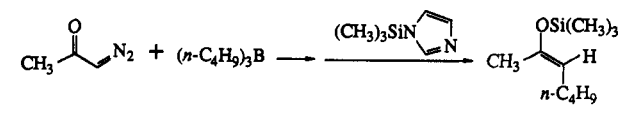
Scheme 99



Scheme 100



Scheme 101



from diazocarbonyl precursors. Significant applications of these intermediates include regiospecific synthesis of α,α-dialkylated ketones (Scheme 96),[230,231] regiospecific synthesis of Mannich bases by reaction with dimethyl(methylene)ammonium iodide (Scheme 97),[232] aldol addition to aldehydes and ketones (Scheme 98),[233] regiospecific synthesis of unsymmetrical acyclic enones by addition of phenylselenyl chloride followed by oxidative elimination (Scheme 99),[234] regiospecific synthesis of 1,3-diketones via boroxazine formation with nitriles (Scheme 100),[235] and regio- and stereocontrolled transformation into enol silyl ethers via reaction with *N*-(trimethylsilyl)imidazole (Scheme 101).[236] In all of these processes a diazocarbonyl precursor was employed to generate the enol borinate.

B. C–H Insertion Reactions

1. Introduction

The past 20 years have witnessed a significant increase in the utilization of diazocarbonyl compounds as precursors in carbon–carbon bond-forming reactions. Intramolecular carbene insertion into C–H bonds has assumed strategic importance in organic synthesis. To demonstrate the broad scope of its applications in synthesis, representative examples of this transformation are highlighted in this section. Insertion reactions of carbenes into C–H bonds have attracted much attention since the first discovery by Meerwein, Rathjen, and Werner.[237] The insertion process can proceed intermolecularly or intramolecularly. From the synthetic point of view, intermolecular C–H insertion is not generally useful because of low selectivity and competition from intramolecular reactions. Therefore, the examples of synthetic applications illustrated here are all intramolecular processes. Intramolecular insertion of keto carbenes into unactivated C–H bonds sometimes allows transformations which would otherwise be difficult to achieve. In this section, reactions have been organized according to the ring size produced on cyclization. In general, five-membered ring formation is the favored process. However, the construction of other ring sizes (in general four- and six-membered rings) by carbene C–H insertion is also possible. The regioselectivity which leads to the control of ring size in a particular molecule depends upon the type of diazo function, the degree of substitution of the carbon where insertion takes place, and steric and electronic factors.

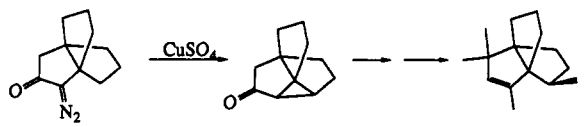
2. Three-Membered Ring Formation

Geometrically rigid structures favor intramolecular insertions. In some special cases C–H insertion results in three-membered ring compounds. For example, diazocamphor **69** was catalytically converted into cyclocamphanone **70** (Scheme 102).[238] The formation of the cyclopropyl ring via C–H insertion has also been used in the stereocontrolled synthesis of (±)-modhephene (**73**, Scheme 103).[239] Thus, treatment of diazo ketone **71** with a copper catalyst afforded the intermediate **72**, which was then converted to **73** via a few subsequent steps.

Scheme 102

69 70

Scheme 103

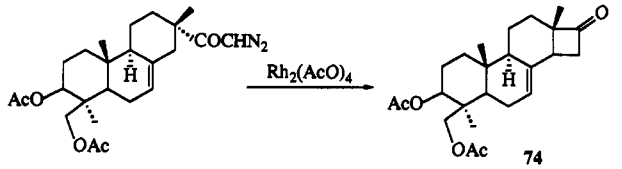


71 72 73

3. Four-Membered Ring Formation

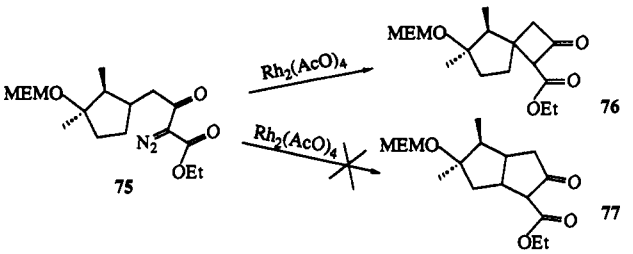
a. Four-Membered Carbocycles. There are few examples of four-membered carbocycle formation via intramolecular C–H insertion.[240–243] It usually is observed as a low-yield product along with five-membered ring formation. However, in some instances with suitable substrates, moderate yields of cyclobutanone products can be obtained. Ceccherelli and co-workers[242] have reported the formation of the D-norsteroid system **74** (yield 53%) (Scheme 104).

Scheme 104



74

Scheme 105

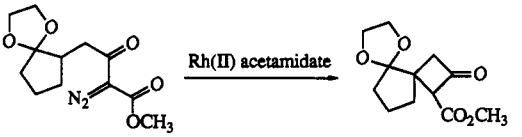


75 76 77

Cane and co-workers[243] reported that catalytic decomposition of diazo ester **75** resulted in spirocyclobutanone **76** in 55% yield; none of the bicycle[3.3.0]-octanone derivative **77** could be detected. It is possible that the combined 1,3-interactions of the MEM ether and the secondary methyl group hinder approach of the carbenoid to the secondary C–H bond, thereby directing attack to the opposite face of the cyclopentane ring on which only a tertiary hydrogen atom is accessible, thus leading to spirocyclobutanone **76** (Scheme 105).

The nature of the transition metal ligands also influence four-membered carbocycle formation. Catalytic decomposition of α-diazo-β-keto ester **78** by rhodium(II) acetamidate[244] favors the formation of a four-membered product **79** (Scheme 106),[245] whereas rhodium(II) triphenylacetate favors cyclopentanone formation.[245]

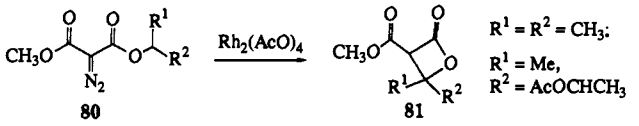
Scheme 106



78 79

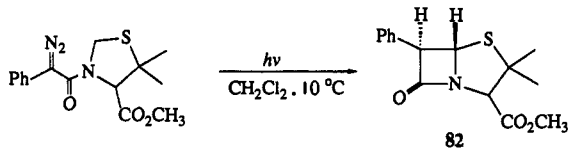
b. Four-Membered Heterocycles. A wide range of four-membered heterocycles are accessible. These include β-lactones,[246,247] β-lactams,[248–264] and 1,2-azaphosphetidines[265] which can be formed via the intramolecular C–H insertion reaction of carbenes or carbenoids derived from α-diazo esters and α-diazo amides. Lee and his co-workers[246] reported that rhodium(II) acetate-catalyzed intramolecular C–H insertion of alkyl methyl diazomalonates **80** results in the formation of β-lactone **81** (Scheme 107). The preference for four-membered ring formation is probably due to the activation of the adjacent oxygen atom and the intrinsic conformational bias of metallocarbenoid spe-

Scheme 107



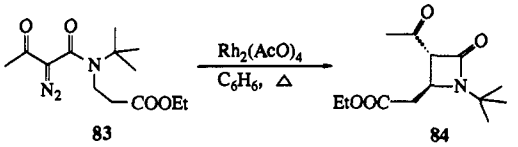
80 81

Scheme 108



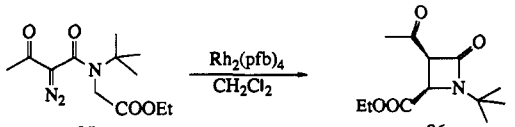
82

Scheme 109



83 84

Scheme 110



85 86

cies formed from diazomalonates. The latter factor may have the more dominant effect. It is noteworthy that a suitably mixed malonate–maloamide-derived diazo precursor undergoes cyclization to the β-lactam in preference to the β-lactone.[247]

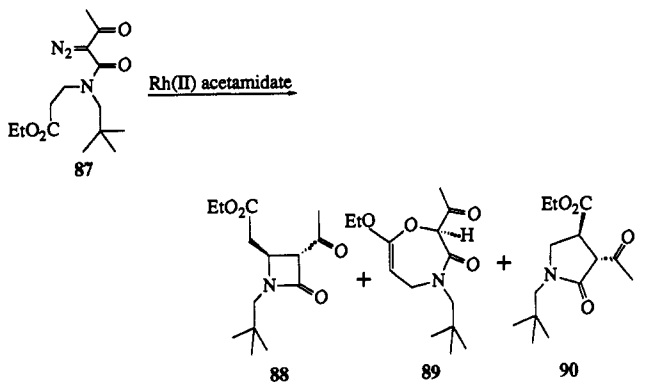
Since Corey's demonstration of the intramolecular C–H insertion reaction in the construction of methyl-6-phenylpenicillinate 82[248] (Scheme 108), the reaction has attracted attention as a versatile procedure for the construction of the β-lactam ring. Earlier work[248–258] was carried out *via* photochemical and thermal decomposition of diazo amides, but suffered from low yields and low selectivities. Since then rhodium(II) acetate has been demonstrated to be the catalyst of choice. A number of examples[259–261] of β-lactam formation have been reported via catalytic decompositions of diazo amides.

Doyle and co-workers[262–264] have demonstrated that the use of rhodium(II) carboxylates as catalysts for the construction of the β-lactam ring via C–H insertion, gives high yields and exceptional selectivity. Decomposition of **83** in refluxing benzene, catalyzed by rhodium(II) acetate, forms β-lactam **84**, solely as the *trans* isomer, in nearly quantitative yield (Scheme 109).[263] In contrast, diazoacetoacetamide **85** with only one methylene group between the ester and nitrogen groups, when treated with $Rh_2(pfb)_4$ in refluxing dichloromethane, underwent conversion to β-lactam **86** (89% yield, *cis* isomer only) (Scheme 110).[263]

Further reports[264] indicate that catalytic decomposition of diazo acetoacetamide **87** forms not only the β-lactam **88**, but also the carbonyl ylide derived product **89** and the γ-lactam insertion product **90** (Scheme 111). However, by employing the electronically selective rhodium(II) acetamidate as catalyst, the β-lactam product **88** was the principal insertion product.

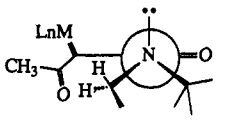
The success of the above transformation was attributed to an activating influence on the C–H bond

Scheme 111



87 88 89 90

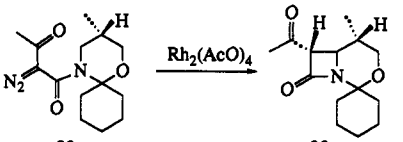
adjacent to the amide nitrogen atom, and conformational preferences which placed the reacting C–H band in close proximity to the carbenoid center as shown in **91**.[263]



91

An example of stereocontrolled C–H insertion with a cyclic diazo amide precursor **92** giving an optically active β-lactam **93** was reported by Brown and Southgate (Scheme 112).[261] The ketone reduction product from **93** is a key intermediate in the synthesis of 1-methyl carbapenems.

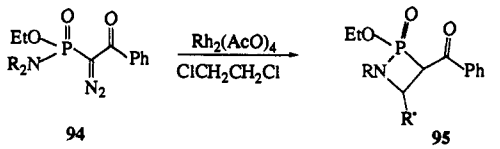
Scheme 112



92 93

Rees and co-workers[265] have reported a catalyzed decomposition of the α-diazo-β-keto phosphonamidates **94** to give the four-membered ring product **95** (Scheme 113). Although the reaction proceeded in low yield, it does provide a ready synthetic approach to 2-oxa-1,2-azaphosphetidine.

Scheme 113

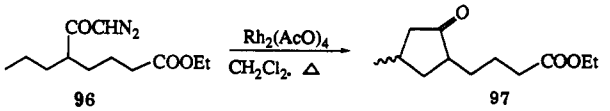


94 95

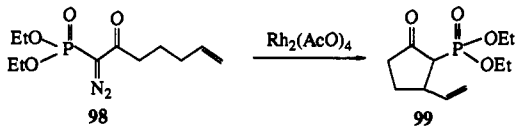
4. Five-Membered Ring Formation

a. Five-Membered Ring Carbocycles. Most methods[266] for five-membered carbocycle construction depend on the joining together of previously functionalized carbon atoms. Catalyzed decomposition of α-diazocarbonyl compounds, involving cyclization to a previously unfunctionalized carbon atom, provides a powerful method for the construction of the five-membered carbocyclic system. This strategy is particularly useful because the diazocarbonyl precursors are readily available and cyclopentanes are important structural units

Scheme 114



Scheme 115



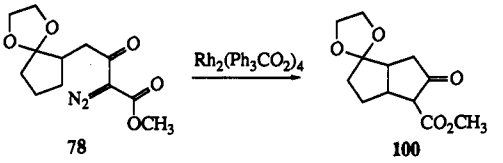
of natural products. This area represents one of the most useful applications of intramolecular diazocarbonyl reactions.

Early work on this type of transformation was based on the use of copper catalysts.[267] Wenkert[240] was the first to report the effectiveness of rhodium(II) carboxylates. Taber and co-workers[268-274] have undertaken a comprehensive examination of the $Rh_2(AcO)_4$-catalyzed intramolecular C–H insertion of α-diazo-β-keto esters into freely rotating aliphatic side chains. The results not only show that cyclization to the five-membered ring is a favored process[268] but also that C–H insertion into a more substituted γ-carbon occurs at a faster rate than insertion into a less substituted γ-carbon.[272] Furthermore, insertion into aliphatic methylenes is favored over allylic and benzylic methylenes.[272,274] These regioselectivities were attributed to electronic effects. Recently, Doyle and co-workers[275] have shown that if the possible sites for insertion cannot present their C–H bonds to the carbene center with equal probability for C–H insertion, regioselectivity is governed more by conformational preference than by electronic preference. Catalytic decomposition of a series of α-diazo ketones bearing two γ centers derived from α,β-unsaturated acids yielding 2-cyclopentenones and 2-alkylidenecyclopentanones have been reported by Ceccherelli and co-workers.[276] In this case, the regioselectivity of the insertion is low. Synthetically this indicates that the electronic effect of the olefinic bond is not generally useful in regiocontrol. Stork and Nakatani[277] reported that electron-withdrawing groups, such as carboxyl functions, can deactivate a C–H insertion site one or two atoms away. Cyclization of **96** with rhodium(II) acetate afforded the cyclopentanone ester **97** as a mixture of two stereoisomers (83% yield) (Scheme 114). This approach to control of regiochemistry could potentially be applied in the construction of more complex substituted carbocycles.

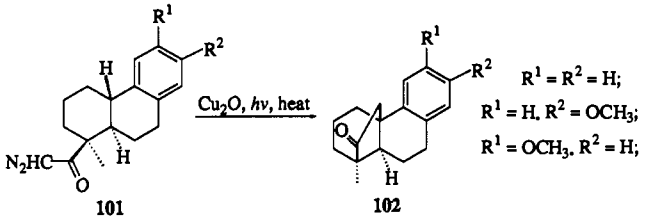
In addition to the preparation of α-carboalkoxy cyclopentanones from the corresponding acyclic α-diazo-β-keto esters, Monteiro[278] has reported that acyclic α-diazo-β-keto phenylsulfones undergo smooth intramolecular carbenoid cyclizations under rhodium(II) catalysis to afford α-phenylsulfonyl cyclopentanones. Also, α-diazo-β-ketoalkylphosphonates and phosphine oxides undergo cyclization to form the corresponding substituted cyclopentanones.[279] Similarly, treatment of **98** with rhodium(II) acetate leads to 2-(diethoxyphosphoryl)-3-vinylcyclopentanone (**99**, Scheme 115). This material was subsequently converted to (±)-sarkomycin in four steps.[280]

Sonawane and co-workers[241] have clearly demonstrated that conformationally rigid carbon frameworks

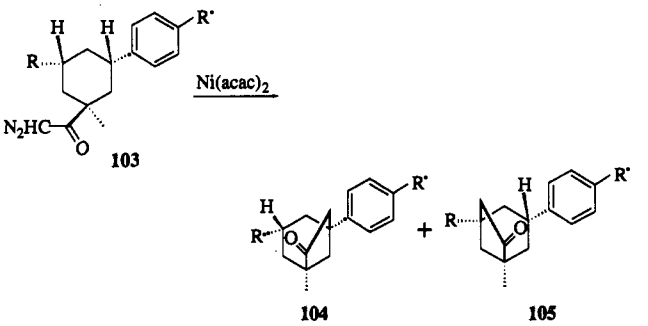
Scheme 116



Scheme 117



Scheme 118



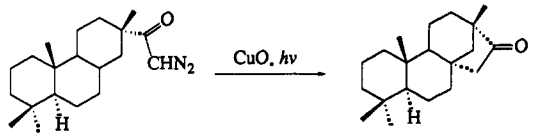
can be advantageously utilized to achieve C–C bond formation by highly selective metal–carbene C–H insertion and in many instances have shown that cyclopentane annulation in the cyclic system can readily be achieved. The ligand on the transition metal, electronic effects, and, in particular, steric factors, play an important role in governing selectivity.

Recent work on the design and synthesis of rhodium(II) catalysts shows that variation of the ligand type of the rhodium(II) catalyst can affect site selectivity. Ikegami and his co-workers[245] found that in the catalytic decomposition of α-diazo-β-keto ester **78**, the rhodium(II) triphenylacetate, which bears a sterically bulky bridging ligand on rhodium, favors the formation of a five-membered ring to form **100** (Scheme 116).[245]

In connection with synthetic studies toward complex diterpenoids, Ghatak and co-workers[281-283] have reported the copper-catalyzed decomposition of the rigid tricyclic diazomethyl ketone **101** to the corresponding tetracyclic bridged ketone **102** in good yield, the product arising from reaction at the benzylic carbon–hydrogen bond (Scheme 117). Ketone **102** served as a key step in the total syntheses of atisine, reatchine, and gibberellin A_{15}.[257-259] Furthermore, the regioselectivity of the carbenoid decomposition of diazocarbonyl precursor **103**, which bears various substituents, forming two types of regioisomer **104**, **105**, has been examined by Ghatak's group (Scheme 118).[284]

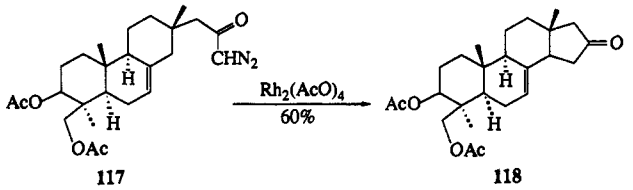
The carbenoid C–H insertion approach provides a general pathway for the preparation of a wide variety of natural products containing a cyclopentane system. The following representative examples, involving carbenoid C–H insertion forming five-membered carbocycles, illustrate the utility of this chemistry.

Scheme 119



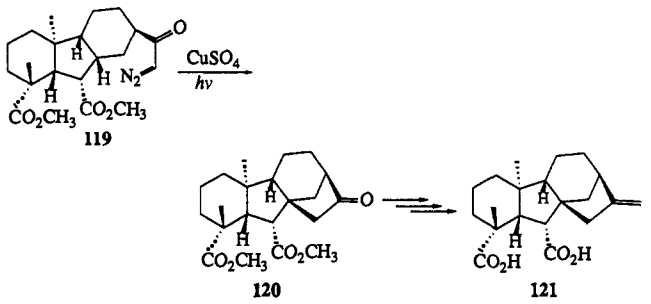
116

Scheme 120



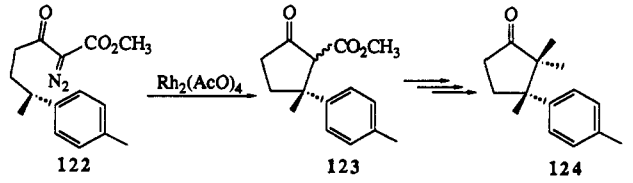
117 118

Scheme 121



119 120 121

Scheme 122



122 123 124

Yoshikoshi and co-workers[235] reported a partial synthesis of isohibaene. It involves, as the key step, the intramolecular insertion reaction of a ketocarbene generated by the cuprous oxide-catalyzed decomposition of diazo ketone **116** under irradiation (Scheme 119).

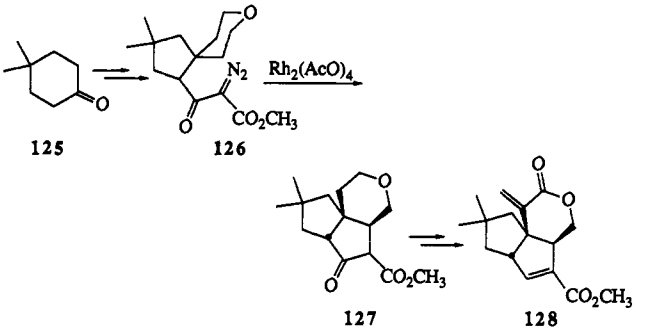
The conversion of an isopimaradiene system **117** into the steroid skeleton **118** was achieved by Wenkert's group (Scheme 120),[240] and carbenoid insertion into the C-8βH bond in **119**, forming the D-ring (**120**), was a crucial step in Nakata and Tahara's synthesis of gibberellin A_{12} (**121**, Scheme 121).[286]

The optically pure α-diazo-β-keto ester **122**, prepared by alkylation of a chiral oxazolidone, on treatment with $Rh_2(AcO)_4$ was converted into **123** with retention of configuration; standard functional group manipulation was used to transform **123** into the (+)-α-cuparenone (**124**, Scheme 122).[271]

Treatment of α-diazo-β-keto ester **126**, prepared in several steps from 4,4-dimethylcyclohexanone (**125**), with catalytic $Rh_2(AcO)_4$ in dichloromethane at room temperature led to smooth conversion to the tricyclic ether **127**, which is a key intermediate in Taber's approach to the synthesis of the sesquiterpene antibiotic pentalenolactone E methyl ester (**128**, Scheme 123).[270]

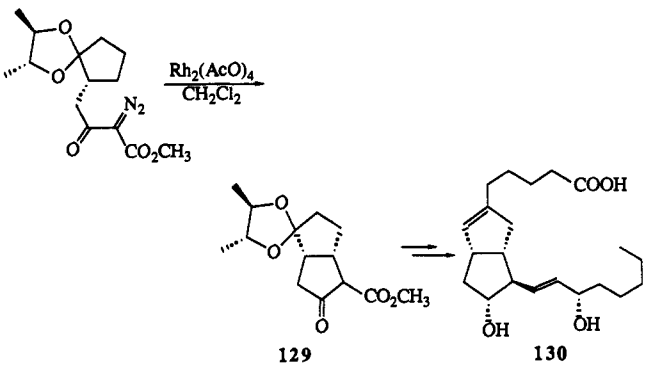
(+)-Isocarbacyclin **130**, one of the most promising therapeutic agents for cardiovascular and circulatory disorders, was synthesized by a sequence[287] in which the key step was the regiocontrolled construction of

Scheme 123



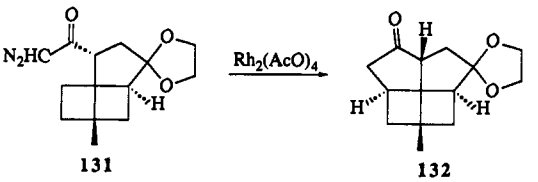
125 126 127 128

Scheme 124



129 130

Scheme 125



131 132

the optically active bicyclic β-oxomethyl ester **129** via rhodium(II)-catalyzed intramolecular C–H insertion (Scheme 124).[268]

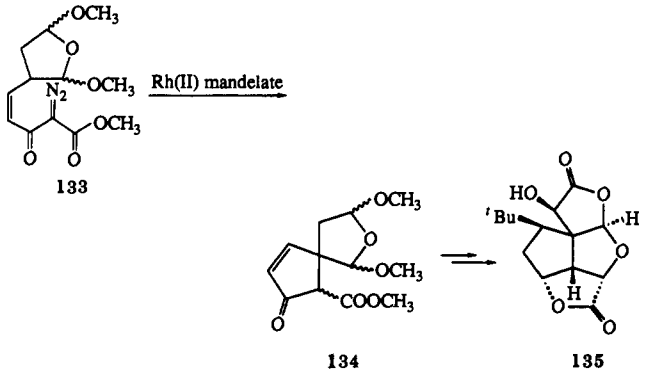
A series [4,4,4,5]fenestrane and [4,4,4,4]fenestrane derivatives have been synthesized via the carbenoid C–H insertion process.[289-291] For example, treatment of diazo ketone **131** with rhodium(II) acetate in dichloromethane caused rapid decomposition and formation of the tetracyclic ketone acetal **132** in good yield (Scheme 125). In general, five-membered ring formation in the construction of this type of polycyclic compound is necessarily stereocontrolled.

Treatment of diazo ester **133** with rhodium(II) mandelate in dichloromethane resulted in formation of the spiroenone **134** in 73% yield. Spiro enone **134** was then transformed into a tetracyclic C_{14} ginkgolide **135** (Scheme 126).[292]

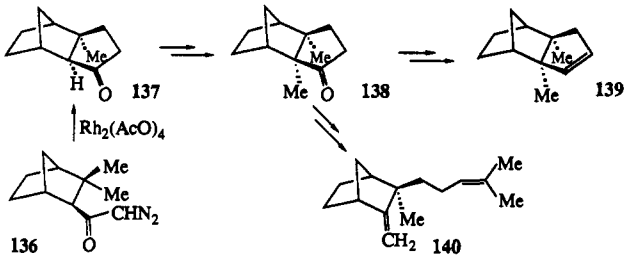
Catalytic decomposition of chiral diazo ketone **136** furnished the enantiomerically pure **137** in high yield. Further functional group manipulation furnished a key intermediate **138**, which was converted to (+)-albene (**139**) and (−)-β-santalene (**140**, Scheme 127).[241]

(±)-Tochuinyl acetate (**143**), recently isolated from the nudibranch *Tochuina tetraquetra*, was synthesized via a sequence in which the crucial step was the formation of a five-membered carbocycle, containing quaternary stereogenic centers via carbenoid C–H insertion.[274] Treatment of diazo ester **141** with Rh(II) catalyst formed ester **142** which is the key intermediate leading to **143** (Scheme 128).

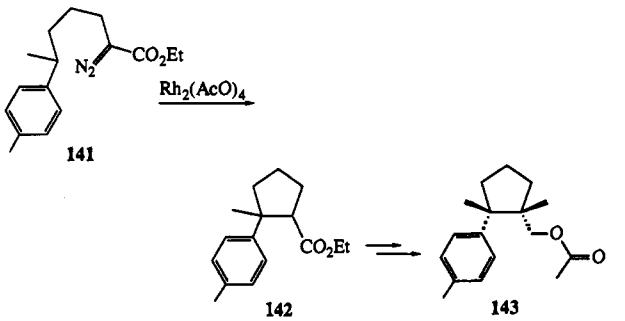
Scheme 126



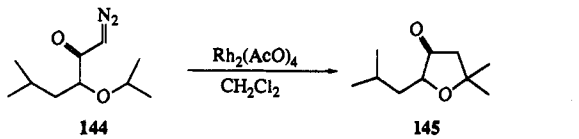
Scheme 127



Scheme 128



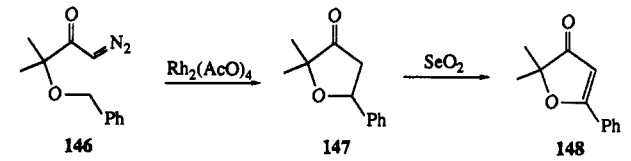
Scheme 129



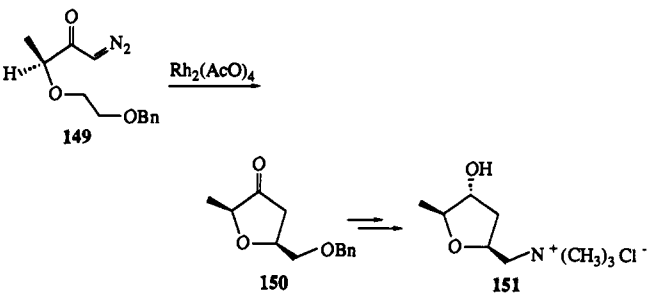
b. Five-Membered Heterocycles. It has been generally recognized[1a] that carbenoid insertion into C–H bonds of heteroatomic compounds proceeds where possible, with a preference for insertion into the C–H bond α to the heteroatom. Adams and co-workers[293,294] reported that the presence of an ether oxygen promotes this type of regioselectivity in carbenoid C–H insertion. The C–H bond adjacent to the ether oxygen is the preferred site of insertion compared to a normal "unactivated" aliphatic carbon–hydrogen bond. For example, rhodium acetate-catalyzed reaction of diazo ketone **144** afforded the corresponding furanone **145** as shown in Scheme 129. This type of reaction has been applied in the synthesis of bullatenone (**148**), a plant metabolite of Myrtus bullata (Scheme 130). Treatment of the alkoxy diazo ketone **146** with a rhodium(II) catalyst at room temperature in dichloromethane afforded the 3(2*H*)-furanone **147**, which was oxidized with SeO_2 to give **148**.

Carbenoid C–H insertion forming disubstituted 2,5-3(2*H*)-furanones exhibits a stereoselection favoring the

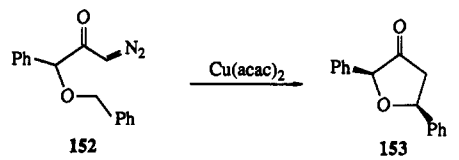
Scheme 130



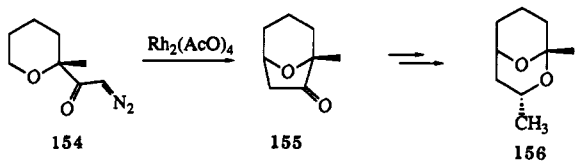
Scheme 131



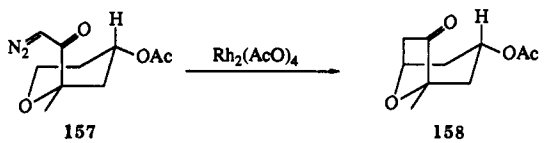
Scheme 132



Scheme 133



Scheme 134



cis isomers.[294] For example, catalytic decomposition of diazo ketone **149** afforded *cis*-enriched disubstituted furanone **150**, which was then transformed into (+)-muscarine (**151**, Scheme 131).

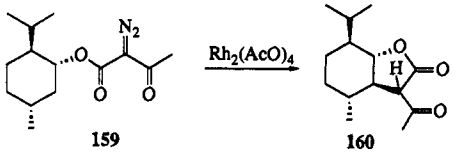
However, the reactivity and selectivity of this type of C–H insertion reaction for the construction of 3(2*H*)-furanones is dependent on the type of catalyst used. Hon and co-workers[295] found that cupric acetylacetonate is the best catalyst for promotion of the C–H insertion reaction from the α-alkoxy-α′-diazo ketone **152**. Side reactions were minimized and the *cis* stereoisomer of the 3(2*H*)-furanone **153** was the favored product (Scheme 132).

endo-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**156**), a pheromone isolated from Norwegian spruce, has been synthesized via a sequence in which the key step was C–H insertion α to an ether oxygen of **154**, forming the bridged bicycle **155** (Scheme 133).[296]

Stereoelectronic factors can also influence regiospecificity. For example, diazo ketone **157**, bearing two different α-C–H bonds, under catalytic decomposition afforded insertion product **158**, regioselectively (Scheme 134).[297]

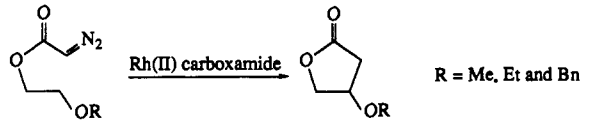
Substituted γ-lactones can be obtained via the carbenoid C–H insertion reaction of corresponding

Scheme 135



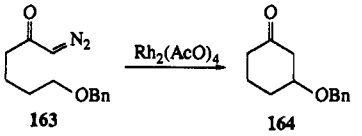
159 160

Scheme 136



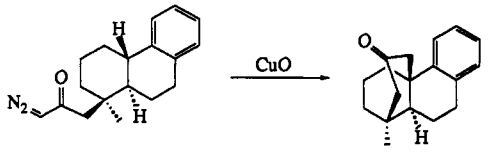
161 162

Scheme 137



163 164

Scheme 138



165 166

α-diazo-β-keto esters[275,298] or diazo esters.[299] Thus treatment of α-diazo-β-keto ester **159** with a rhodium(II) catalyst afforded the bicyclic γ-lactone **160** in high yield and with a high degree of regiocontrol (Scheme 135).[275,298] Similarly, treatment of diazo ester **161** with a rhodium(II) catalyst under reflux in dichloromethane provided the corresponding 3-substituted γ-butyrolactones **162** in moderate to high yields (Scheme 136).[299]

5. Six-Membered Ring Formation

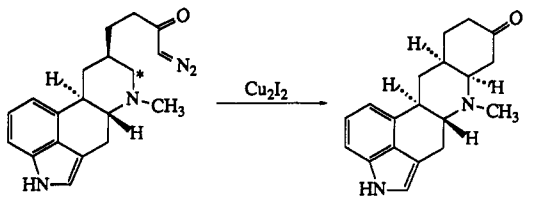
The regioselectivity of carbenoid C–H insertion strongly depends on the type of diazocarbonyl precursor. In certain circumstances, six-membered annulation can compete effectively with five-membered annulation.

a. Six-Membered Carbocycles. It is well known that the intramolecular C–H insertion of α-diazocarbonyl compounds into freely rotating aliphatic chains forms five-membered carbocycles. However, when a δ-carbon–hydrogen bond is activated by one adjacent heteroatom, the C–H insertion results in a six-membered ring. For example, catalytic decomposition of α-diazo ketone **163** afforded substituted cyclohexanone **164** as the major product (Scheme 137).[293]

The bridged bicyclo[3.3.1]nonanone system **166**, related to the insect attractant (±)-9a-carbomorphinan, was synthesized via an intramolecular C–H insertion process. Decomposition of diazo ketone **165** in a dilute cyclohexane–THF solvent system in the presence of an "activated CuO catalyst" under irradiation with a tungsten lamp gave the bridged ketone **166** (Scheme 138).[300]

A key intermediate **168**, required for the synthesis of conformationally blocked ergoline derivatives, has been synthesized via intramolecular carbenoid C–H insertion.[301] Reaction of diazo ketone **167** in refluxing

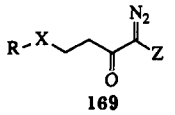
Scheme 139



167 168

diethylene glycol dimethyl ether, catalyzed by Cu_2I_2, gave **168**, which now possesses the additional D ring of the ergoline skeleton (Scheme 139). This cyclohexanone annulation can be explained by electronic effects. The starred C*–H bond adjacent to the basic nitrogen atom is activated, resulting in six-membered ring formation as the favored process. There is an antiperiplanar relationship between the N lone pair and the C*–H axial bond. This stereoelectronic requirement may be responsible for the preferred formation of the *cis*-fused ring. Basic nitrogen groups form complexes with rhodium(II) carboxylates and carboxamides rendering such catalysts unsuitable for the type of transformation shown in Scheme 139.

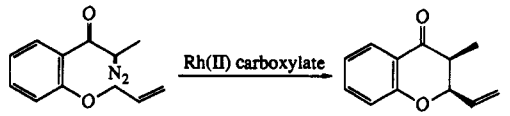
b. Six-Membered Heterocycles. It is known that when there is a heteroatom at the γ position of precursors of type **169**, the resulting catalytic decom-



169

position products are generally produced via ylide formation (see section III.E). However, the regioselectivity of the carbenoid reaction strongly depends upon the type of diazocarbonyl precursor. This laboratory[41] has reported the synthesis of six-membered oxygen heterocycles via the intramolecular C–H insertion reaction of α-diazo ketones catalyzed by rhodium(II) carboxylates. Decomposition of diazo ketone **170**, with rhodium(II) carboxylate in dichloromethane at 0 °C, furnished substituted chromanone **171** in 97% yield. The *cis*-fused disubstituted isomer was the major product (92%) (Scheme 140).

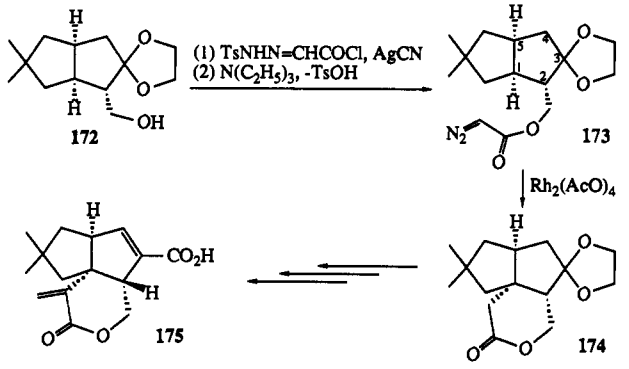
Scheme 140



170 171

Diazo acetate **173**, prepared from alcohol **172** according to House's method,[70,71] in the presence of $Rh_2(AcO)_4$ in an inert Freon solvent, undergoes an intramolecular carbenoid insertion at the adjacent C-1 bridgehead C–H bond to generate a δ-lactone ring of **174** in satisfactory yield. The δ-lactone **174** was then converted to pentalenolactone E (**175**)[243] (Scheme 141). Two factors favor this key intramolecular C–H insertion process. Firstly, a tertiary C–H bond favors formation of the six-membered lactone via insertion. Secondly, competing insertion at C-2 to generate the γ-lactone

Scheme 141



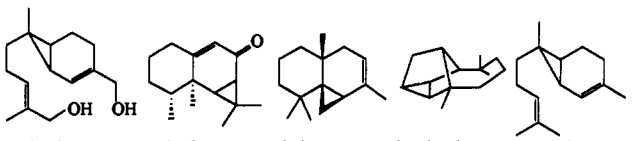
ring is disfavored due to steric effects, and insertion to C-5 leads to a seven-membered ring.

C. Cyclopropanation and Related Reactions

Due to their occurrence in natural products, biological significance, and synthetic utility, cyclopropanes have received considerable attention during the past several decades. Transition metal catalytic decomposition of diazocarbonyl compounds in the presence of alkenes provides a facile and powerful means of constructing cyclopropanes. The literature up to 1985 on intermolecular and intramolecular cyclopropanation, including mechanistic aspects and choice of catalysts, has been reviewed in detail by Maas.[1b] In this section we will review recent applications of cyclopropanation and some of the subsequent ring cleavage reactions used in synthesis. The main emphasis will focus on the construction of natural products as well as other biologically active compounds.

1. Synthesis of Cyclopropane-Containing Products via Diazocarbonyl Intermediates

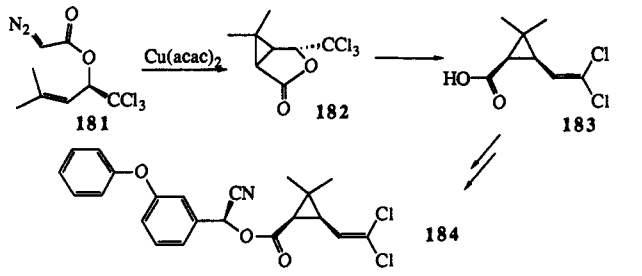
Many natural products which contain the cyclopropyl ring have been synthesized through reaction of a carbenoid with a carbon–carbon double bond. Some target molecules which were synthesized in this manner are sirenin (**176**), aristolone (**177**), thujopsene (**178**), longicyclene (**179**), and sesquicarene (**180**). This work



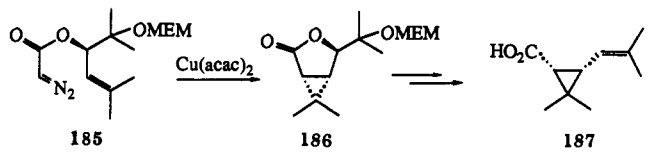
has been reviewed by Burke and Grieco.[267] Hatch and Baum[302] have reported the total synthesis of the potent synthetic pyrethroid NRDC 182 (**184**), involving stereospecific carbenoid cyclopropanation as the key step. Treatment of the chiral diazo ester **181** with a copper catalyst resulted in the stereospecific formation of the bicyclic lactone **182**. Cleavage of the bicyclic lactone **182** gave the permethrinic acid **183** which was then converted to **184** (Scheme 142).

Recently, Yadav and co-workers[303] have used the same strategy in the synthesis of (1*R*)-*cis*-chrysanthemic acid (**187**) from (*R*,*R*)-tartaric acid. The crucial step was carbenoid cyclopropanation of the chiral diazo ester **185** to afford the optically active bicyclic lactone **186**

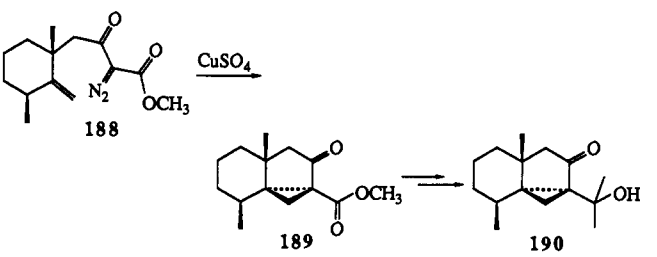
Scheme 142



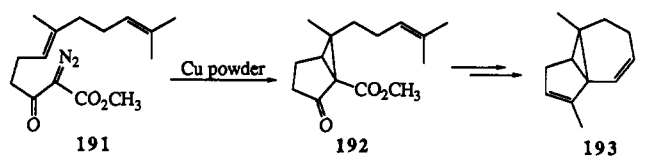
Scheme 143



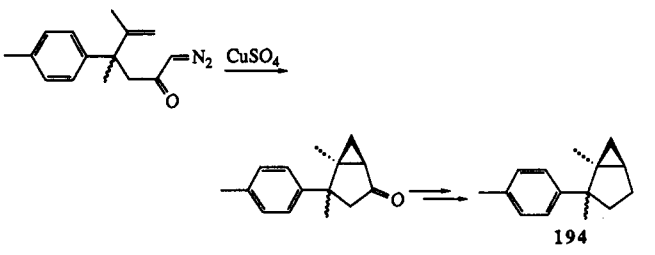
Scheme 144



Scheme 145



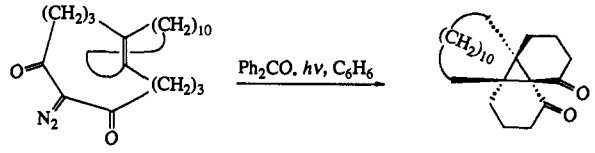
Scheme 146



(Scheme 143). Both permethrinic acid (**183**) and chrysanthemic acid (**187**), are valuable precursors for the synthesis of pyrethroids.[304,305] The tricyclic compound **189**, which is the key intermediate for the total synthesis of the sesquiterpenoid (±)-cycloeudesmol (**190**),[306] was constructed via the catalytic decomposition of the α-diazo-β-keto ester **188** (Scheme 144). Similarly, the bicyclo[3.1.0]hexane derivative **192** was synthesized from the corresponding diazocarbonyl precursor **191** via the catalytic method and was converted into (±)-trinoranastreptene **193** (Scheme 145).[307]

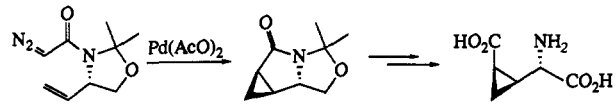
(±)-Cyclolaurene **194**, isolated from the sea hare *Aplysia dactylomela*, has been synthesized via intramolecular cyclopropanation as the key step (Scheme 146).[308] Fused polycyclic compounds, for example, *trans,cis,cis*-[10,4,4]triannulane-16,18-dione (**196**), can be prepared from an appropriate α-diazocarbonyl precursor, e.g. **195**. Irradiation of **195** in benzene using

Scheme 147



195 196

Scheme 148



197 198

benzophenone as a photosensitizer produced **196** via transannular cyclopropanation (Scheme 147).[309] α-(Carboxycyclopropyl)glycine (**198**), which has been isolated from the Spindaceae family by Fowden and co-workers,[310] was synthesized by Yamanoi and Ohfune[311] via a sequence which involved stereoselective carbenoid cyclopropanation of **197** (Scheme 148). Conformationally constrained analogues of L-glutamate[311-314] and substituted cyclopropanes containing dipeptide mimics[315-317] have also been synthesized via an inter- or intramolecular cyclopropanation.

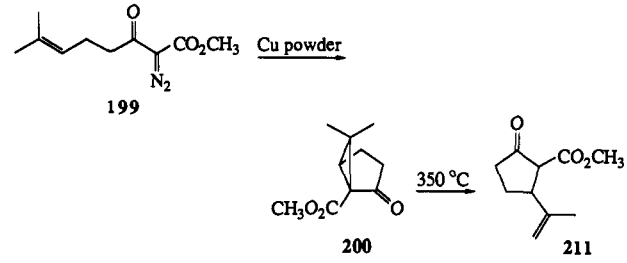
2. Cyclopropanation and Subsequent Reactions in Synthesis

Cyclopropane derivatives undergo a variety of ring-opening reactions. The use of cyclopropane derivatives as intermediates in organic synthesis has already been well established,[318-325] and so it is not surprising that the carbenoid cyclopropanation, followed by ring-opening reactions, have become a valuable tool in the construction of many compounds other than those containing cyclopropanes. Some important examples taken from the literature to demonstrate the versatility of this synthetic strategy are shown below. These examples are roughly divided into three subsections according to the types of product derived from cyclopropyl ring fragmentation.

a. Construction of Monocyclic Systems via Cyclopropanation Followed by Ring Fragmentation. α-Diazocarbonyl precursors containing a freely rotating aliphatic chain with a carbon–carbon double bond in an appropriate position can undergo catalytic intramolecular cyclopropanation leading to five- or six-membered bicyclic systems. Fragmentation of the cyclopropyl ring can then lead to substituted monocyclic products. Trost and co-workers[326] have reported a sequence involving the above strategy to construct substituted cyclopentanones. Catalytic decomposition of α-diazo-β-keto ester **199** afforded cyclopropyl ketone **200**; thermolytic opening of **200** gave cyclopentanone **201** (Scheme 149). Intramolecular cyclopropanation of the chiral α-diazo-β-keto ester **202** proceeded to bicyclic keto ester **203** with a diastereomeric excess of 60%.[327] Treatment of enantiomerically pure **203** with lithium divinylcuprate furnished **204**, which, following further synthetic modification, led to (+)-isoneonepetalactone (**205**), a constituent of the essential oil of *Actinidia polygama* (Scheme 150).[327]

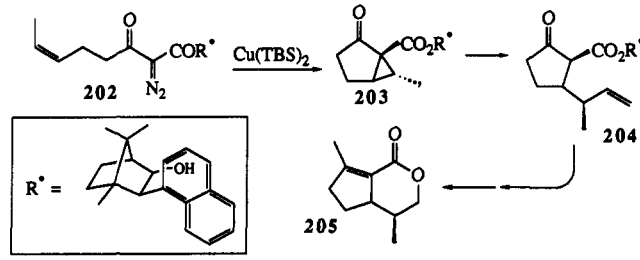
Intramolecular cyclopropanation of dienoic diazo ketone **206** resulted in the formation of *cis*-methylvinylcyclopropane **207** which underwent a controlled

Scheme 149



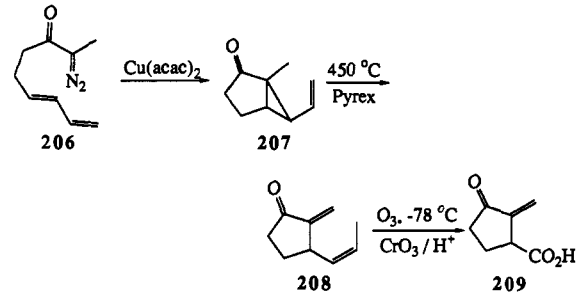
199 200 211

Scheme 150



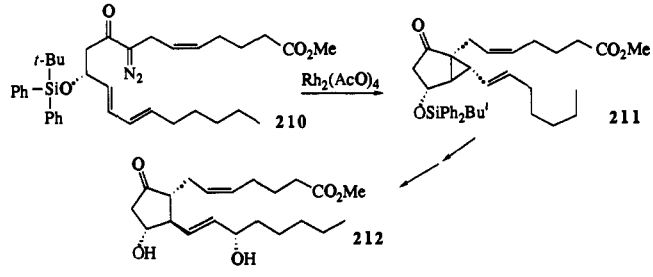
202 203 204 205

Scheme 151



206 207 208 209

Scheme 152



210 211 212

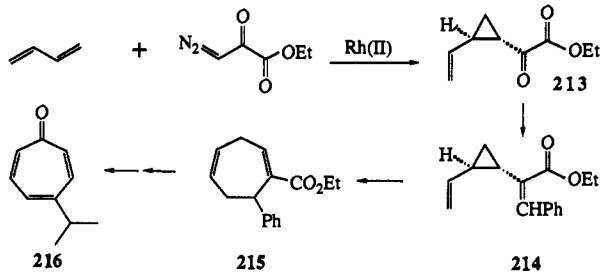
pyrolysis to afford enone **208**.[328] Selective ozonolysis of enone **208** leads to antibiotic (±)-sarkomycin (**209**, Scheme 151).[329]

Prostaglandin E_2 methyl ester (**212**) has been synthesized via a sequence involving an intramolecular cyclopropanation process. Thus, treatment of diazocarbonyl precursor **210** with rhodium(II) acetate in dichloromethane furnished the bicyclic adduct **211**, which was then transformed into **212** (Scheme 152).[330]

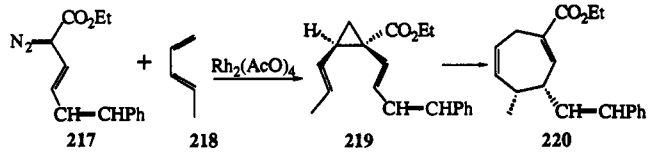
Intermolecular cyclopropanation and subsequent ring fragmentation has also been employed in the synthesis of monocyclic compounds. Rhodium(II)-catalyzed reaction of 1,3-butadiene with ethyl 3-diazopyruvate leads to acylcyclopropane **213** which with a Wittig reagent gave **214**; Cope rearrangement of **214** afforded cycloheptadienecarboxylate **215**, which was then transformed to nezukone (**216**, Scheme 153).[331]

The Cope rearrangement of divinylcyclopropanes has been extensively used for the synthesis of seven-membered cyclic compounds. Davies and co-workers[332]

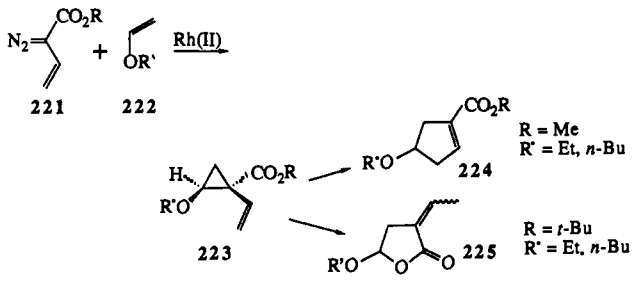
Scheme 153



Scheme 154



Scheme 155

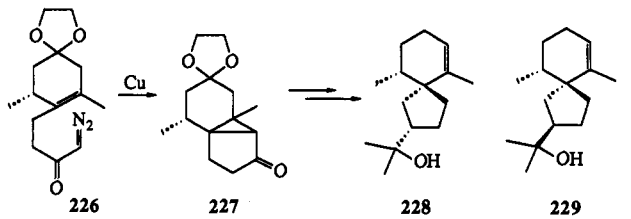


have reported the stereoselective synthesis of the substituted seven-membered carbocycle **220** via a sequence involving the tandem cyclopropanation/Cope rearrangement. Addition of unsaturated diazocarbonyl compound **217** to acyclic diene **218** generated divinylcyclopropane **219**, which then undergoes Cope rearrangement to afford **220** (Scheme 154). Rhodium(II)-catalyzed decomposition of vinyl diazo ester **221** in the presence of vinyl ether **222** gave the cyclopropane carboxylate **223**. The cleavage of the cyclopropyl ring of **223** resulted in a five-membered carbocyclic compound **224** or lactone **225**. The rearrangement chemistry of **223** is highly dependent on the presence of the ester functionality (Scheme 155).[333,334]

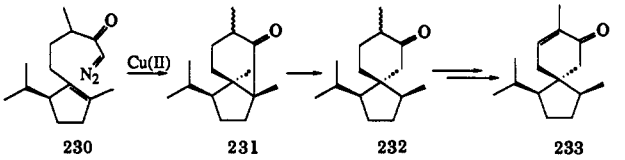
b. Construction of Spiro Frameworks via Cyclopropanation Followed by Ring Fragmentation. Products of intramolecular addition of a diazocarbonyl to a cyclic olefin can undergo cleavage of the exterior cyclopropane bond to produce a spiro framework. This synthetic strategy has been used as a key step in the construction of a number of naturally occurring spiro sesquiterpenes. An elegant application of this spiro framework formation protocol, which led to the total synthesis of (±)-hinesol (**228**) and (±)-epihinesol (**229**), was achieved by Deslongchamps and co-workers[335] (Scheme 156). Catalytic decomposition of ketal diazo ketone **226** gave tricyclic ketal ketone **227**. Functional group manipulation involving the opening of the cyclopropyl ring furnished **228** and **229**.

The spiroannulation process has also been investigated by White and co-workers.[336] Applications include the stereocontrolled synthesis of (−)-acorenone B (**233**) and (±)-α-chamigrene (**237**) (Schemes 157 and 158).[337] Catalytic intramolecular cyclopropanation of diazo ketones **230** and **234** led to the corresponding tricyclic

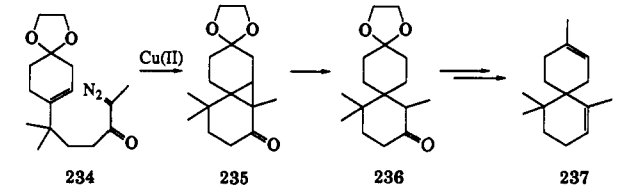
Scheme 156



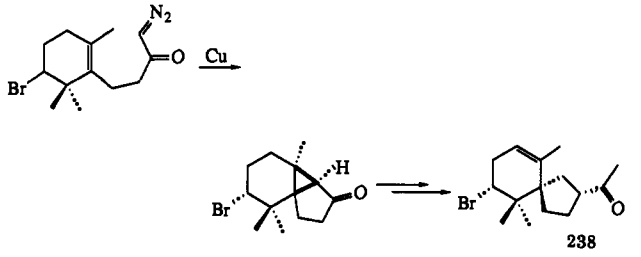
Scheme 157



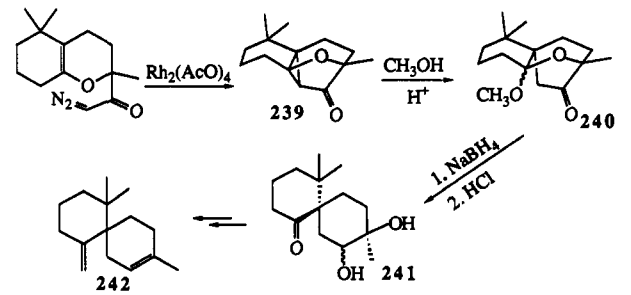
Scheme 158



Scheme 159



Scheme 160

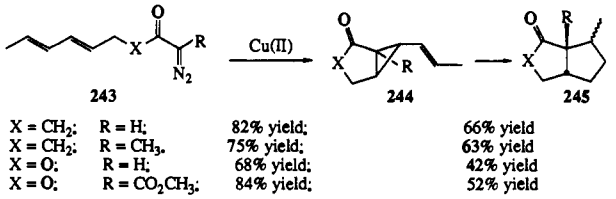


ketones **231** and **235**. Cleavage of the cyclopropyl ring led to the spirocyclic ketones **232** and **236** which were then transformed into **233** and **237**, respectively.

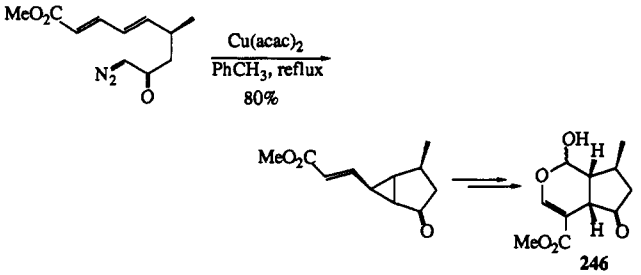
(±)-Spirolaurenone (**238**), an antifungal compound isolated from the red alga *Laurencia glandulifera*, has been synthesized via the same spiroannulation strategy involving carbenoid cyclopropanation–fragmentation (Scheme 159).[338] The transannular cyclopropanation of a keto carbenoid to a bicyclic dihydropyran nucleus generated by rhodium(II) catalysis provided a key oxa tricyclic keto intermediate **239** for the construction of the [6.6]-spirocyclic skeleton. Regiospecific cleavage of cyclopropane **240** followed by hydrolytic cleavage of the C–O bond provided spirocyclic **241**, which was then transformed to β-chamigrene (**242**, Scheme 160).[339]

c. Construction of Fused and Bridged Polycyclic Systems via Cyclopropanation Followed by Ring Fragmentation. Metal-catalyzed decomposition of

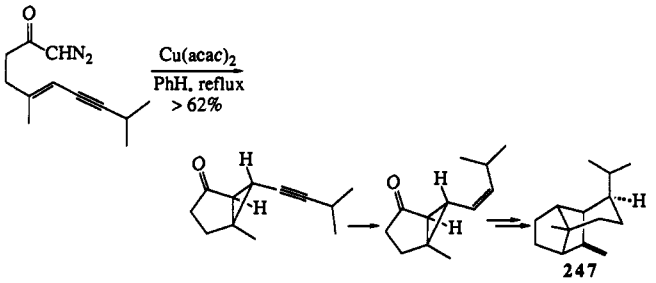
Scheme 161



Scheme 162



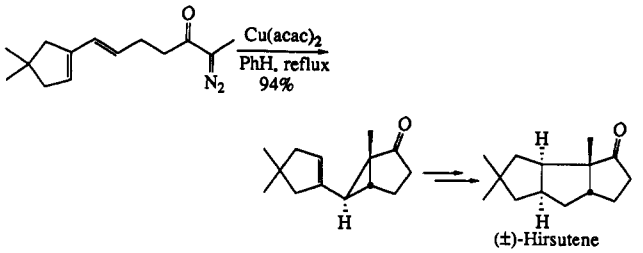
Scheme 163



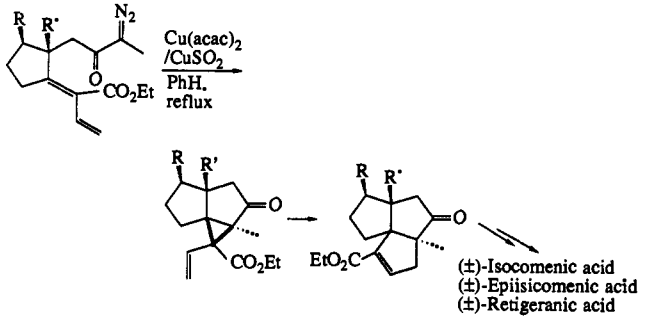
dienoic diazocarbonyls gives vinyl cyclopropanes, pyrolysis of which results in cyclopentene annulation. The cyclopropanation step is ring-size dependent, and only closures of five- and six-membered rings prove synthetically useful. $Cu(acac)_2$-catalyzed decomposition of diazocarbonyl **243** furnished vinyl cyclopropane **244** in high yield. Rearrangement of vinyl cyclopropane **244** produced bicyclic adduct **245** (Scheme 161).[340-343] An interesting application of this method is found as a step in a synthetic entry to (−)-verbenalol (**246**, Scheme 162).[344] A further example is found in a synthesis of (±)-sinularene **247** where the vinyl cyclopropane was again obtained via copper catalysis. In this case, the diazo ketone bears a carbon–carbon triple bond as a masked *cis* double bond which meets the requirement for further stereocontrolled rearrangement (Scheme 163).[345]

When the diene function is attached to, or is part of, a carbocyclic system, the vinyl cyclopropanation formation and rearrangement affords a reliable approach to the formation of tricyclic carbocycles. Some elegant demonstrations of the use of this methodology in the total synthesis of fused cyclopentanoid terpenes come from the research of Hudlicky and co-workers.[341,346-352] (±)-Hirsutene,[346] (±)-isocomenic acid,[347] (±)-epiisocomenic acid,[347] (±)-epiisocomene,[348] pentalenic acid,[349,350] pentalenene,[349,350] and retigeranic acid[351,352] have been successfully synthesized via sequences involving the cyclopropanation–cyclopentene annulation protocol (Schemes 164–167). In the cases where these diazo ketones contain a carboxylate-substituted double bond of a diene, the promotion of effective intramolecular cyclopropanation requires the combination of $CuSO_4/Cu(acac)_2$ as catalyst.

Scheme 164

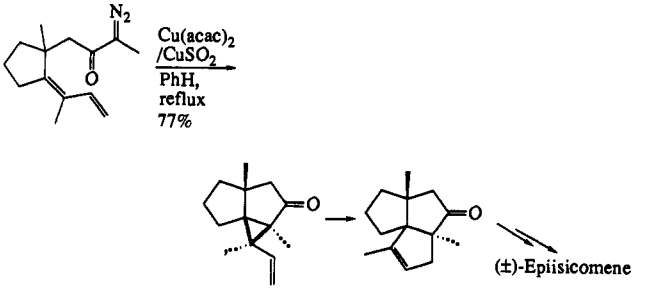


Scheme 165

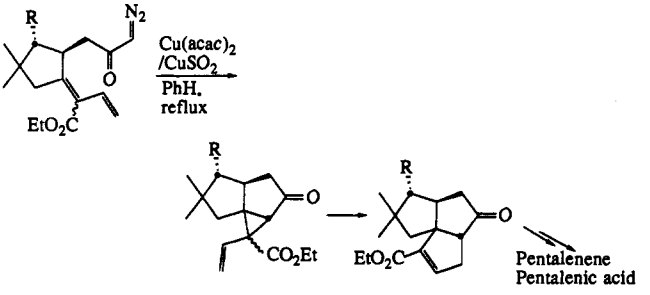


R = CH_3, R' = H, 70-75% yield; R = H, R' = CH_3, 61% yield

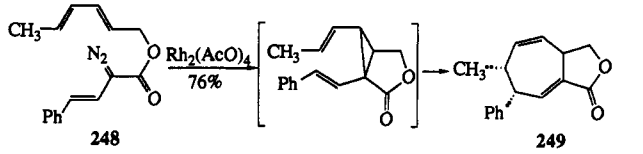
Scheme 166



Scheme 167

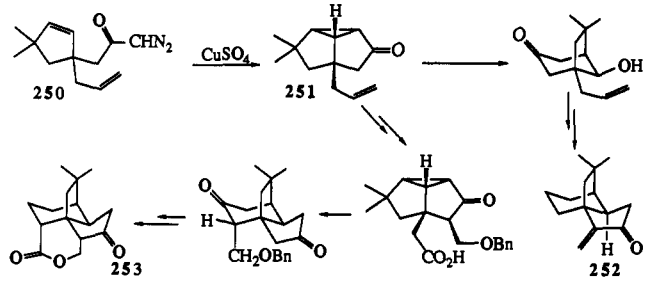


Scheme 168

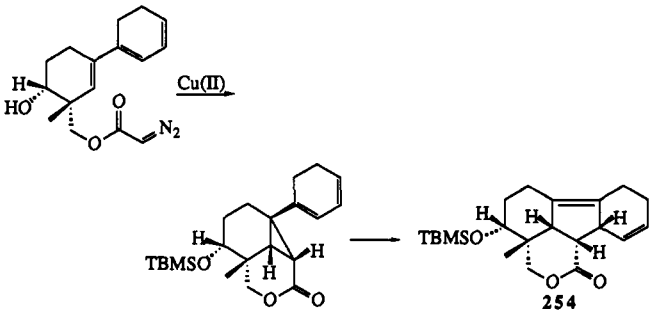


Divinylcyclopropanes, which can be generated by the intramolecular cyclopropanation of diazocarbonyl precursors, undergo a Cope rearrangement leading to the formation of fused seven-membered rings. For example, decomposition of the 2*E*,4*E*-diene **248** by rhodium(II) acetate in refluxing dichloromethane resulted in the formation of a fused cycloheptadiene **249** (Scheme 168).[353] The scope and stereochemistry of this sequence has been extensively studied by Davies and co-workers.[332,353,354]

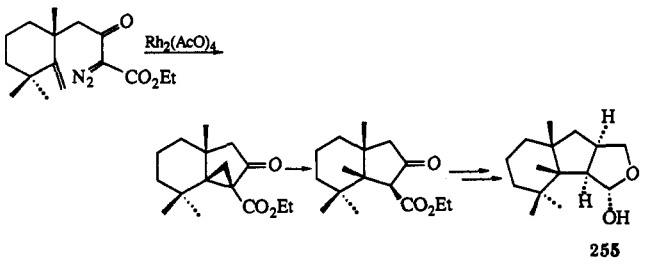
Scheme 169



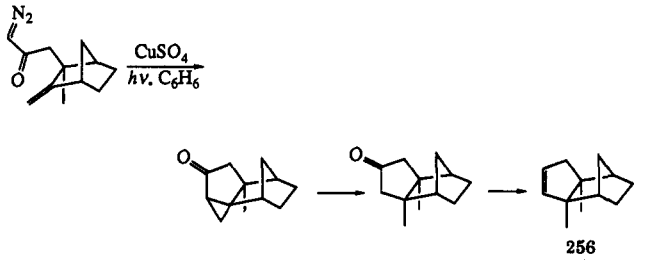
Scheme 170



Scheme 171



Scheme 172



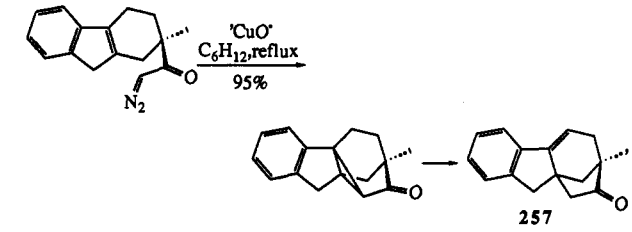
Both (±)-quadrone[355] (**253**) and (±)-descarboxyquadrone[356] (**252**) have been synthesized via a key intermediate tricyclo[3.3.0.0^{2,8}]octan-3-one **251** which was derived from an intramolecular cyclopropanation of diazocarbonyl precursor **250** (Scheme 169).

Antheridic acid, the antheridium-inducing factor of the fern *Anemia phyllitidis*, has been synthesized via a stereocontrolled and enantioselective process.[357-359] The key intermediate **254** was constructed via a sequence involving an intramolecular cyclopropanation followed by a vinylcyclopropane–cyclopentene rearrangement (Scheme 170).

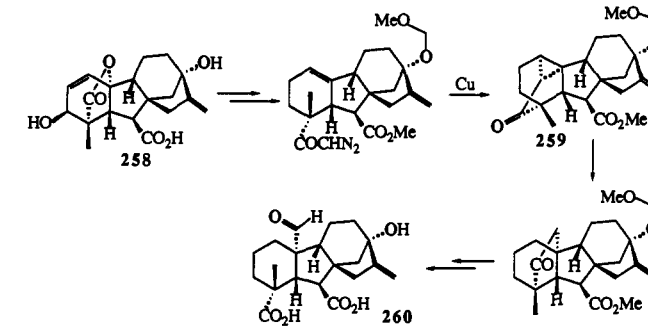
Intramolecular cyclopropanation of a γ,δ-unsaturated diazo ketone with subsequent cleavage of the cyclopropane ring has been used as the key step in the total synthesis of thapsane (**255**)[360] and (±)-albene (**256**)[361] (Schemes 171 and 172).

The intramolecular cyclopropanation of appropriate γ,δ-unsaturated α-diazo ketones followed by stereoselective catalytic reduction of the cyclopropyl ketone provided a useful approach in diterpenoid synthesis. Some bridged tetracyclic compounds, for example gibbenes **257**, have been synthesized *via* this strategy (Scheme 173).[382]

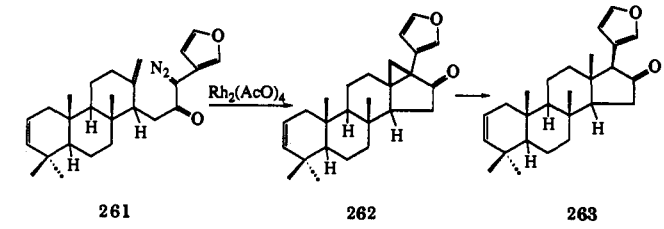
Scheme 173



Scheme 174



Scheme 175

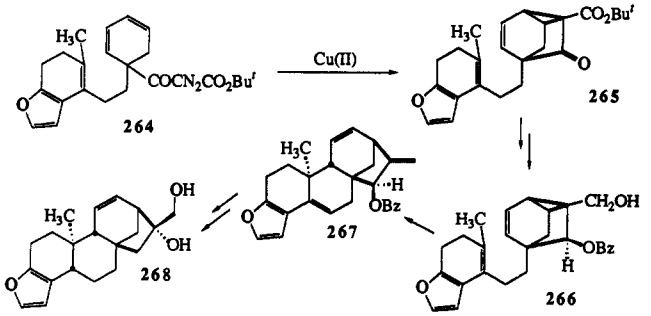


The intramolecular cyclopropanation of a diazo ketone derived from gibberellic acid (**258**), followed by reductive cleavage of the cyclopropyl group in **259** has been used as the key step in Mander's stereocontrolled synthesis of gibberellin A_{19} (**260**, Scheme 174).[363] Similarly, two C_{20} gibberellins, A_{36} and A_{37}, have also been synthesized via a sequence involving the cyclopropanation–reductive cleavage approach.[364]

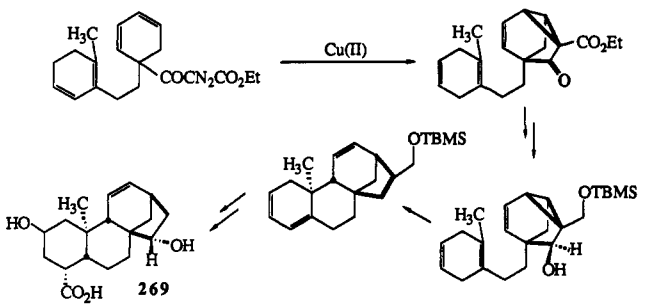
The 13-*epi*-limonoid skeleton **263** has been synthesized via a sequence shown in Scheme 175. Rhodium(II) acetate-catalyzed decomposition of the diazocarbonyl **261** proceeded selectively to cyclopropyl ketone **262**, which was converted cleanly to **263** by lithium–ammonium reduction.[365]

Two elegant examples of the application of the selective carbenoid cyclopropanation were used by Corey in the total synthesis of (±)-cafestol (**268**)[366] and (±)-atractyligenin (**269**).[367] Copper-catalyzed decomposition of diazo ketone **264** gave cyclopropyl keto ester **265**. The cyclopropyl keto ester **265** was converted to alcohol **266** in two further steps. Cyclization of **266** to pentacycle **267** leads to the required ring system directly and stereoselectively. The pentacycle **267** was functionalized to give (±)-cafestol **268** (Scheme 176). This synthetic strategy was further employed in the total synthesis of (±)-atractyligenin (**269**, Scheme 177).

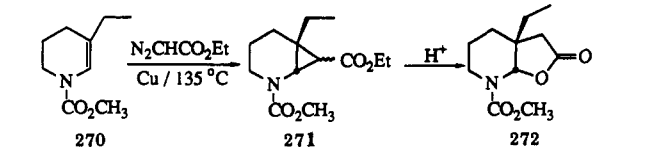
Scheme 176



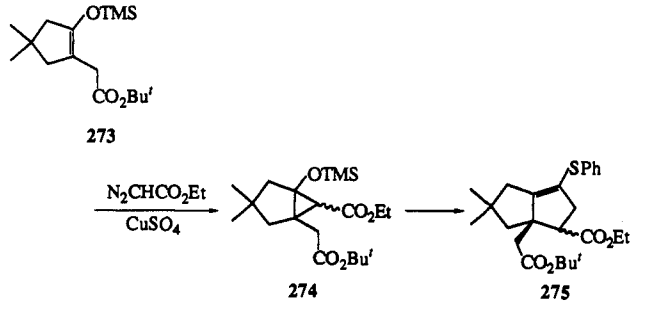
Scheme 177



Scheme 178



Scheme 179



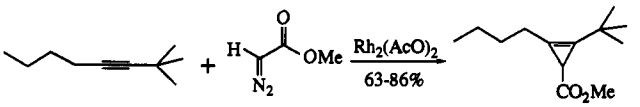
Intermolecular cyclopropanation of enamide **270** using ethyl diazoacetate gave cyclopropane **271**. Acid-catalyzed ring opening of **271** afforded lactone **272** which was the key intermediate of the synthesis of eburnamonine and of dehydroaspidospermidine (Scheme 178).[368]

Marino and co-workers[369] applied the carbenoid cyclopropanation followed by a cyclopentaannulation reaction in the total synthesis of pentalenolactone E methyl ester. Thus, treatment of trimethylsilyl enol ether **273** with ethyl diazoacetate gave the (silyloxy) cyclopropane **274**, which was then fragmented to afford the key bicyclo[3.3.0]octene **275** (Scheme 179). Further chemical manipulation completed the total synthesis.

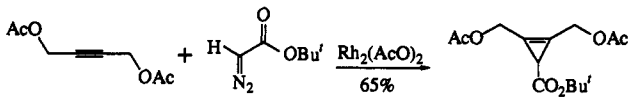
3. Cyclopropenation of Alkynes and Related Reactions

Early studies by Doering and Pomerantz[370] established that methyl diazoacetate adds to 2-butyne photolytically to furnish a cyclopropene adduct. Metal-catalyzed decomposition of diazo esters in the presence

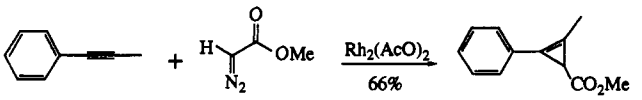
Scheme 180



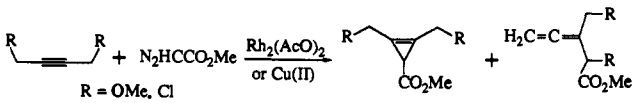
Scheme 181



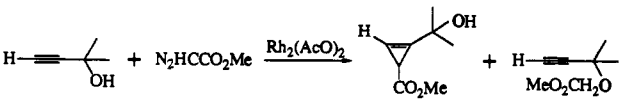
Scheme 182



Scheme 183



Scheme 184

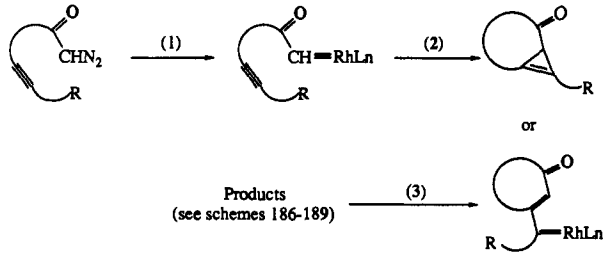


of alkynes is now the preferred route to cyclopropenecarboxylates.[1b,371] Rhodium(II) carboxylates are the catalysts of choice, having largely replaced traditional copper catalysts which often required higher temperatures thereby exposing the primary reaction products to thermal or catalytic ring opening. Bicyclobutanes, arising from cyclopropanation of the product cyclopropenes, are infrequently formed and usually in very low yields.[372] A few representative examples of intermolecular cycopropenation are shown in Schemes 180–182.[68,373–375] For examples of asymmetric cyclopropenation using chiral rhodium(II) catalysts see section III.L.

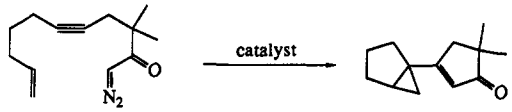
Functionalized alkynes may also undergo cyclopropenation, although depending on the nature of the additional groups in the substrate, other product types are possible. For example, ylide-derived minor products may arise with propargyl chlorides and ethers (Scheme 183),[93,376] and O–H insertion competes with cyclopropenation with propargyl alcohols as substrates (Scheme 184).[93]

There is a growing number of mechanistically complex, intramolecular reactions of α-diazocarbonyls containing suitably positioned alkyne functions which show great potential for the construction of polycyclic molecules from acyclic precursors. These catalysed reactions, which come largely from the work of Hoye[377] and Padwa[1b] and their co-workers, are believed to be initiated by formation of a metal carbene from the diazocarbonyl group in the usual way (Scheme 185, step 1). There follows addition to the alkyne to produce a vinyl carbenoid directly via insertion or indirectly via a highly strained cyclopropene intermediate (step 2). The vinyl carbenoid can then proceed intramolecularly to products which depend on its structure and immediate environment or intermolecularly by reaction with external carbenophiles (step 3). Although most

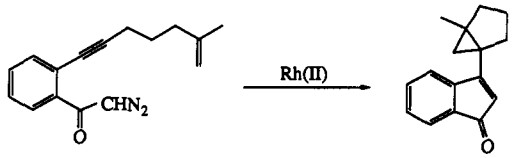
Scheme 185



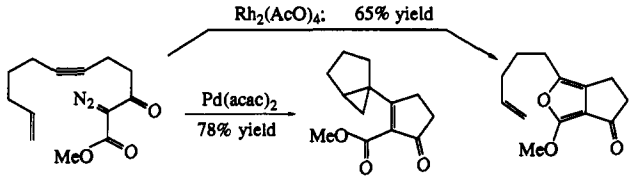
Scheme 186



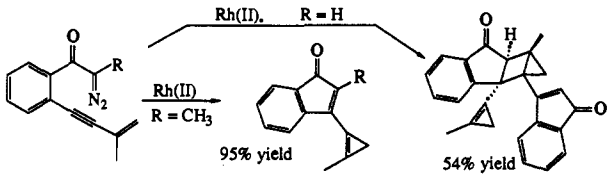
Scheme 187



Scheme 188



Scheme 189

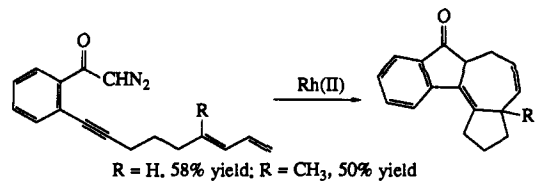


studies are based on rhodium(II) catalysis, Hoye's work shows that product types and yields are very metal dependent, emphasizing that metalated species are involved in product-determining steps.[377]

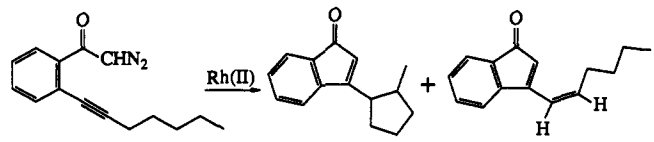
Of the various intramolecular processes open to the putative vinyl carbenoid intermediate in Scheme 185, that of cyclopropanation of a distal double bond in the side chain has proved to be especially effective. Typical examples are shown in Schemes 186[377] and 187.[378] The behavior of the substrate in Scheme 188[377] illustrates the catalyst dependence of the fate of the vinyl carbenoid, whereas use of $Pd(acac)_2$ leads to efficient cyclopropanation of the distal double bond, $Rh_2(AcO)_4$ catalyzes the formation of a fused furan system, presumably from interception of the vinyl carbenoid by the ester carbonyl oxygen atom. When the alkene trap is placed adjacent to the carbenoid carbon atom, as should be the case with the precursor in Scheme 189,[379] the product of its participation is now a vinylcyclopropene which, in the case in hand, with R = CH_3 was isolable, although in the related case with R = H the product isolated was a dimer derived from a [2+2] cycloaddition process.[379]

Yet another variation is possible when the side chain contains a butadiene moiety with the *E* geometry shown in Scheme 190.[378] Here internal cyclopropanation

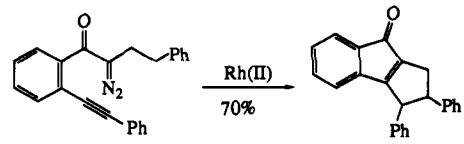
Scheme 190



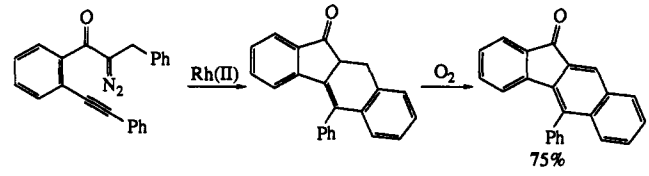
Scheme 191



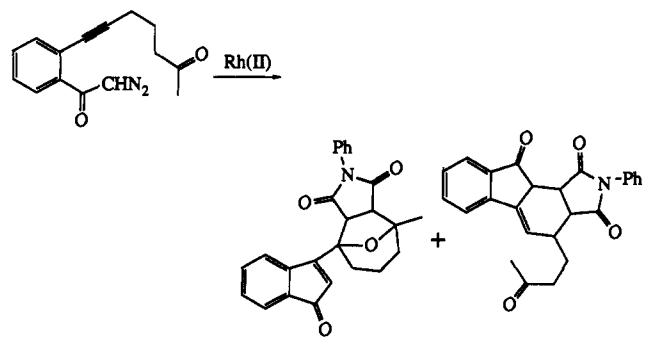
Scheme 192



Scheme 193



Scheme 194

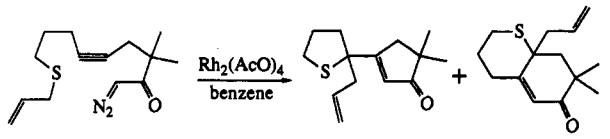


produces a divinylcyclopropane with the correct stereochemistry for Cope rearrangement and the ultimate products are the fused cycloheptatrienes (R = H and R = CH_3). With simple alkyl side chains as in Scheme 191,[380] the vinyl carbene formed on cyclization of the alkyne exhibits characteristic behavior, viz. 1,2-hydrogen shift to form a diene and C–H insertion to form a cyclopentane ring.

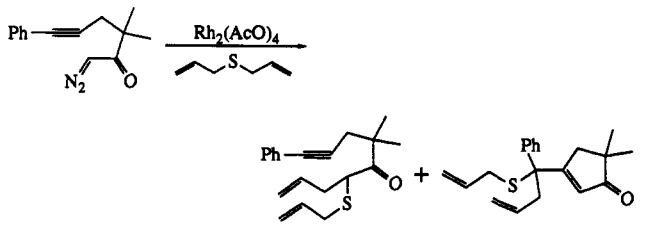
Intramolecular C–H insertion is the preponderant mode of reaction in the example in Scheme 192[381] where formation of the cyclopentane ring results from insertion into the benzylic bond. Intramolecular trapping with an aromatic ring suitably located in the side chain is also possible. For example, treatment of the diazo ketone in Scheme 193[381] with rhodium(II) acetate furnished the tetracyclic ketone shown, attack by the vinyl carbenoid on the distal benzene ring completing the formation of three new fused rings; the primary reaction product was easily oxidized by air to the fully aromatized system.

The behavior of the diazo ketones in Schemes 194[378] and 195[382] on exposure to rhodium(II) acetate dem-

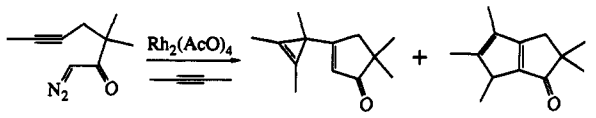
Scheme 195



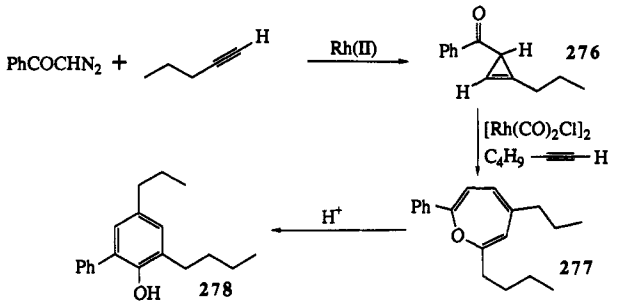
Scheme 196



Scheme 197



Scheme 198



onstrates that vinyl carbenoids are also vulnerable to trapping by heteroatoms. In Scheme 194, a neighboring carbonyl group sequesters the carbenoid in a carbonyl ylide which can be trapped externally in a cycloaddition reaction with *N*-phenylmaleimide. The second product probably results from capture, by *N*-phenylmaleimide, of a diene formed by a 1,2-hydrogen shift in the vinyl carbenoid. In Scheme 195, an allyl sulfide moiety acts as the intramolecular trap for the vinyl carbenoid and the resulting sulfonium ylide undergoes sigmatropic rearrangement to furnish the sulfur heterocycles shown.

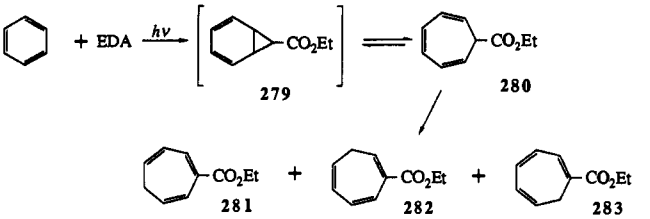
Hoye and Dinsmore[382] have extended the chemistry illustrated in Scheme 195[382] to include the combination of intramolecular formation of a vinyl carbenoid with intermolecular trapping by an external reagent to include diazo ketone decomposition in the presence of diallyl sulfide, as for example in Scheme 196.[382] Here the rhodium(II)-induced bimolecular alkyne insertion–allyl sulfonium ylide rearrangement proceeds efficiently to give γ-allylthio cyclic enones. These workers also demonstrated that when the acetylenic diazo ketone shown in Scheme 197[383] was treated with rhodium(II) acetate in the presence of 2-butyne a double alkyne insertion occurred. Subsequent catalytic ring opening, also brought about by rhodium(II), furnished the dihydropentalenone shown. Padwa and Xu[364] have developed a new phenol synthesis which combines the use of diazo ketone-derived vinyl carbenoids with terminal alkynes. Thus the precursor for the rhodium vinyl carbenoids was prepared by treating α-diazo benzoyl ketone (Scheme 198) with a terminal alkyne. The resulting cyclopropene **276** was allowed to react with another terminal alkyne in the presence of 10 mol % of tetracarbonyldichlorodirhodium to produce oxepin (**277**). Treatment of **277** with a catalytic amount of hydrochloric acid completed the transformation to the phenol **278**. A typical example is shown in the Scheme 198.

D. Reactions with Aromatics

1. Benzene and Its Derivatives

Shortly after Curtius announced his synthesis of ethyl diazoacetate (EDA) in 1893,[2] Buchner commenced an investigation of its reactions with alkenes, alkynes, and aromatics that was to continue for 30 or more years.[385-399] Initially, Buchner believed that thermal decomposition of EDA in benzene furnished a single product to which he assigned the norcaradiene structure, although he was later to discover that hydrolysis of the product yielded a mixture of four isomeric carboxylic acids. The norcaradiene formulation persisted until the 1950s when Doering reexamined the reaction.[400] We now know that the Buchner reaction in its original form produces four cycloheptatrienyl esters **280–283** in Scheme 199.[400]

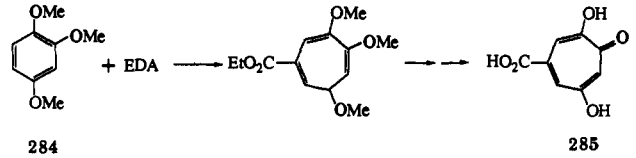
Scheme 199



Photochemically, the reaction behaves in much the same way. The contemporary interpretation of both processes is that carbethoxycarbene addition to benzene proceeds via an unstable norcaradiene intermediate **279** which is in mobile equilibrium with the more stable cycloheptatriene tautomer **280**; the remaining products, **281–283**, are isomers of **280** formed by thermally or photochemically induced sigmatropic rearrangement.

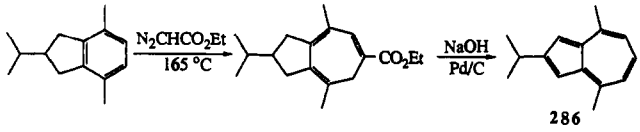
Much of the early work on thermal or photochemical Buchner reactions was characterized by the isolation of complex mixtures of cycloheptatrienyl esters which usually were neither separated nor individually identified. Toluene and EDA produce three ring-expanded products,[401] and a recent reinvestigation of the reaction with anisole revealed the formation of seven products.[402] Low yields and separation problems notwithstanding, the original Buchner reaction represented a singularly direct route to a vast range of seven-membered carbocycles many of which, as mixtures of isomers, were suitable for further elaboration into natural products and unnatural azulenes. The relationship between the anisole–EDA reaction and tropone derivatives was first recognized by Johnson and co-workers[403] who used it as a model for their synthesis of stitipatic acid (**285**) from 1,2,4-trimethoxybenzene (**284**, Scheme 200); for convenience only the cycloheptatriene ester appropriate to the synthesis is shown. Application of the Buchner reaction to bi- and tricyclic aromatics opened up new routes to condensed cycloheptatrienyl systems which were often transformed through decarboxylation–dehydrogenation into azulenes. A typical sequence leading to vetivazulene **286** is shown in Scheme 201.[404]

Scheme 200



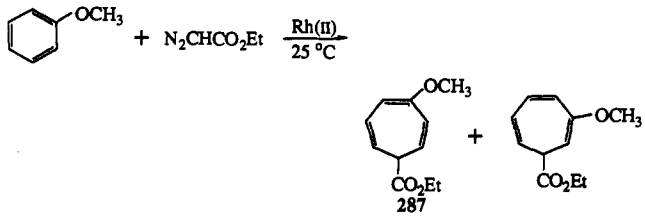
284 285

Scheme 201



286

Scheme 202



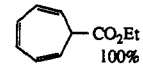
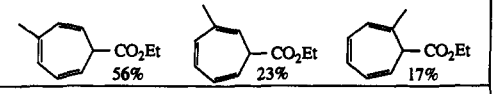
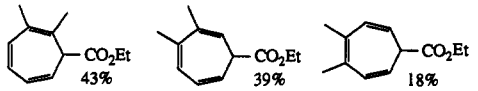
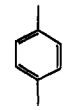
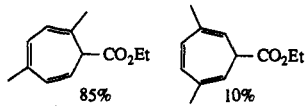
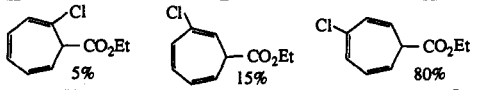
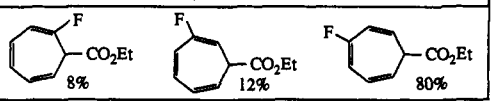
287

The problems endemic to the thermal and photochemical reactions were solved comprehensively in 1980 when the Belgian group extended their study of rhodium catalysis of diazocarbonyl reactions to include the Buchner process.[89,91] The measure of improvement can be quickly appreciated by comparing the thermal reaction of EDA with anisole (seven products, 35% yield) with its rhodium trifluoroacetate-catalyzed counterpart (two products, 73% yield, Scheme 202). And although the methoxy substituent clearly exerts a directive effect in favor of the 4-isomer **287**, both products of the latter (room temperature) reaction are kinetically controlled unconjugated esters, neither of which was even detected in the thermal reaction.

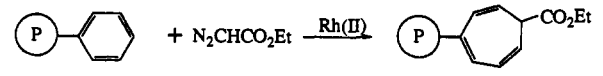
In general, rhodium(II)-catalyzed decomposition of alkyl diazoacetates in a large excess of aromatic substrate at room temperature produces kinetically controlled cycloheptatrienyl esters in excellent yield; a summary of the behavior of several aromatics with EDA is shown in Table 3.[89,91] The regioselectivities observed among isomeric products have been interpreted in terms of attack by a highly electrophilic rhodium carbenoid on the aromatic ring, yield being highest with electron-rich substrates. The catalyzed reaction of EDA with polystyrene (Scheme 203) represents an interesting extention of the Buchner process to the formation of a cycloheptatriene polymer.[89] Cycloaddition of diazo ketones and aromatics is also known. A useful additional feature of the ketone series is that the cycloheptatrienes produced are susceptible to ready ring contraction to benzene ketones in the presence of trifluoroacetic acid (Scheme 204);[405] in some cases aromatization occurs spontaneously. The combination of these two processes has been used to synthesize optically pure α-substituted benzyl ketones from diazo ketones derived from homochiral α-amino acids and α-chloropropionic acid. Illustrative examples are shown in Scheme 205.[150]

Only a few examples of intramolecular Buchner reactions were known prior to the introduction of rhodium catalyst. All employed copper in one form or another, and although yields of ring-expanded bicyclic

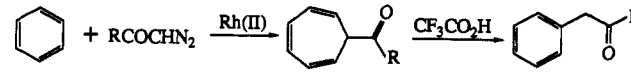
Table 3. Reactions of Ethyl Diazoacetate with Aromatics

Precursor	Products
	 100%
	 56% 23% 17%
	 43% 39% 18%
	 85% 10%
	 5% 15% 80%
	 8% 12% 80%

Scheme 203

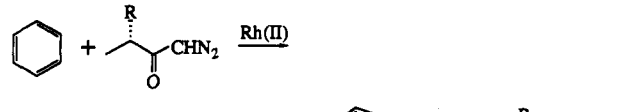


Scheme 204



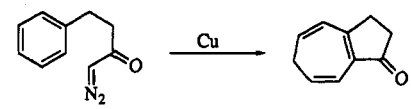
R = CH_3, CH_3OCH_2, CH_3CHBr, CH_2ClCH_2

Scheme 205



R = Cl; R = N-phthaloyl

Scheme 206

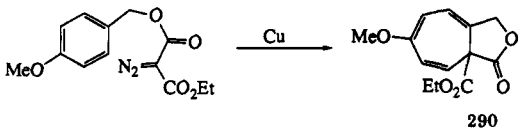


288 289

products were low, the process was recognized as a potentially useful route to a variety of novel structures. Cyclization of 1-diazo-4-phenylbutan-2-one (**288**) with a copper catalyst in hot decalin furnished a mixture of products from which azulenone (**289**) was isolated in 13% yield (Scheme 206).[406] Benzyl diazomalonate, on the other hand, produced bicyclic lactone **290** in 60% yield,[407] movement of the double bonds in **290** being prevented by the bridgehead substituent (Scheme 207). Vogel employed copper powder in refluxing benzene to produce the bridged annulene shown in Scheme 208.[408]

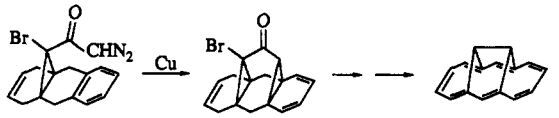
We now return to the parent system. Clearly, trienone **289** is the result of sigmatropic shifts within the cycloheptatrienyl system. Scott reinvestigated the reaction at lower temperatures and detected by ^1H

Scheme 207

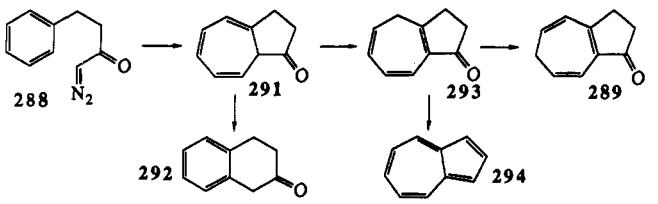


290

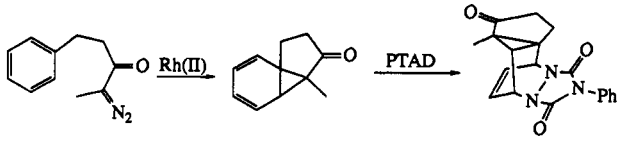
Scheme 208



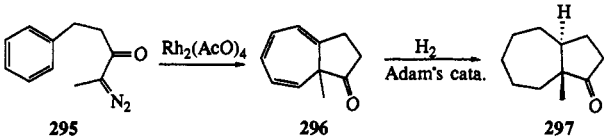
Scheme 209



Scheme 210



Scheme 211

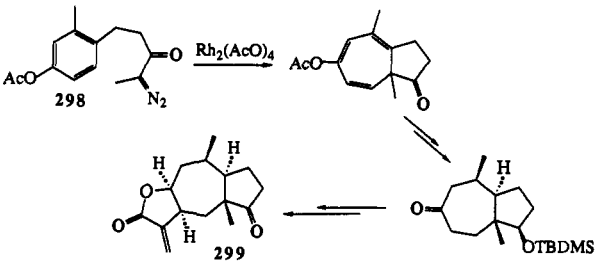


295 296 297

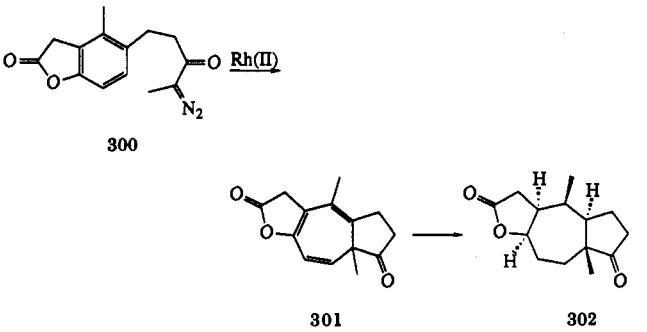
NMR the kinetically formed trienone **291**, but this isomer was transformed into the more conjugated trienone **293** during the isolation procedure.[409-411] Dehydration of **293** with phosphorus pentoxide in methanesulfonic acid produced azulene (**294**) to complete a synthesis which Scott later demonstrated was ideally suited to the production of ^{13}C labeled azulenes.[410,411] The kinetically controlled trienone **291** was finally uncovered by rhodium catalysis for when diazo ketone **288** was exposed to rhodium(II) acetate in dichloromethane at room temperature **291** was the only trienone isolated in 95% yield.[412,413] With triethylamine catalysis, **291** isomerized to Scott's trienone **293**. In contrast, trifluoroacetic acid caused **291** to rearrange quantitatively to 2-tetralone (**292**), an aromatization process that probably proceeds via the norcaradiene valence tautomer presumed to be in equilibrium with the trienone. All these transformations are summarized in Scheme 209. In a related example Saba has shown that the norcaradiene form can be detected by low-temperature NMR and can be trapped in a Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (Scheme 210).[414,415]

A study of substituent effects on this catalyzed intramolecular Buchner reaction shows that a methyl can be accommodated on the diazo carbon atom as in Scheme 211, hydrogenation of the product **296** opening up a short stereospecific route to the *trans*-perhydroazulenone system **297** (60% yield from the diazo ketone **295**).[416] Recently this route has been applied to the synthesis of the pseudoguaianolide sesquiterpene, (±)-confertin (**299**), from diazo ketone **298** (Scheme 212).[417,418] More highly substituted aromatics have also been studied in the course of guaianolide and pseudoguaianolide synthesis. For example, rhodium(II) mandelate-catalyzed cyclization of diazo ketone **300** produced the ring-expanded product **301** which on hydrogenation furnished the tricyclic lactone **302** (Scheme 213).[416] With para phenolic groups in the diazo ketone yet another cyclization pathway may be followed.[419-423] For example, diazo ketone **303** on exposure to copper(I) chloride furnishes both spirodienone **304** and cycloheptatrienone **305**; depending on reaction conditions the spirodienone **304** may be the sole product (Scheme 214).[419] Other active catalysts include rhodium and palladium carboxylates.[421] This route to spirodienones has been employed in synthetic studies directed toward the solavetivone, aphidicolane, and stemodane sesquiterpenes.[421-423]

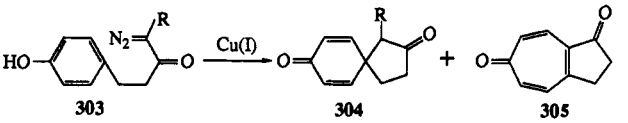
Scheme 212



Scheme 213

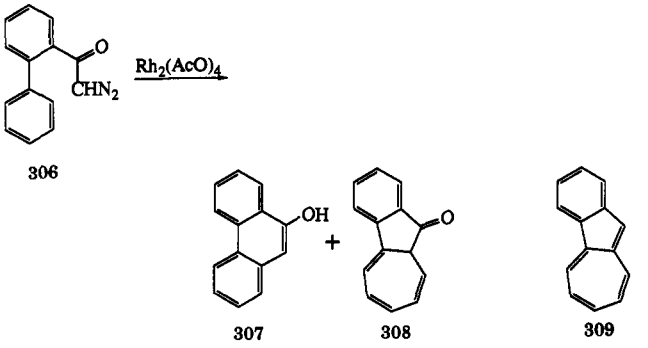


Scheme 214

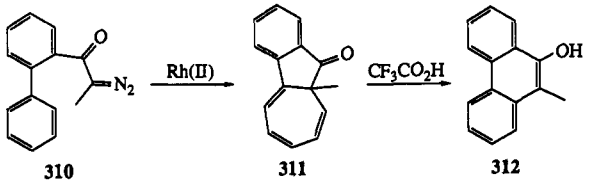


As we have just seen with diazo ketone **288** (Scheme 209), the mild conditions associated with rhodium catalysis, as compared with copper, do provide more favorable circumstances for observing unstable primary reaction products. Another case in point is the formation of phenanthrol **307** from biphenyl diazo ketone **306** under copper catalysis.[424] Superficially the reaction may appear to be an aromatic C–H insertion process; its behavior under rhodium catalysis suggests a Buchner-type reaction. The crude product from rhodium(II)-catalyzed decomposition of **306** contained about 15% of an unstable substance which slowly rearranged into phenanthrol on standing at room temperature. Furthermore, lithium aluminum hydride reduction of the product mixture gave benzazulene (**309**, 5%), suggesting that the minor component is indeed the Buchner product **308** (Scheme 215).[425]

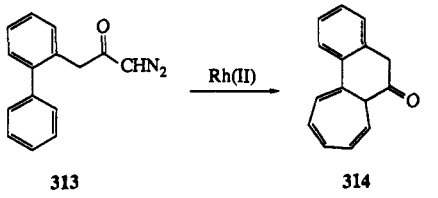
Scheme 215



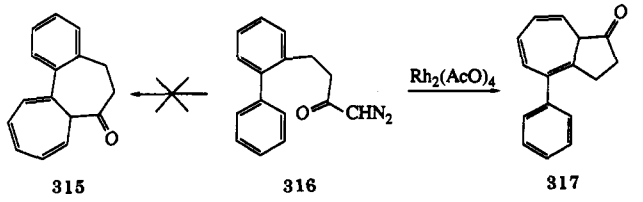
Scheme 216



Scheme 217



Scheme 218

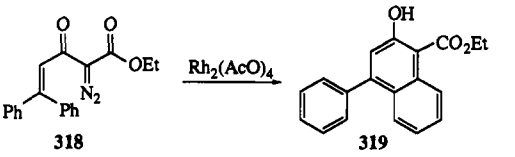


Interestingly, a major change of behavior occurs in the biphenyl series when a methyl substituent is added to the diazo carbon atom of **306**.[425] Decomposition of diazo ketone **310** employing rhodium(II) mandelate furnished as the sole product the stable tricyclic azulenone **311** (Scheme 216). Furthermore, this product did not rearomatize easily, requiring treatment with hot trifluoroacetic acid to bring about conversion to 10-methyl-9-phenanthrol (**312**).

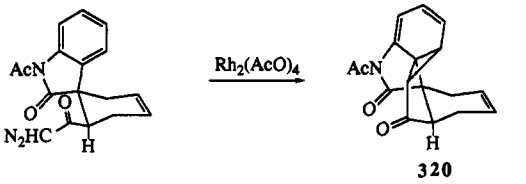
Diazo ketone **313**, a simple homologue of **306** with a longer side chain, also underwent smooth catalyzed decomposition to the ring-expanded ketone **314** in 95% yield (Scheme 217).[425] The next homologue in the biphenyl series, diazo ketone **316**, did not, however, continue the trend and produce the colchicine-like benzodicycloheptyl system **315** in Scheme 218. Rather the product was the bicyclic phenylazulenone (**317**), indicating that the distal benzene ring in **316** acts as a substituent in the reaction and not as a site for carbenoid attack.[425]

A contrasting picture is observed in the rhodium(II) acetate-catalyzed decomposition of diazo ketone **318**, which furnished the naphthol **319** exclusively (Scheme 219).[426] It is quite possible that this product is formed via a norcaradiene-like intermediate which would be expected to aromatized readily rather than undergo ring expansion. There is at least one example of

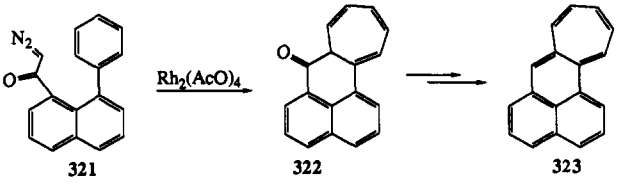
Scheme 219



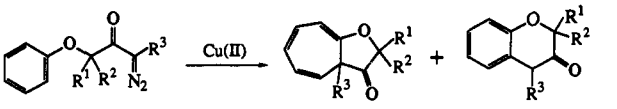
Scheme 220



Scheme 221



Scheme 222

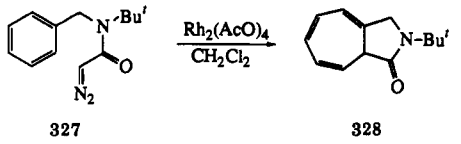


$R^1 = R^2 = H$, $R^3 = CH_3$, yield = 65% (325/326 = 2/3)
$R^1 = R^2 = R^3 = CH_3$, yield = 95% (325/326 = 9/1)
$R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$, yield = 95% (325 only)
$R^1 = C_6H_5$, $R^2 = H$, $R^3 = CH_3$, yield = 88% (325 only)

isolation of a stable norcaradiene from a catalyzed decomposition of a diazo ketone. Wenkert and Liu[427] found that decomposition of the diazo ketone in Scheme 220 using rhodium(II) acetate furnished **320** in 80% yields. A final example of the use in synthesis of intramolecular carbocyclic ring expansion is the construction by Murata and co-workers[428] of cyclohepta[*a*]phenylene (**323**), a highly electron-donating nonalternant hydrocarbon. Rhodium(II) acetate-catalyzed decomposition of diazo ketone **321** furnished the necessary tetracyclic framework **322** in 89% yield and reductive removal of the oxygen function followed by dehydrogenation completed the synthesis of **323** (Scheme 221).

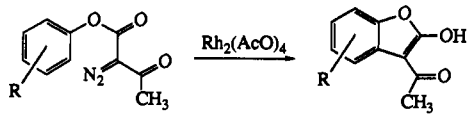
There are now several examples of catalyzed aromatic cycloadditions, all intramolecular, leading to heterocyclic systems. Saba and co-workers[429] found that diazo ketones **324** with α-phenoxy substituents of the type shown in Scheme 222 undergo cyclization catalyzed by bis(hexafluoroacetonate)copper(II) to furnish mixtures of cycloheptafuranones **325** and chromanones **326** whose compositions were influenced by the degree and position of substituents in the precursors. The cycloheptafuranones **325** were observed to rearomatize easily to chromanones **326**, e.g. in contact with silica gel, an instability reminiscent of their carbocyclic counterparts, the azulenones, discussed earlier. Doyle's group[430] has examined similar routes to *N*-heterocycles using as substrates *N*-alkyl-*N*-benzyldiazoacetamides and rhodium(II) acetate as the catalyst. With the *N*-*tert*-butyl precursor **327** (Scheme 223) cyclization proceeded

Scheme 223

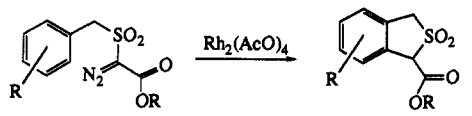


327 328

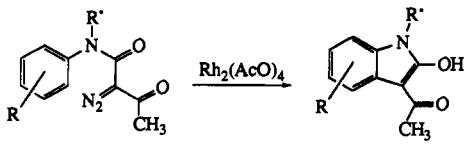
Scheme 224



Scheme 225



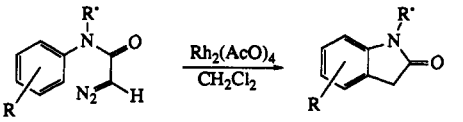
Scheme 226



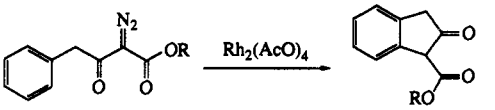
quantitatively to afford azabicyclo[5.3.0]decatrienone **328**. Cyclization occurred with comparable efficiency in the *N*,*N*-dibenzyl precursor but with the *N*-methyl precursor cyclization occurred in much lower yield, although it did improve on changing the catalyst to rhodium(II) perfluorobutyrate. Unlike their oxygen and carbon counterparts, these azabicycles did not rearomatize even on prolonged exposure to either strong protonic or Lewis acids.

Regardless of the relative stabilities of the cycloheptatrienyl adducts, the processes described above can be classified as aromatic cycloadditions of keto carbenoids. There is another related intramolecular reaction of diazocarbonyl compounds bearing aromatic substituent which leads to bicyclic aromatic products apparently without the intervention of ring-expanded intermediates. This latter process is often referred to as aromatic C–H insertion of carbenoids although mechanistically electrophilic aromatic substitution may more accurately characterize the transformation. Experiments designed to allow a distinction between these two processes appear not to have been conducted. However, it is probably significant that some examples in which rhodium(II) carboxylates are catalytically active can also be brought about by protonic acids, suggesting that acid-promoted electrophilic aromatic substitution is an alternative to the carbenoid C–H insertion pathway. The common feature of these reactions is annulation of an aromatic system with a five-membered carbocyclic or heterocyclic ring. Durst and his co-workers[431–434] have studied these annulations extensively employing α-diazo-β-keto esters (Scheme 224), α-diazo-β-sulfonyl esters (Scheme 225), and α-diazo-β-keto amides (Scheme 226). Doyle and coworkers[435] have independently studied *N*-aryldiazoacetamides and *N*-aryldiazoacetoacetamides (Schemes 226 and 227). Aromatic substrates include simple monosubstituted benzenes, thiophenes, and indoles.[433] The preferred catalyst was rhodium(II) acetate or trifluoroacetate. The perfluorosulfonic acid, Nafion-H, also catalyzed the cyclization of Doyle's diazoacetamides, but not diazoacetoacetamides, and yields of 2-indolinones were higher than those obtained with rhodium(II) acetate.[435] Taber[272] has used rhodium(II) acetate to catalyze the formation of 1-carboxy-2-indanone from the diazo keto ester in Scheme 228, and this catalyst was also used by Nakatani[436] to form the tricyclic indanone in Scheme 229.

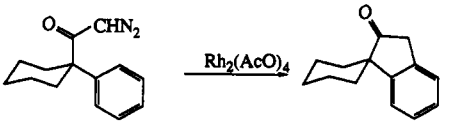
Scheme 227



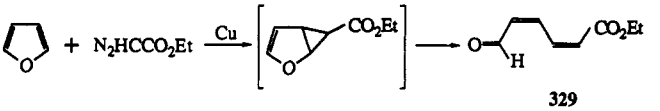
Scheme 228



Scheme 229

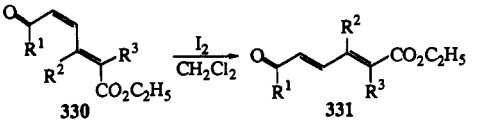


Scheme 230



329

Scheme 231



330 331

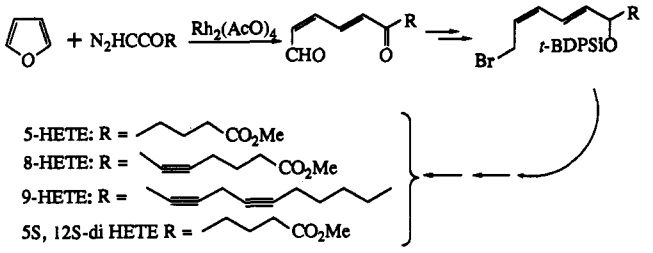
$R^1 = R^2 = CH_3$, $R^3 = H$;
$R^1 = CH_3$, $R^2 = R^3 = H$;
$R^1 = R^2 = H$, $R^3 = CH_3$

2. Heteroaromatic Compounds

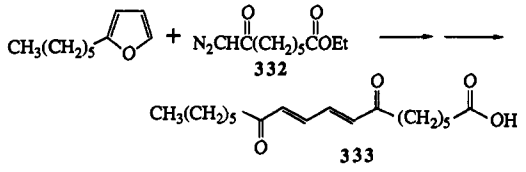
Among other aromatics whose reactions with diazocarbonyls have found applications in synthesis are furan, pyrrole, and thiophene. In an early study using copper catalysis Novac and Sorm[437] observed that cyclopropanation of furan with ethyl diazoacetate is possible (Scheme 230), but that the initially formed cycloadduct undergoes a ready ring-opening process to afford the *Z*,*E*-diene adduct **329**. Several groups have recognized the synthetic potential of this short route to functionalized dienes, although most of the more recent applications use rhodium rather than copper catalysts. Although some of the cycloadducts are isolable, notable those derived from ethyl diazoacetate, in most cases they spontaneously ring open under the reaction conditions or can be induced to do so by the addition of an acid. The fact that the resulting *Z*,*E*-dienes **330** can be readily isomerized to *E*,*E*-isomers **331** (Scheme 231)[438,439] further enhances the usefulness of this synthesis.

The rhodium-induced furan–diazocarbonyl unraveling process has been applied with notable success to

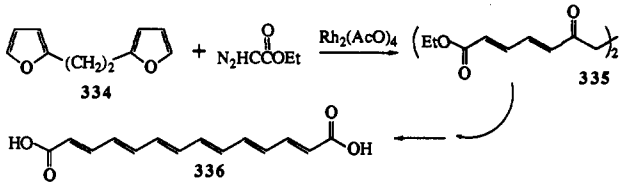
Scheme 232



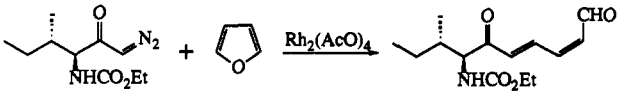
Scheme 233



Scheme 234



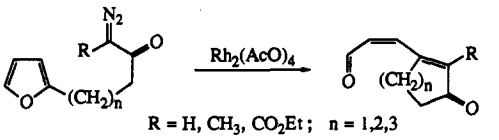
Scheme 235



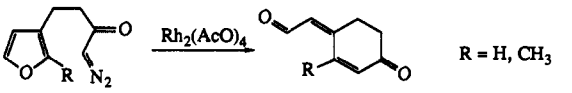
leukotriene synthesis by a Merck Frost Canadian group.[440-442] In each case the aldehyde released in the ring-opening process was used to attach the remainder of the polyene system. Some representative examples are shown in Scheme 232. Total synthesis of ostopanic acid (**333**), a plant cytotoxin, has been achieved (Scheme 233),[443] in a similar way from 2-*n*-hexylfuran and the diazo ketone **332**, the *E,E*-diene having been produced by iodine-catalyzed isomerization of the *Z,E* isomer. Wenkert and co-workers[439] have combined the products of furan–diazoacetate reactions with Wittig reagents to form 1,6-diacyl-1,3,5-hexatrienes and segments of retinol and β-carotene. The same group in their synthesis of corticrocin (**336**),[439] a fungal pigment, employed a double unraveling of a difurylethane **334** (Scheme 234) with ethyl diazoacetate to furnish the tetraene **335** suitable for conversion to the natural product by reduction of the two keto functions followed by double dehydration of the resulting diol. Optically pure diazo ketones derived from natural amino acids have been combined with furan under rhodium catalysis to produce aldehydes suitable for elaboration, via Wittig reactions, into optically pure α-amino keto polyene systems of the type shown in Scheme 235.[444]

The intramolecular version of the furan–diazocarbonyl reaction is an attractive route to carbocycles. Furans with side chains at C(2) of various lengths terminating in diazomethyl keto functions are known to undergo rhodium-catalyzed unraveling with the production of 2-cyclopentenones, 2-cyclohexanones, and 2-cycloheptenones to each of whose olefinic β-carbon atoms is a attached an acrylaldehyde unit.[445,446] Some representative examples from the work of Wenkert[445,446]

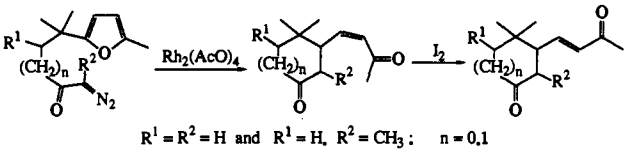
Scheme 236



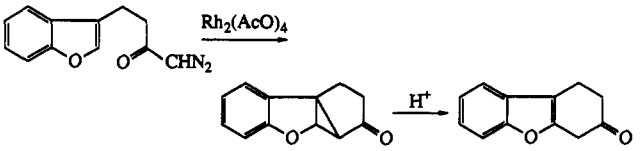
Scheme 237



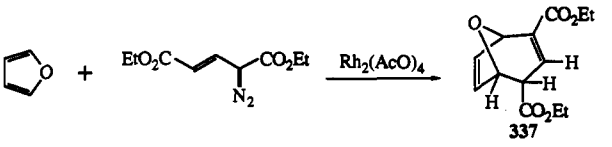
Scheme 238



Scheme 239



Scheme 240

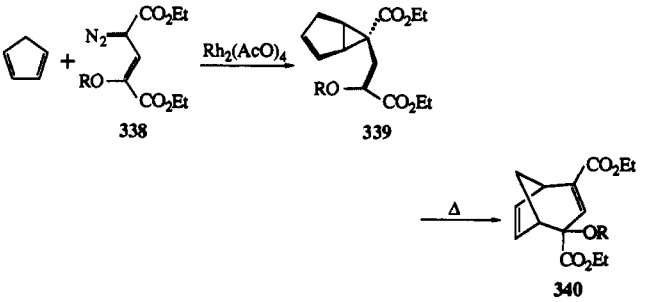


and Padwa[447,448] and their respective groups are shown in Schemes 236–239.

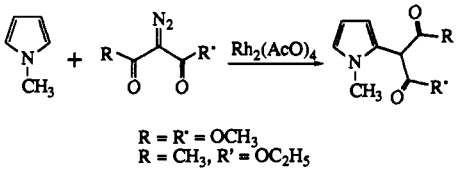
Yet another pathway for furan–diazocarbonyl cycloadditions is the [3 + 4] combination explored in detail by Davies and his group.[449] They argued that while vinyl carbenes have a strong propensity for intramolecular reactions, their reactivity might be quite different if they were generated as metal carbenoid complexes by metal-catalyzed decomposition of vinyl diazo precursors. Such complexes should be more stable than free vinyl carbenes. Undesirable intramolecular side reactions should therefore be minimized. Davies tested this idea by preparing the vinyl diazo ester in Scheme 240 (from commercially available diethyl glutaconate via diazo transfer using *p*-(*n*-dodecylphenyl)sulfonyl azide) and exposing it to rhodium(II) acetate in the presence of furan at room temperature. The major reaction product was the bicyclic adduct **337**, clearly demonstrating that a stereospecific [4 + 3] cycloaddition between a vinyl carbenoid and a furan is feasible. Subsequent studies revealed that formation of adducts of type **340** is the result of a tandem cyclopropanation–Cope rearrangement process, divinylcyclopropanes **339** having been isolated as intermediates (Scheme 241) from the reaction of the vinyl diazo ester **338** and cyclopentadiene.[450]

Pyrrole and its derivatives exhibit a range of reactivity in catalyzed reactions with diazocarbonyls. This heterocycle possesses the additional feature that the electron supply can be modulated by N-substitution. Unlike furan, pyrrole, and its *N*-alkyl derivatives favor ring alkylation rather than cyclopropanation. In fact

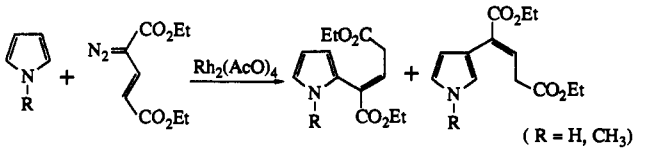
Scheme 241



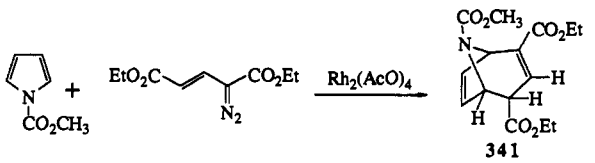
Scheme 242



Scheme 243

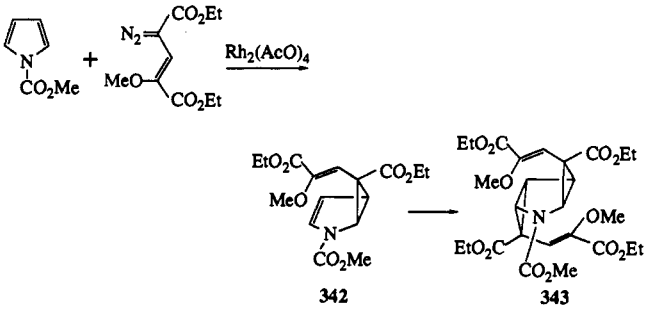


Scheme 244

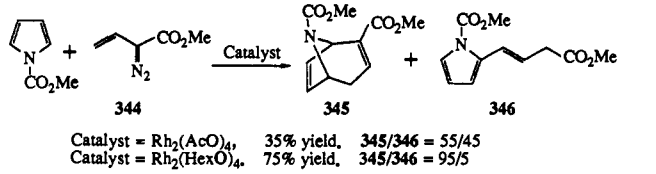


the copper-catalyzed reaction of ethyl diazoacetate with pyrrole or pyrrole derivatives has long been recognized as one of the most reliable routes to pyrrole-2-acetic ester.[451-456] Substitution at the 2-position is preferred, although not exclusively so. For example, *N*-methylpyrrole and ethyl diazomalonate give products of both 2- and 3-substitution in a 10:1 ratio. As part of research directed toward improved synthetic processes for tolmetin and zomepirac, Maryanoff[454-456] has carried out a detailed study of the reaction of ethyl diazoacetate, dimethyl diazomalonate, and ethyl 2-diazoacetoacetate with *N*-methylpyrrole. All reactions showed high regiochemical preference for the formation of 2-substituent adducts. Rhodium(II) acetate resulted in high yield products from the dimethyl diazomalonate and ethyl 2-diazoacetoacetate (Scheme 242). For the reaction of ethyl diazoacetate, copper(II) compounds are the catalysts of choice.[458] Substitution reactions with pyrrole and alkylpyrroles are presumably favored because the electron-releasing ability of the nitrogen atom stabilizes a zwitterionic intermediate and consequently cyclopropanation does not occur. Alternatively, cyclopropanation may occur but is rapidly followed by ring opening. The preference for ring alkylation of pyrrole and *N*-methylpyrrole is also observed with the vinyl carbenoid precursors of Davies (Scheme 243).[457] However, on changing the substrate to N-(methoxycarbonyl)pyrrole (Scheme 244), where the ability of the nitrogen atom to stabilize a positive charge is considerably diminished, the tandem cyclopropanation–Cope rearrangement process takes over, providing a direct entry to the tropane skeleton **341**.

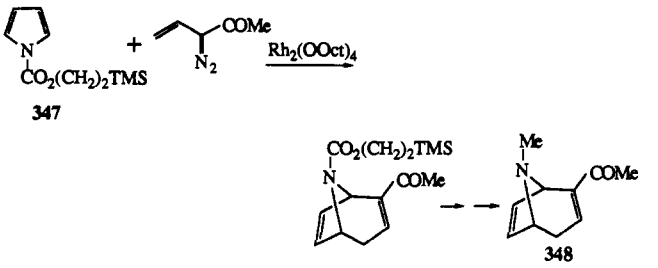
Scheme 245



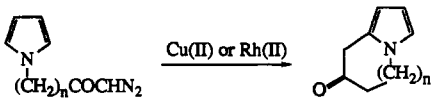
Scheme 246



Scheme 247



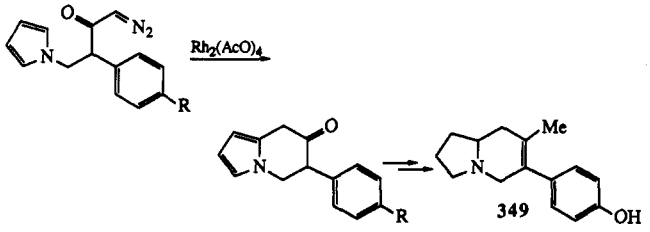
Scheme 248



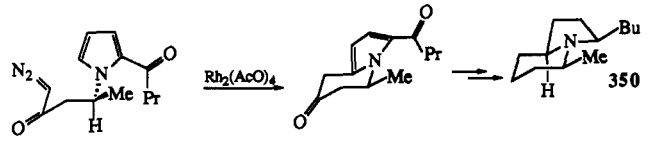
An interesting reaction was observed on decomposition of the bulky vinyldiazomethane in Scheme 245 in the presence of *N*-(methoxycarbonyl)pyrrole. In this case the initially formed divinylcyclopropane **342** was sterically too constrained to undergo Cope rearrangement, and instead further reaction of **342** produced the dicyclopropane adduct **343**. In the case of a vinyl diazocarbonyl with a single electron-withdrawing group, as in **344**, reaction with the N-acylated pyrrole to form the tropane system **345** (Scheme 246) was strongly catalyst dependent, with rhodium(II) hexanoate in hexane furnishing a much higher conversion to **345** than rhodium(II) acetate in dichloromethane.[458] The efficacy of this approach to tropane alkaloids has been demonstrated by Davies[458] in a short synthesis of (±)-ferruginine **348** from the N-acylated pyrrole **347** in Scheme 247. In this case the key cyclization step was accomplished using rhodium(II) octanoate.

The intramolecular version of the pyrrole–diazocarbonyl alkylation reaction has been explored by Jefford and Johncock[459] in a very efficient route to another important group of alkaloids, the indolizidines. These workers were among the first to show that simple *N*-alkylpyrroles having the diazocarbonyl moiety in the side chain of the type shown in Scheme 248 undergo very efficient intramolecular alkylation to form pyrrolizinones with either copper[459] or rhodium catalysis.[460-464] Applications of this route to the synthesis of (±)-ipalbidine (**349**), (+)-monomorine (**350**), (−)-

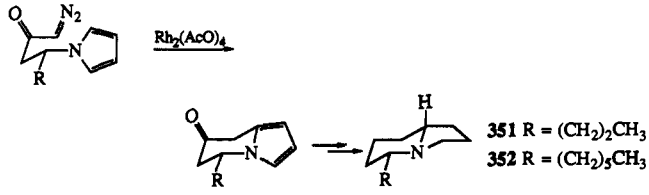
Scheme 249



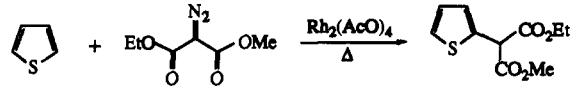
Scheme 250



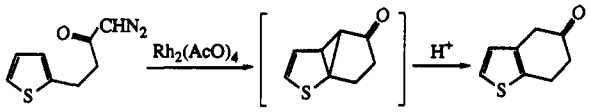
Scheme 251



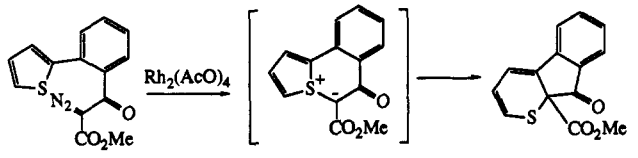
Scheme 252



Scheme 253



Scheme 254

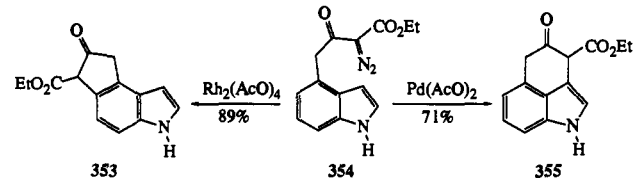


indolizidine 167B (**351**), and (−)-indolizidine 209D (**352**) are shown in Schemes 249–251; the enantiospecific routes in the latter two cases were constructed using *N*-alkylpyrroles derived from optically active amino acids.[461–464]

Catalytic reaction between thiophenes and diazocarbonyls has been known for several years. Rhodium(II) salts are the catalysts of choice for this reaction type.[465] In general, three possible processes, ylide formation, cyclopropanation, and C–H insertion, may be involved in the reaction; also ylide formation may be responsible for the C–H insertion and cyclopropanation.[465,466] The outcome of the reaction depends upon the diazocarbonyl precursors and reaction conditions. In addition, the intramolecular version of this reaction is also possible.[447,448,467] Some representative examples are shown in Schemes 252–254.

Finally, the outcome of intramolecular aromatic cycloaddition not only depends upon the nature of the diazocarbonyl precursor, but also depends upon the catalyst employed in the reaction. Decomposition of

Scheme 255

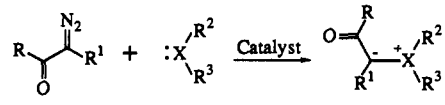


diazocarbonyl **354** with rhodium(II) acetate and palladium(II) acetate led to regioisomers **353** and **355**, respectively (Scheme 255).[468]

E. Ylide Formation and Subsequent Reactions

Carbenoids derived from α-diazocarbonyl compounds exhibit highly electrophilic properties. They can readily react with an available heteroatom to effect ylide formation (Scheme 256). Chemical transformations of

Scheme 256



ylides have shown great versatility in the synthesis of natural products as well as other complex molecules. Recently, ylides derived from α-diazocarbonyl compounds have received considerable attention and there are numerous examples in the literature concerning the application of ylide generation via catalytic methods.

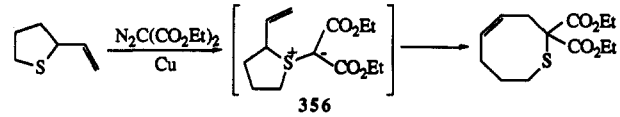
In this section we will briefly review formation from diazocarbonyl compounds and their subsequent reactions. The main emphasis will be placed on synthetic applications.

1. [2,3]-Sigmatropic Rearrangements

Symmetry-allowed [2,3]-sigmatropic rearrangement is a facile bond reorganization process with catalytically generated ylides.[469] Transition metal-catalyzed reactions of diazocarbonyl compounds with a broad selection of allylic substrates result in products derived from [2,3]-sigmatropic rearrangement of intermediate allylic ylides.

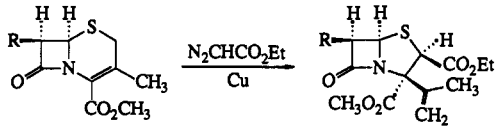
Catalytic decomposition of diazocarbonyl compounds in the presence of allylic sulfides, ethers, selenides, amines, and halides may form allylic ylides. Vedejs and Hagen[470] reported the application of the [2,3]-sigmatropic rearrangement in the ring expansion of an allylic sulfide substrate **356**, derived from the copper-catalyzed decomposition of diazomalonate (Scheme 257).

Scheme 257



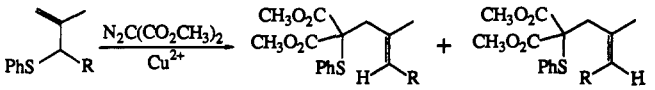
The [2,3]-sigmatropic rearrangement of an allylic sulfur ylide, generated by catalytic decomposition of ethyl diazoacetate, has also been used in the stereocontrolled conversion of the cephalosporin (**357**) to the penicillin ring system **358** (Scheme 258).[469] Another interesting application (Scheme 259) of the [2,3]-sigmatropic rearrangement of allylic sulfur ylides derived from carbenoids is in the synthesis of trisub-

Scheme 258



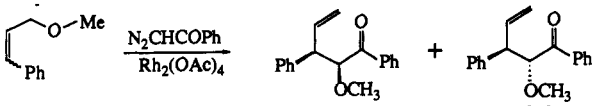
357 358

Scheme 259



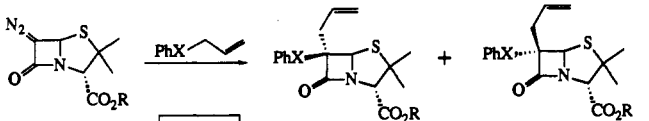
E 359 *Z* 360

Scheme 260



361 362 363

Scheme 261



364 365 366

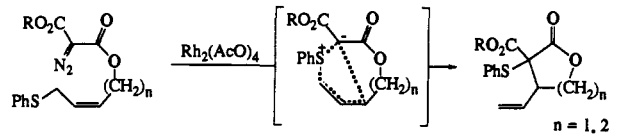
stituted olefins. There is a high level of stereoselectivity in this transformation, leading to a 9:1 ratio of (*E*)- and (*Z*)-olefins (**359** and **360**, respectively, Scheme 259).[471] The strong preference for the *E* isomer is clearly a general attribute of the [2,3]-sigmatropic rearrangement process. Doyle and co-workers[472] reported the formation of allylic oxonium ylides via catalytic reaction of diazo ketones with allyl methyl ethers. The resulting [2,3]-sigmatropic rearrangement products **362** and **363** showed high degrees of diastereoselectivity, the preference depending on the geometry of the allyl methyl ether **361** (Scheme 260). These results can be explained by steric influences in the transition state.

Allylic selenium ylides, derived from the catalytic reaction of diazocarbonyl compounds **364** with allylic selenides, also undergo a [2,3]-sigmatropic rearrangement. Thomas and coworkers[473,474] have utilized both allylic sulfur and allylic selenium ylides in the synthesis of 6-substituted penicillin analogues **365** and **366** (Scheme 261).

The intermolecular reaction of carbenoids derived from diazocarbonyl compounds with allylic amines and allylic halides (Cl, Br, and I) to form the corresponding allylic ylides and their subsequent [2,3]-sigmatropic rearrangement is also known. The scope of these ylide formations and the influence of catalysts have been studied by Doyle's group.[475,476] Allylamines and iodides give the corresponding sigmatropic rearrangement product exclusively, whereas allyl bromides and chlorides undergo catalytic cyclopropanation in competition with ylide formation and rearrangement.

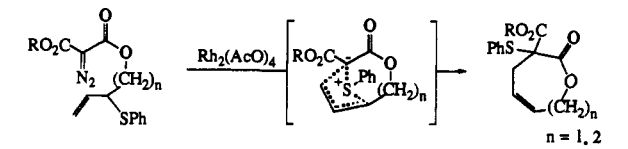
Catalytic decomposition of diazocarbonyl compounds containing heteroatoms in intramolecular allylic systems is also known. These ylides and their subsequent [2,3]-sigmatropic rearrangements provide a convenient and powerful tool for the construction of natural products, as well as other carbonyl compounds possessing interesting molecular frameworks.

Scheme 262



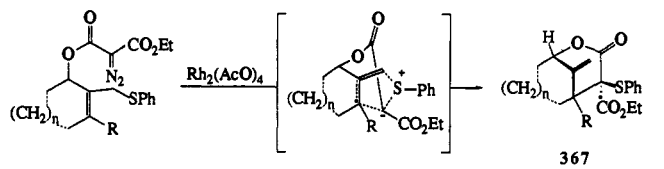
n = 1, 2

Scheme 263



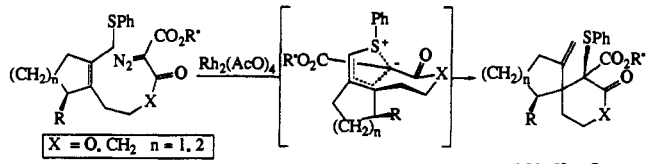
n = 1, 2

Scheme 264



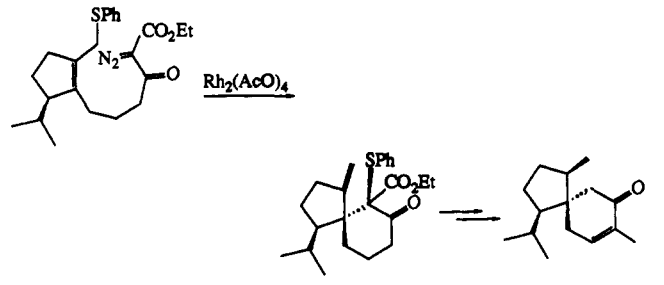
367

Scheme 265



368 369: X = O 370: X = CH_2

Scheme 266

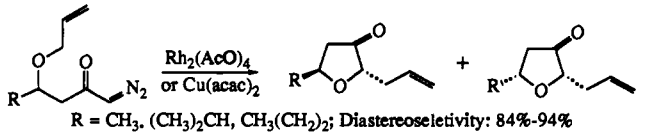


371

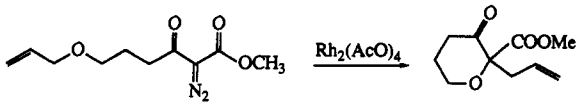
For example, an attractive method for construction of five- to eight-membered lactones, based on intramolecular allylic sulfur ylide formation and subsequent [2,3]-sigmatropic rearrangement, has been reported by Kido and Yoshikoshi's group (Schemes 262 and 263).[477-480] This synthetic methodology has been extended to the efficient synthesis of bridged δ-lactones **367**,[481] spiro-fused five- and six-membered lactones[482] (**369**, X = O), and spiro carbocyclic compounds (**370**, X = CH_2)[483] (Schemes 264 and 265). Because the [2,3]-sigmatropic rearrangement usually proceeds through a highly ordered cyclic transition state, conformational analysis may be applied to predict and control the stereochemical outcome.[484]

This method of constructing spiro carbocyclic compounds (**370**, X = CH_2) has also been used in the stereoselective synthesis of the sesquiterpene (+)-acorenone B (**371**)[483] (Scheme 266). The remarkable stereoselectivity in the rearrangement process may result from the carbenoid approaching the sulfonium reaction site from the less hindered side, away from the R substituent (isopropyl group), as seen in the transition state **368** (Scheme 265).

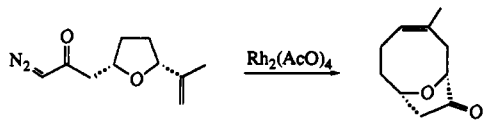
Scheme 267



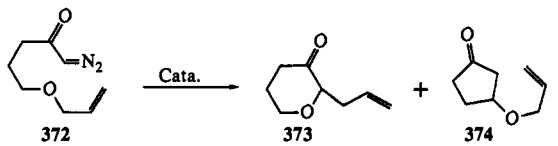
Scheme 268



Scheme 269



Scheme 270

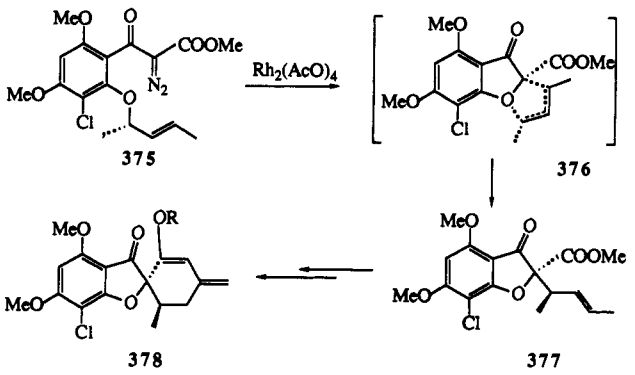


Catalyst	yield	yield
$Rh_2(AcO)_4$	37%	22%
$Cu(hfacac)_2$	83%	0%

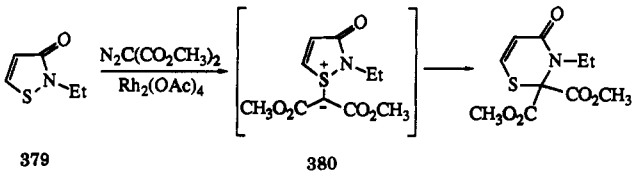
Generation of allylic oxonium ylides derived from intramolecular carbenoid addition to an ether oxygen atom, followed by concerted [2,3]-sigmatropic rearrangement provides novel methodology for the construction of five-, six-, and eight-membered oxygen heterocycles. Some representative examples carried out by Pirrung's,[485] Johnson's,[486] and Clark's[487] research groups are illustrated in Schemes 267–269. Recently, Clark and co-workers[488] have demonstrated that the intramolecular oxonium ylide formation process, in some cases, is catalyst dependent. Copper(II) hexafluoroacetylacetonate [Cu(hfacac)$_2$] provided exceptional chemoselectivity in the cyclization of diazo ketone **372** to give the solo product **373** from ylide generation (Scheme 270). Seven- and eight-membered ring ethers have also been synthesized via this methodology in 76% and 40%, respectively. The intramolecular generation and [2,3]-sigmatropic rearrangement of oxonium ylides was also used by Pirrung and co-workers[489] in the preparation of (+)-griseofulvin (**378**). Decomposition of diazocarbonyl precursor **375** using rhodium(II) pivalate as the catalyst in refluxing benzene provided the sigmatropically rearranged product **377** which served as a key step in the total synthesis. The stereochemistry of this process can be understood in terms of a transition-state model **376** that resembles an oxabicyclo[3.3.0]octane ring system with the key stereochemistry-defining methyl group located on the convex face (Scheme 271).

Effective allylic oxonium ylide generation in the transition metal-catalyzed reactions of diazocarbonyl compounds depends on the catalyst, the type of diazo carbonyl compound, and competition with other transformations.[41] Although copper catalysts are in general less efficient for carbenoid transformations when compared to their rhodium counterparts, they usually favor the ylide formation process.[145]

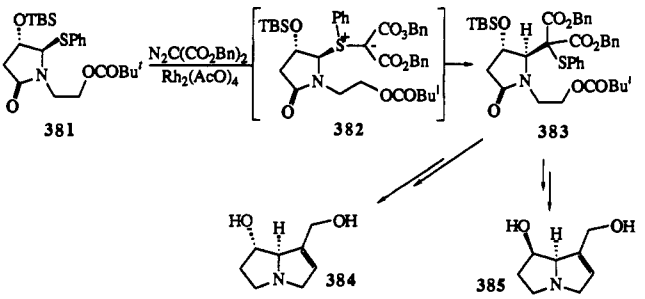
Scheme 271



Scheme 272



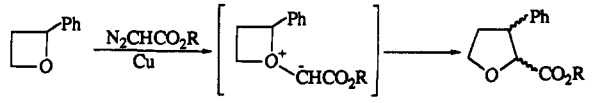
Scheme 273



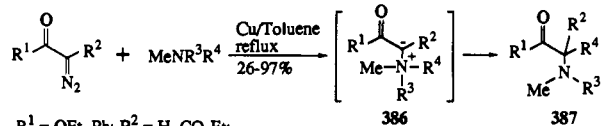
2. [1,2]-Sigmatropic Rearrangements

There have been many reports of ylide formation by catalytic methods, followed by Stevens [1,2]-shift leading to the formation of new carbon–carbon bonds. Although concerted [1,2]-shifts are forbidden processes according to the Woodward–Hoffmann rules,[490] the many reports of apparent [1,2]-shift of ylides derived from reaction of carbenoids and heteroatoms suggest the rearrangements occur via a homolysis–recombination mechanism. Ylides derived from catalytic reactions of diazo carbonyl compounds which undergo [1,2]-shift processes are becoming increasingly useful in synthetic chemistry. Most applications of this sequence involve the intramolecular mode. However, a few examples of applications of intermolecular ylide formation followed by [1,2]-shift are summarized here. The carbenoid derived from rhodium(II) acetate-catalyzed decomposition of dimethyl diazomalonate reacts with *N*-ethylisothiazol-3(2*H*)-one (**379**) to form the sulfide ylide **380**, which then undergoes ring expansion via a [1,2]-shift process (Scheme 272).[491] Two pyrrolizidine alkaloids, (+)-heliotridine (**384**) and (+)-retronecine (**385**), have recently been synthesized by Kametani's group (Scheme 273).[492] The crucial step of both synthetic sequences was stereoselective formation of the sulfur ylide **382** via rhodium acetate-catalyzed decomposition of diazomalonate in the presence of the optically active sulfide **381**, followed by [1,2]-shift to afford the key intermediate **383**. Further functional group manipulations furnished both target alkaloids.

Scheme 274

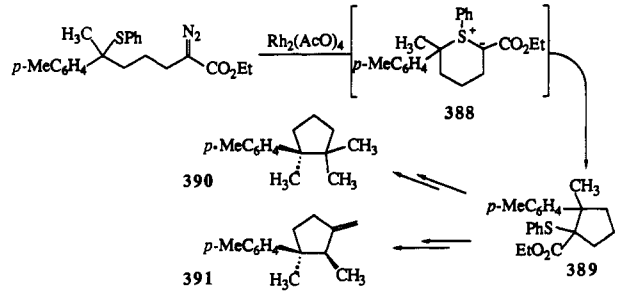


Scheme 275



R^1 = OEt, Ph; R^2 = H, CO_2Et;
R^3 = Me. CH_2CO_2Et; R^4 = CH_2Ph, CH_2CO_2Et, $CH(CO_2Et)_2$

Scheme 276



Nozaki and co-workers[493] have reported the intermolecular formation of an oxonium ylide from a cyclic ether via catalysis. [1,2]-Shift of the ylide afforded the ring-enlargement products (Scheme 274). Recently, West and co-workers[494] have reported a sequence leading to the construction of tertiary α-amino ketones and α-amino esters from amines and diazocarbonyl compounds. Thus, copper-catalyzed decomposition of simple diazocarbonyls in the presence of tertiary amines gave corresponding ammonium ylides **386** which underwent facile [1,2]-shift to give α-substituted α-amino ketones or α-amino esters **387** (Scheme 275).[494]

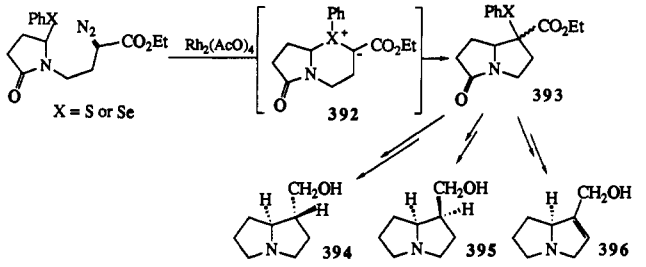
The intramolecular addition of a carbenoid to a heteroatom lone pair has proven to be an efficient, direct route to the formation of cyclic ylides under mild conditions. The [1,2]-shift process of the cyclic ylide has recently received considerable attention. Two aromatic sesquiterpenes, (±)-cuparene (**390**) and (±)-laurene (**391**), were synthesized by a sequence[495,496] in which the key step was the formation a new carbon–carbon bond at a benzylic position by formation of the sulfur ylide **388** followed by the [1,2]-shift process to give **389** (Scheme 276).

Sulfur or selenium ylide **392**, derived from the intramolecular catalytic method, undergoes a [1,2]-shift process to form a new five-membered ring **393**. This synthetic strategy[497,498] was employed in the construction of three pyrrolizidine alkaloids, (±)-trachelanthamidine (**394**), (±)-isoretronecanol (**395**), and (±)-supinidine (**396**) (Scheme 277).

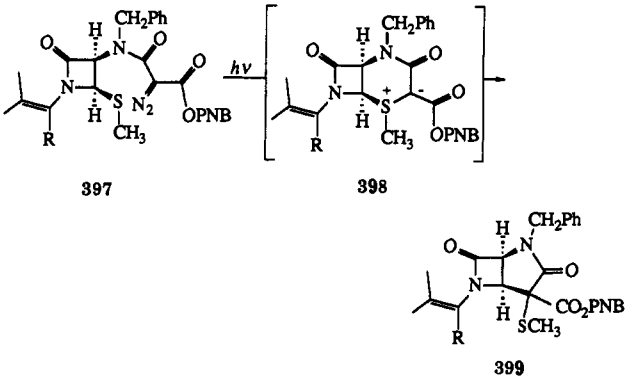
A similar strategy has been used in the synthesis of the bicyclic β-lactam **399**.[499] The carbene generated by the irradiation of diazo ester **397** reacts to give the cyclic sulfur ylide **398**, which undergoes a [1,2]-shift to **399** with the desired chirality (Scheme 278).

Cyclic oxonium ylides are readily generated from the intramolecular catalytic reaction of diazocarbonyl compounds containing ethereal oxygen groups. The [1,2]-shift pathways of the cyclic oxonium ylide offers a novel approach to the construction of substituted

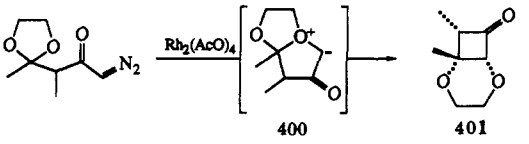
Scheme 277



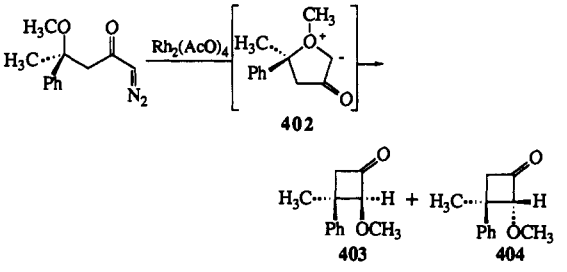
Scheme 278



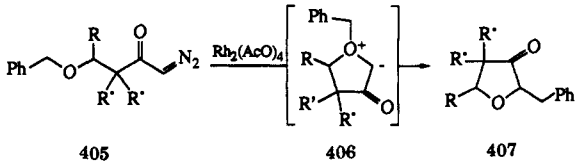
Scheme 279



Scheme 280



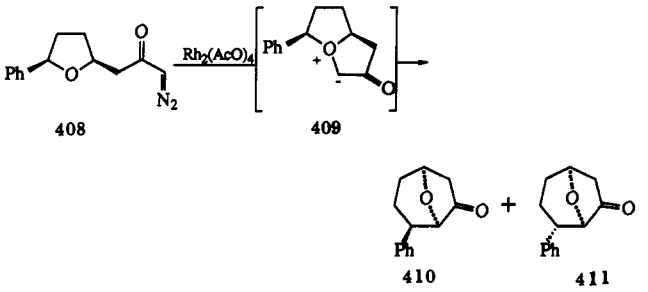
Scheme 281



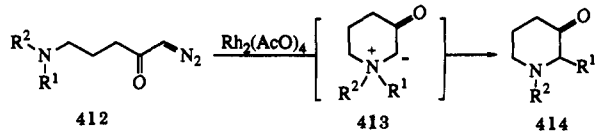
carbocycles[486] and substituted cyclic ethers.[500–502] This synthetic strategy has been exploited in the synthesis of substituted cyclobutanones **401**, **403**, and **404** from the corresponding cyclic oxonium ylides (**400** and **402**) by Roskamp and Johnson (Schemes 279 and 280).[486]

West and coworkers[500] have successfully utilized the tandem cyclic oxonium ylide generation–Stevens [1,2]-shift protocol in the synthesis of functionalized tetrahydrofuranones. Catalytic decomposition of ω-alkoxy-α'-diazo ketone **405** forms the cyclic oxonium ylide **406** with subsequent generation of cyclic ether **407** (Scheme 281). The formation of the cyclic ether **407** in good yield by this [1,2]-shift approach was attributed to the presence of a benzylic migrating group. O-Bridged

Scheme 282



Scheme 283



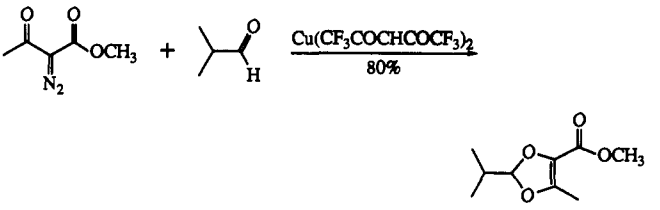
medium-sized carbocyclic rings have been synthesized via same methodology. Fused bicyclic oxonium ylide **409**, generated with catalytic rhodium acetate from diazo ketone **408**, undergoes a [1,2]-shift to give O-bridged seven-membered carbocycles **410** and **411** with a high degree of stereoselectivity (**410**/**411** = 15–19/1) (Scheme 282).[501] Similarly, catalytic decomposition of the diazocarbonyl compound **412** bearing dialkylamino substituents six centers away from the carbenoid center forms the corresponding ammonium ylide **413** which undergoes the Stevens [1,2]-shift of one of the exocyclic groups to form the six-membered nitrogen heterocycle **414** (Scheme 283).[502]

3. Reactions of Carbonyl and Thiocarbonyl Ylides Derived from Diazocarbonyl Precursors

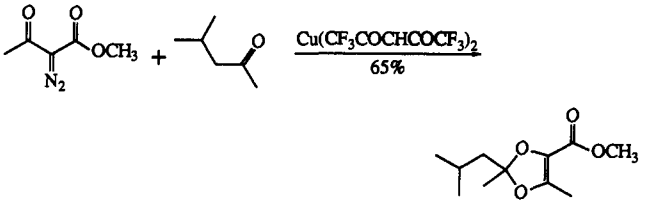
Carbonyl ylide generation from the reaction of carbenes and carbenoids with carbonyl compounds has received considerable attention, from both a mechanistic and a synthetic point of view. The largest contribution to this field is that of Padwa and co-workers, whose work has recently been summarized in a short review.[503] In this section an outline of the use of carbonyl ylide in organic synthesis is presented. One of the simplest routes to the generation of carbonyl ylides involves the addition of a carbene or carbenoid onto the oxygen atom of a carbonyl group. In many cases, this can be readily achieved via catalytic decomposition of a diazocarbonyl compound in the presence of a carbonyl group. Carbonyl ylides are efficiently trapped by dipolarophiles (*vide infra*). However, in the absence of trapping agents, the fate of carbonyl ylides has not been thoroughly studied.[504]

Diazocarbonyl compounds react with ketones or aldehydes to furnish products which strongly depend on the nature of diazocarbonyl and reaction conditions. Use of simple diazo esters results in homologation products under Lewis acid catalysis.[505] In the presence of organotellurium reagents, e.g. dibutyl telluride, and catalytic amounts of copper(I), dimethyl diazomalonate, or ethyl diazoacetate, reacts with aldehydes to afford olefination products.[506] However, certain diazocarbonyl compounds, e.g. 2-diazo-3-oxobutyrate or 3-diazo-2,4-pentanedione, react with aldehydes and ketones in the presence of a copper(II) catalyst to give corresponding 1,3-dioxoles.[507-509] The yields of the reaction depend on the nature of catalyst ligands. The reaction is

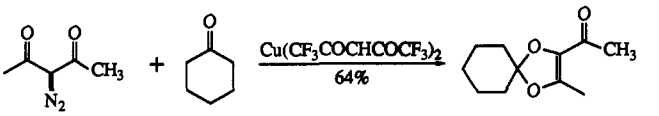
Scheme 284



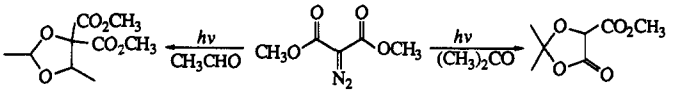
Scheme 285



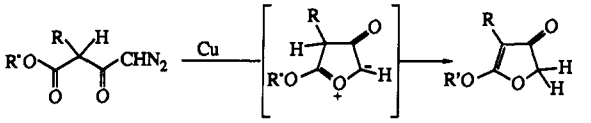
Scheme 286



Scheme 287



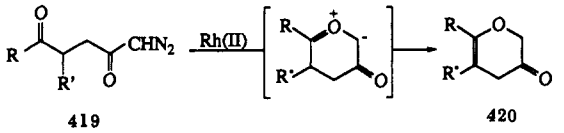
Scheme 288



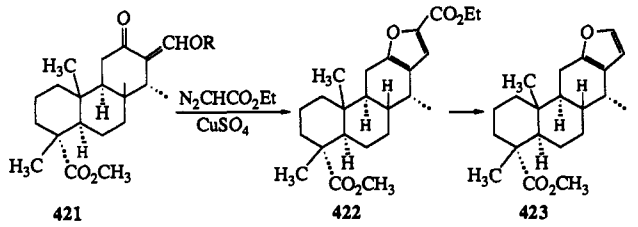
believed to involve initial formation of a carbonyl ylide which undergoes an intramolecular cyclization to afford the dioxole. Some representative examples from the work of Alonso and his co-workers[507-509] are shown in Schemes 284–286. Similarly, photolytic decomposition of dimethyl diazomalonate in neat acetone afforded dioxole adduct **416** via an intramolecular cyclization process (Scheme 287). On the other hand, the dimethyl diazomalonate reaction with acetaldehyde does not undergo an intramolecular cyclization process; instead an intermolecular reaction with another molecule of acetaldehyde gives dioxole **415** (Scheme 287).[510] The reaction of dicarbomethoxycarbene with aromatic aldehydes via carbonyl ylide process has been studied by Huisgen and de March.[511]

One of the useful chemical transformations of the carbonyl ylides derived from the intramolecular reaction of a diazocarbonyl compound containing a carbonyl group consists of a hydrogen-migration process.[471] Bien and Gillon[513] have used this reaction in the synthesis of 3(2*H*)-furanones. Thus treatment of diazo ketone **417** with a copper catalyst produced the furanone **418** (Scheme 288). The proton-transfer process in this reaction occurs very rapidly; even in the presence of a variety of dipolarophiles, the reaction still proceeds with the formation of 3(2*H*)-furanones.[514] Similarly, Padwa and co-workers[515] have demonstrated that the hydrogen-migration process is also successful in the six-membered carbonyl ylide series. The decomposition of diazo

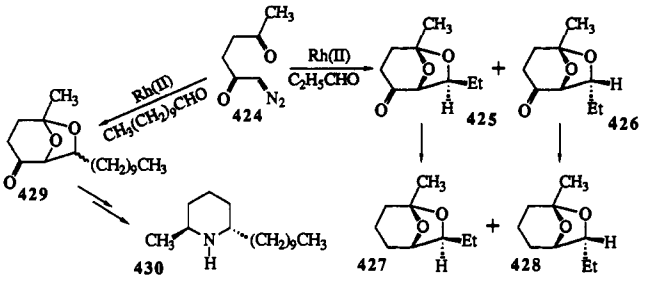
Scheme 289



Scheme 290



Scheme 291



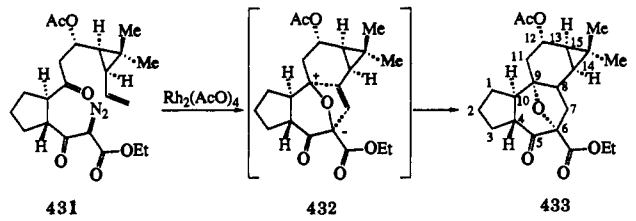
ketone **419** results in the formation of the cyclic enol ether **420** (Scheme 289).

Cyclization of carbonyl ylides containing an α,β-unsaturated carbon–carbon bond provides a facile route for the construction of the furan ring. This method has served as a key step in the total synthesis of the tetracyclic furanoid diterpene methyl vinhaticoate (**423**).[516] Reaction of the ketone **421** with the carbenoid derived from ethyl diazoacetate furnished the key intermediate **422**, which was then selectively hydrolyzed and decarboxylated to give **423** (Scheme 290).

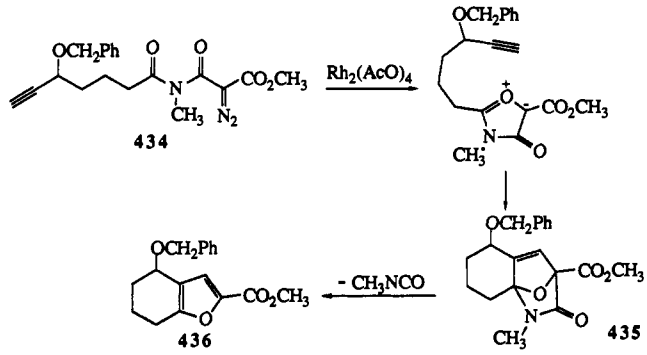
Carbonyl ylides derived via catalysis are readily trapped by dipolarophiles to form oxygen based heterocyclic compounds. The scope and mechanistic details of the intramolecular carbonyl ylide formation and subsequent 1,3-dipolar cycloaddition have been extensively studied.[503,517,518] Bimolecular reaction of cyclic ylides with dipolarophiles is an attractive protocol for the synthesis of tetrahydrofurans. This methodology has been used in the synthesis of brevicomin,[519,520] a key component of the aggregation pheromone of the female Western pine beetle. Thus, treatment of diazo dione **424** with rhodium(II) acetate, in the presence of propionaldehyde, afforded bicyclic compounds as a chromatographically separable mixture of *exo* and *endo* isomers (**425** and **426**, respectively). Reduction leads to *exo*- and *endo*-brevicomin (**427** and **428**, respectively). Similarly, 6,8-dioxabicyclo[3,2,1]octane **429**, the precursor for the synthesis of solenopsis A (**430**), was prepared by the same methodology (Scheme 291).[519,520]

The intramolecular trapping of carbonyl ylide dipoles with an alkene or alkyne represents an effective method for the synthesis of complex polycyclic heterocycles. Varying the length of the group which separates the olefin or the alkyne from the carbonyl ylide dipoles allows for the synthesis of a variety of interesting oxopolycyclic ring systems.[503] An interesting application of this method is found as the central step in

Scheme 292



Scheme 293

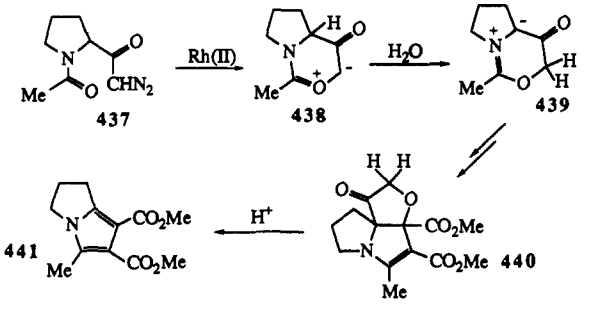


Dauben's synthesis of the tigliane ring system.[521] Thus, carbonyl ylide **432**, generated from the diazocarbonyl **431** in the presence of a catalytic amount of rhodium(II) acetate, underwent an intramolecular addition with the olefin to form the C_6,C_9-oxido-bridged tigliane ring system **433** (Scheme 292). The two new stereocenters at C-8 and C-9 were formed with the correct configurations relative to C-14 and C-15 presented by the natural tigliane compounds. The high stereospecificity in the ring-closure reaction could be related to steric interactions and/or the introduction of conformational strain in the tether which does not favor a transition state that leads the cyclopropane ring and the oxido bridge to be on the same side of the molecule.

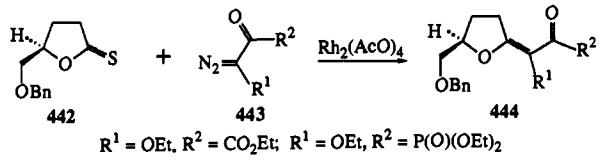
The 1,3-oxazolium 4-oxides (isomünchnones) are readily obtained through the catalytic cyclization of a suitable diazoimide. This type of mesoionic oxazolium ylide corresponds to the cyclic equivalent of a carbonyl ylide and undergoes 1,3-dipolar cycloaddition. Intramolecular cycloaddition of isomünchnones containing π-bonds suitably placed within the molecule have been examined in some detail.[522–526] This cycloaddition protocol emerged as an attractive sequence. For example, reactions of acetylenic isomünchnones afforded annulated furans. Thus, catalytic decomposition of diazoimide **434** with rhodium(II) acetate in refluxing toluene, furnished cycloadduct **435**, which then underwent a subsequent cycloreversion reaction to give furan **436** (Scheme 293).[523]

The carbonyl ylide dipole, generated by rhodium(II)-catalyzed diazo ketone cyclization onto a neighboring amide carbonyl group, can undergo a proton shift to form the thermodynamically more stable azomethine ylide. The 1,3-dipolar cycloaddition of the azomethine ylide and subsequent rearrangement provides a potentially useful method for the synthesis of nitrogen-based heterocycles.[527–529] Pyrrole **441** was synthesized via azomethine ylide formation and subsequent rearrangement. Thus, catalytic decomposition of diazo ketone **437** produced the carbonyl ylide **438** which isomerized to the azomethine ylide **439**. 1,3-Dipolar cycloaddition and subsequent 1,3-alkoxy shift generated

Scheme 294

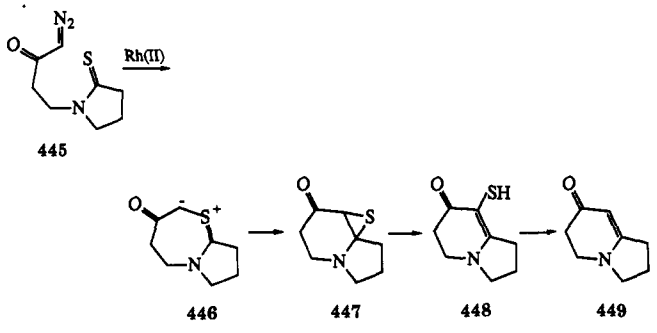


Scheme 295



R^1 = OEt, R^2 = CO_2Et; R^1 = OEt, R^2 = P(O)(OEt)$_2$

Scheme 296



the tricyclic dihydropyrrolizine **440** which fragmented to produce pyrrole **441** (Scheme 294).[527-529]

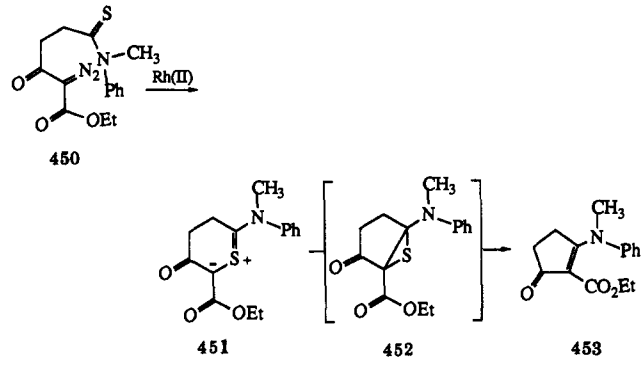
Thiocarbonyl ylides have been the subject of much interest in recent years, due to their potential role as intermediates in a variety of reactions, including the formation of episulfides and novel heterocyclic ring systems. One efficient method for the generation of thiocarbonyl ylides involves the addition of carbenoid onto the sulfur atom of a thiocarbonyl group. Takano and co-workers[530] have reported the intermolecular formation of the thiocarbonyl ylide via a diazocarbonyl intermediate. Reaction of (*R*)-5-[(benzyloxy)methyl])-tetrahydro-2-furanthione (**442**) with the diazocarbonyl compound **443** in the presence of rhodium(II) acetate afforded the 2-(acylmethylene)tetrahydrofuran derivative **444** in good yield (Scheme 295).

Danishefsky and co-workers[531-535] reported the construction of nitrogen heterocyclic compounds via the thiocarbonyl ylide formation process. Intramolecular reaction of the keto carbenoid derived from diazo ketone **445** gave the cyclic thiocarbonyl ylide **446**. Cyclization then led to **447**, which was isomerized to product **448**; the latter was transformed to dihydropyridone **449** by treatment with partially deactivated W-2 Raney nickel (Scheme 296).

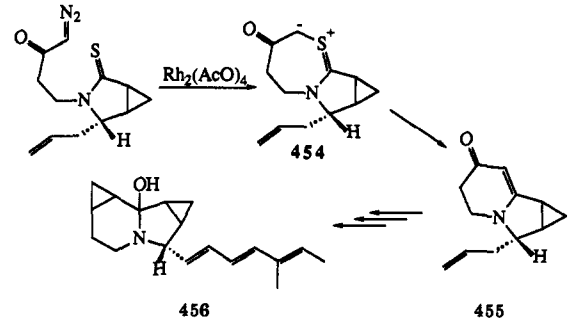
Similarly, Padwa and co-workers reported that thiocarbonyl ylide **451** derived from α-diazo-β-keto ester **450**, cyclizes to produce a transient episulfide **452**, which subsequently eliminates sulfur to give vinylogous amide **453** (Scheme 297).[536]

A key step in Danishefsky's total synthesis of indolizomycin (**456**)[534] involved the formation of thio-

Scheme 297



Scheme 298



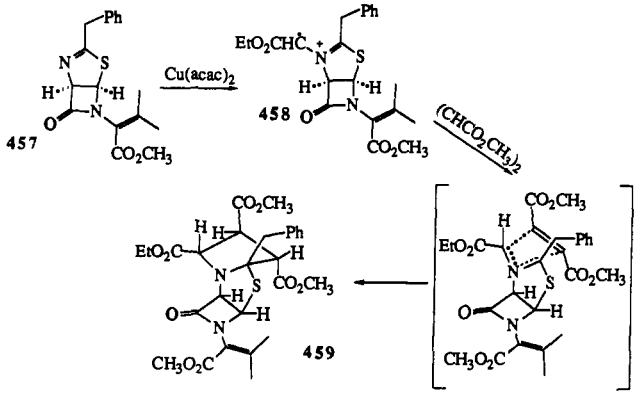
carbonyl ylide **454**, which subsequently afforded vinylogous amide **455** (Scheme 298).

4. Reactions of Nitrogen Ylides Derived from Diazocarbonyl Precursors

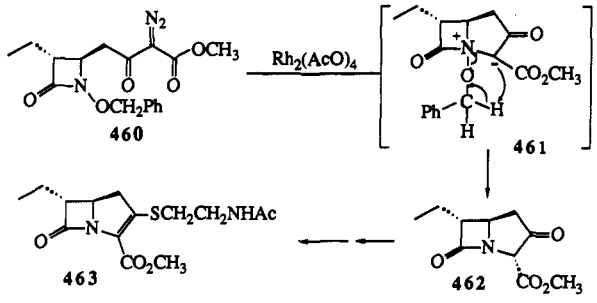
Azomethine ylides undergo facile 1,3-dipolar cycloadditions with π-bonds to give pyrrolidines which are useful in the synthesis of alkaloids. One simple method for the generation of the azomethine ylide involves the addition of carbenoid to a C–N bond. In some cases it can be prepared via isomerization of carbonyl ylides, which in turn are available from the catalytic decomposition of appropriate diazocarbonyl compounds.[537] The reaction of thiazoloazetidinone **457** with carbenoids and subsequent 1,3-dipolar cycloaddition has been investigated by Thomas and co-workers.[538] Thus, treatment of **457** with ethyl diazoacetate in the presence of a copper catalyst and dimethyl fumarate afforded adduct **459** stereoselectively. This sequence involves the addition of the carbenoid onto the thiazoline nitrogen to form the azomethine ylide **458**, which undergoes 1,3-dipolar cycloaddition with dimethyl fumarate from the less hindered side of **458** (Scheme 299).

The intramolecular reaction of carbenoids derived from α-diazo-β-keto esters with an *N*-alkoxy β-lactam provides a novel ring-forming methodology. This cyclization protocol involves interaction of an initially generated carbenoid with the *N*-alkoxy lactam electron lone pair to form the ylide. Abstraction of a proton from the alkoxy group, followed by carbonyl formation and N–O bond cleavage, affords the cyclized product. Miller and co-workers[539,540] have applied this methodology to the asymmetric synthesis of a key intermediate **462** for the preparation of β-lactam antibiotic PS-5 **463**. Thus, rhodium-catalyzed cyclization of optically active diazocarbonyl **460** afforded carbapenam **462**, which was

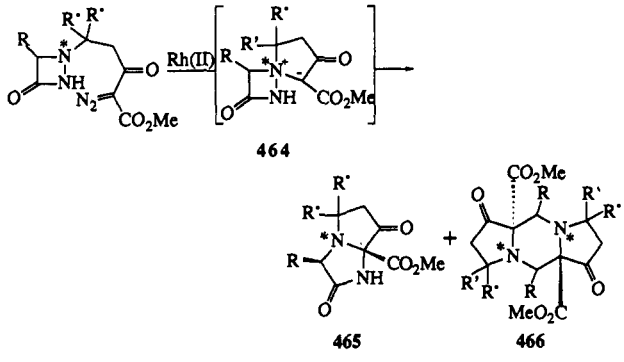
Scheme 299



Scheme 300



Scheme 301

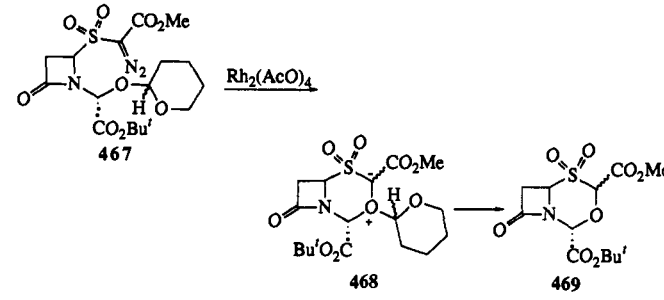


then converted to **463**.[541] The formation of the intermediate nitrogen-based ylide **461** was the key step of this cyclization (Scheme 300).

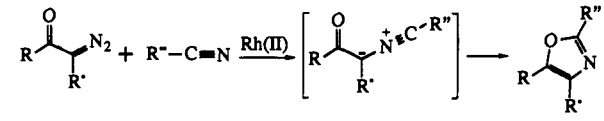
Rhodium(II)-catalyzed decomposition of the diazocarbonyl in Scheme 301 resulted in two products, **465** and **466**.[542] Both products appear to result from formation of ylide **464** in which the carbenoid bonds to the more nucleophilic of the two nitrogen atoms (starred in **464**). Product **465** is that of sigmatropic rearrangement of the ylide, whereas product **466** may result from fragmentation of the ylide followed by dimerization. There was no evidence of product arising from N–H insertion into the amide group (Scheme 301).

The formation of nitrogen ylides strongly depends on the nature of the diazocarbonyl precursor, although, in some cases, stereochemical or steric effects may inhibit intramolecular ylide formation. Rhodium(II)-catalyzed decomposition of the diazocarbonyl **467** gave the oxacepham **469** which is the result of formation of the oxygen ylide **468** rather than a nitrogen ylide. The ylide may decompose by proton abstraction leading to fragmentation to the oxacepham and dihydropyran (Scheme 302).[543]

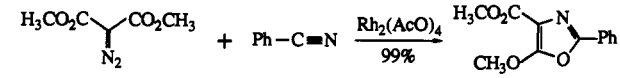
Scheme 302



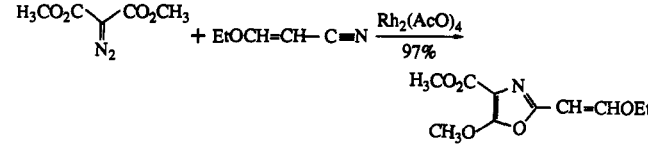
Scheme 303



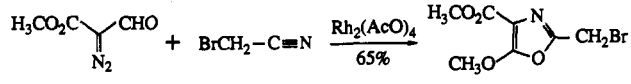
Scheme 304



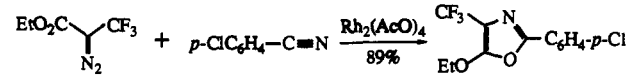
Scheme 305



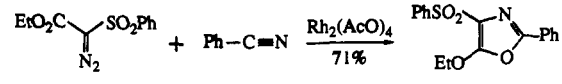
Scheme 306



Scheme 307

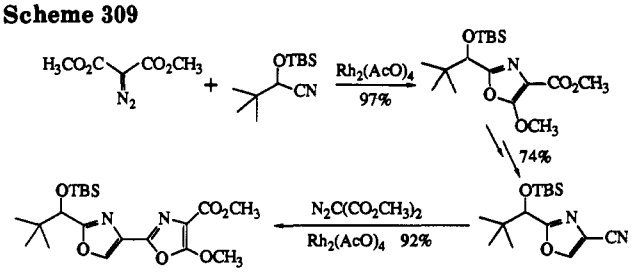


Scheme 308



Diazocarbonyl compounds react with nitriles under diverse reaction conditions to produce oxazoles.[544,545] Lewis acid-promoted reaction of α-diazocarbonyl compounds with nitriles to give oxazoles will be reviewed in section III.J. Transition metal-catalyzed decomposition of diazocarbonyl compounds in nitrile solvents provide direct access to oxazoles. Rhodium salts as catalysts produce the highest yield.[546–552] Kinetic studies of the diazo compound in the presence of nitrile by using the laser flash photolysis technique have shown that the reaction involves the formation of nitrile ylide.[553–555] A stable nitrile ylide in some cases can be isolated from reaction of a diazo compound with nitrile.[556] It is now believed that carbenoids derived from the diazocarbonyl compounds react with nitriles to yield a nitrile ylide which then undergoes a cycloaddition reaction (Scheme 303). Some representative examples taken from the literature[546–552] are shown in Schemes 304–309.

Scheme 309

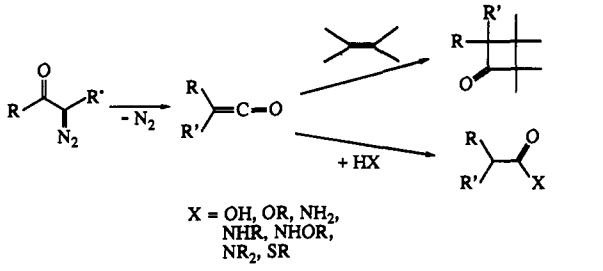


F. The Wolff Rearrangement

1. Introduction

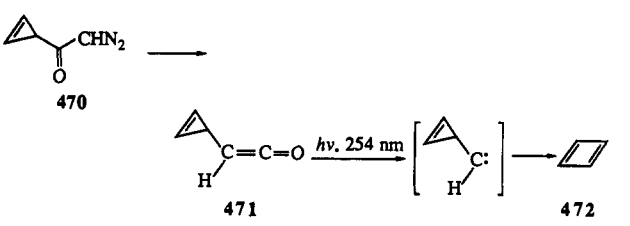
In outline, the Wolff rearrangement of a diazo ketone is a specific 1,2-rearrangement, accompanying or following loss of nitrogen, to a ketene which may undergo further reactions such as nucleophilic attack by water, alcohols or amines, or cycloaddition to unsaturated systems (Scheme 310). Wolff discovered the rearrangement in 1912,[557] many years before reliable synthetic routes to acyclic and alicyclic α-diazo ketones became available. When the methods of diazomethane acylation and diazo transfer were introduced the potential of the Wolff rearrangement was quickly appreciated.[1b,558-568] The literature is replete with examples of its use, not just as a step in the Arndt–Eistert homologation reaction, but also as a powerful means of imposing angle strain on cyclic systems through ring contraction and, more recently, as a means of generating highly unstable systems in isolated circumstances at low temperatures where they can be scrutinized spectroscopically.

Scheme 310

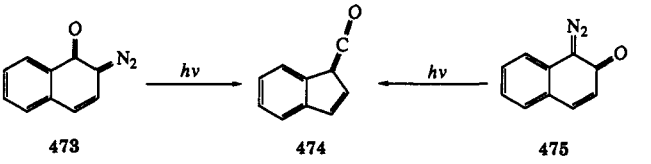


Rearrangement may be initiated by thermolysis, photolysis, or metal ion catalysis, the latter two being the more widely employed. An important mechanistic question, which has received widespread experimental and theoretical examination, centers on whether loss of nitrogen and rearrangement occur sequentially or in concert. The question of ketene formation is long settled and very unstable ketenes can now be generated at low temperatures. Maier,[569] for example, has shown that cyclopropenyl ketene **471** can be produced on matrix photolysis of diazo ketone **470** and observed to decarbonylate to cyclobutadiene **472** (Scheme 311). Other examples of similar studies include those of Pacansky[570,571] and Turro[572] on production, photolytically at 77 K, of indenylketenes **474** from diazonaphthalenones **473** or **475** in which products were identified spectroscopically by infrared and ultraviolet spectroscopy (Scheme 312). These studies, although confirming ketene formation, do not comment on the nature of the preceding steps.

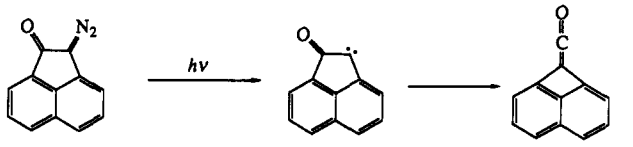
Scheme 311



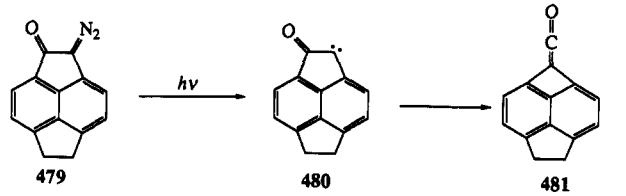
Scheme 312



Scheme 313



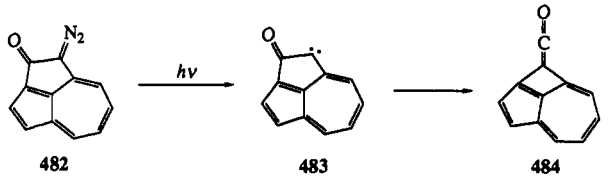
Scheme 314



The most illuminating study of the photochemically induced Wolff rearrangement was that of Chapman and co-workers[573] who combined matrix isolation with low-temperature spectroscopy to follow the decomposition pathways of diazo ketones **476**, **479**, and **482**. These precursors were chosen wisely for Shechter[574] and Trost[575,576] had already found that increasing the transition-state energy for ring contraction in similar systems tends to inhibit Wolff rearrangement. The absence of rearrangement products from diazo ketone **476**, either thermally or photochemically at ordinary temperatures, suggested that this precursor should be an ideal substrate for imposing increasingly severe strain limitations. These expectations were fulfilled: employing photochemical extrusion of nitrogen from diazo ketones **476**, **479**, and **482** in a matrix at 10–15 K, Chapman obtained spectroscopic evidence for the formation of keto carbenes **477**, **480**, and **483** which were further characterized by trapping experiments with oxygen and carbon monoxide. Further irradiation of these keto carbenes led to Wolff rearrangement (**477** → **478**; **480** → **481**; **483** → **484**). These transformations thus represent the first clear-cut examples of nonconcerted Wolff rearrangement (Schemes 313–315).

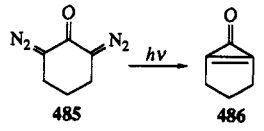
The formation of cyclopropenones from bis diazo ketones followed from a suggestion by Trost[577] to the effect that the product composition from photolysis of **485** was best accommodated by a bicyclopropenone intermediate **486**. This suggestion gained considerable support when Trost isolated diphenylcyclopropenone **488** from the acyclic precursor **487** (Schemes 316 and

Scheme 315



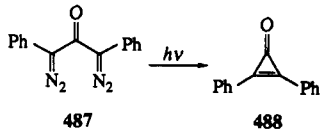
482 483 484

Scheme 316



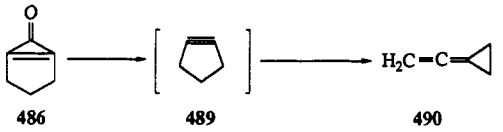
485 486

Scheme 317



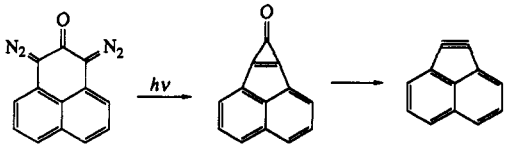
487 488

Scheme 318



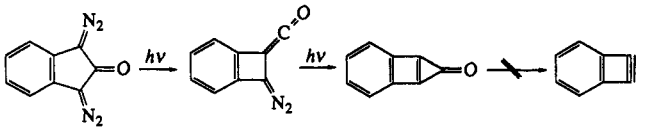
486 489 490

Scheme 319



491 492

Scheme 320

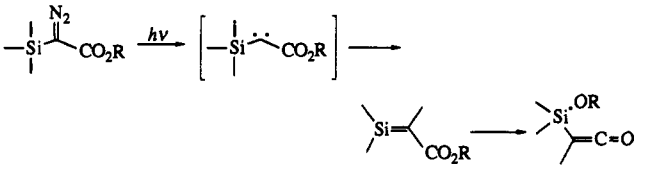


493 494 495 496

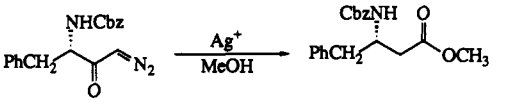
317). Chapman[578] subsequently applied the low-temperature matrix-isolation technique to these systems and, commencing with **485** at 8 K, was able to observe by IR spectroscopy the changes illustrated in Scheme 318, terminating in a stable allenic product **490** which was assumed to have been formed from cyclopentyne **489** via a 1,3-sigmatropic shift, although this intermediate was not detected (Scheme 318).

Arguing that a cycloalkyne intermediate which did not have access to a 1,3-sigmatropic shift should have a greater lifetime, Chapman repeated the study with the tricyclic bis diazo ketone **491**, photolysis of which could be followed in well-resolved stages by IR analysis (Scheme 319). The cycloalkyne **492** was indeed observed, and it was further characterized by its reactions with water, oxygen, and itself (trimerization). Recently, Tomioka[579] and his co-workers have carried out an investigation of photodecomposition of 1,3-bis(diazo)-indan-2-one (**493**). The diazo ketene **494** derived from the Wolff rearrangement in an Ar matrix at 10 K, was converted photolytically to the cyclopropenone **495**. However, the synthesis of benzocyclobutenyne **496** from **495** was not successful (Scheme 320).

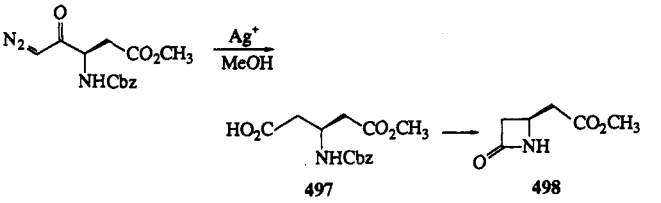
Scheme 321



Scheme 322



Scheme 323



497 498

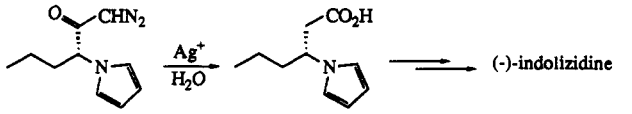
Among other notably unstable systems that have been probed via Wolff rearrangement are molecules containing the silicon–carbon double bond. Ando[580] suggested originally that photolysis of (trimethylsilyl)-diazoacetates proceeds via keto carbene intermediates, Wolff rearrangement of a methyl group then forming an unsaturated silicon–carbon bond as shown in Scheme 321; additional evidence, gained later, supports this interpretation.[581-586]

2. Synthetic Applications

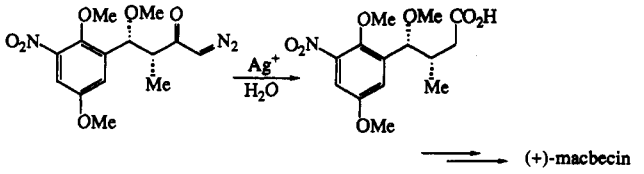
We now return to the synthetic applications of Wolff rearrangement. The key feature of Wolff rearrangement is the formation of ketene. The subsequent reaction of the ketene is determined by its structure and the reaction conditions. In the following, a selection of examples from the recent literature is divided into four subsections to illustrate the versatility of Wolff rearrangement in modern organic synthesis.

a. Arndt–Eistert Homologation and Related Reactions. The Arndt–Eistert synthesis, in effect, is a one-carbon homologation for which many hundreds of examples have been published. Silver ion catalysis or photolysis are the favored methods for effecting the reaction. Newman and Beale[587] developed a procedure for carrying out the reaction in homogeneous solution under mild conditions. The catalytic system involves a solution of silver benzoate in triethylamine. Under these conditions, the reactions of chiral diazo ketones are also completely stereospecific with retention of configuration. Many of the β-amino acids which have served as replacement residues in studies of the biological activity of peptide analogues have been prepared via Arndt–Eistert synthesis.[588-591] Scheme 322 shows the synthesis of Cbz-protected β-phenylalanine methyl ester.[592] β-Amino acid formation via the Arndt–Eistert reaction has shown considerable synthetic utility in natural product synthesis. β-Amino acid **497** derived from D-aspartic acid via Arndt–Eistert homologation served as the chiral building block in the construction of 2-azetidinone **498** (Scheme 323).[593] Two recent examples of Arndt–Eistert homologation in the total

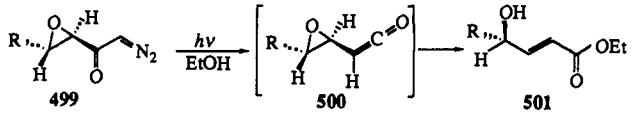
Scheme 324



Scheme 325



Scheme 326

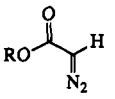


R = $C_{10}H_{21}$, C_4H_9, C_5H_{11}, $CH_3CH(OAc)CH_2CH_2$,

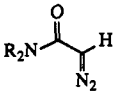
synthesis of natural products are shown in Schemes 324[594] and 325.[595]

Epoxy diazomethyl ketones of type **499** undergoes an interesting photoinduced rearrangement leading to γ-hydroxy α,β-unsaturated ester.[596,597] Initially, an epoxy ketene **500** is formed, which subsequently reacts with an alcoholic solvent to give a hydroxyalkene ester **501** (Scheme 326). Optically active diazo ketone **499** can be prepared from an allylic alcohol using the Sharpless epoxidation, with subsequent oxidation to the corresponding oxiranecarboxylic acid and conversion to diazo ketone **499** via standard procedures. This γ-hydroxy α,β-unsaturated ester formation methodology has been applied in the total synthesis of various naturally occurring macrocyclic lactones.[598-603]

Extention of the Arndt–Eistert homologation to the open-chain diazo ester **502** and diazoamide **503** systems,



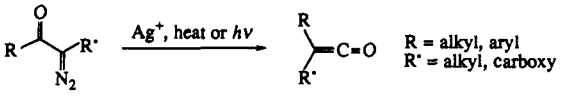
502



503

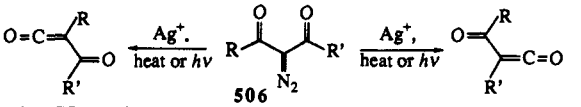
in general, affords lower yield of products due to the alkoxy and amino group being less favored migrating groups. These transformations[566] have received much less attention synthetically due to the competing reactions of the carbene precursor. The α-diazocarbonyl of type **504**, bearing two substituted functional groups other than hydrogen, also undergoes Wolff rearrangement to form ketene **505** (Scheme 327).[604-607]

Scheme 327



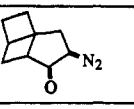
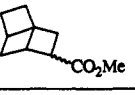
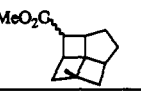
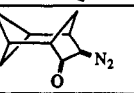
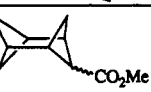
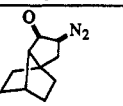
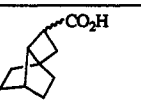
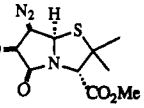
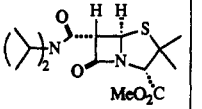
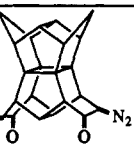
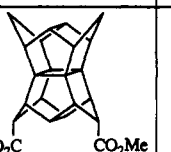
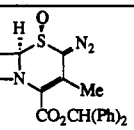
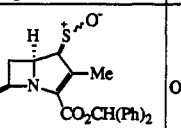
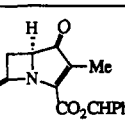
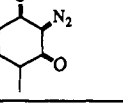
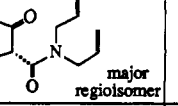
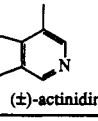
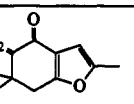
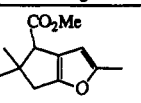
Unsymmetrical 2-diazo-1,3-dicarbonyl compounds of general type **506** can give rise to two ketene products (Scheme 328) under Wolff rearrangement[608-611] and an

Scheme 328



R = CO_2Me, R' = Me; R = CO_2Me, R' = OMe; R = OMe, R' = SPh;

Table 4. Ring Contraction Strategy in Synthesis

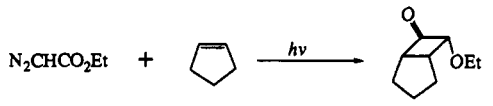
entry	Diazocarbonyl	Product	Target molecule	Ref.
1				612
2				613 614
3				615
4				616
5				617
6				618 619
7				620
8				610 611
9				621

example involving ring contraction is shown in Table 4, entry 8.[610,611]

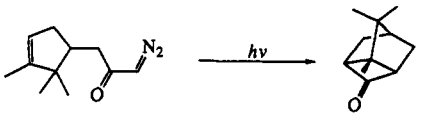
b. Ring Contraction Reactions. Application of the Wolff rearrangement to ring contraction has proved an effective methodology for the synthesis of strained isolable systems at less extreme temperatures. Although there are no limitations in the formation of various ring sizes via the Wolff rearrangement protocol, very few examples of the formation of three-membered rings and large cyclic systems have been reported. Some examples have been discussed in sections III.F.1. A selection of examples from the recent literature is summarized in Table 4.

Four-membered carbocyclic and heterocyclic systems are readily accessible from cyclopentyl precursors (entries 1–5). Entries 1[612] and 2[613,614] show how ring contraction has been employed to produce fused, polycyclic systems in which angle strain forces the central quaternary carbon atom more and more toward an energetically unfavorable planar geometry. Entry 4 is a particularly good example from the work of Eaton

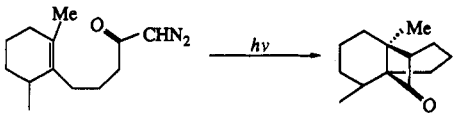
Scheme 329



Scheme 330



Scheme 331



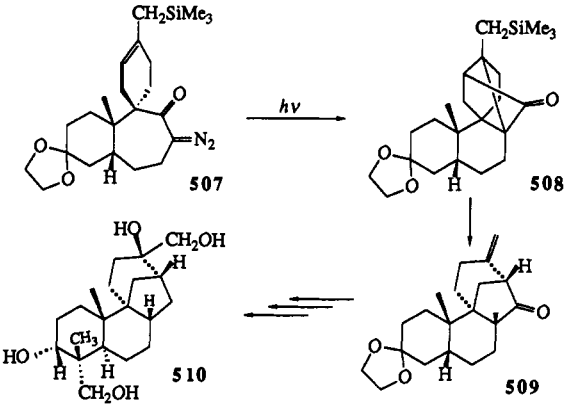
and co-workers,[616] the very unfavorable dihedral angle between the 1- and 7-positions of norbornane making the resulting cyclobutane derivative exceedingly distorted. Entry 5[617] provided a new synthetic route to β-lactams that involves the photolytic ring contraction of 4-diazopyrrolidine-2,3-diones to 3-carboxy-2-azetidinones. Similarly, five-membered systems are also constructed efficiently by ring contraction (entries 6–9). Entry 7[620] illustrates the Wolff rearrangement in a bicyclic system containing a β-lactam in which the carbapenem skeleton can be prepared through a photolytic rearrangement of a readily available 2-diazoceph-3-em 1-oxide. Entry 8[610,611] shows that a Wolff rearrangement applied to the diazo diketone in the presence of diallylamine gave a 1.6/1.0 mixture of two regioisomeric amides. The major regioisomeric amide was isolated in 56% yield and could further be transformed to the monoterpene alkaloid, (±)-actinidine. Finally, entries 3[615] and 6[618,619] through the syntheses of diasterane and pagodane demonstrates that the ring contraction strategy is an effective method in the construction of highly strained and chemically versatile carbon frameworks.

c. Wolff Rearrangement with Cycloaddition Reactions. Ketenes derived from the Wolff rearrangement of diazocarbonyls can undergo cycloaddition reactions. [2 + 2] thermal cycloadditions of ketenes to olefins are well understood and have been used for the synthesis of four-membered rings.[622] Both intermolecular[623] and intramolecular[624–629] additions of ketenes to olefins have been studied. Some representative examples are shown in Schemes 329–331.

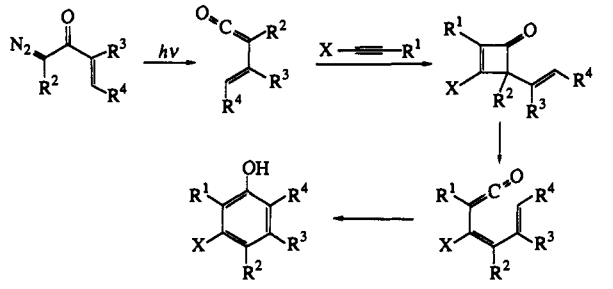
The combination of ring contraction and [2 + 2] cycloaddition reaction strategy has been used in Ireland's total synthesis of (±)-aphidicolin (**510**, Scheme 332).[630] The photochemical decomposition of diazo ketone **507** afforded the corresponding silylcyclobutanone derivative **508** which subsequently rearranged to ketone **509**. The ketone **509** contains the desired bicyclo[3.2.1]octane ring system of aphidicolin (**510**).

Danheiser and his co-workers[631] have invented a new aromatic annulation method which is based on the photochemical Wolff rearrangement of unsaturated α-diazo ketones to generate vinyl- or arylketenes, followed by a cascade of three pericyclic reactions (Scheme 333). A variety of highly substituted polycyclic aromatic and heteroaromatic compounds can be prepared using this method. The marine alkaloid

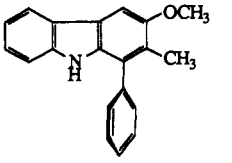
Scheme 332



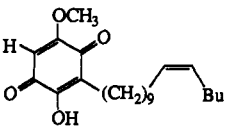
Scheme 333



hyellazole (**511**)[631] and the host defense stimulant maesanin (**512**)[632] are two such examples.



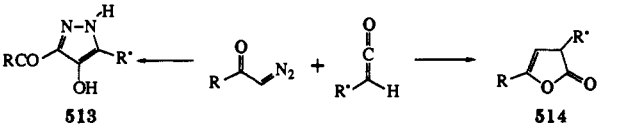
511



512

Other types of double or triple bonds are suitable for trapping the ketene ensuing from Wolff rearrangement. The rather labile aldoketenes react with intact α-diazo ketone to give butenolides **514** or pyrazoles **513** (Scheme 334).[566] Staudinger[633] reported the first example of

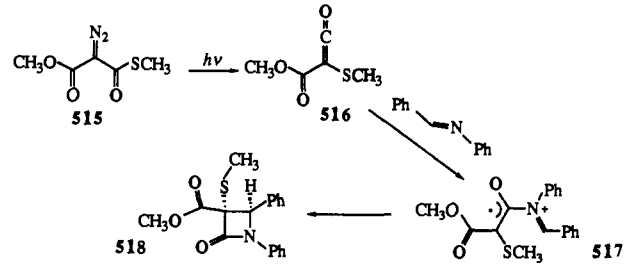
Scheme 334



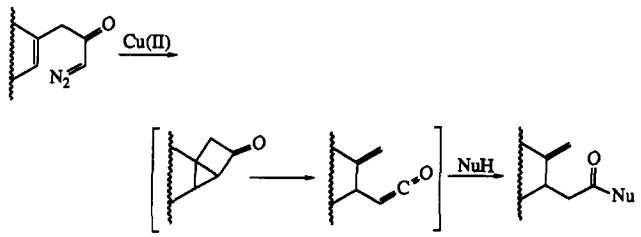
ketene addition to a carbon–nitrogen double bond to give a β-lactam. This cycloaddition reaction is a two-step process involving a zwitterionic species (**517**) as intermediate[634,635] as shown in Scheme 335. The ketene **516** derived from the α-diazo thioester **515** adds to an imine acceptor, giving β-lactam **518** stereoselectivity.[608,609] However, the ketene cycloaddition to π-bonds containing heteroatoms has scarcely been exploited synthetically.

d. The Vinylogous Wolff Rearrangement. From the late 1950s to early 1970s, a few research groups discovered that β,γ-unsaturated diazo ketones not only undergo the normal Wolff rearrangement leading to homologated acids but also yield, via novel skeletal rearrangement, abnormal isomeric products.[636–642] A

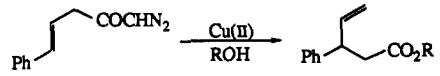
Scheme 335



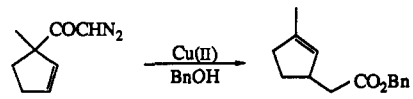
Scheme 336



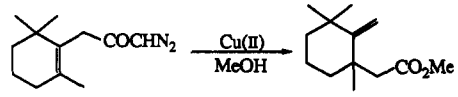
Scheme 337



Scheme 338



Scheme 339



systematic study of the decomposition of β,γ-unsaturated diazo ketones revealed that copper catalysts favor the abnormal product formation. This transformation, which has been termed the vinylogous Wolff rearrangement, represents a synthetic alternative to the Claisen-type rearrangement.[643-646]

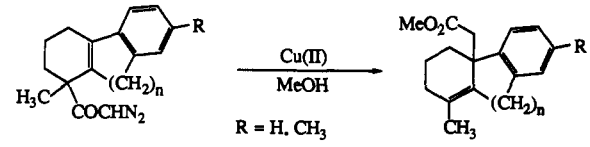
The initial reaction of the vinylogous Wolff rearrangement is probably a cyclopropanation reaction to give a bicyclic product. Fragmentation of this intermediate leads to a β,γ-unsaturated ketene which in turn can be captured by an available nucleophile to afford the γ,δ-unsaturated carboxylic acid derivative (Scheme 336).

The copper salt-catalyzed decomposition of monocyclic and acyclic β,γ-unsaturated diazo ketones in the presence of a nucleophile leading to the respective γ,δ-unsaturated carboxylic acid derivatives has been extensively studied.[598-601] Some representative examples are shown in Schemes 337–339.

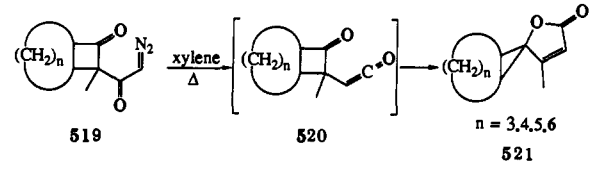
To rigid β,γ-unsaturated diazo ketone systems, the vinylogous Wolff rearrangement is also applicable.[647-650] Scheme 340 shows the flexibility of the vinylogous Wolff rearrangement in the introduction of an angularly functionalized two-carbon residue from appropriately substituted polycyclic β,γ-unsaturated diazo ketones.[648,649]

e. Miscellaneous. Among the applications that do not fall into the preceding categories are the thermal rearrangement of 2-(diazoacetyl)cyclobutanones and

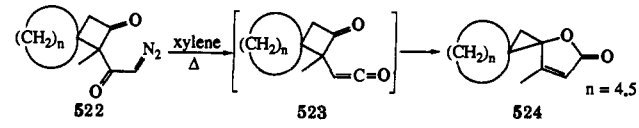
Scheme 340



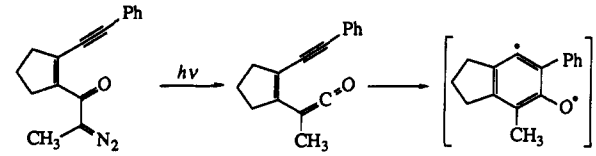
Scheme 341



Scheme 342



Scheme 343



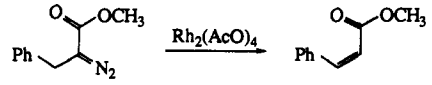
the formation of ene–yne–ketene for DNA cleavage. Miller and co-workers[651] have reported the development of a synthetic route to a variety of substituted α-ketenylcyclobutanones (**520** and **523**) from the pyrolysis or photolysis of corresponding 2-[(diazomethyl)-carbonyl]cyclobutanone derivatives (**519** and **522**). Facile thermal rearrangement of the α-ketenylcyclobutanones (**520** and **523**) gave the corresponding 5-spirocyclopropyl-$\Delta^{\alpha,\beta}$-butenolides (**521** and **524**). The yield of the rearrangement product is high, and the reaction is completely stereospecific (Schemes 341 and 342). Recently an example of photoinduced DNA cleavage by diazo ketone (**525**) containing an ene–yne moiety has been reported (Scheme 343).[652] DNA cleavage is probably due to the hydrogen abstraction from the DNA sugar backbone by σ-sp^2 diradical **527** spontaneously formed from ene–yne–ketene **526**.

G. β-Hydride Elimination Leading to Alkene Formation

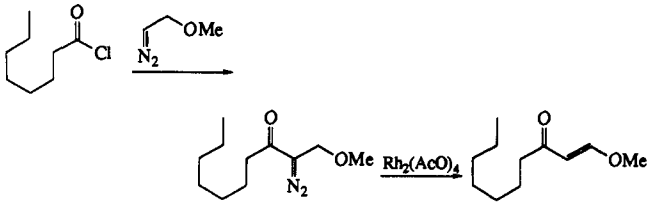
Metal-catalyzed decomposition of a diazo ketone or diazo ester containing a β-hydrogen atom can lead rapidly to alkene formation. In some cases the reaction takes this course exclusively, but examples are known in which it occurs competitively with another catalyzed process such as Wolff rearrangement, C–H insertion or cyclopropanation. In the former category Ganem and co-workers[653] found that certain acyclic α-diazo esters on exposure to rhodium(II) acetate in benzene produced *cis*-enoates, an illustrative example being the quantitative conversion to *cis*-methyl cinnamate shown in Scheme 344.

Hudlicky and his co-workers[654] have developed a general synthesis of β-methoxy-enones, presumably also

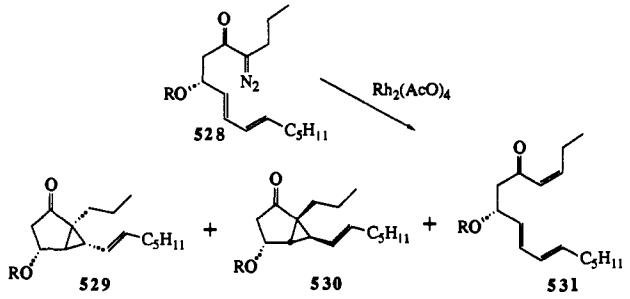
Scheme 344



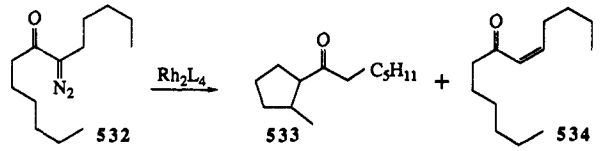
Scheme 345



Scheme 346



Scheme 347



via β-elimination of an intermediate carbenoid, from 2-diazo-1-methoxyethyl ketones. These precursors, obtained from the acyl chloride and 2-diazo-1-methoxyethane, on treatment with rhodium(II) acetate in benzene furnished *trans*-methoxy-enones exclusively. In the example shown in Scheme 345 no competing C–H insertion was observed.

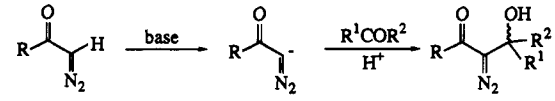
In contrast, Taber and his co-workers have found examples in which cyclopropanation[330] or C-H insertion[274] competes with β-elimination. In the course of an enantioselective synthesis of (−)-PGE_2 methyl ester, Taber found that rhodium(II) acetate catalyzed the conversion of diazo ketone **528** in Scheme 346 into the cyclopropanes **529** and **530** (55% yield), whereas when the catalyst was rhodium(II) trifluoroacetate the sole product **531** (in 90% yield) was that of elimination. That the nature of the ligand on the rhodium(II) catalyst had an influence on the extent of β-elimination was also demonstrated in the conversion of diazo ketone **532** in Scheme 347 into the C–H insertion product **533** and the elimination product **534**: with rhodium acetate there was a 70/30 preference for **533** while with the corresponding trifluoroacetate there was a 62/38 preference for **534**. In both these examples β-elimination led to *cis*-alkene exclusively. These and other results suggest that β-elimination is favored by electron-withdrawing ligands on the metal. Early examples of β-elimination in competition with Wolff rearrangement were reported by Franzen,[655] although the geometry of the alkenes formed is not reported.

H. Reactions with Aldehydes and Ketones

In reactions of aldehydes and ketones with keto carbenoids (section III.E.3) the carbonyl functions act as a nucleophile in donating electrons to the electron-deficient carbenoid center. There are other reactions of aldehyde and ketones in which the carbon–oxygen double bond participates in a cycloaddition (see section III.I). In yet another group to be discussed here, the carbonyl component acts as the electrophile while the diazocarbonyl acts in a nucleophilic capacity. There are two broad categories of such reactions of α-diazocarbonyls with aldehydes and ketones, one an aldol-type addition promoted by base with retention of the diazo function, the other a related process of β-dicarbonyl formation with loss of nitrogen which requires a Lewis acid. In many cases the products of the former can be converted into those of the latter by exposure to catalytic amounts of rhodium(II) acetate. Purely thermal reactions with aldehydes and ketones are known, but they tend to be unselective and are of only limited use in synthesis.

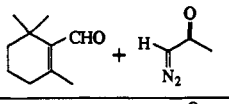
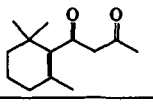
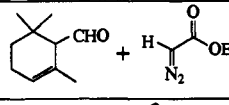
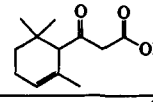
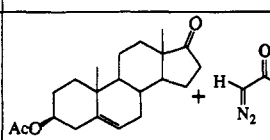
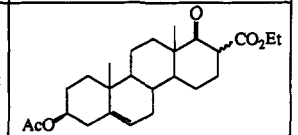
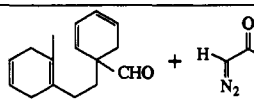
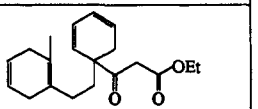
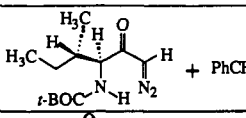
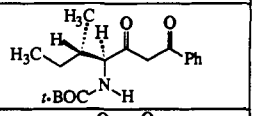
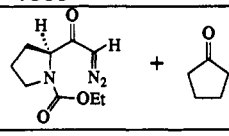
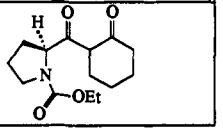
For aldol-type additions the diazocarbonyl precursor must be capable of base-promoted ionization to the α-diazocarbonyl anion (Scheme 348). There follows

Scheme 348

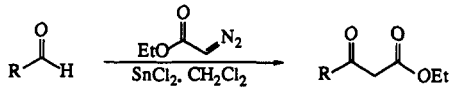


addition of the anion to the aldehyde or ketone. Early work by Schölkopf and Frasnelli[656] described the formation of ethyl lithiodiazoacetate from ethyl diazoacetate and *n*-butyllithium at low temperature and its addition to several carbonyl compounds. Shortly thereafter Wenkert and McPherson[657,658] examined a range of bases for the deprotonation step, including *n*-butyllithium and lithium diisopropylamide (LDA), and recommended that a dilute solution of potassium hydroxide in methanol or ethanol was the combination of choice. However, in more recent studies, especially those following the work of Pellicciari and co-workers,[659–667] LDA has been by far the most widely employed base for diazocarbonyl deprotonation. The Italian group has used lithiated diazo esters and diazo ketones to convert aldehydes and ketones into α-diazo-β-hydroxycarbonyl adducts suitable for subsequent transformations into nitrogen-free products, a particularly attractive version of the latter being β-dicarbonyl compounds produced by the catalytic action of rhodium(II) acetate. Examples of this methodology are summarized in Table 5, entry 1, showing the use of diazolithioacetone to transform β-cyclocitral into a β-diketone suitable for elaboration into β-damascone.[664,665] α-Cyclocitral combines with ethyl diazolithioacetate to afford a product which on exposure to rhodium(II) acetate produces the β-keto ester in entry 2.[660] The process is also applicable to ring expansion of cyclic ketones, an illustrative example (entry 3) being the transformation of 3-acetoxyestrone into a D-homoestrone derivative.[667] Corey's synthesis of (±)-atractyligenin employed this two-step sequence to add a β-keto ester side chain to the bicyclic aldehyde in entry 4.[668] The β-keto ester moiety was then used to set the scene for an intramolecular copper(II)-catalyzed

Table 5. Synthesis of β-Dicarbonyl Compounds

Entry	Reactants	Products
1		
2		
3		
4		
5		
6		

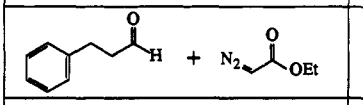
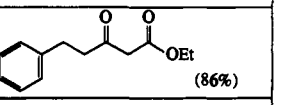
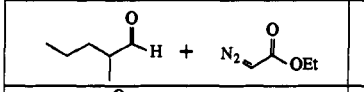
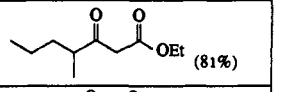
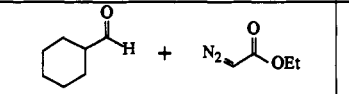
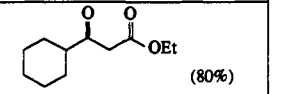
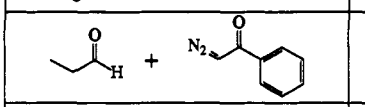
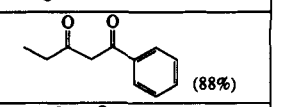
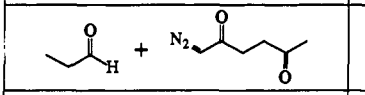
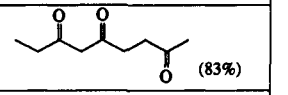
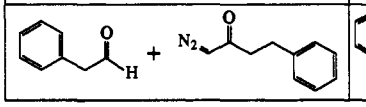
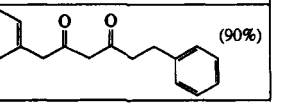
Scheme 349



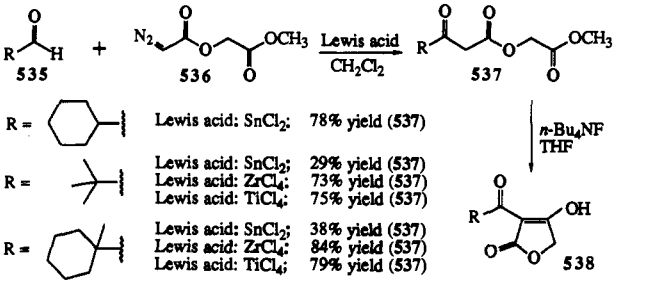
cyclopropanation by reintroducing a diazo group between the two carbonyl groups. Entries 5 and 6 demonstrate the application of this methodology to the elaboration of optically active amino acids using lithiated N-protected diazo amino ketones; these reactions have been shown to be free of racemization.[16] Kim and co-workers[669] in a detailed study of the second, catalyzed stage of the above processes have found that catalysis is not confined to rhodium(II) acetate. Other active salts include palladium and cobalt chloride and tris (triphenylphosphine)rhodium(I) chloride. Furthermore, the migratory aptitudes of the α- and α′-hydrogens in diazo adducts derived from unsymmetrical ketones were catalyst dependent. A final useful application of additions of lithiated diazocarbonyls is to be found in Moody's synthesis of oxygen, nitrogen, and sulfur heterocycles (see section III.A.4) where the acyclic precursors were conveniently prepared by addition of ethyl lithiodiazoacetate to γ- and δ-lactones, thiolactones, and lactams.[670]

Acid-promoted reactions of aldehydes and ketones lead directly to nitrogen-free β-dicarbonyl products (Scheme 349). Examples employing ketonic substrates are more numerous than those with aldehydes, although the recent work of Holmquist and Roskamp[671] and of Padwa and co-workers[672] has demonstrated that aldehydes are efficiently converted into β-keto esters or β-diketones with diazocarbonyls in the presence of tin(II) chloride. A few representative examples are shown in Table 6. The process occurs readily in dichloromethane at or below room temperature and shows a sensitivity toward aldehyde structures sufficient to allow differential reaction between aliphatic (the more reactive) and aromatic aldehydes. For example, a

Table 6. Synthesis of β-Dicarbonyl Compounds via Tin(II) Chloride-Catalyzed Reaction

Reactants	Products (yield)
	 (86%)
	 (81%)
	 (80%)
	 (88%)
	 (83%)
	 (90%)

Scheme 350



reaction performed on a 1:1:1 mixture of benzaldehyde, 3-phenylpropionaldehyde, and ethyl diazoacetate gave a 1:30 ratio of β-keto esters at −15 °C.[671] Yields of diketones were found to be significantly lower when aromatic aldehydes were used. For example, treatment of 1-diazo-4-phenylbutan-2-one with benzaldehyde in the presence of $SnCl_2$ afforded H–Cl insertion adducts rather than β-diketones. The preparation of β-keto ester from aldehydes has been used as a step in the synthesis of *ent*-cholesterol[673] and (±)-leuhistin.[674] Very recently, Nomura and co-workers[675] have applied this Lewis acid-promoted β-keto ester formation protocol to the synthesis of γ-unsubstituted α-acyl-β-tetronic acids **538** (Scheme 350). They claimed that the Sn(II) catalytic reactions of tertiary aldehydes **535** with diazo ester **536** resulted in a poor yield of dicarbonyl products **537**, whereas the $ZrCl_4$ and $TiCl_4$ catalysts are quite effective in the reaction of sterically hindered aldehydes (Scheme 350).[673]

In later work Holmquist and Roskamp[676] demonstrated that this Lewis acid-promoted reaction could be extended to include conversion of alkenes into β-keto esters, using ozonolysis to first generate the aldehyde which in turn condenses with ethyl diazoacetate. Here tin(II) chloride plays a dual role, acting as a reducing agent to convert the ozonide to the aldehyde and as a Lewis acid to assist the addition of diazo ester. Several examples of this two-stage transformation are shown in Table 7.

Among other novel addition reactions of diazo esters are Wittig-like olefinations mediated by a combination

Table 7. Conversion of Olefins to β-Keto Esters

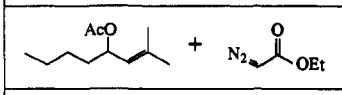
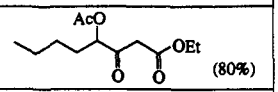
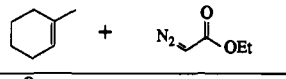
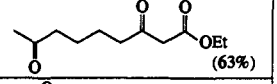
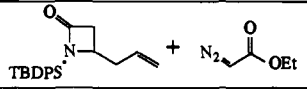
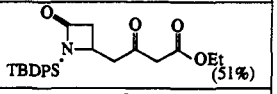
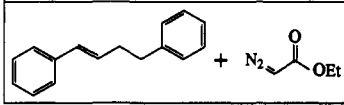
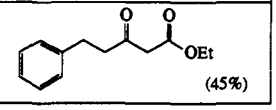
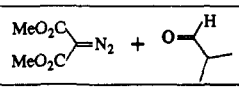
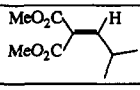
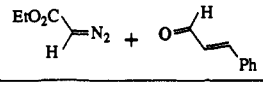
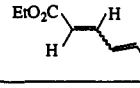
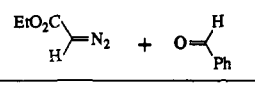
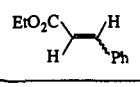
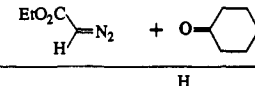
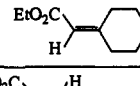
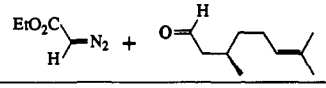
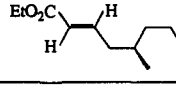
Reactants	Products (yield)
	 (80%)
	 (63%)
	 (51%)
	 (45%)

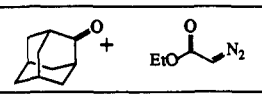
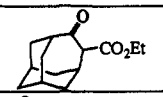
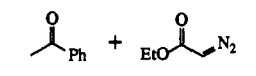
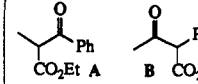
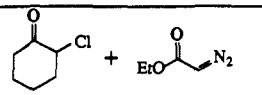
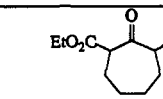
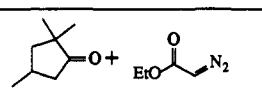
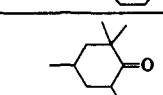
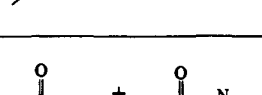
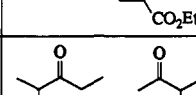
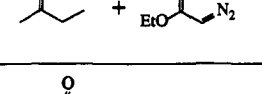
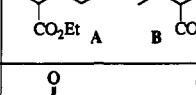
Table 8. Olefination of Diazocarbonyls with Carbonyl Compounds

Reactants	Products (yield)
	 79%
	 97%
	 80%
	 88%
	 89%

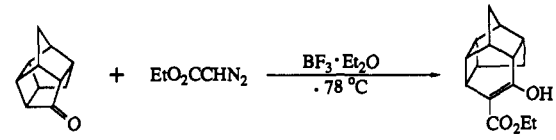
of tributylstibine and copper(I) iodide[677] or catalyzed by methyltrioxorhenium.[678] The former are also applicable to both aldehydes and ketones, whereas the latter appear to have been observed with aldehydes only. Examples of both processes are shown in Table 8.

Addition of diazocarbonyls to ketones promoted by Lewis acids has been used extensively as a means of homologation or ring expansion. The most widely employed Lewis acid appears to be boron trifluoride etherate, although Mock and Hartman[679] have advocated the use of triethyloxonium fluoroborate. With unsymmetrical ketones, whether acyclic or cyclic, questions of regioselectivity rise in homologation due to different migratory aptitudes of the groups flanking the carbonyl function. Liu and co-workers[680] studied the BF_3·Et_2O-catalyzed addition of ethyl diazoacetate to a series of cycloalkanones with different substitution patterns at the α- and α′-positions and concluded that the migratory aptitudes were uniformly such that the less substituted carbon atom migrates preferentially. Studies by Mock and Hartman[679] with triethyloxonium fluoroborate as catalyst revealed a similar trend in migratory aptitude in reactions which gave good to excellent yields of homologated ketones. Some examples taken from both studies are shown in Table 9. However, there are cases where the regiochemical outcome is catalyst dependent. Furthermore, recently studies on the Lewis acid-promoted ring homologation of ketone **539** with ethyl diazoacetate at lower temperatures shows higher regioselectivity (Scheme 351).[681]

Table 9. Homologation of Ketones

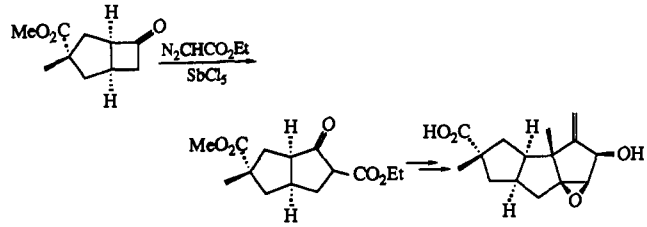
Reactants	Products (A/B ratio, yield)
	 63%
	 A/B = 1/9 78%
	 74%
	 69%
	 A/B = 1/1 89%
	 A/B = 7/3 95%

Scheme 351



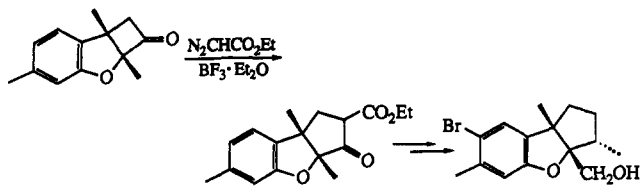
539

Scheme 352



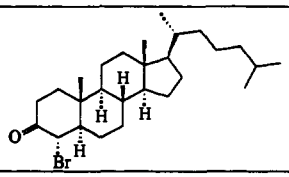
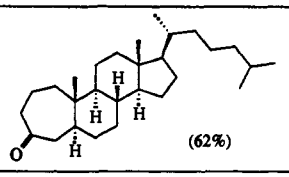
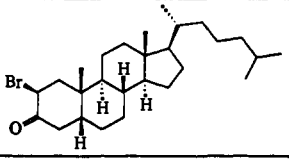
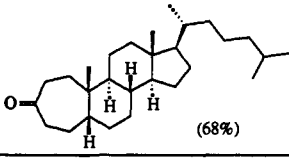
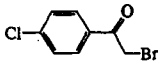
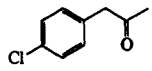
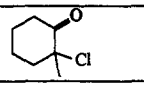
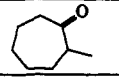
540 541

Scheme 353

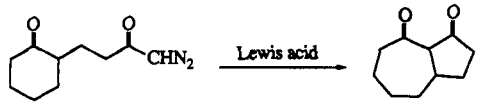


Greene and co-workers[682] found, for example, that whereas addition of ethyl diazoacetate to the cyclobutanone in Scheme 352 with either boron trifluoride etherate or triethyloxonium fluoroborate as catalyst proceeded with poor selectivity, use of antitimony pentachloride in dichloromethane resulted in a highly regioselective ring expansion to give the product **540** (Scheme 352). This ring-expansion adduct (**540**) was then transformed into hirsutic acid C (**541**). A similar application of cyclobutanone ring expansion has been used in a total synthesis of (±)-aplysin[683] (Scheme 353). In this case, the cyclobutanone ring expansion was catalyzed by BF_3·Et_2O regioselectively.

Table 10. Regiospecific Homologation of Unsymmetrical Ketones

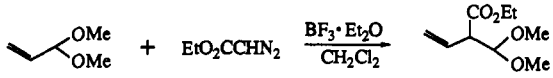
Reactants	Products (yield)
	 (62%)
	 (68%)
	 (61%)
	 (67%)

Scheme 354

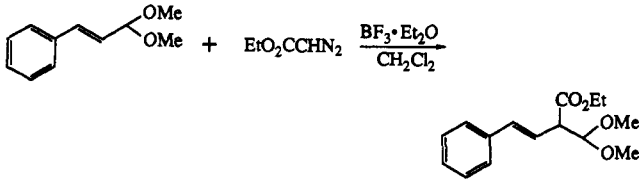


542 543

Scheme 355



Scheme 356



Dave and Warnoff[684] have developed an approach to regiospecific homologation of unsymmetrical, unhindered ketones based on the imposition of a bias against migration of one of the two α-substituents. The procedure consists of preparation of a pure α-bromo or α-chloro ketone, reaction of this derivative with ethyl diazoacetate and boron trifluoride, and removal of the halogen by zinc reduction and removal of the ethoxycarbonyl group by heating with water in a sealed tube at 230 °C. The regiospecificity of the homologation rests on the electron-withdrawing power of the α-halogen atom which prevents migration of the carbon atom to which it is attached. Examples of this approach are shown in Table 10. Intramolecular ring expansion of ketones is known. Treatment of diazo ketone **542** with boron trifluoride etherate[679] or tin(II) chloride[672] afforded the rearranged diketone **543** (Scheme 354). α,β-Unsaturated ketones and aldehydes are not amenable to homologation with diazocarbonyl compounds.[679] Doyle's group, however, has found that the acetals of α,β-unsaturated carbonyl compounds do undergo homologation with ethyl diazoacetate in the presence of boron trifluoride etherate to produce, in good yields, β,γ-unsaturated acetals. Two examples of this transformation are illustrated in Schemes 355 and 356.[685]

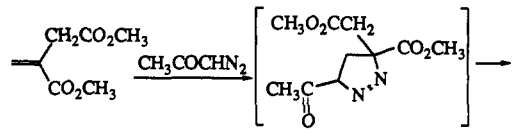
I. Cycloaddition Reactions of Diazocarbonyls

α-Diazocarbonyl compounds are capable of numerous intermolecular and intramolecular cycloadditions, as exemplified for cyclopropanation of alkenes and aromatics in sections III.C and III.D. In these processes bond formation takes place exclusively at the carbenic carbon. Other types of cycloaddition to be discussed in this section may occur directly onto the diazocarbonyl precursor with retention of nitrogen or via the keto carbenoid functionality as a 1,3-dipole. Cycloaddition via ketenes arising from Wolff rearrangement has been considered in section III.F.2.c.

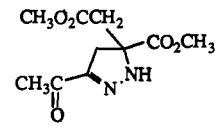
1. Diazocarbonyl Compounds as 1,3-Dipoles in the [3 + 2] Cycloadditions[686]

In the absence of catalysts, a wide variety of α-diazocarbonyls undergo 1,3-dipolar cycloaddition reactions with double bonds conjugated with carbonyl,[687-691] amine,[692] nitrile,[687] nitro[693] groups, or double bonds as a part of a strained ring system,[694-698] without loss of nitrogen to furnish Δ^1-pyrazolines. For example, reaction of dimethyl itaconate **544** and 1-diazo-2-propanone furnishes the Δ^1-pyrazoline **545**, which undergoes spontaneous tautomerization to afford the Δ^2-pyrazoline **546** in good yield (Scheme 357).[691] The same type of

Scheme 357



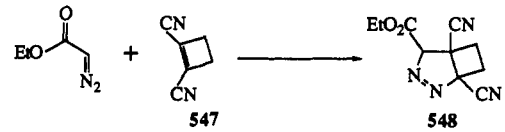
544 545



546

reaction has been observed in the reaction of 1-diazo-2-propanone with the enolate double bond generated from β-dicarbonyl compounds in the presence of base.[699] Disubstituted cyclobutene **547** adds ethyl diazoacetate to give the cycloadduct **548** in 53% yield as shown in Scheme 358.[647]

Scheme 358

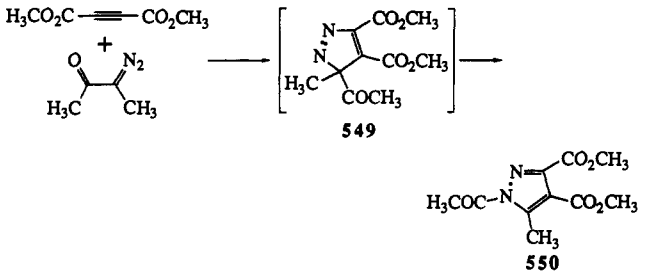


547 548

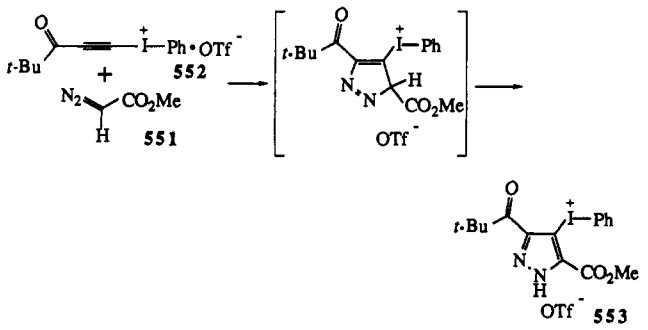
Similarly, 1,3-dipolar cycloaddition reactions occur with carbon–carbon triple bonds conjugated with carbonyl groups.[700-705] 2-Diazo-3-butanone reacts with dimethyl acetylene dicarboxylate to form the unstable pyrazolenine **549**, which undergoes a transposition leading to N(2)-substituted pyrazole **550** by a specific [1,5]-migration of the acyl group to N(2) (Scheme 359).[702] Recently, Mass and co-workers[705] have shown that the diazo esters such as **551** undergo [3 + 2]-cycloaddition to the (alkynyl)(phenyl)iodonium salt **552** to give a (4-pyrazolyl)phenyl iodonium salt **553** (Scheme 360).

Cycloaddition of α-diazocarbonyl compounds with hetero double or triple bonds is a minor process. In

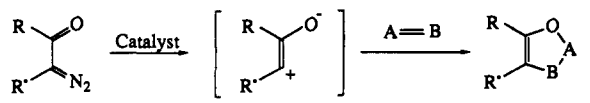
Scheme 359



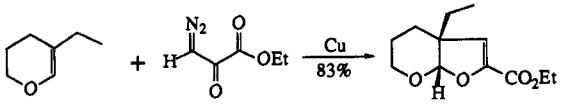
Scheme 360



Scheme 361



Scheme 362



many cases nucleophilic attack on the electrophilic C–X bond by the diazocarbonyl occurs instead of 1,3-dipolar cycloaddition.[686]

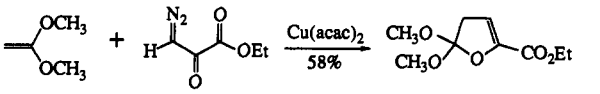
2. Cycloaddition with Participation of Both the Carbenic Carbon and the Carbonyl Oxygen Atoms

Carbenes and carbenoids derived from α-diazocarbonyl compounds can add to multiple bonds with participation of both the carbenic carbon and carbonyl oxygen to form five-membered heterocycles (Scheme 361). The reaction proceeds as a [3 + 2]-cycloaddition. Alternatively, the five-membered heterocyclic product may arise from thermal rearrangement of primary species derived from carbene (or carbenoid) interaction with multiple bonds. Whatever the mechanism, this transformation has been extensively used in the synthesis of dihydrofuran and furan.

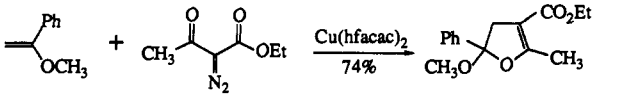
It is known that the carbenoid derived from the alkyl diazoacetates or diazomalonates reacts with alkyl vinyl ethers to form β-oxycyclopropane adducts.[706] By contrast, the reaction between alkyl vinyl ethers and certain diazo ketones, for example, alkyl 2-diazo-3-oxobutyrates or 3-diazo-2,4-pentandione, furnished dihydrofurans.[707–716] The dihydrofurans obtained from the cycloaddition can be further transformed, e.g. into furoic ester and furanones. Some representative examples are shown in Schemes 362–367.

Similarly, diazodimedone (**554**) reacts with substituted pyrrole **555** to give the cycloadduct **556** (Scheme

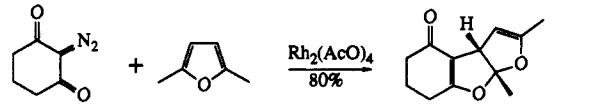
Scheme 363



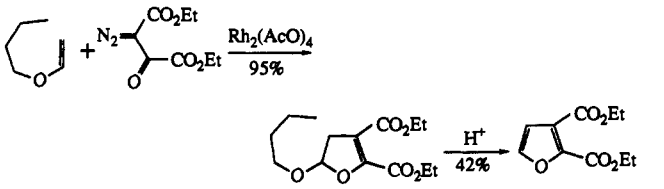
Scheme 364



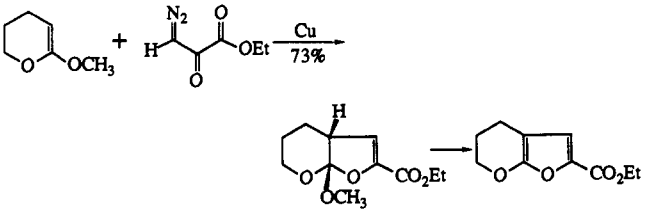
Scheme 365



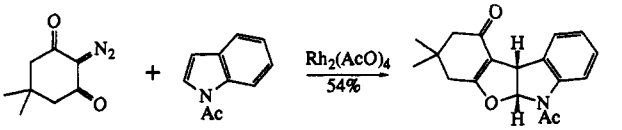
Scheme 366



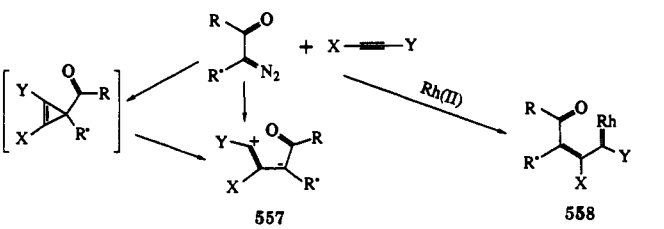
Scheme 367



Scheme 368

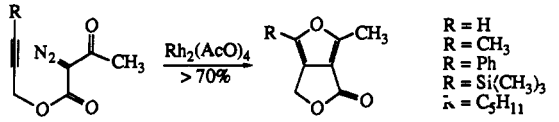


Scheme 369

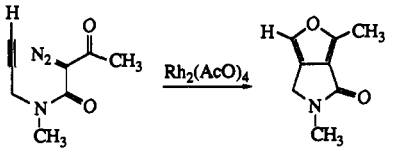


368).[716] Diazocarbonyl compounds with appropriate substituents can react with the carbon–carbon triple bond to afford corresponding substituted furans. Both inter- and intramolecular processes are possible. Intermediate **558**,[717] derived from the addition of an initially formed metal carbenoid onto the alkyne unit, and the dipolar intermediate **557**,[718] which is derived either by ring opening of an initially formed cyclopropene or directly from the reaction of a carbenoid with an alkyne, may be involved in the processes (Scheme 369). Some representative examples from the work of Padwa[717] and Davies[718] and their respective groups are shown in Schemes 370–372.

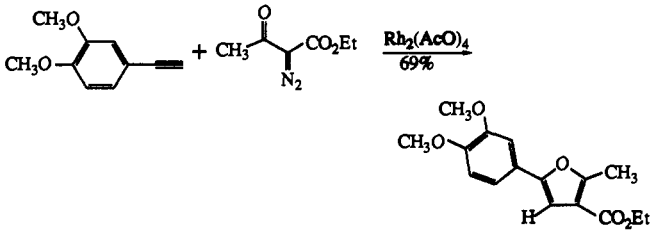
Scheme 370



Scheme 371



Scheme 372



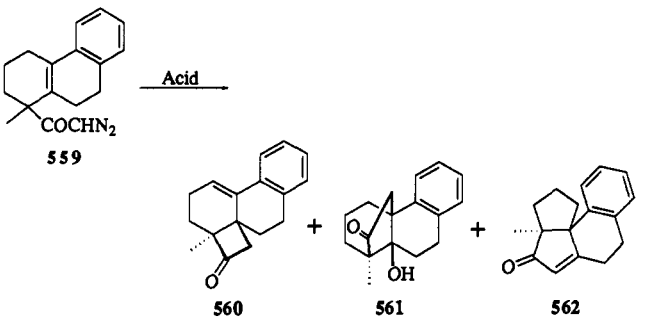
J. Acid-Catalyzed Cyclization of Unsaturated and Aromatic Diazo Ketones

Cyclization processes in which a new bond is formed by nucleophilic addition to an ionizing center provide important routes to carbocycles and heterocycles. Diazocarbonyls with suitably positioned internal nucleophiles display this type of behavior under acid catalysis. Nucleophiles include olefinic, acetylenic, and aromatic groups as well as heteroatoms such as oxygen, nitrogen, and sulfur. Of these, π-route cyclizations of alkenes and aromatics have had the most impact on synthesis, and this section is devoted to unsaturated and aromatic diazo ketones. Cyclizations involving heteroatom participation are included in the section on α,α-substitution.

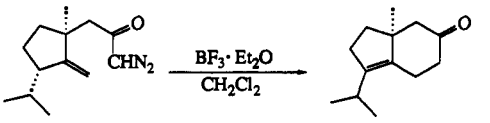
π-Route cyclization is believed to proceed via initial protonation (with Brönsted acids) or complexation (with Lewis acids) of the diazocarbonyl function followed by, or possibly accompanied by, π-electron participation in the very electrophilic species, leading to loss of nitrogen and a cyclized cation which leads to product, typically by proton elimination. π-Route cyclization has been applied very successfully, not just to simple carbocyclic systems, but to many multiring and bridged-ring molecules. The literature up to 1979 has been reviewed in detail by Burke and Grieco[267] and Smith[719] has summarized his own work and that of Mander on multiple π-route cyclizations including aromatics. A few examples will suffice here to demonstrate the power of the process including recent variations.

Cyclobutanones are accessible; diazo ketone **559** furnishes the cyclized product **560** on treatment with either perchloric or fluoroboric acid in benzene or chloroform. However, the course of cyclization in this system is catalyst dependent: use of fluoroboric acid led to cyclopentanone **561** predominantly, whereas in nitromethane perchloric acid furnished **562**, the product of cyclization and rearrangement (Scheme 373).[720] Mehta's group[721,722] have used π-route cyclization to construct the cyclopentanone ring of the hydrindanone shown in Schemes 374 and 375. The adducts **563** was

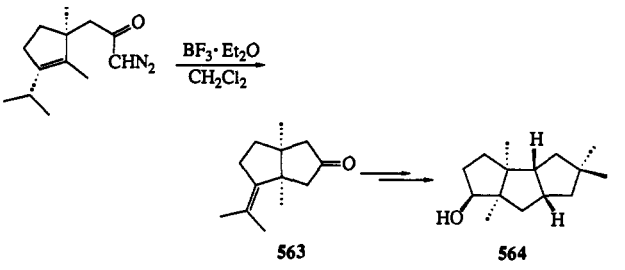
Scheme 373



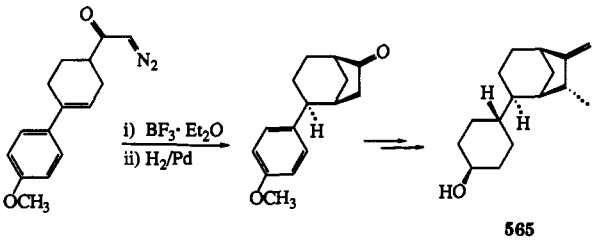
Scheme 374



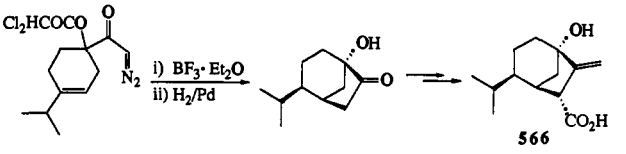
Scheme 375



Scheme 376



Scheme 377

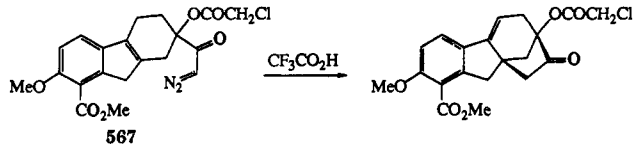


the key intermediate of the total synthesis of (−)-ceratopicanol (**564**).[722]

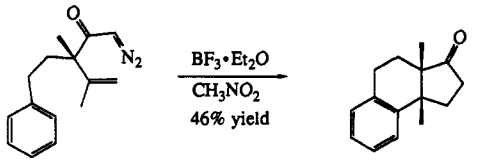
The most impressive application of this annulation process is undoubtedly Mander's synthesis of gibberellic acid.[723] Following extensive studies of the scope of π-route cyclizations in bridged-ring systems, which included the synthesis of helminthsporic acid analogues, e.g. **565** and **566** (Schemes 376 and 377),[724] Mander and co-workers[723] applied the process to construction of the characteristic bicyclo[3.2.1]octane framework of gibberellic acid by trifluoroacetic acid-catalyzed cyclization of the diazo ketone **567** in Scheme 378.

Further aspects of π-route diazocarbonyl cyclizations are worthy of note in systems where more than one olefinic group participates and in systems in which the participating π-electrons are supplied by an aromatic ring. Smith and co-workers[725] have provided several

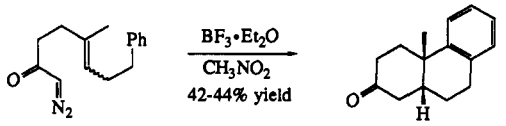
Scheme 378



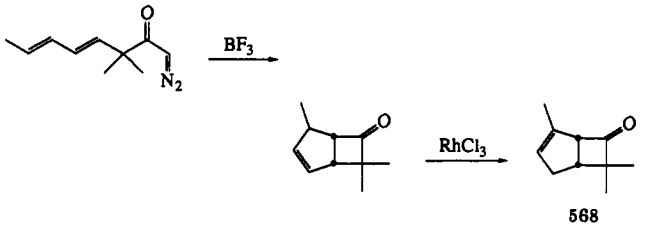
Scheme 379



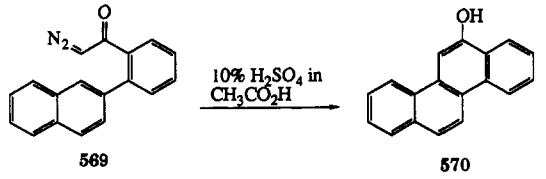
Scheme 380



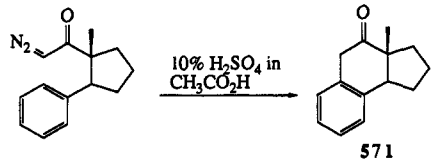
Scheme 381



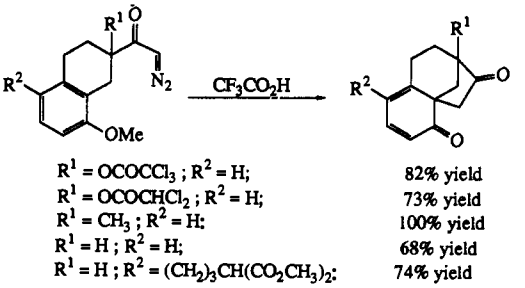
Scheme 382



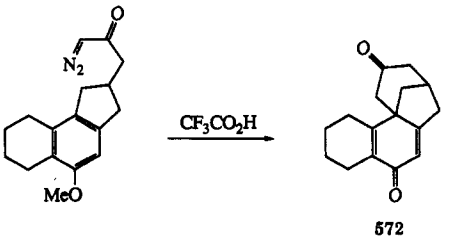
Scheme 383



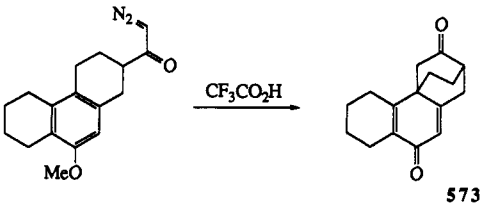
Scheme 384



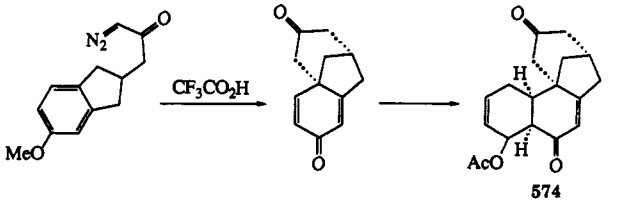
Scheme 385



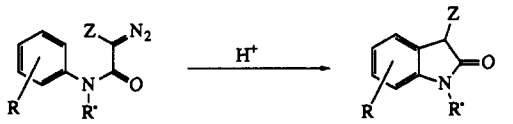
Scheme 386



Scheme 387



Scheme 388

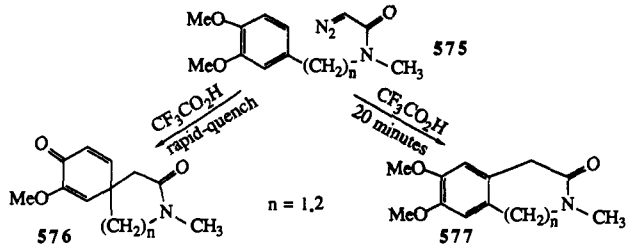


demonstrations of polyolefinic cationic cyclizations of α-diazo ketones. Two typical examples are shown in Schemes 379 and 380. The optimal combination of acid and solvent proved to be boron trifluoride etherate in nitromethane or dichloromethane. Small ring bicycles are also accessible, Hudlicky and Kutchan[726] having demonstrated the construction of a cyclobutanone fused to a cyclopentene ring in their synthesis of (±)-filifolone (**568**, Scheme 381).

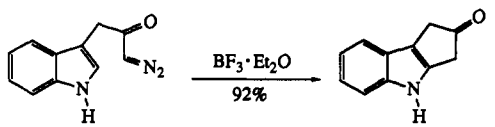
Aryl participation in acid-promoted diazo ketone decomposition has been known for many years. Early examples include the synthesis of 2-chrysenol (**570**) from the diazo ketene **569** in Scheme 382[727] and of the tricyclic ketone **571** in Scheme 383,[728] both reactions having been catalyzed by sulfuric acid in acetic acid. Numerous, more recent studies of π-route participation in aromatic precursors with appropriately placed hydroxy or methoxy groups confirm that this is a very versatile route to bridged-ring cyclohexadienones bearing angular substituents. Illustrative examples from Mander's work, in which trifluoroacetic acid was used as catalyst, are shown in Scheme 384.[729-731] Maity and Mukerjee[732] have used this approach to synthesize tetracyclic dienones (**572** and **573**) related to diterpenes, e.g. the transformation shown in Schemes 385 and 386, as did Nicolaou and Zipkin[733] in their synthesis of the ring system (**574**) of aphidicolin and related natural products (Scheme 387).

Several types of heterocycles are also accessible by acid-catalyzed cyclization of α-diazocarbonyl precursors. Although probably different mechanistically, these reactions provide products similar to those obtained in some rhodium(II)-catalyzed processes (see section III.D). For example, Doyle and co-workers[435] found that the solid-phase sulfonic acid resin Nafion catalyzed the cyclization of diazoacetamides of the type shown in Scheme 388, as did rhodium(II) acetate, to form 2(3*H*)-indolinone derivatives. Similar cyclizations

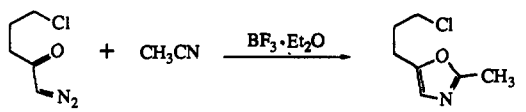
Scheme 389



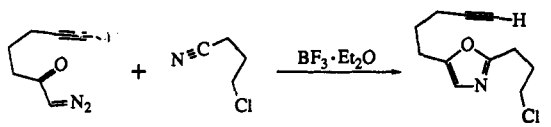
Scheme 390



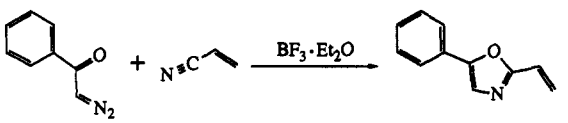
Scheme 391



Scheme 392



Scheme 393



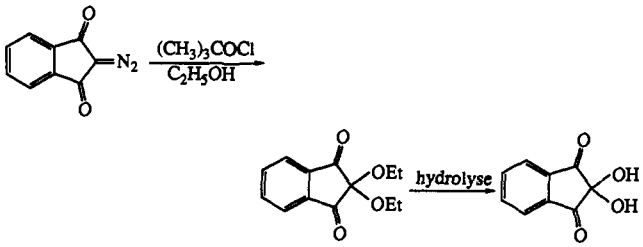
of diazocarbonyls of type **575** catalyzed by trifluoroacetic acid, resulted in two heterocycles (**576** and **577**) (Scheme 389). The reaction course in this case depends on the reaction conditions employed.[734] Furthermore, Pellicciari and co-workers[735] used boron trifluoride etherate to bring about the formation, in 92% yield, of the tricyclic indolone derivative in Scheme 390.

Intermolecular acid-catalyzed reactions of α-diazocarbonyls with π-electron systems are less common than intramolecular processes. Reaction with nitriles, catalyzed by boron trifluoride etherate or aluminum chloride, offers a direct route to substituted oxazoles.[736-740] Several examples are shown in Schemes 391–393. The process is reasonably explained by a stepwise mechanism in which a Lewis acid–diazonium ion complex is attacked by the nitrogen atom of the nitrile followed by intramolecular attack by the oxygen atom to complete the heterocyclic ring.

K. Oxidations of Diazocarbonyl Compounds

Several reagents are available for oxidation of the diazo function of α-diazocarbonyl compounds, the nature of the product depending on the choice of oxidant and the substitution pattern of the substrate. Peroxy acids react with disubstituted diazo ketones to form α-diketones which may react further with this oxidant.[741,742] *tert*-Butyl hypochlorite in ethanol oxidizes 2-diazoindanedione to a trione monoketal which on hydrolysis furnishes ninhydrin hydrate (Scheme 394). Oxidation of primary diazo ketones with ozone can lead

Scheme 394



Scheme 395

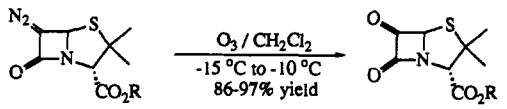
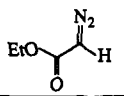
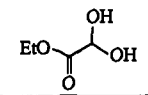
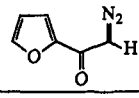
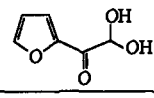
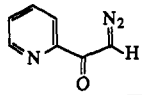
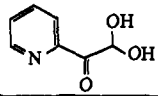
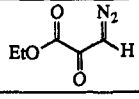
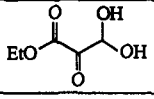


Table 11. Oxidation of Diazocarbonyls by DMD

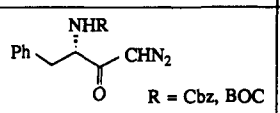
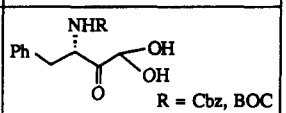
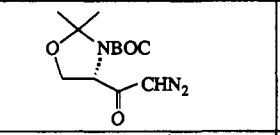
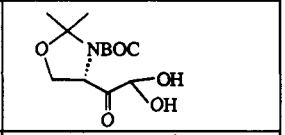
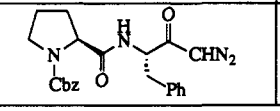
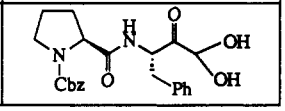
Diazocarbonyls	Products
	
	
	
	

to products resulting from C–H bond cleavage of the initially formed glyoxal.[743] However, when this complication is absent, as with 6-diazo-APA (Scheme 395), cleavage by ozone to the α-diketone can be very efficient.[744]

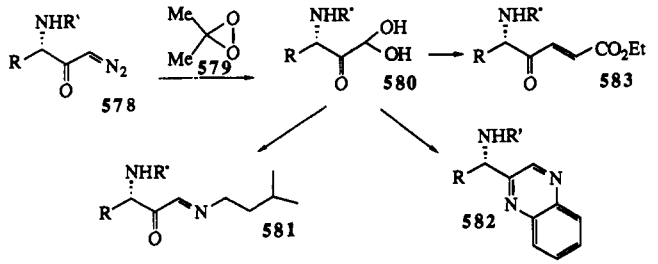
Perhaps the most synthetically useful diazocarbonyl oxidation is through the use of dioxiranes, notably dimethyldioxirane (DMD) **579**. This oxidant, which can be readily prepared and distilled as a dilute solution in acetone,[745,746] converts diazo ketones into diketones or glyoxals in essentially quantitative yield.[747] Products are obtained in a high state of purity since there are no byproducts other than nitrogen and acetone; glyoxals are usually isolated in hydrated form. Some examples are shown in Table 11. Particularly noteworthy are the diazo ketones with oxidizable heterocyclic substitutents where reaction occurs exclusively at the diazo group. This process has been used recently to produce homochiral N-protected amino acids and dipeptides (Table 12).[748] By combining the oxidation process with a Wittig olefination routine, it is possible to bring about one-pot conversions of chiral diazo ketones **578** into optically pure enones of the type **583** shown in Scheme 396. Alternatively, the glyoxals **580** can be combined with isoamylamine or 1,2-aminobenzene to furnish optically pure imine **581** or quinoxaline **582**, respectively (Scheme 396).[748]

A final application of DMD oxidation of diazocarbonyl is illustrated in Scheme 397 for the synthesis of optically pure N-protected β-amino-α-keto esters from natural amino acids or dipeptides.[749] Previous syntheses of these compounds proceeded with extensive racemization. In the first step in Scheme 397 an amino

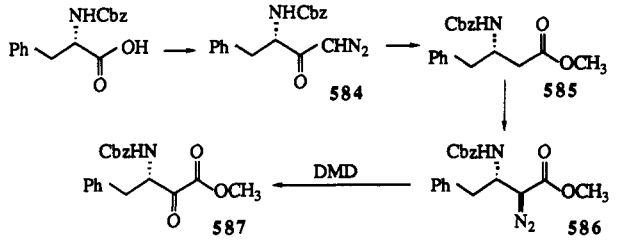
Table 12. Oxidation of N-Protected Amino Acid-Derived Diazo Ketones by DMD

Diazoketones	Products
	
	
	

Scheme 396



Scheme 397

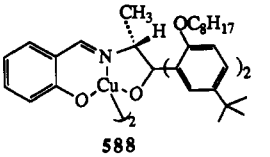


acid-derived diazo ketone, e.g. diazo ketone **584**, is subjected to Wolff rearrangement using silver benzoate in methanol. The resulting β-amino ester **585** is then transformed via the Danheiser procedure[23] into a diazo ester **586**. Finally DMD oxidation converts the diazo ester **586** into the α-keto ester **587**, none of the stages showing any degree of racemization.

L. Asymmetric Synthesis in Diazocarbonyl Reactions

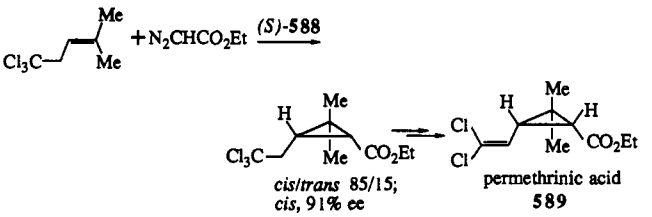
The possibilities for asymmetric synthesis employing diazocarbonyl compounds are numerous, and although this aspect of their use as reaction intermediates is a relatively recent pursuit, very substantial progress has been made especially in enantioselective cyclopropanation. Although the option of covalently attaching chiral auxiliaries to diazocarbonyl precursors or to substrates, e.g. alkenes for cyclopropanation, has been examined in several C–C bond forming reactions, the fact that many of the processes require metal catalysis makes the alternative option of using chiral catalysts particularly attractive and potentially more rewarding for commercial exploitation. The double option of combining the use of a chiral catalyst with a substrate carrying a chiral auxiliary is also available.

Essentially all of the early studies were directed toward enantioselective cyclopropanation and Maas has throughly reviewed the literature up to 1985.[1b] The most successful of these early studies were those of Aratani[7150–753] who developed a series of chiral copper(II) chelates of type **588** from salicyaldehyde and

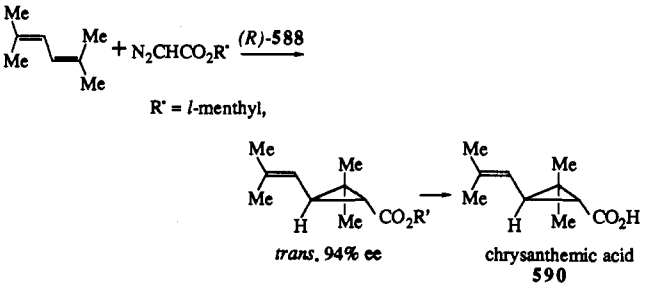


optically active amino alcohols with which to catalyze intermolecular cyclopropanation of alkenes and dienes with diazo esters. Enantioselectivities exceeding 90% ee could be achieved in selected cases (Schemes 398–400) including the synthesis of permethrinic acid (**589**),

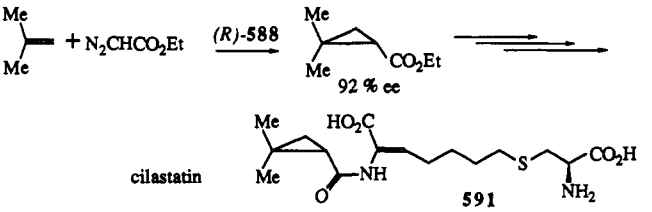
Scheme 398



Scheme 399

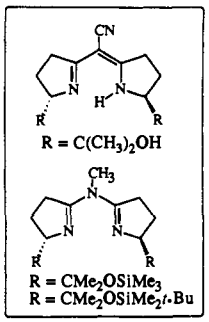


Scheme 400

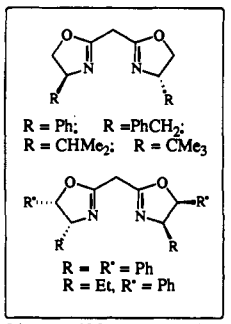


trans-chrysanthemic acid (**590**), and the 2,2-dimethylcyclopropane carboxylate of cilastatin **591**. The commercialization of the Aratani route to cilastatin represents a nobtable achievement for the asymmetric catalysis methodology involving diazocarbonyls.

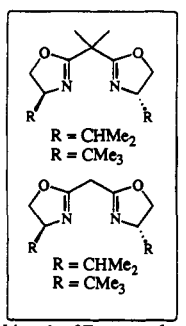
There are now several catalysts available which are capable of achieving high levels (>90%) of enantioselectivity in cyclopropanation over a range of alkenes. The most successful of these are those with chiral ligands **592**, **593**, and **594**. The catalysts of Pfaltz **592**,[754–759] Masamune **593**,[760,761] and Evans **594**[762,763] are all based on copper(II) or copper(I) with C_2-symmetric semicorrin or bisoxazoline auxiliaries, whereas Doyle's catalysts **595**[1b,244,299,764–768] are rhodium(II) complexes bearing chiral carboxamide ligands. The active form of the former catalysts is copper(I); reduction of copper(II) prior to use is therefore necessary. Enantioselectivities greater than 90% have been realized



Ligands of Pfaltz catalyst
592



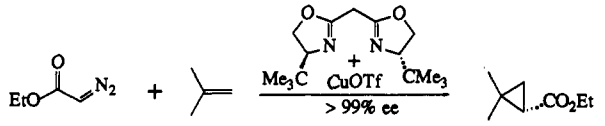
Ligands of Masamune catalyst
593



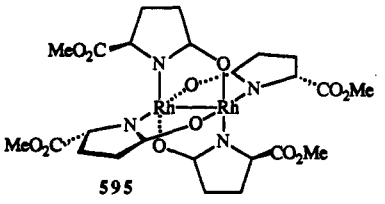
Ligands of Evans catalyst
594

with monosubstituted alkenes and dienes using the Pfaltz catalyst **592**, but di- and trisubstituted alkenes exhibited selectivities and yields inferior to those produced with the Aratani catalyst (**588**). Similar levels of enantiocontrol were obtained with the chiral bisoxazolone catalysts, a notable illustration being the >99% ee for the cyclopropanation of isobutene with ethyl diazoacetate (Scheme 401). Very recently, Ito

Scheme 401

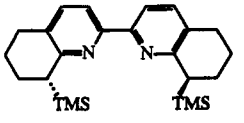


and Katsuki[769] have reported that the copper-based chiral bipyridine **596** as a catalyst gives high levels of



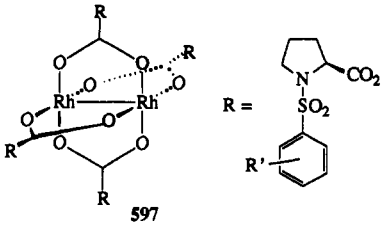
595

Doyle's catalyst : Rh(II)-MEPY



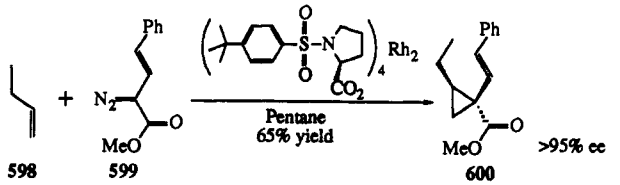
596

asymmetric induction in the cyclopropanation of styrene (66–99% ee), but the enantiomeric pure ligand suffers from the disadvantage of being accessible from the racemate only by HPLC. However, there is one report, due to Matlin,[770] of the use of a copper(II) chelate possessing rigid (+)-(trifluoroacetyl)camphor ligands for the cyclopropanation of styrene with 2-diazodimedone. Although an optical yield of 100% was reported, there have been no other reports that would have allowed further assessment of this catalyst. Doyle's Rh(II)-MEPY systems are also very effective catalytically for cyclopropanation of monosubstituted alkenes with (+)- or (−)-menthyl diazoacetate or ethyl diazoacetate, although the levels of stereocontrol have not yet reached those produced with the chiral copper systems.[764] McKervey and co-workers[41,771] have developed prolinate derivatives of rhodium(II) **597** as



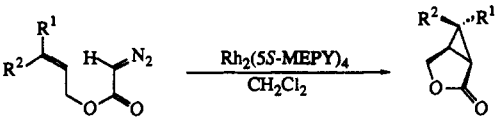
597

Scheme 402



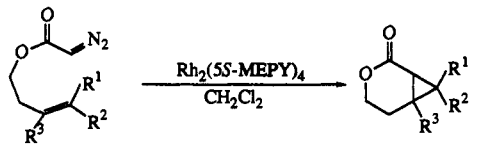
598 599 600 >95% ee

Scheme 403



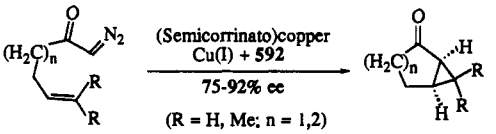
$R^1 = R^2 = Me$	98.6% ee
$R^1 = H$; R^2 = Ph, Et, $PhCH_2$ or $(n\text{-}Bu)_3Sn$	> 98.6% ee
R^1 = Ph; n-Pr; $R^2 = H$	65-75% ee

Scheme 404



$R^1 = R^2 = Me$; $R^3 = H$.	77% ee
R^1 = Et, Ph, Bn, TMS; $R^2 = R^3 = H$.	80-90% ee
$R^1 = H$; R^2 = Et, Ph; $R^3 = H$.	73-82% ee
$R^1 = R^2 = H$; R^3 = Me.	79% ee

Scheme 405

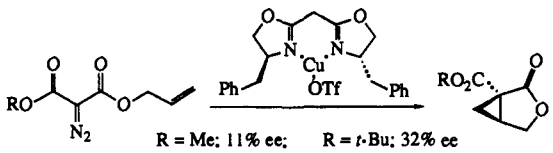


homochiral catalyst for the intramolecular carbenoid transformation (*vide infra*). Davies[772] has applied this type of catalyst to the reactions of vinyldiazocarbonyl **599** with monosubstituted alkene **598** to give (*E*)-vinylcyclopropane adduct **600** with high enantioselectivity (Scheme 402).

There have been equally important developments in intramolecular cyclopropanation, an area where Doyle's catalysts (**595**) show outstanding capabilities for enantiocontrol in the cyclization of allyl and homoallyl diazo esters to bicyclic γ- and δ-lactones, respectively (Schemes 403 and 404).[765,773] The data also reveal that intramolecular cyclopropanation of (*Z*)-alkenes is generally more enantioselective than that of (*E*)-alkenes in bicyclic γ-lactone formation.[765] Both Rh(II)-MEPY enantiomers are available, and through their use enantiomeric products are accessible. In preparative-scale reactions, less than 0.25 mol % of catalyst is adequate for high yields of pure products with >95% ee values. In a few selected cases, the Pfaltz catalyst results in high-level enantioselectivity in intramolecular cyclopropanation (Scheme 405).[759] On the other hand, the Aratani catalyst is less effective than the Doyle catalyst or Pfaltz catalyst (**592**) in asymmetric intramolecular cyclopropanations.[774] In addition, the bisoxazoline-derived copper catalyst shows lower enantioselectivity in the intramolecular cyclopropanation of allyl diazomalonate (Scheme 406).[775]

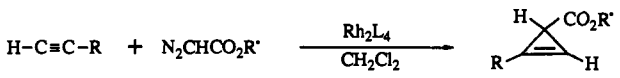
Asymmetric cyclopropenation is a related area where chiral catalysts are begining to show promise. In the

Scheme 406



R = Me; 11% ee; R = *t*-Bu; 32% ee

Scheme 407



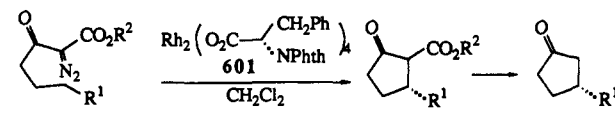
R = CH_3OCH_2;	R* = (+)-menthyl;	L = 5*R*-MEPY;	Yield = 43%;	de = 98%
R = CH_3OCH_2;	R* = (-)-menthyl;	L = 5*S*-MEPY;	———	de = 98%
R = $AcOCH_2$;	R* = (-)-menthyl;	L = 5*S*-MEPY;	Yield = 30%;	de = 98%
R = CH_3OCH_2;	R* = ethyl;	L = 5*R*-MEPY;	Yield = 73%;	ee = 69%
R = $(CH_3)_3C$;	R* = ethyl;	L = 5*R*-MEPY;	Yield = 85%;	ee = 57%

Scheme 408

intermolecular mode, 1-alkynes react with (+)- or (−)-menthyl diazoacetate or ethyl diazoacetate (Scheme 407) in the presence of Rh_2(5*S*-MEPY)$_4$ or Rh_2(5*R*-MEPY)$_4$ to furnish cyclopropenes with moderate to high diastereoselectivity and/or enantioselectivity.[766] Propargyl methyl ether or propargyl acetate, for example, reacts with (−)-menthyl diazoacetate in the presence of Rh_2(5*S*-MEPY)$_4$ to produce the corresponding cyclopropenes in 98% de. These cyclopropenations are subjected to significant double diastereoselection with (+)- and (−)-menthyl diazoacetate.

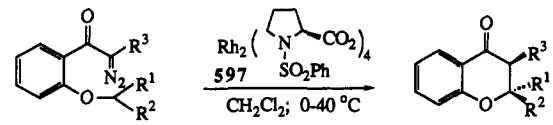
There are four other processes presumed to involve carbenoids which have been screened for catalyzed asymmetric synthesis: viz. C–H insertion, ylide formation coupled with sigmatropic rearrangement, aromatic cycloaddition, and dipolar cycloaddition. Unfortunately, the copper-based complexes which are so successful in catalytic asymmetric cyclopropanation have limited chemical reactivity and are more or less inert in these other carbenoid reactions. However, the Rh(II)-MEPY catalysts are effective in intramolecular C–H insertion. On the other hand, as we have emphasized in earlier sections, rhodium(II) carboxylates are catalytically active across the entire spectrum of carbenoid reactions including C–H insertion. Furthermore, rhodium(II) carboxylates are efficient for decomposition of diazo dicarbonyl compounds such as diazoacetoacetic ester and diazomalonate where the rhodium carboxamides usually fail. The question naturally arose therefore as to the efficacy of chiral rhodium(II) carboxylates for catalyzed asymmetric synthesis. The first reports of enantioselective C–H insertion reactions employed chiral rhodium(II) carboxylates derived from (*S*)-mandelic acid, *N*-(phenylsulfonyl)-L-proline and *N*-acetyl-L-phenylalanine.[771] Although very efficient cyclization leading to substituted cyclopentanones did occur, see for example Scheme 408, the enantiomeric excesses of the products were low (12% ee). Several other amino acid-based chiral Rh(II) catalysts are also now available.[776,777] Catalytic decomposition of α-diazo-β-keto ester in the presence of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-

Scheme 409



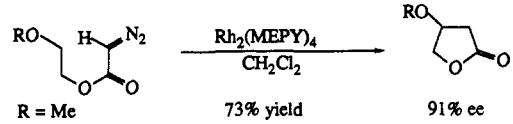
R^1 = Ph; R^2 = Me;	96% yield	46% ee
R^1 = Ph; R^2 = *i*-Pr_2CH;	86% yield	76% ee
R^1 = Ph; R^2 = *i*-Pr_2CMe;	57% yield	75% ee
R^1 = 2-naphthyl; R^2 = *i*-Pr_2CH;	72% yield	64% ee
R^1 = CH_2=CH; R^2 = *i*-Pr_2CH;	61% yield	53% ee

Scheme 410



R^1 = R^2 = R^3 = Me;	70% ee
R^1 = H, R^2 = R^3 = Me;	82% ee
R^1 = H, R^2 = Ph, R^3 = Me;	62% ee
R^1 = H, R^2 = CH_2=CH, R^3 = Me;	79% ee
R^1 = H, R^2 = CH_2=CH, R^3 = Ph;	45% ee

Scheme 411

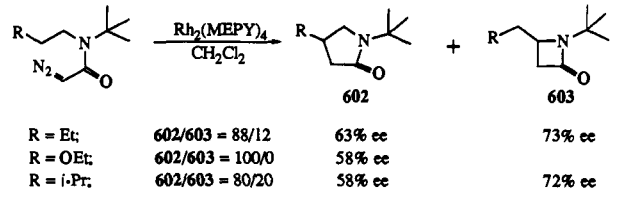


R = Me	73% yield	91% ee
R = Et	64% yield	89% ee
R = Bn	69% yield	87% ee

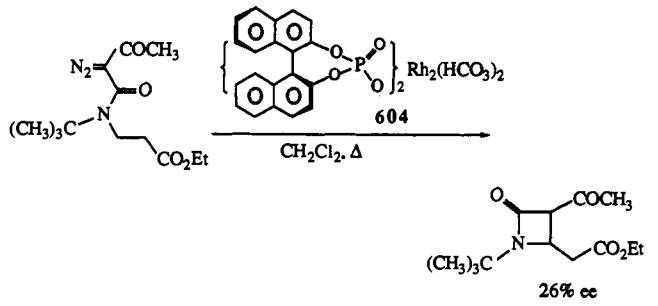
phenylalaninate] (**601**) to give cyclopentanones with moderate to high enantioselectivity (Scheme 409).[776] Here the nature of the alkoxy substituent of the ester group strongly influenced the enantioselectivity. More recent work has shown that C–H insertion reactions can, in suitably formulated precursors, be used to construct six-membered oxygen heterocycles and that high levels of enantioselectivity can be obtained using the rhodium(II) L-prolinate catalyst **597**. For example, treatment of the precursors shown in Scheme 410 with this catalyst (1–2% by mass) in dichloromethane led to the formation of substituted chromanones (90–100% yield) with enantiomeric excess values in the range 45–82%.[41] Doyle's Rh(II)-MEPY catalyst was also catalytically active in this C–H insertion series, but its ability to promote enantioselective was inferior to the prolinate catalyst.

There is, however, a group of intramolecular C–H insertions leading to γ-lactones where the Rh_2(MEPY)$_4$ catalysts (**595**) show great promise. This is evident from the results with a series of 2-alkoxyethyl diazoacetates (Scheme 411) where enantiomeric excesses are at the 90% level.[299] Rather similar C–H insertions, also catalyzed by Rh(II)-MEPY, occur with diazoacetamides of the type shown in Scheme 412,[767] although the γ-lactams **582** produced have enantioselectivities inferior to those obtained in the γ-lactone series (Scheme 411). In these cyclizations β-lactam (**603**) formation (Scheme 412), competes with γ-lactam formation because of the activating influence of the amide nitrogen atom on the adjacent C–H bond.[778,779] Although the β-lactams show significant levels of enantiocontrol, they are very much minor products of the cyclization process. Much higher conversions to *trans*-β-lactams (catalyzed

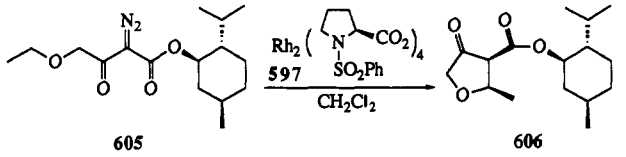
Scheme 412



Scheme 413



Scheme 414

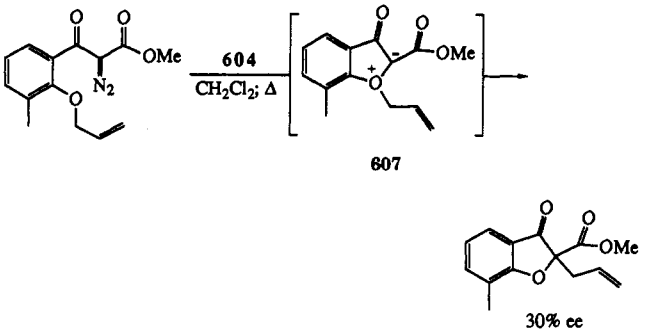


by achiral rhodium(II) carboxylates) are possible with certain diazo dicarbonyls of the type shown in Scheme 413. Very recently a new type of chiral rhodium(II) catalyst, Rh(II)-phos **604**, derived from (+)-binaphthyl phosphoric acid, has been introduced, showing a broad spectrum of reactivity in diazocarbonyl reactions. When applied to the β-lactam synthesis in Scheme 413, the Rh(II)-phos catalyst produced an ee value of 26%.[780] Combinations of chiral substrates and chiral catalysts have also been studied in C–H insertion reactions. In a recent example, the α-diazo-β-keto ester **605** in Scheme 414 was cyclized in the presence of rhodium(II) L-prolinate to afford the furanone **606** with 61% diastereoselectivity. This cyclization could also be brought about with rhodium(II) acetate, but the achiral catalyst produced a much lower diastereoselectivity (18%).[781]

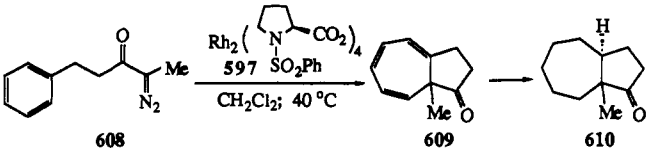
The Rh(II)-phos catalyst **604** is beginning to show promise in some other areas, notably asymmetric sigmatropic rearrangement of oxonium ylides. The question of the extent of metal involvement in catalyzed diazocarbonyl reactions terminating in [2,3]-sigmatropic rearrangement has been raised by several workers. One view is that after forming the carbenoid the metal departs the scene mechanistically and takes no further part in the subsequent stages. However, it has been observed that when the Rh(II)-phos catalyst (**604**) was used to bring about the cyclization reaction shown in Scheme 415 the product (of [2,3]-sigmatropic rearrangement) had an ee value of 30%.[780] Although modest, this stereocontrol suggests that the metal, and its ligands, exert some influence on formation of the oxonium ylide **607**, presumed to proceed the sigmatropic rearrangement step.

Catalytic asymmetric synthesis involving the two diazo ketone precursors **608** and **611** in Schemes 416 and 417 has also been observed in intramolecular aromatic cycloaddition. With the simple benzene

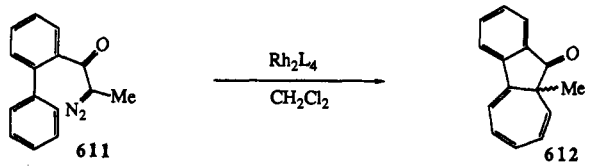
Scheme 415



Scheme 416



Scheme 417



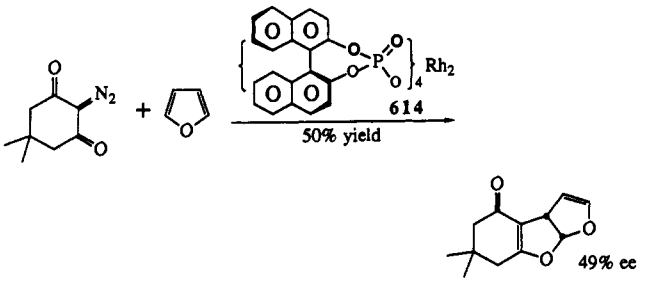
Cata.: Rh_2(5S-MEPY)$_4$;	Reaction temp.: 0 °C	2% ee
Cata.: Rh_2[(+)-mandelate]$_4$;	Reaction temp.: 0 °C	8% ee
Cata.: Rh_2(L-Prolinate)$_4$ (**597**);	Reaction temp.: -30 °C	79% ee
Cata.: Rh_2[(+)-Phos]$_4$;	Reaction temp.: -30 °C	60% ee
Cata.: Rh_2(**613**)$_4$	Reaction temp.: -30 °C	71% ee

derivative **608** a 33% ee was realized employing rhodium(II) L-prolinate (**597**). Hydrogenation of the product **609** over palladium furnished (+)-*trans*-1-methylbicyclo[5.3.0]decan-3-one (**610**, 33% ee) in 93% yield, thus completing a short partial asymmetric synthesis of this bicyclic ketone from a readily accessible precursor.[771] In the biphenyl series **611**, excellent conversions to tricyclic ketone **612** were observed with a range of chiral rhodium(II) catalysts. The stereocontrol in the latter reaction was very catalyst dependent (Scheme 417). Rh(II)-MEPY resulted in an ee value of only 2% and rhodium(II) mandelate was equally poor. Much better ee values were obtained with Rh(II)-phos (**604**) and with a new rhodium(II) carboxylate **613** derived from the (+)-enantiomer of a bicyclic amino acid. The highest value, however, of 79% ee was achieved employing the rhodium(II) L-prolinate catalyst (**597**) at −30 °C.[145,220]

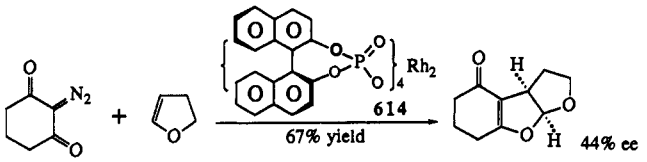
Chiral rhodium(II) catalysts also show promise in the dipolar cycloaddition of diazocarbonyls to heterocycles. Pirrung and Zhang[781] have demonstrated that chiral dirhodium tetrakisbinaphthol phosphate **614** promotes dipolar cycloaddition to furan and 2,3-dihydrofuran with good asymmetric induction (Schemes 418 and 419).

Although we have emphasized the chiral catalyst approach to asymmetric synthesis in this brief summary, it would be misleading to leave the impression that

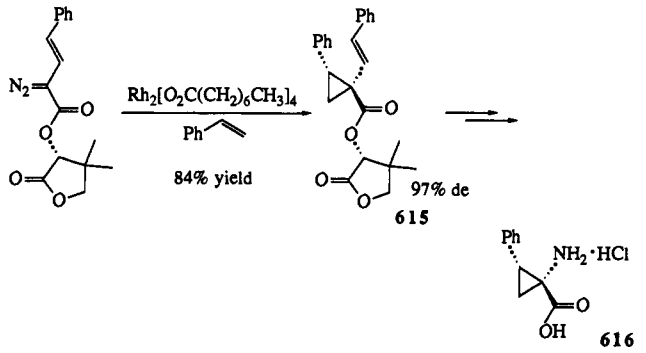
Scheme 418



Scheme 419



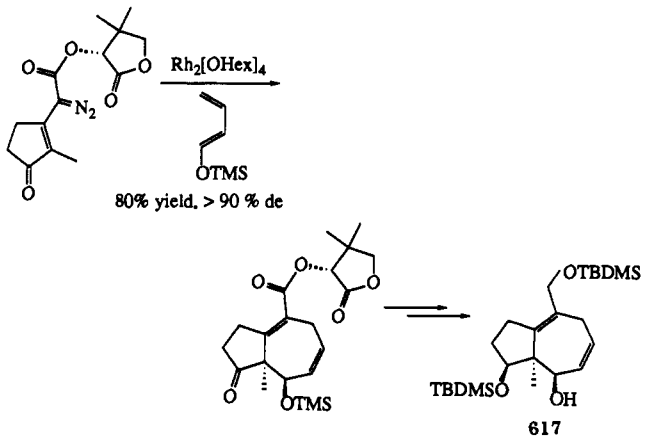
Scheme 420



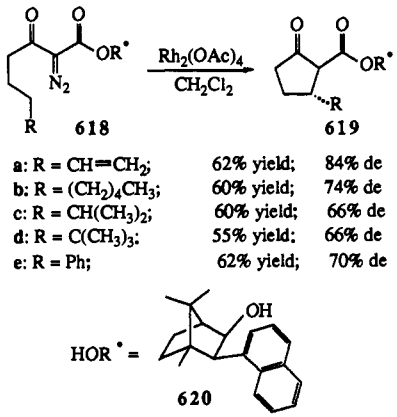
other approaches have not been pursued. In fact, there have been several investigations of systems in which an achiral catalyst was used to bring about reaction of a substrate containing a covalently bound chiral auxiliary. In general, however, applications to cyclopropanation have not been very successful. Only very low enantiomeric excesses were obtained when styrene, for example, was cyclopropanated with diazo esters derived from (+)- or (−)-borneol or (−)-menthol.[782] Optical induction in cyclopropanation of styrene with a chiral diazoacetamide was similarly small.[24] However, there is one exception, in which the (*R*)-(−)-pantolactone was a chiral auxiliary, where a diastereomeric excess for intermolecular cyclopropanation of 97% was recorded[783,784] (Scheme 420). The cyclopropane adduct **615** was further converted to the cyclopropane amino acid **616** by oxidative cleavage of the vinyl group followed by a Curtius rearrangement. By combining the asymmetric cyclopropanation with a subsequent Cope rearrangement, enantioselective synthesis of hydroazulene **617** has been achieved by Davies and coworkers (Scheme 421).[764]

Taber and Raman[269] have conducted a very successful investigation of enantioselective intramolecular C–H insertion reactions leading to optically active disubstituted cyclopentanones. The precursors were β-keto diazo esters of the type **618** show in Scheme 422 in which a chiral auxiliary (**620**) based on (+)- or (−)-camphor was incorporated into the alkoxy moiety of the ester. Cyclization was brought about by rhodium(II) acetate with the results shown in Scheme 422. Diastereoselectivity was good in all cases, the highest

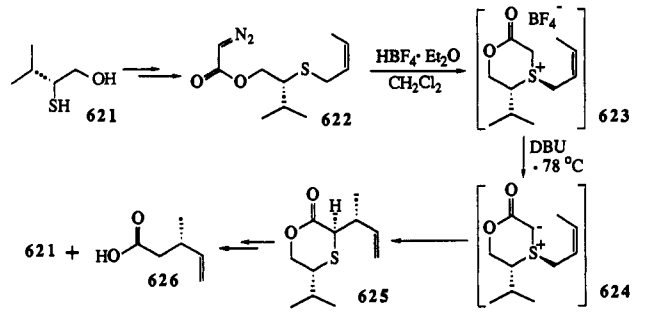
Scheme 421



Scheme 422



Scheme 423



value being found with the vinyl precursor **618a**, the product of which was later transformed into (+)-estrone methyl ether in 91% ee.[785] The diastereoisomers were separable by chromatography, and substituted cyclopentanones of high optical purity were thus accessible.

Asymmetric induction via ylide formation and tandem [2,3]-sigmatropic rearrangement should be possible through the use of chiral auxiliaries incorporated into diazocarbonyl precursors. Kurth and co-workers[786] have reported the utilization of a thioxanone-based [2,3]-sigmatropic rearrangement strategy to construct chiral 3-methylpent-4-enoic acid **626**. Thus, diazocarbonyl **622** derived from the chiral auxiliary **621** was treated with a Lewis acid to give the corresponding thioxonium salt **623** which was then transformed to ylide **624** by treatment of base. The ylide underwent the [2,3]-sigmatropic rearrangement to give **625** in 66% yield with 88% de. The thioxonone **625** was finally disassembled to give the chiral 3-methyl-4-pentenoic acid **626** (Scheme 423).

IV. Conclusion

It is now more than a century since Buchner began his systematic study of organic synthesis using α-diazocarbonyls as intermediates. It is clear from the variety of studies in the more than 700 publications that we have surveyed here that modern organic synthesis continues to benefit from the outstanding versatility of this class of compounds. The rapid recent development of diazocarbonyl chemistry is due in no small measure to the pioneering research of Teyssié, Hubert, and Noels[85-93] that led to the discovery of the rhodium carboxylate catalysts.

V. References and Footnotes

(1) (a) α-Diazocarbonyl compounds are but one of a group of compounds within the vast array of diazoorganic molecules. Diazoorganophosphorus and diazoorganosulfur compounds have been investigated extensively but their applications in synthesis are, as yet, not very well developed. For comprehensive accounts of these and other aspects of diazoorganic compounds including diazoalkanes, see: Weygand, F.; Bestmann, H. J. *New. Methods of Prep. Org. Chem.* **1964**, *3*, 451. Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971. Jones, M.; Moss, R. A. *Carbenes*; Wiley & Sons: New York, 1973; Vol. 1. Regitz, M. *Diazoalkanes*; Thieme Verlag: Stuttgart, 1977. Patai, S. *The Chemistry of Diazonium and Diazo Groups*; John Wiley & Sons: New York, 1978; Vols. 1 and 2. Wulfman, D. S.; Poling, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1980; Chapter 5, p 321. Regitz, M.; Maas, G. *Aliphatic Diazo Compound-Properties and Synthesis*; Academic Press: New York, 1986. (b) For recent reviews of diazocarbonyl chemistry which concentrate on metal-catalyzed carbenoid processes, see: Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75. Demonceau, A.; Noels, A. F.; Hubert, A. J. In *Aspects of Homogeneous Catalysis*; Ugo, R., Ed.; Reidel, D. Publishing Company: Lancaster, 1988; Vol. 6, p 199. Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. Taber, D. F. In *Comprehensive Organic Synthesis; Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 4.2. Davies, H. M. L. In *Comprehensive Organic Synthesis; Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 4.8. Doyle, M. P. *Recl. Trav. Chim. Pays-Bas.* **1991**, *110*, 305. Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385.

(2) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230.

(3) Anrdt, F.; Eistert, B.; Partale, W. *Ber. Dtsch. Chem. Ges.* **1927**, *60B*, 1364.

(4) Arndt, F.; Amende, J. *Ber. Dtsch. Chem. Ges.* **1928**, *61B*, 1122.

(5) Arndt, F.; Eistert, B.; Amende, J. *Ber. Dtsch. Chem. Ges.* **1928**, *61B*, 1949.

(6) Bradley, W.; Robinson, R. *J. Chem. Soc.* **1928**, 1310.

(7) Pettit, G. R.; Nelson, P. S. *J. Org. Chem.* **1986**, *51*, 1282.

(8) DeWald, H. A.; Moore, A. M. *J. Am. Chem. Soc.* **1958**, *80*, 3941.

(9) Weygand, F.; Bestmann, H.; Klieger, E. *Chem. Ber.* **1958**, *91*, 1037.

(10) Pettit, G. R.; Nelson, P. S. *J. Org. Chem.* **1983**, *48*, 741.

(11) Bradley, W.; Robinson, R. *J. Am. Chem. Soc.* **1930**, *52*, 1558.

(12) Weygand, F.; Bestmann, H. *J. Angew. Chem.* **1960**, *72*, 535.

(13) Hodson, D.; Holt, G.; Hall, D. K. *J. Chem. Soc.* **1970**, 971.

(14) Zwanenburg, B.; Thijs, L. *Tetrahedron Lett.* **1974**, *9*, 2459.

(15) Thijs, L.; Smeets, F. L. M.; Gillissen, P. J. M.; Harmsen, J.; Zwanenburg, B. *Tetrahedron* **1980**, *36*, 2141.

(16) Ye, T.; McKervey, M. A. *Tetrahedron* **1992**, *48*, 8007.

(17) Wilds, A. L.; Meader, A. L. *J. Org. Chem.* **1948**, *13*, 763.

(18) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733.

(19) Regitz, M. *Synthesis* **1972**, 351.

(20) Regitz, M.; Menz, F. *Chem. Ber.* **1968**, *101*, 2622.

(21) Regitz, M.; Rüter, J. *Chem. Ber.* **1968**, *101*, 1263.

(22) Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.

(23) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

(24) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663.

(25) Norbeck, D. W.; Kramer, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 7217.

(26) Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144.

(27) Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 833.

(28) Regitz, M.; Rüter, J.; Liedhegener, A. *Org. Synth.* **1971**, *51*, 86.

(29) Regitz, M.; Liedhegener, A. *Chem. Ber.* **1966**, *99*, 3128.

(30) Koskinen, A. M. P.; Muñoz, L. *J. Chem. Soc., Chem. Commun.* **1990**, 652.

(31) Ledon, H. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 414.

(32) Benalloum, A.; Villemin, C. *Synth. Commun.* **1989**, *19*, (13-14), 2567.

(33) Popic, V. V.; Korneev, S. M.; Nikolaev, V. A.; Korobitsyna, I. K. *Synthesis* **1991**, 195.

(34) Rao, Y. K.; Nagarajan, M. *Indian J. Chem., Sect. B* **1986**, *25*, 735.

(35) McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1983**, *48*, 2675.

(36) Ledon, H. *Synthesis* **1974**, 347.

(37) Lombardo, L.; Mander, L. N. *Synthesis* **1980**, 368.

(38) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(39) Regitz, M. *Tetrahedron Lett.* **1964**, 1403.

(40) Regitz, M. *Chem. Ber.* **1965**, *98*, 1210.

(41) McKervey, M. A.; Ye, T. *J. Chem. Soc., Chem. Commun.* **1992**, 823.

(42) von E Doering, W.; DePuy, C. H. *J. Am. Chem. Soc.* **1953**, *75*, 5955.

(43) Hazen, G. G.; Weinstock, L. M.; Connell, R.; Bollinger, F. W. *Synth. Commun.* **1981**, *11*(12), 947.

(44) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 179.

(45) Curphey, T. J. *Org. Prep. Proced. Int.* **1981**, *13*, 112.

(46) Spencer, H. *Chem. Ber.* **1981**, *17*, 106.

(47) Rewicki, D.; Tuchscherer, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 44.

(48) Roush, W. R.; Feitler, D.; Rebek, J. *Tetrahedron Lett.* **1974**, *15*, 1391.

(49) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.

(50) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17* (14), 1709.

(51) Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. *J. Org. Chem.* **1989**, *54*, 930.

(52) Davies, H. M. L.; Saikali, E.; Clark, T. J.; Chee, E. H. *Tetrahedron Lett.* **1990**, *31*, 6299.

(53) McGuiness, M.; Shechter, H. *Tetrahedron Lett.* **1990**, *31*, 4987.

(54) See refs 49-52, and references cited therein.

(55) Balli, H.; Löw, R.; Müller, V.; Rempfler, H.; Sezen-Gezgin, A. *Helv. Chim. Acta* **1978**, *61*, 97.

(56) Balli, H.; Müller, V.; Sezen-Gezgin, A. *Helv. Chim. Acta* **1978**, *61*, 104.

(57) Balli, H.; Felder, L. *Helv. Chim. Acta* **1978**, *61*, 108.

(58) Kokel, B.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 716.

(59) Cava, M. P.; Litle, R. L.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2257.

(60) Allinger, N. L.; Freiberg, L. A. *J. Org. Chem.* **1962**, *27*, 1490.

(61) Muchowski, J. M. *Tetrahedron Lett.* **1966**, 1773.

(62) Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1967**, *50*, 1327.

(63) Searle, N. E. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 424.

(64) Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* **1975**, *31*, 227.

(65) Ehrlich, J.; Anderson, L. E.; Coffey, G. L.; Nilleges, A. B.; Knudsen, M. P.; Koepsell, H. J.; Kohberger, D. L.; Oyaas, J. E. *Nature* **1954**, 71.

(66) Bartz, Q. R.; Eicher, C. L.; Frohardt, R. P.; Fusari, S. A.; Haskell, T. H.; Johannessen, D. W.; Ryder, A. *Nature* **1954**, 73.

(67) Ehrlich, J.; Knudsen, M. P.; Quentin, R.; Bartz, S. A.; Fusari, A.; Haskell, T. H.; Moore, J. A. U.S.P. 2,996,500, 1956 (Parke, Davis and Co.).

(68) Nishimura, M.; Nakada, H.; Tabase, S.; Katayama, A.; Goto, T.; Tanaka, H.; Hashimoto, M. *J. Antibiotics* **1989**, *42*, 549.

(69) Challis, B. C.; Latif, F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1005.

(70) House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 53.

(71) Blankely, C. J.; Scuter, F. J.; House, H. O. *Org. Synth.* **1969**, *49*, 22.

(72) Sen, R.; Carriker, J. D.; Balogh-Nair, V.; Nakanishi, K. *J. Am. Chem. Soc.* **1982**, *104*, 3214.

(73) Sen, R.; Widlanski, T. S.; Balogh-Nair, V.; Nakanishi, K. *J. Am. Chem. Soc.* **1983**, *105*, 5160.

(74) Keilbaugh, S. A.; Thornton, E. R. *J. Am. Chem. Soc.* **1983**, *105*, 3283.

(75) Ok, H.; Cadwell, C.; Schroeder, D. R.; Singh, A. K.; Nakanishi, K. *Tetrahedron Lett.* **1988**, *29*, 2275.

(76) Ouihia, A.; René, L.; Badet, B. *Tetrahedron Lett.* **1992**, *33*, 5509.

(77) Ouihia, A.; René, L.; Guilhem, J.; Pascard, C.; Badet, B. *J. Org. Chem.* **1993**, *58*, 1641.

(78) Fink, J.; Regitz, M. *Synthesis* **1985**, 569.

(79) Yates, P.; Garneau, F. X.; Lokensgard, J. P. *Tetrahedron* **1975**, *31*, 1979.

(80) Schöllkopf, U.; Bánhidai, B.; Frasnelli, H.; Meyer, R.; Beckhaus, H. *Liebigs Ann. Chem.* **1974**, 1767.

(81) Schöllkopf, U.; Rieber, N. *Chem. Ber.* **1969**, *102*, 488.

(82) Schöllkopf, U.; Gerhart, F.; Reetz, M.; Frasnelli, H.; Schumacher, H. *Liebigs Ann. Chem.* **1968**, *716*, 204.
(83) Gerhart, F.; Schöllkopf, U.; Schumacher, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 74.
(84) Schöllkopf, U.; Tonne, P.; Schäfer, H.; Markush, P. *Liebegs Ann. Chem.* **1969**, *722*, 45.
(85) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssié, Ph. *Tetrahedron Lett.* **1973**, 2233.
(86) Paulissen, R.; Hayez, E.; Hubert, A. J.; Teyssié, Ph. *Tetrahedron Lett.* **1974**, 607.
(87) Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssié, Ph. *Synthesis* **1976**, 600.
(88) Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssié, Ph. *Tetrahedron Lett.* **1978**, *19*, 1239.
(89) Anciaux, A. J.; Demonceau, A.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, Ph. *J. Chem. Soc., Chem. Commun.* **1980**, 765.
(90) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, Ph. *J. Org. Chem.* **1980**, *45*, 695.
(91) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssié, Ph. *J. Org. Chem.* **1981**, *46*, 873.
(92) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssié, Ph. *J. Chem. Soc., Chem. Commun.* **1981**, 688.
(93) Noels, A. F.; Petiniot, D. N.; Hubert, A. J.; Teyssié, Ph. *Tetrahedron* **1982**, *38*, 2733.
(94) Taylor, T. W. J.; Forscey, L. A. *J. Chem. Soc.* **1930**, 2272.
(95) Clayton, J. P. *J. Chem. Soc. (C)* **1969**, 2123.
(96) Volkmann, R. A.; Carroll, R. D.; Drolet, R. B.; Elliott, M. L.; Moore, B. S. *J. Org. Chem.* **1982**, *47*, 3344.
(97) Kapur, J. C.; Fasel, H. P. *Tetrahedron Lett.* **1985**, *26*, 3875.
(98) Rosati, R.; Kapili, L. V.; Morrissey, P.; Retsema, J. A. *J. Med. Chem.* **1990**, *33*, 291.
(99) Sacripante, G.; Just, G. *J. Org. Chem.* **1987**, *52*, 3659.
(100) Belinzoni, D. U.; Mascaretti, O. A.; Alzari, P. M.; Punte, G.; Faerman, C.; Podjarny, A. *Can. J. Chem.* **1985**, *63*, 3177.
(101) Leroy, J.; Wakselman, C. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1224.
(102) Patrick, T. B.; Scheibel, J. J.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 3917.
(103) Olah, G. A.; Welch, J. *Synthesis* **1974**, 896.
(104) Mata, E. G.; Setti, E. L.; Mascaretti, O. A. *J. Org. Chem.* **1990**, *55*, 3674.
(105) Wolff, L.; Greulich, R. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 23.
(106) Knunyants, I. L.; Kisel, Y. M.; Bykhovskaya. *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.* **1956**, 363.
(107) Brewster, P.; Hughes, E. D.; Ingold, C. K.; Rao, P. A. D. S. *Nature* **1950**, *166*, 178.
(108) Larchevêque and Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993.
(109) Faustini, F.; Munari, S.; De Panzeri, A.; Villa, V.; Gandolfi, C. A. *Tetrahedron Lett.* **1981**, *22*, 4533.
(110) Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, 316.
(111) Schurig, V.; Leyrer, U.; Wistuba, D. *J. Org. Chem.* **1986**, *51*, 242.
(112) Lerchen, H.-G.; Kunz, H. *Tetrahedron Lett.* **1985**, *26*, 5257.
(113) Anderson, R. J.; Adams, K. G.; Henrick, C. A. *J. Agric. Food. Chem.* **1985**, *33*, 508.
(114) Cignarella, G.; Pifferi, G.; Testa, E. *J. Org. Chem.* **1962**, *27*, 2668.
(115) McMillan, I.; Stoodley, R. J. *J. Chem. Soc. (C)* **1968**, 2533.
(116) Ernest, I.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6301.
(117) Keith, D. D.; Tengi, J.; Rossman, P.; Todaro, L.; Weigele, M. *Tetrahedron* **1983**, *39*, 2445.
(118) Brennan, J.; Hussain, F. H. S. *Synthesis* **1985**, 749.
(119) McKervey, M. A.; O'Sullivan, M. B.; Myers, P. L.; Green, R. H. *J. Chem. Soc., Chem. Commun.* **1993**, 94.
(120) Shute, R. E.; Dunlap, B.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 71.
(121) Hsiao, C.-N.; Leanna, M. R.; Bhagavatula, L.; Lara, E. De; Zydowsky, T. M.; Horrom, B. W.; Morton, H. E. *Synth. Commun.* **1990**, *20*, 3507.
(122) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872.
(123) Rauber, P.; Angliker, H.; Walker, B.; Shaw, E. *Biochem. J.* **1986**, *239*, 633.
(124) Wagner, R. W.; Tome, J. M. *J. Am. Chem. Soc.* **1950**, *72*, 3477.
(125) Giddings, P. J.; John, D. I.; Thomas, E. J. *Tetrahedron Lett.* **1978**, 995.
(126) Baumann, B. C.; MacLeod, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 6223.
(127) Ganem, B.; Ikota, N.; Muralidharan, V. B.; Wade, W. S.; Young, S. D.; Yukimoto, Y. *J. Am. Chem. Soc.* **1982**, *104*, 6787.
(128) Teng, C.-Y. P.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 2463.
(129) Hoare, J. H.; Policastro, P. P.; Berchtold, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6264.
(130) Chouinard, P. M.; Bartlett, P. A. *J. Org. Chem.* **1986**, *51*, 75.
(131) Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765.
(132) Wood, H. B.; Buser, H.-P.; Ganem, B. *J. Org. Chem.* **1992**, *57*, 178.
(133) Marshall, J. R.; Walker, J. *J. Chem. Soc.* **1952**, 467.
(134) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.
(135) Heslin, J. C.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1986**, *27*, 1403.
(136) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1987**, *28*, 5351.
(137) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417.
(138) Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 721.
(139) Davies, M. J.; Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2473.
(140) Davies, M. J.; Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1.
(141) Davies, M. J.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 9.
(142) Kulkowit, S.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1981**, 616.
(143) Erickson, J. L. E.; Dechary, J. M.; Kesling, M. R. *J. Am. Chem. Soc.* **1951**, *73*, 5301.
(144) Wolfrom, M. L.; Thompson, A.; Evans, E. F. *J. Am. Chem. Soc.* **1945**, *67*, 1793.
(145) Ye, T.; McKervey, M. A. Unpublished results.
(146) Canet, J. L.; Fadel, A.; Salaun, J. *J. Org. Chem.* **1992**, *57*, 3463.
(147) Ogawa, K.; Terada, T.; Muranaka, Y.; Hamakawa, T.; Ohta, S.; Okamoto, M.; Fujii, S. *Chem. Pharm. Bull. Tokyo* **1987**, *35*, 3276.
(148) Hua, D. H.; Peacock, N. J.; Meyers, C. Y. *J. Org. Chem.* **1980**, *45*, 1717.
(149) Charlton, J. L.; Lai, H. K.; Lypka, G. N. *Can. J. Chem.* **1980**, *58*, 458.
(150) Collins, J. C.; Dilworth, B. M.; Garvey, N. T.; Kennedy, M.; McKervey, M. A.; O'Sullivan, M. B. *J. Chem. Soc., Chem. Commun.* **1990**, 362.
(151) Sumner, T.; Ball, L. E.; Platner, J. *J. Org. Chem.* **1959**, *24*, 2017.
(152) Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.
(153) Flowers, W. T.; Holt, G.; McCleery, P. P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1485.
(154) Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 3457.
(155) Ando, W. In *The Chemistry of Diazonium and Diazo groups*; Patai, S., Ed.; John Wiley & Sons: New York, 1978; Chapter 9, p 445.
(156) Sheehan, J. C.; Commons, T. J.; Lo, Y. S. *J. Org. Chem.* **1977**, *42*, 2224.
(157) Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 5376.
(158) McKervey, M. A.; Ratananukul, P. *Tetrahedron Lett.* **1982**, *23*, 2509.
(159) McKervey, M. A.; Cronin, J. P. Unpublished results.
(160) McKervey, M. A.; Dilworth, B. M. Unpublished results.
(161) Moody, C. J.; Taylor, R. J. *Tetrahedron* **1990**, *46*, 6501.
(162) Ando, W.; Yagihara, T.; Tozune, S.; Imai, I.; Suzuki, J.; Toyama, T.; Hakaido, S.; Migita, T. *J. Org. Chem.* **1972**, *37*, 1721.
(163) Weygand, F.; Bestmann, H. J. *Z. Naturforsch., Tei B* **1955**, *10b*, 296.
(164) McKervey, M. A.; Ratananukul, P. *Tetrahedron Lett.* **1983**, *24*, 117.
(165) Cronin, J. P.; Dilworth, B. M.; McKervey, M. A. *Tetrahedron Lett.* **1986**, *27*, 757.
(166) Pellicciari, R.; Curini, M.; Ceccherelli, P.; Fringuelli, R. *J. Chem. Soc., Chem. Commun.* **1979**, 440.
(167) Giddings, P. J.; John, D. I.; Thomas, E. J. *Tetrahedron Lett.* **1980**, *21*, 395, 399.
(168) Buckley, D. J.; Kulkowit, S.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1980**, 506.
(169) Buckley, D. J.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2193.
(170) Back, T. G.; Kerr, R. G. *J. Organomet. Chem.* **1985**, *286*, 171.
(171) Usuki, Y.; Iwaoka, M.; Tomoda, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1148.
(172) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, 4233.
(173) Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. *Tetrahedron Lett.* **1966**, 6131.
(174) Nicoud, J. F.; Kagan, H. B. *Tetrahedron Lett.* **1971**, 2065.
(175) Moore, J. A.; Medeiros, R. W. *J. Am. Chem. Soc.* **1959**, *81*, 6026.
(176) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
(177) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783.
(178) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.
(179) Berges, D. A.; Spines, E. R.; Chan, G. W.; Kingsbury, W. D.; Kinzig, C. M. *Tetrahedron Lett.* **1981**, *22*, 3557.
(180) Kametani, T.; Honda, T.; Nakayama, A.; Sakai, Y.; Mochizuki, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1884; 2228.
(181) Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765.
(182) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293.
(183) Ueda, Y.; Damas, C. E.; Belleau, B. *Can. J. Chem.* **1983**, *61*, 1996.
(184) Andrus, A.; Christensen, B. G.; Heck, J. V. *Tetrahedron Lett.* **1984**, *25*, 595.
(185) Ona, H.; Uyeo, S. *Tetrahedron Lett.* **1984**, *25*, 2237.
(186) Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936.
(187) Hirai, H.; Sawada, K.; Aratani, M.; Hashimoto, M. *Tetrahedron Lett.* **1984**, *25*, 5075.
(188) Knierzinger, A.; Vasella, A. *J. Chem. Soc., Chem. Commun.* **1984**, 9.

(189) Shih, D. H.; Cama, L. D.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.
(190) Buynak, J. D.; Rao, M. N.; Pajouhesh, H.; Chandrasekaran, R. Y.; Finn, K.; de Meester, P.; Chu, S. C. *J. Org. Chem.* **1985**, *50*, 4245.
(191) Aratani, M.; Hirai, H.; Sawada, K.; Yamada, A.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 223.
(192) Shih, D. H.; Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1985**, *26*, 587.
(193) Dhtani, M.; Watanabe, F.; Narisada, M. *J. Antibiot.* **1985**, *38*, 610.
(194) Nakai, T.; Chiba, T.; Nagatsuma, M. *Chem. Lett.* **1985**, *9*, 1343.
(195) Koga, K.; Ikota, N.; Shibata, H. *Chem. Pharm. Bull. Tokyo* **1985**, *33*, 3299.
(196) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 3119.
(197) Deziel, R.; Endo, M. *Tetrahedron Lett.* **1988**, *29*, 61.
(198) Endo, M.; Droghini, R. *Can. J. Chem.* **1988**, *66*, 1400.
(199) Georg, G.; Kant, J. *J. Org. Chem.* **1988**, *53*, 692.
(200) Kita, Y.; Tamura, O.; Shibata, N.; Miki, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1862.
(201) Andreoli, P.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1991**, *56*, 5984.
(202) Mastalerz, H.; Menard, M.; Ruediger, E.; Fung-Tomc, J. *J. Med. Chem.* **1992**, *35*, 953.
(203) Brennan, J.; Pinto, I. L. *Tetrahedron Lett.* **1983**, *24*, 4731.
(204) MaK, C. P.; Mayerl, C.; Fliri, H. *Tetrahedron Lett.* **1983**, *24*, 347.
(205) Heck, J. V.; Christensen, B. G. *Tetrahedron Lett.* **1981**, *22*, 5027.
(206) Heck, J. V.; Szymonifka, M. J.; Christensen, B. G. *Tetrahedron Lett.* **1982**, *23*, 1519.
(207) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193.
(208) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3787.
(209) Bodurow, C. C.; Boyer, B. D.; Brennan, J.; Bunnell, C. A.; Burks, J. E.; Carr, M. A.; Doecke, C. W.; Eckrich, T. M.; Fisher, J. W.; Gardner, J. P.; Graves, B. J.; Hines, P.; Hoying, R. C.; Jackson, B. G.; Kinick, M. D.; Kochert, C. D.; Lewis, J. S.; Luke, W. D.; Moore, L. L.; Morin, J. M., Jr.; Nist, R. L.; Prather, D. E.; Sparks, D. L.; Vladuchick, W. C. *Tetrahedron Lett.* **1989**, *30*, 2321.
(210) Habich, D.; Hartwig, W. *Tetrahedron* **1984**, *40*, 3667.
(211) Yamamoto, S.; Itani, H.; Takahashi, H.; Tsuji, T.; Nagata, W. *Tetrahedron Lett.* **1984**, *25*, 4545.
(212) Okonogi, T.; Shibahara, S.; Murai, Y.; Inouye, S.; Kondo, S.; Christensen, B. G. *Heterocycles* **1990**, *31*, 791.
(213) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073.
(214) Emmer, G. *Tetrahedron* **1992**, *48*, 7165.
(215) McKervey, M. A.; Dilworth, B. M.; Collins, J. C. Unpublished results. [See: Dilworth, B. M. Ph.D. Thesis, NUI, 1987. Collins, J. C. Ph.D. Thesis, NUI, 1990.)
(216) Hanessian, S.; Fu, J.-M.; Chiara, J.-L.; Di Fabio, R. *Tetrahedron Lett.* **1993**, *34*, 4157.
(217) Burger, K.; Rudolph, M.; Fehn, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 285.
(218) Ko, K.-Y.; Lee, K.-I.; Kim, W-J. *Tetrahedron Lett.* **1992**, *33*, 6651.
(219) Polozov, A. M.; Polezhaeva, N. A.; Mustaphin, A. H.; Khotinen, A. V.; Arbuzov, B. A. *Synthesis* **1990**, 515.
(220) McKervey, M. A.; McCarthy, N.; Rafferty, D. Unpublished results.
(221) Bagheri, V.; Doyle, M. P.; Taunton, J.; Claxton, E. E. *J. Org. Chem.* **1988**, *53*, 6158.
(222) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936.
(223) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 6891.
(224) Hooz, J.; Gunn, D. M. *Tetrahedron Lett.* **1969**, 3455.
(225) Hooz, J.; Morrison, G. F. *Can. J. Chem.* **1970**, *48*, 868.
(226) Hooz, J.; Gunn, D. M. *J. Chem. Soc., Chem. Commun.* **1969**, 139.
(227) Hooz, J.; Gunn, D. M. *J. Am. Chem. Soc.* **1969**, *91*, 6195.
(228) Newman, H. *Chem. Phys. Lipids.* **1974**, *12*, 48.
(229) Newman, H. *J. Org. Chem.* **1974**, *39*, 100.
(230) Pasto, D. J.; Wojtkowski, P. W. *Tetrahedron Lett.* **1970**, 215.
(231) Pasto, D. J.; Wojtkowski, P. W. *J. Org. Chem.* **1971**, *36*, 1790.
(232) Hooz, J.; Bridson, J. N. *J. Am. Chem. Soc.* **1973**, *95*, 602.
(233) Hooz, J.; Oudenes, J.; Roberts, J. L.; Benderly, A. *J. Org. Chem.* **1987**, *52*, 1347.
(234) Hooz, J.; Oudenes, J. *Synth. Commun.* **1980**, *10*, 667.
(235) Hooz, J.; Oudenes, J. *Synth. Commun.* **1982**, *12*, 189.
(236) Hooz, J.; Oudenes, J. *Tetrahedron Lett.* **1983**, *24*, 5695.
(237) Meerwein, H.; Rathjen, H.; Werner, H. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1610.
(238) Yates, P.; Danishefsky, S. *J. Am. Chem. Soc.* **1962**, *84*, 879.
(239) Wrobel, J.; Takahashi, K.; Honkan, V.; Lannoye, G.; Cook, J. M.; Bertz, S. H. *J. Org. Chem.* **1983**, *48*, 139.
(240) Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3243.
(241) Sauawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **1991**, *56*, 1434.
(242) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron* **1991**, *47*, 7403.
(243) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295.
(244) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906.
(245) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709.
(246) Lee, E.; Jung, K. W.; Kim, Y. S. *Tetrahedron Lett.* **1990**, *31*, 1023.
(247) Box, V. G. S.; Marinovic, N.; Yiannikouros, G. P. *Heterocycles* **1991**, *32*, 245.
(248) Corey, E. J.; Felix, A. M. *J. Am. Chem. Soc.* **1965**, *87*, 2518.
(249) Rando, R. R. *J. Am. Chem. Soc.* **1970**, *92*, 6706.
(250) Rando, R. R. *J. Am. Chem. Soc.* **1972**, *94*, 1629.
(251) Brunwin, D. M.; Lowe, G.; Parker, J. *J. Chem. Soc. C.* **1971**, 3756.
(252) Brunwin, D. M.; Lowe, G.; Parker, J. *J. Chem. Soc. D.* **1971**, 865.
(253) Lowe, G.; Parker, J. *J. Chem. Soc. D.* **1971**, 577.
(254) Franich, R. A.; Lowe, G.; Parker, J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2034.
(255) Lowe, G.; Ramsay, M. V. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 479.
(256) Golding, R. T.; Hall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1517.
(257) Tomioka, H.; Kitagawa, H.; Izawa, Y. *J. Org. Chem.* **1979**, *44*, 3072.
(258) Tomioka, H.; Kondo, M.; Izawa, Y. *J. Org. Chem.* **1981**, *46*, 1090.
(259) Ponsford, R. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1979**, 846.
(260) Smale, T. C. *Tetrahedron Lett.* **1984**, *25*, 2913.
(261) Brown, P.; Southgate, R. *Tetrahedron Lett.* **1986**, *27*, 247.
(262) Doyle, M. P.; Shanklin, M. S.; Oon, S.-M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384.
(263) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397.
(264) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.
(265) Afarinkia, K.; Cadogan, J. I. G.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1992**, 285.
(266) For recent reviews on cyclopentane annulation, see: (a) Ramaiah, M. *Synthesis* **1984**, 529. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (c) Hudlicky, T.; Price, J. O. *Chem. Rev.* **1989**, *89*, 1467.
(267) Burke, S. D.; Grieco, P. A. *Org. React. (N.Y.)* **1979**, *26*, 361.
(268) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.
(269) Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935.
(270) Taber, D. F.; Schuchardt, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 5289.
(271) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
(272) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686.
(273) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28.
(274) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436.
(275) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.
(276) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1991**, *56*, 7065.
(277) Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.
(278) Monteiro, H. J. *Tetrahedron Lett.* **1987**, *28*, 3459.
(279) Corbel, B.; Hernot, D.; Haelters, J.-P.; Sturtz, G. *Tetrahedron Lett.* **1987**, *28*, 6605.
(280) Mikolajczyk, M.; Zurawinski, R.; Kielbasinski, P. *Tetrahedron Lett.* **1989**, *30*, 1143.
(281) Ghatak, U. R.; Chakrabarty, S. *J. Am. Chem. Soc.* **1972**, *94*, 4756.
(282) Ghatak, U. R.; Chakrabarty, S. *J. Org. Chem.* **1976**, *41*, 1089.
(283) Ghatak, U. R.; Alam, S. K.; Ray, J. K. *J. Org. Chem.* **1978**, *43*, 4598.
(284) Chakraborti, A. K.; Ray, J. K.; Kundu, K. K.; Chakrabarty, S.; Mukherjee, D.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 261.
(285) Kitadani, M.; Ito, K.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3431.
(286) Nakata, T.; Tahara, A. *Tetrahedron Lett.* **1976**, 1515.
(287) Hashimoto, S.; Shinoda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1137.
(288) Hashimoto, S.; Shinoda, T.; Shimada, Y.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1987**, *28*, 637.
(289) Rao, V. B.; Wolff, S.; Agosta, W. C. *Tetrahedron* **1986**, *42*, 1549.
(290) Rao, V. B.; Geroge, C. F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 5732.
(291) Rao, V. B.; Wolff, S.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1984**, 293.
(292) Corey, E. J.; Kamiyama, K. *Tetrahedron Lett.* **1990**, *31*, 3995.
(293) Adams, J.; Poupart, M. A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749.
(294) Adams, J.; Poupart, M. A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753.
(295) Hon, Y. S.; Chang, R. C.; Chau, T. Y. *Heterocycles* **1990**, *31*, 1745.
(296) Adams, J.; Frenette, R. *Tetrahedron Lett.* **1987**, *28*, 4773.
(297) Spero, D. M.; Adams, J. *Tetrahedron Lett.* **1992**, *33*, 1143.
(298) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001.
(299) Doyle, M. P.; Oeveren, A. V.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982.
(300) Ray, C.; Saha, B.; Ghatak, U. R. *Tetrahedron* **1990**, *46*, 2857.
(301) Ballabio, M.; Malatesta, V.; Ruggieri, D.; Temperilli, A. *Gazz. Chim. Ital.* **1988**, *118*, 375.
(302) Hatch, C. E., III; Baum, J. S. *J. Org. Chem.* **1980**, *45*, 3281.
(303) Yadav, J. S.; Mysorekar, S. V.; Rao, A. V. R. *Tetrahedron* **1989**, *45*, 7353.

(304) Bowers, W. S., Ebing, W., Martin, D., Wegler, R., Eds. *Chemistry of Plant Protection, Synthetic Pyrethroid insecticides: Structures and Properties*; Springer: Berlin, 1990; Vol. 4.
(305) Artt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 703.
(306) Chen, E. Y. *Tetrahedron Lett.* **1982**, *23*, 4769; *J. Org. Chem.* **1984**, *49*, 3245.
(307) Kang, S. H.; Kim, W. J.; Chae, Y. B. *Tetrahedron Lett.* **1988**, *29*, 5169.
(308) Srikrishna, A.; Krishnan, K. *Tetrahedron* **1992**, *48*, 3429.
(309) Marshall, J. A.; Peterson, J. C.; Lebioda, L. *J. Am. Chem. Soc.* **1983**, *105*, 6515.
(310) Fowden, L.; Smith, A.; Millington, D. S.; Sheppard, R. C. *Phytochemistry* **1969**, *8*, 437.
(311) Yamanoi, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 1181.
(312) Schimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1989**, *30*, 3803.
(313) Pellicciari, R.; Natalini, B.; Marinozzi, M.; Monahan, J. B.; Snyder, J. P. *Tetrahedron Lett.* **1990**, *31*, 139.
(314) Schimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4049.
(315) Martin, S. F.; Austin, R. E.; Oalmann, C. J. *Tetrahedron Lett.* **1990**, *31*, 4731.
(316) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; deLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710.
(317) Martin, S. F.; Oalmann, C. J.; Liras, S. *Tetrahedron* **1993**, *49*, 3521.
(318) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.
(319) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73.
(320) Reissig, H.-U. *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Part 1, p 375.
(321) Vehre, R.; De Kimpe, N. *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Part 1, p 445.
(322) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.
(323) Salaün, J. *Chem. Rev.* **1989**, *89*, 1247.
(324) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; *Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 899.
(325) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React.*; John Wiley & Sons: New York, 1992; Vol. 41, p 1.
(326) Trost, B. M.; Vladuchick, W. C. *J. Org. Chem.* **1979**, *44*, 148.
(327) Taber, D. F.; Amedio, J. C., Jr.; Raman, K. *J. Org. Chem.* **1988**, *53*, 2984.
(328) Hudlicky, T.; Koszyk, F. J. *Tetrahedron Lett.* **1980**, *21*, 2487.
(329) Govindan, S. V.; Hudlicky, T.; Koszyk, F. J. *J. Org. Chem.* **1983**, *48*, 3581.
(330) Taber, D. F.; Hoerrner, R. S. *J. Org. Chem.* **1992**, *57*, 441.
(331) Wenkert, E.; Greenberg, R.; Kim, H.-S. *Helv. Chim. Acta* **1987**, *70*, 2159.
(332) Davies, H. M. L.; Clark, T. J.; Smith, H. D. *J. Org. Chem.* **1991**, *56*, 3817.
(333) Davies, H. M. L.; Hu, B. *J. Org. Chem.* **1992**, *57*, 4309.
(334) Davies, H. M. L.; Hu, B. *Tetrahedron Lett.* **1992**, *33*, 453.
(335) Lafontaine, J.; Mongrain, M.; Sergent-Guay, M.; Ruest, L.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 2460.
(336) Ruppert, J. F.; White, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 1808.
(337) White, J. D.; Ruppert, J. F.; Avery, M. A.; Torii, S.; Nokami, J. *J. Am. Chem. Soc.* **1981**, *103*, 1813.
(338) Murai, A.; Kato, K.; Masamune, T. *Tetrahedron Lett.* **1982**, *23*, 2887.
(339) Adams, J.; Lepine-Frenette, C.; Spero, D. M. *J. Org. Chem.* **1991**, *56*, 4494.
(340) Hudlicky, T.; Sheth, J. P. *Tetrahedron Lett.* **1979**, *29*, 2667.
(341) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020.
(342) Hudlicky, T.; Reddy, D. B.; Govindan, S. V.; Kulp, T.; Still, B.; Sheth, J. P. *J. Org. Chem.* **1983**, *48*, 3422.
(343) Hudlicky, T.; Govindan, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166.
(344) Laabassi, M.; Grée, R. *Tetrahedron Lett.* **1988**, *29*, 611.
(345) Piers, E.; Jung, G. L. *Can. J. Chem.* **1985**, *63*, 996.
(346) Hudlicky. T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351.
(347) Short, R. P.; Revol, J.-M.; Ranu, B. C.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453.
(348) Hudlicky, T.; Kwart, L. D.; Tiedje, M. H.; Ranu, B. C.; Short, R. P.; Frazier, J. O.; Rigby, H. L. *Synthesis* **1986**, 716.
(349) Hudlicky, T.; Natchus, M. G.; Sinai-Zingde, G. *J. Org. Chem.* **1987**, *52*, 4641.
(350) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G.; Ranu, B. C.; Papadopolous, P. *Tetrahedron* **1987**, *43*, 5687.
(351) Hudlicky, T.; Short, R. P. *J. Org. Chem.* **1982**, *47*, 1522.
(352) Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691.
(353) Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. *J. Org. Chem.* **1989**, *54*, 930.
(354) Davies, H. M. L.; Oldenburg, C. E. M.; McAfee, M. J.; Nordahl, J. G.; Henretta, J. P.; Romines, K. R. *Tetrahedron Lett.* **1988**, *29*, 975.
(355) Imanishi, T.; Matsui, M.; Yamashita, M.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1987**, 1802.
(356) Imanishi, T.; Matsui, M.; Yamashita, M.; Iwata, C. *Tetrahedron Lett.* **1986**, *27*, 3161.
(357) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.
(358) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574.
(359) Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025.
(360) Srikrishna, A.; Krishnan, K. *J. Chem. Soc., Chem. Commun.* **1991**, 1693.
(361) Srikrishna, A.; Nagaraju, S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 657.
(362) Ranu, B. C.; Sarkar, M.; Chakraborti, P. C.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 865.
(363) Dawe, R. D.; Mander, L. N.; Turner, J. V. *Tetrahedron Lett.* **1985**, *26*, 363.
(364) Dawe, R. D.; Mander, L. N.; Turner, J. V.; Pan, X. *Tetrahedron Lett.* **1985**, *26*, 5725.
(365) Corey, E. J.; Reid, G. J.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 918.
(366) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717.
(367) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187.
(368) Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953.
(369) Marino, J. P.; Silveira, C.; Comasseto, J.; Petragnani, N. *J. Org. Chem.* **1987**, *52*, 4139.
(370) Doering, W. v. E.; Pomerantz, M. *Tetrahedron Lett.* **1964**, 961.
(371) Protopopova, M. N.; Shapiro, E. A. *Russ. Chem. Rev.* **1989**, *58*, 667.
(372) Shapiro, E. A.; Lun'kova, G. V.; Nefedov, A. O.; Dolgii, I. E.; Nefedov, O. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, 2535.
(373) Donaldson, W. A.; Hughes, R. P. *J. Am. Chem. Soc.* **1982**, *104*, 4846.
(374) Dowd, P.; Garner, P.; Schappert, R.; Irngartinger, H.; Goldman, A. *J. Org. Chem.* **1982**, *47*, 4240.
(375) Domnin, I. N.; Zhuravleva, E. F.; Pronina, N. V. *Zh. Org. Khim.* **1978**, *14*, 2323.
(376) Dowd, P.; Schappert, R.; Garner, P.; Go, C. L. *J. Org. Chem.* **1985**, *50*, 44.
(377) Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. *J. Org. Chem.* **1990**, *55*, 4518.
(378) Padwa, A.; Krumpe, K. E.; Gareau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523.
(379) Padwa, A.; Austin, D. J.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 4103.
(380) Padwa, A.; Krumpe, K. E.; Kassir, J. M. *J. Org. Chem.* **1992**, *57*, 4940.
(381) Mueller, P. H.; Kassir, J. M.; Semones, M. A.; Weingarten, M. D.; Padwa, A. *Tetrahedron Lett.* **1993**, *34*, 4285.
(382) Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1992**, *33*, 169.
(383) Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1991**, *32*, 3755.
(384) Padwa, A.; Xu, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5881.
(385) Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2371; 2377.
(386) Buchner, E. *Liebigs Ann. Chem.* **1893**, *273*, 214; **1894**, *27*, 3250; **1896**, *29*, 106; **1897**, *30*, 632; **1898**, *31*, 2241.
(387) Buchner, E.; Papandieck, A. *Liebigs Ann. Chem.* **1893**, *273*, 233.
(388) Buchner, E.; Lingg, F. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 402.
(389) Braren, W.; Buchner, E. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 684; 3553; **1901**, *34*, 982.
(390) Buchner, E.; Lehmann, L. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 35.
(391) Buchner, E.; Hediger, S. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3502.
(392) Buchner, E.; Feldmann, L. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3509.
(393) Buchner, E.; Geronimus, J. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3782.
(394) Buchner, E.; Scheda, K. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 931.
(395) Buchner, E.; Delbruck, K. *Liebegs Ann. Chem.* **1907**, *358*, 1.
(396) Buchner, E.; Schulze, P. *Liebegs Ann. Chem.* **1910**, *377*, 259.
(397) Buchner, E.; Weigand, W. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 759; 2108.
(398) Buchner, E.; Rehorst, K. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 2680.
(399) Buchner, E.; Schottenhammer, K. *Ber. Dtsch. Chem. Ges.* **1920**, *53*, 865.
(400) von E. Doering, W.; Laber, G.; Vonderwahl, R.; Chamberlain, N. F.; Williams, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 5448.
(401) Alder, K.; Muders, R.; Krane, W.; Wirtz, P. *Liebegs Ann. Chem.* **1959**, *627*, 59.
(402) Garst, M. E.; Roberts, V. A. *J. Org. Chem.* **1982**, *47*, 2188.
(403) Bartels-Keith, J. R.; Johnson, A. W.; Taylor, W. I. *J. Chem. Soc.* **1951**, 2352.
(404) Pfau, A. St.; Plattner, Pl. A. *Helv. Chim. Acta* **1939**, *22*, 202.
(405) McKervey, M. A.; Russell, D. N.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1985**, 491.
(406) Costantino, A.; Linstrumelle, G.; Julia, S. *Bull. Soc. Chim. Fr.* **1970**, 907.
(407) Ledon, H.; Cannic, G.; Linstrumelle, G.; Julia, S. *Tetrahedron Lett.* **1970**, 3971.
(408) Vogel, E.; Reel, H. *J. Am. Chem. Soc.* **1972**, *94*, 4388.
(409) Scott, L. T. *J. Chem. Soc., Chem. Commun.* **1973**, 882.
(410) Scott, L. T.; Minton, M. A. *J. Org. Chem.* **1977**, *42*, 3757.
(411) Scott, L. T.; Minton, M. A.; Kirms, M. A. *J. Am. Chem. Soc.* **1980**, *102*, 6311.

(412) McKervey, M. A.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1984**, 129.
(413) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1047.
(414) Saba, A.; De Lucchi, O. *Heterocycles* **1987**, *26*, 2339.
(415) Saba, A. *Tetrahedron Lett.* **1990**, *31*, 4657.
(416) Duddeck, H.; Ferguson, G.; Kaitner, B.; Kennedy, M.; McKervey, M. A.; Maguire, A. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1055.
(417) Kennedy, M.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1028.
(418) Kennedy, M.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2565.
(419) Iwata, C.; Yamada, M.; Shinoo, Y.; Kobayashi, K.; Okada, H. *Chem. Pharm. Bull. Tokyo* **1980**, *28*, 1932.
(420) Iwata, C.; Fusaka, T.; Fujiwara, K.; Tomita, K.; Yamada, M. *J. Chem. Soc., Chem. Commun.* **1981**, 463.
(421) Iwata, C.; Morie, T.; Maezaki, N.; Shimamura, H.; Tanaka, T.; Imanishi, T. *J. Chem. Soc., Chem. Commun.* **1984**, 930.
(422) Iwata, C.; Miyashita, K.; Imao, T.; Masuda, K.; Kondo, N.; Uchida, S. *Chem. Pharm. Bull. Tokyo* **1985**, *33*, 853.
(423) Iwata, C.; Morie, T.; Tanaka, T. *Chem. Pharm. Bull. Tokyo* **1985**, *33*, 944.
(424) Chattergee, J. N.; Sinha, A. K.; Bhakta, C. *Indian J. Chem., Sect. B* **1979**, *17*, 329.
(425) Duddeck, H.; Kennedy, M.; McKervey, M. A.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1988**, 1586.
(426) Taylor, E. C.; Davies, H. M. L. *Tetrahedron Lett.* **1983**, *24*, 5453.
(427) Wenkert, E.; Liu, S. *Synthesis* **1992**, 323.
(428) Sugihara, Y.; Yamamoto, H.; Mizoue, K.; Murata, I. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1247.
(429) Pusino, A.; Saba, A.; Rosnati, V. *Tetrahedron Lett.* **1986**, *42*, 4319.
(430) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q. *Tetrahedron Lett.* **1988**, *29*, 2639.
(431) Hrytsak, M.; Etkin, N.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 5679.
(432) Hrytsak, M.; Durst, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1150.
(433) Babu, S. D.; Hrytsak, M.; Durst, T. *Can. J. Chem.* **1989**, *67*, 1071.
(434) Etkin, N.; Babu, S. D.; Fooks, C. J.; Durst, T. *J. Org. Chem.* **1990**, *55*, 1093.
(435) Doyle, M. P.; Shanklin, M. S.; Pho, H. O.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017.
(436) Nakatani, K. *Tetrahedron Lett.* **1987**, *28*, 165.
(437) Novac, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1958**, *23*, 1126.
(438) Lucien, T.; Guenther, V. Ger. Offen. 2,652,356, 18 May, 1978; *Chem. Abstr.* **1978**, *89*, 110052p.
(439) Wenkert, E.; Guo, Ming.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem.* **1990**, *55*, 6203.
(440) Rokach, J.; Adams, J.; Perry, R. *Tetrahedron Lett.* **1983**, *24*, 5185.
(441) Adams, J.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 35.
(442) Adams, J.; Leblanc, Y.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 1227.
(443) Sheu, J.-H.; Yen, C.-F.; Huang, H.-C.; Hong, Y.-L. Vincent. *J. Org. Chem.* **1989**, *54*, 5126.
(444) McKervey, M. A.; O'Sullivan, M. B. Unpublished results.
(445) Wenkert, E.; Guo, Ming.; Pizzo, F.; Ramachandran, K. *Helv. Chim. Acta* **1987**, *70*, 1429.
(446) Wenkert, E.; Decorzant, R.; Näf, F. *Helv. Chim. Acta* **1989**, *72*, 756.
(447) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1986**, *51*, 5036.
(448) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299.
(449) Davies, H. M. L.; Clark, D. M.; Smith, T. K. *Tetrahedron Lett.* **1985**, *26*, 5659.
(450) Davies, H. M. L.; Smith, H. D.; Korkor, O. *Tetrahedron Lett.* **1987**, *28*, 1853.
(451) Nenitzescu, C. D.; Solomonica, E. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 1924.
(452) Gossauer, A. *Die Chemie der Pyrrole (The Chemistry of Pyrrole)*; Springer Verlag: Berlin, 1974; pp 126–127.
(453) Jones, R. A.; Bean, G. P. *The chemistry of pyrroles*; Academic Press: London, 1977; pp 269–270.
(454) Maryanoff, B. E. *J. Heterocycl. Chem.* **1977**, *14*, 177.
(455) Maryanoff, B. E. *J. Org. Chem.* **1979**, *44*, 4410.
(456) Maryanoff, B. E. *J. Org. Chem.* **1982**, *47*, 3000.
(457) Davies, H. M. L.; Young, W. B.; Smith, H. D. *Tetrahedron Lett.* **1989**, *30*, 4653.
(458) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696.
(459) Jefford, C. W.; Johncock, W. *Helv. Chim. Acta* **1983**, *66*, 2666.
(460) Jefford, C. W.; Zaslona, A. *Tetrahedron Lett.* **1985**, *26*, 6035.
(461) Jefford, C. W.; Kubota, T.; Zaslona, A. *Helv. Chim. Acta* **1986**, *69*, 2048.
(462) Jefford, C. W.; Tang, Q.; Zaslona, A. *Helv. Chim. Acta* **1989**, *72*, 1749.
(463) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513.
(464) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119.
(465) Gillespie, R. J.; Porter, A. E. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2624.
(466) Chan, L.; Matlin, S. A. *Tetrahedron Lett.* **1981**, *22*, 4025.
(467) Stoflor, H.; Skramstad, J.; Nordenson, S. *J. Chem. Soc., Chem. Commun.* **1984**, 208.
(468) Matsumoto, M.; Watanabe, N.; Kubayashi, H. *Heterocycles* **1987**, *26*, 1479.
(469) Yoshimoto, M.; Ishihara, S.; Nakayama, E.; Soma, N. *Tetrahedron Lett.* **1972**, 2923.
(470) Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878.
(471) Grieco, P. A.; Boxler, D.; Hiroi, K. *J. Org. Chem*, **1973**, *38*, 2572.
(472) Doyle, M. P.; Bagheri, V.; Harn, N. K. *Tetrahedron Lett.* **1988**, *29*, 5119.
(473) Giddings, P. J.; John, D. I.; Thomas, E. J. *Tetrahedron Lett.* **1980**, 359.
(474) Giddings, P. J.; John, D. I.; Thomas, E. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2757.
(475) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094.
(476) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917.
(477) Kido, F.; Sinha, S. C.; Abiko, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1989**, *30*, 1575.
(478) Kido, F.; Sinha, S. C.; Abiko, T.; Watanabe, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 418.
(479) Kido, F.; Sinha, S. C.; Abiko, T.; Watanabe, M.; Yoshikoshi, A. *Tetrahedron* **1990**, *46*, 4887.
(480) Kido, F.; Kazi, A. B.; Yoshikoshi, A. *Chem. Lett.* **1990**, 613.
(481) Kido, F.; Kawada, Y.; Kato, M.; Yoshikoshi, A. *Tetrahedron Lett.* **1991**, *32*, 6159.
(482) Kido, F.; Abiko, T.; Kazi, A. B.; Kato, M.; Yoshikoshi, A. *Heterocycles* **1991**, *32*, 1487.
(483) Kido, F.; Abiko, T.; Kato, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 229.
(484) A review on 2,3-Wittig sigmatropic rearrangements in organic synthesis: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.
(485) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060.
(486) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.
(487) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193.
(488) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385.
(489) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561.
(490) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511.
(491) Crow, W. D.; Gosney, I.; Ormiston, R. A. *J. Chem. Soc., Chem. Commun.* **1983**, 643.
(492) Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1988**, 685.
(493) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655.
(494) West, F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis* **1993**, 977.
(495) Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1324.
(496) Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 193.
(497) Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1986**, 651.
(498) Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 833.
(499) Kametani, T.; Nakayama, A.; Itoh, A.; Honda, T. *Heterocycles* **1983**, *20*, 2355.
(500) Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479.
(501) West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2857.
(502) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177.
(503) Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22.
(504) Rodgers, J. D.; Caldwell, G. W.; Gauthier, A. D. *Tetrahedron Lett.* **1992**, *33*, 3273.
(505) See section III.H.
(506) Zhou, Z.-L.; Huang, Y.-Z.; Shi, L.-L. *Tetrahedron* **1993**, *49*, 6821.
(507) Alonso, M. E.; Jano, P. *J. Heterocycl. Chem.* **1980**, *17*, 721.
(508) Alonso, M. E.; Chitty, A. W. *Tetrahedron Lett.* **1981**, *22*, 4181.
(509) Alonso, M. E.; García, M. d. C.; Chitty, A. W. *J. Org. Chem.* **1985**, *50*, 3445.
(510) L'Esperance, R. P.; Ford, T. M.; Jones, M., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 209.
(511) Huisgen, R.; de March, P. *J. Am. Chem. Soc.* **1982**, *104*, 4953.
(512) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q. *J. Org. Chem.* **1991**, *56*, 820.
(513) Bien, S.; Gillon, A. *Tetrahedron Lett.* **1974**, 3073.
(514) Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhang, Z. J. *J. Org. Chem.* **1991**, *56*, 3271.
(515) Fairfax, D. J.; Austin, D. J.; Xu, S. L.; Padwa, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2837.
(516) Spencer, T. A.; Villarica, R. M.; Storm, D. L.; Weaver, T. D.; Friary, R. J.; Posler, J.; Shafer, P. R. *J. Am. Chem. Soc.* **1967**, *89*, 5497.
(517) Ibata, T.; Toyoda, J.; Sawada, M.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1266.
(518) Ibata, T.; Toyoda, J. *J. Bull. Chem. Soc. Jpn.* **1986**, *59*, 2489 and references cited therein.
(519) Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 1491.
(520) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.

(521) Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.* **1993**, *58*, 7635.
(522) Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, *29*, 1677.
(523) Maier, M. E.; Schöffling, B. *Chem. Ber.* **1989**, *122*, 1081.
(524) Padwa, A.; Hertzog, D. L.; Chinn, R. L. *Tetrahedron Lett.* **1989**, *30*, 4077.
(525) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.
(526) Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett.* **1992**, *33*, 4731.
(527) Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1989**, *111*, 6451.
(528) Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1992**, *114*, 593.
(529) Rodgers, J. D.; Caldwell, G. W.; Gauthier, A. D. *Tetrahedron Lett.* **1992**, *33*, 3273.
(530) Takano, S.; Tomita, S.; Takahashi, M.; Ogasawara, K. *Synthesis* **1987**, 1116.
(531) Fang, F. G.; Prato, M.; Kim, G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3625.
(532) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 2747.
(533) Fang, F. G.; Maier, M. E.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 831.
(534) Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 2003.
(535) Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30.
(536) Padwa, A.; Kinder, F. R.; Zhi, L. *Synlett* **1991**, April, 287.
(537) See section III.E.3.
(538) Mara, A. M.; Singh, O.; Thomas, E. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2169.
(539) Williams, M. A.; Miller, M. J. *Tetrahedron Lett.* **1990**, *31*, 1807.
(540) Williams, M. A.; Hsiao, C.-N.; Miller, M. J. *J. Org. Chem.* **1991**, *56*, 2688.
(541) Favara, D.; Omodei-Sale, A.; Consonni, P.; Depaoli, A. *Tetrahedron Lett.* **1982**, *23*, 3105.
(542) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113.
(543) Crackett, P. H.; Sayer, P.; Stoodley, R. J.; Greengrass, C. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1235.
(544) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliott, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657 and references cited therein.
(545) Tuichi, I. J., Ed. *Oxazoles*; Wiley Interscience: New York, 1986.
(546) Connell, R.; Scavo, F.; Helquist, P.; Åkermark, B. *Tetrahedron Lett.* **1986**, *27*, 5559.
(547) Shi, G.; Xu, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 607.
(548) Connell, R.; Tebbe, M.; Helquist, P.; Åkermark, B. *Tetrahedron Lett.* **1991**, *32*, 17.
(549) Yoo, S.-K. *Tetrahedron Lett.* **1992**, *33*, 2159.
(550) Doyle, K. J.; Moody, C. J. *Tetrahedron Lett.* **1992**, *33*, 7769.
(551) Gangloff, A. R.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1992**, *57*, 4797.
(552) Connell, R.; Tebbe, M.; Gangloff, A. R.; Helquist, P.; Åkermark. B. *Tetrahedron* **1993**, *49*, 5445.
(553) Grasse, P. B.; Brauer, B. E.; Zupancic, J. J.; Kaufmann, K. J.; Schuster, G. B. *J. Am. Chem. Soc.* **1983**, *105*, 6833.
(554) Barcus, R. L.; Hadel, L. M.; Johnston, L. J.; Platz, M. S.; Savino, T. G.; Scaiano, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3928.
(555) Abdel-Wahab, A. A.; Doss, S. H.; Dürr, H.; Turro, N. J.; Gould, I. R. *J. Org. Chem.* **1987**, *52*, 429.
(556) Janulis, E. P., Jr.; Wilson, S. R.; Arduengo, A. J. *Tetrahedron Lett.* **1984**, *25*, 405.
(557) Wolff, L. *Liebigs Ann. Chem.* **1912**, *394*, 23.
(558) Bachmann, W. E.; Struve, W. S. *Org. React.*; John Wiley & Sons: New York, 1942; Vol. 1, p 38.
(559) Eistert, B. In *Newer Methods of Preparative Organic Chemistry*; Interscience: New York, 1948; Vol. 1, p 513.
(560) Weygand, F.; Bestmann, H. J. *Angew. Chem.* **1960**, *72*, 535.
(561) Weygand, F.; Bestmann, H. J. In *Newer Methods of Preparative Organic Chemistry*; Academic Press: New York, 1964; Vol. 3, p 451.
(562) Mustafa. *Adv. Photochem.* **1964**, *2*, 113.
(563) Rodina, L. L.; Korobitsyna, I. K. *Russ. Chem. Rev.* (*Engl. Transl.*) **1967**, *36*, 260.
(564) Eistert, B.; Regitz, M.; Heck, G.; Schwall, H. *Method. Org. Chem.* (*Houben-Weyl*) **1968**, *10* (4), 473.
(565) Fridman, A. L.; Ismagilova, G. S.; Zalesov, V. S.; Novikov, S. S. *Russ. Chem. Rev.* (*Engl. Transl.*) **1972**, *41*, 371.
(566) Meier, H.; Zeller, K.-P. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 32.
(567) Meier, H.; Zeller, K.-P. In *New Synthetic Methods*; Verlag Chemie: Weinheim/Bergstr., Germany, 1979; Vol. 4, Chapter 1.
(568) Gill, G. B. In *Comprehensive Organic Synthesis*; *Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 887.
(569) Maier, G.; Hoppe, M.; Lanz, K.; Reisenauer, H. P. *Tetrahedron Lett.* **1984**, *25*, 5645.
(570) Pacansky, J.; Johnson, D. *J. Electrochem. Soc.* **1977**, *124*, 865.
(571) Pacansky, J.; Coufal, H. *J. Am. Chem. Soc.* **1980**, *102*, 410.
(572) Hacker, N. P.; Turro, N. J. *Tetrahedron Lett.* **1982**, *23*, 1771.
(573) McMahon, R. J.; Chapman, O. L.; Hayes, R. A.; Hess, T. C.; Krimmer, H.-P. *J. Am. Chem. Soc.* **1985**, *107*, 7597.
(574) Chang, S.-J.; Shanker, B. K. R.; Shechter, H. *J. Org. Chem.* **1982**, *47*, 4226.
(575) Trost, B. M.; Kinson, P. L. *Tetrahedron Lett.* **1973**, 2675.
(576) Trost, B. M.; Kinson, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 2438.
(577) Trost, B. M.; Whitman, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 7421.
(578) Chapman, O. L.; Gano, J.; West, P. R.; Regitz, M.; Mass, G. *J. Am. Chem. Soc.* **1981**, *103*, 7033.
(579) Murata, S.; Yamamoto, T.; Tomioka, H. *J. Am. Chem. Soc.* **1993**, *115*, 4013.
(580) Ando, W.; Hagiwara, T.; Migita, T. *J. Am. Chem. Soc.* **1973**, *95*, 7518.
(581) Ando, W.; Sekiguchi, A.; Hagiwara, T.; Migita, T.; Chowdhry, V.; Westheimer, F. H.; Kammula, S. L.; Green, M.; Jones, M., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 6393.
(582) Ando, W.; Sekiguchi, A.; Sato, T. *J. Am. Chem. Soc.* **1981**, *103*, 5573.
(583) Ando, W.; Sekiguchi, A.; Sato, T. *J. Am. Chem. Soc.* **1982**, *104*, 6830.
(584) Sekiguchi, A.; Ando, W. *J. Am. Chem. Soc.* **1984**, *106*, 1486.
(585) Sekiguchi, A.; Ando, W. *Tetrahedron Lett.* **1985**, *26*, 2337.
(586) Mass, G.; Schneider, K.; Ando, W. *J. Chem. Soc., Chem. Commun.* **1988**, 72.
(587) Newman, M. S.; Beale, P. E., III. *J. Am. Chem. Soc.* **1950**, *72*, 5163.
(588) Ondetti, M. A.; Pluscec, J.; Weaver, E. R.; Williams, N.; Sabo, E. E.; Kocy, O. In *Chemistry and Biology of Peptides*; Meienhofer, J., Ed.; Ann Arbor Science Publishers: Ann Arbor, MI, 1972; p 525.
(589) Ondetti, M. A.; Engel, S. L. *J. Med. Chem.* **1975**, *18*, 761.
(590) Stachowiak, K.; Khosla, M. C.; Plucinska, K.; Khairallah, P. A.; Bumpus, F. M. *J. Med. Chem.* **1979**, *22*, 1128.
(591) Plucinska, K.; Liberek, B. *Tetrahedron* **1987**, *43*, 3509.
(592) Nishi, T.; Morisawa, Y. *Heterocycles* **1989**, *29*, 1835.
(593) Pellicciari, R.; Natalini, B.; Ursini, A. *Gazz. Chim. Ital.* **1986**, *116*, 607.
(594) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513.
(595) Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471.
(596) van Haard, P. M. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1975**, 803.
(597) Thijs, L.; Dommerholt, F. J.; Leemhuis, F. M. C.; Zwanenburg, B. *Tetrahedron Lett.* **1990**, *31*, 6589.
(598) Thijs, L.; Stokkingreef, E. H. M.; Lemmens, J. M.; Zwanenburg, B. *Tetrahedron* **1985**, *41*, 2949.
(599) Waanders, P. P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 2409.
(600) Thijs, L.; Egenberger, D. M.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 2153.
(601) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1495.
(602) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1499.
(603) Leemhuis, F. M. C.; Thijs, L.; Zwanenburg, B. *J. Org. Chem.* **1993**, *58*, 7170.
(604) Gallucci, R. R.; Jones, M., Jr. *J. Org. Chem.* **1985**, *50*, 4404.
(605) Hauptmann, S.; Hirschberg, K. *J. Prakt. Chem.* **1966**, *34*, 262.
(606) Dean, F. M.; Robertson, A. *J. Chem. Soc.* **1948**, 1674.
(607) Kuo, Y.-C.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 526, 2787.
(608) Georgian, V.; Boyer, S. K.; Edwards, B. *Heterocycles* **1977**, 1003.
(609) Georgian, V.; Boyer, S. K.; Edwards, B. *J. Org. Chem.* **1980**, *45*, 1688.
(610) Cossy, J.; Belotti, D. *Tetrahedron Lett.* **1988**, *29*, 6113.
(611) Cossy, J.; Belotti, D.; Leblanc, C. *J. Org. Chem.* **1993**, *58*, 2351.
(612) Wiberg, K. B.; Olli, L. K.; Golembeski, N.; Adams, R. D. *J. Am. Chem. Soc.* **1980**, *102*, 7467.
(613) Rao, V. B.; Wolff, S.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1984**, 293.
(614) Rao, V. B.; George, C. F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 5732.
(615) Otterbach, A.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 554.
(616) Eaton, P. E.; Jobe, P. G.; Reingold, I. D. *J. Am. Chem. Soc.* **1984**, *106*, 6437.
(617) Moore, H. W.; Arnold, M. J. *J. Org. Chem.* **1983**, *48*, 3365.
(618) Fessner, W. D.; Prinzbach, H.; Richs, G. *Tetrahedron Lett.* **1983**, *24*, 5857.
(619) Fessner, W. D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H. *J. Am. Chem. Soc.* **1987**, *109*, 4626.
(620) Rosati, R. L.; Kapili, L. V.; Morrissey, P.; Bordner, J.; Subramanian, E. *J. Am. Chem. Soc.* **1982**, *104*, 4262.
(621) Rao, Y. K.; Nagarajan, M. *J. Org. Chem.* **1989**, *54*, 5678.
(622) Corey, E. J.; Arnold, Z.; Hutton, J. *Tetrahedron Lett.* **1970**, 307.
(623) Dominh, T.; Strausz, O. P. *J. Am. Chem. Soc.* **1970**, *92*, 1766.
(624) Yates, P.; Fallis, A. G. *Tetrahedron Lett.* **1968**, 2493.
(625) Becker, D.; Nagler, M.; Birnbaum, D. *J. Am. Chem. Soc.* **1972**, *94*, 4771.
(626) Geisel, M.; Grob, C. A.; Santi, W.; Tschudi, W. *Helv. Chim. Acta* **1973**, *56*, 1046.
(627) Becker, D.; Harel, Z.; Birnbaum, D. *J. Chem. Soc., Chem. Commun.* **1975**, 377.
(628) Becker, D.; Birnbaum, D. *J. Org. Chem.* **1980**, *45*, 570.

(629) Stevens, R. V.; Bisacchi, G. S.; Goldsmish, L.; Strouse, C. E. *J. Org. Chem.* **1980**, *45*, 2708.
(630) Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001.
(631) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.
(632) Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527.
(633) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51.
(634) Haddadin, M.; Hassner, A. *J. Org. Chem.* **1973**, *38*, 2650.
(635) Pacansky, J.; Chang, J. S.; Brown, D. W.; Schwarz, W. *J. Org. Chem.* **1982**, *47*, 2233.
(636) Blades, C. E.; Wilds, A. L. *J. Org. Chem.* **1956**, *21*, 1013.
(637) Wilds, A. L.; Berghe, J. V. D.; Winestock, C. H.; von Treba, R. L.; Woolsey, N. F. *J. Am. Chem. Soc.* **1962**, *84*, 1503.
(638) Wilds, A. L.; Woolsey, N. F.; Berghe, J. V. D.; Winestock, C. H. *Tetrahedron Lett.* **1965**, 4841.
(639) Wilds, A. L.; von Trebra, R. L.; Woolsey, N. F. *J. Org. Chem.* **1969**, *34*, 2401.
(640) Lokensgard, J. P.; O'Dea, J.; Hill, E. A. *J. Org. Chem.* **1974**, *39*, 3355.
(641) Zimmerman, H. E.; Little, R. D. *J. Am. Chem. Soc.* **1974**, *96*, 4623.
(642) Smith, A. B., III. *J. Chem. Soc., Chem. Commun.* **1974**, 695.
(643) Smith, A. B., III; Toder, B. H.; Branca, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 7456.
(644) Branca, S. J.; Lock, R.; Smith, A. B., III. *J. Org. Chem.* **1977**, *42*, 3165.
(645) Smith, A. B., III; Toder, B. H.; Branca, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 3995.
(646) Smith, A. B., III; Toder, B. H.; Richmond, R. E.; Branca, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 4001.
(647) Ceccherelli, P.; Curini, M.; Porter, B.; Wenkert, E. *J. Org. Chem.* **1984**, *49*, 2052.
(648) Saha, B.; Bhattacharjee, G.; Ghatak, U. R. *Tetrahedron Lett.* **1986**, *27*, 3913.
(649) Saha, B.; Bhattacharjee, G.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 939.
(650) Ray, C.; Saha, B.; Ghatak, U. R. *Synth. Commun.* **1991**, *21*, 1223.
(651) Miller, R. D.; Theis, W.; Heilig, G.; Kirchmeyer, S. *J. Org. Chem.* **1991**, *56*, 1453.
(652) Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I. *Tetrahedron Lett.* **1994**, *35*, 605.
(653) Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4163.
(654) Hudlicky, T.; Olivo, H. H.; Natchus, M. G.; Umpierrez, E. F.; Pondolfi, E.; Volonterio, C. *J. Org. Chem.* **1990**, *55*, 4767.
(655) Frazen, V. *Liebegs Ann. Chem.* **1957**, *602*, 199.
(656) Schöllkopf, U.; Frasnelli, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 301.
(657) Wenkert, E.; McPherson, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 8084.
(658) Wenkert, E.; McPherson, C. A. *Synth. Commun.* **1972**, *2*, 331.
(659) Pellicciari, R.; Natalini, B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1823.
(660) Pellicciari, R.; Castagnino, E.; Corsano, S. *J. Chem. Res.* **1979** (S), 76.
(661) Pellicciari, R.; Natalini, B.; Taddei, M.; Ricci, A.; Bistocchi, G. A.; De Meo, G. *J. Chem. Res.* **1979** (S), 142.
(662) Pellicciari, R.; Castagnino, E.; Fringuelli, R.; Corsano, S. *Tetrahedron Lett.* **1979**, 481.
(663) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 595.
(664) Pellicciari, R.; Fringuelli, R.; Sisani, E. *Tetrahedron Lett.* **1980**, 4039.
(665) Pellicciari, R.; Fringuelli, R.; Curini, M.; Sisani, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2566.
(666) Pellicciari, R.; Natalini, B.; Cecchetti, S.; Fringuelli, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 493.
(667) Pellicciari, R.; Natalini, B.; Fringuelli, R. *Steroids* **1987**, *49*, 433.
(668) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187.
(669) Nagao, K.; Chiba, M.; Kim, S.-W. *Synthesis* **1983**, 197.
(670) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1987**, *28*, 5351.
(671) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.
(672) Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297.
(673) Rychnovsky, S. D.; Mickus, D. E. *J. Org. Chem.* **1992**, *57*, 2732.
(674) Hecker, S. J.; Werner, K. M. *J. Org. Chem.* **1993**, *58*, 1762.
(675) Nomura, K.; Iida, T.; Hori, K.; Yoshii, E. *J. Org. Chem.* **1994**, *59*, 488.
(676) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1990**, *31*, 4991.
(677) Liao, Y.; Huang, Y.-Z. *Tetrahedron Lett.* **1990**, *31*, 5897.
(678) Wolfgang, A.; Wang, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1641.
(679) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459.
(680) Liu, H. J.; Majumdar, S. P. *Synth. Commun.* **1975**, *5*, 125.
(681) Marchand, A. P.; Reddy, S. P.; Rajapaksa, D.; Ren, C.-T.; Watson, W. H.; Kashyap, R. P. *J. Org. Chem.* **1990**, *55*, 3493.
(682) Greene, A. E.; Luche, M.-J.; Serra, A. A. *J. Org. Chem.* **1985**, *50*, 3957.
(683) Ghosh, A.; Biswas, S.; Venkateswaran, R. V. *J. Chem. Soc., Chem. Commun.* **1988**, 1421.
(684) Dave, V.; Warnhoff, E. W. *J. Org. Chem.* **1983**, *48*, 2590.
(685) Doyle, M. P.; Trudell, M. L.; Terpstra, J. W. *J. Org. Chem.* **1983**, *48*, 5146.
(686) For a comprehensive review on the cycloaddition of diazoalkanes, see: Regitz, M.; Heydt, H. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons, Inc.: New York, 1984; Vol. 1, p 393.
(687) Sheehan, J. C.; Chaeko, E.; Lo, Y. S.; Ponzi, D. R.; Sato, E. *J. Org. Chem.* **1978**, *43*, 4856.
(668) Noels, A. F.; Braham, J. N.; Hubert, A. J.; Teyssié, Ph. *J. Org. Chem.* **1977**, *42*, 1527; *Tetrahedron* **1978**, *34*, 3495.
(689) Eberhard, P.; Huisgen, R. *Tetrahedron Lett.* **1971**, 4337.
(690) Schöllkopf, U.; Hoppe, D.; Rieber, N.; Jacobi, V. *Liebigs Ann. Chem.* **1969**, *730*, 1.
(691) Ghandour, N. El.; Soulier, J. *C. R. Acad. Sci. Paris* **1971**, *272*, 243.
(692) Huisgen, R.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 330.
(693) Parham, W. E.; Bleasdale, J. L. *J. Am. Chem. Soc.* **1950**, *72*, 3843.
(694) Aue, D. H.; Helwig, G. S. *Tetrahedron Lett.* **1974**, 721.
(695) Aue, D. H.; Lorens, R. B.; Helwig, G. S. *J. Org. Chem.* **1979**, *44*, 1202.
(696) Franck-Neumann, M.; Buchecker, C. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 240.
(697) Cobb, R. L.; Mahan, J. E. *J. Org. Chem.* **1977**, *42*, 2597.
(698) Wulfman, D. S.; McDaniel, R. S., Jr. *Tetrahedron Lett.* **1975**, 4523.
(699) Hampel, W. *J. Prakt. Chem.* **1969**, *311*, 1058.
(700) Huttel, R. *Ber. Dtsch. Chem. Ges.* **1941**, *74*, 1680.
(701) Ried, W.; Omran, J. *Liebigs Ann. Chem.* **1963**, *666*, 144.
(702) Franck-Neumann, M.; Buchecker, C. *Tetrahedron Lett.* **1972**, 937; **1976**, 2069.
(703) Korobizina, I. K.; Bulusheva, V. V.; Rodina, L. L. *Khim. Heterocycl. Comp.* **1978**, *5*, 579.
(704) Huisgen, R.; Reissig, H.-U.; Huber, H. *J. Am. Chem. Soc.* **1979**, *101*, 3647.
(705) Maas, G.; Regitz, M.; Moll, U.; Rahm, R.; Krebs, F.; Hector, R.; Stang, P. J.; Crittell, C. M.; Williamson, B. L. *Tetrahedron* **1992**, *48*, 3527.
(706) See sections III.C and III.D.
(707) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778.
(708) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.
(709) Wenkert, E. *Heterocycles* **1980**, *14*, 1703.
(710) Wenkert, E.; Halls, T. D. J.; Kwart, L. D.; Magnusson, G.; Showalter, H. D. H. *Tetrahedron* **1981**, *37*, 4017.
(711) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Sanchez, E. L. *J. Am. Chem. Soc.* **1983**, *105*, 2021.
(712) Wenkert, E.; Ananthanarayan, T. P.; Ferreira, V. F.; Hoffmann, M. G.; Kim, H. S. *J. Org. Chem.* **1990**, *55*, 4975.
(713) Alonso, M. E.; Morales, A.; Chitty, A. W. *J. Org. Chem.* **1982**, *47*, 3747.
(714) Alonso, M. E.; Jano, P.; Hernandez, M. I.; Greemberg, R. S.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 3047.
(715) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorrow, R. L. *Organometallics* **1984**, *3*, 53.
(716) Pirrung, M. C.; Zhang, J.; McPhail, A. T. *J. Org. Chem.* **1991**, *56*, 6269.
(717) Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21.
(718) Davies, H. M. L.; Romines, K. R. *Tetrahedron* **1988**, *44*, 3343.
(719) Smith, A. B., III; Dieter, R. K. *Tetrahedron* **1981**, *37*, 2407.
(720) Satyanarayana, G. O. S. V.; Roy, S. C.; Ghatak, U. R. *J. Org. Chem.* **1982**, *47*, 5353.
(721) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765.
(722) Mehta, G.; Karra, S. R. *J. Chem. Soc., Chem. Commun.* **1991**, 1367.
(723) Hook, J. M.; Mander, L. N.; Urech, R. *J. Org. Chem.* **1984**, *49*, 3250.
(724) Mander, L. N.; Palmer, L. T. *Aust. J. Chem.* **1979**, *32*, 823.
(725) Smith, A. B., III; Dieter, R. K. *J. Am. Chem. Soc.* **1981**, *103*, 2009; 2017.
(726) Hudlicky, T.; Kutchan, T. *Tetrahedron Lett.* **1980**, *21*, 691.
(727) Cook, J. W.; Schoental, R. *J. Chem. Soc.* **1945**, 288.
(728) Newman, M. S.; Eglinton, G.; Grotta, H. M. *J. Am. Chem. Soc.* **1953**, *75*, 349.
(729) Blair, I. A.; Ellis, A.; Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1978**, *31*, 405.
(730) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626.
(731) Mander, L. N.; Pyne, S. G. *J. Am. Chem. Soc.* **1979**, *101*, 3373.
(732) Maity, S. K.; Mukherjee, D. *Tetrahedron* **1984**, *40*, 757.
(733) Nicolaou, K. C.; Zipkin, R. E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 785.
(734) Rishton, G. M.; Schwartz, M. A. *Tetrahedron Lett.* **1988**, *29*, 2643.
(735) Franceschetti, L.; Garzon-Aburbeh, A.; Mahmoud, M. R.; Natalini, B.; Pellicciari, R. *Tetrahedron Lett.* **1993**, *34*, 3185.
(736) Doyle, M. P.; Oppenhuizen, M.; Elliott, R. C.; Boelkins, M. R. *Tetrahedron Lett.* **1978**, *26*, 2247.
(737) Ibata, T.; Sato, R. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3597.
(738) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliott, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657.
(739) Ibata, T.; Isogami, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 618.
(740) Vedejs, E.; Piotrowski, D. W. *J. Org. Chem.* **1993**, *58*, 1341.

(741) Curci, R.; Di Furia, F.; Marcuzzi, F. *J. Org. Chem.* **1971**, *36*, 3774.
(742) Curci, R.; Di Furia, F.; Ciabattoni, J.; Concannon, P. W. *J. Org. Chem.* **1974**, *39*, 3295.
(743) Bailey, P. S.; Reader, A. M.; Kolsaker, P.; White, H. M.; Barborak, J. C. *J. Org. Chem.* **1965**, *30*, 3042.
(744) Ursini, A.; Pellicciari, R.; Tamburini, B.; Carlesso, R.; Gaviraghi, G. *Synthesis* **1992**, 363.
(745) Murray, R. W.; Jeyaraman, J. *J. Org. Chem.* **1985**, *50*, 2847.
(746) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.
(747) Ihmels, H.; Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1991**, *32*, 6215.
(748) Darkins, P.; McCarthy, N.; McKervey, M. A.; Ye, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1222.
(749) Darkins, P.; McCarthy, N.; McKervey, M. A.; O'Donnell, K.; Ye, T.; Walker, B. *Tetrahedron: Asymmetry* **1994**, *5*, 195.
(750) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1975**, 1707.
(751) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1977**, 2599.
(752) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1982**, *23*, 685.
(753) Aratani, T. *Pure Appl. Chem.* **1985**, 1839.
(754) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1005.
(755) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A.; Keller, W.; Kratky, Ch. *Helv. Chim. Acta* **1988**, *71*, 1541.
(756) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553.
(757) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.
(758) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.
(759) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.
(760) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.
(761) Lowenthal, R. W.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.
(762) Evans, D. A.; Woerpel, K. A.; Himman, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.
(763) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430.
(764) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett.* **1990**, *31*, 6613.
(765) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423.
(766) Protopopova, M. N.; Doyle, M. P.; Müller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755.
(767) Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L. *Tetrahedron Lett.* **1992**, *33*, 7819.
(768) Doyle, M. P.; Eismont, M. Y.; Berbreiter, D. E.; Gray, H. N. *J. Org. Chem.* **1992**, *57*, 6103.
(769) Ito, K.; Katsuki, T. *Tetrahedron Lett.* **1993**, *34*, 2661.
(770) Matlin, S. A.; Lough, W. J.; Chan, L.; Abram, D. M. H.; Zhou, Z. *J. Chem. Soc., Chem. Commun.* **1984**, 1038.
(771) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 361.
(772) Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243.
(773) Martin, S. F.; Oalmann, C. J.; Liras, S. *Tetrahedron Lett.* **1992**, *33*, 6727.
(774) Dauben, W. G.; Hendricks, R. T.; Luzzio, M. J.; Ng, H. P. *Tetrahedron Lett.* **1990**, *31*, 6969.
(775) Koskinen, A. M. P.; Hassila, H. *J. Org. Chem.* **1993**, *58*, 4479.
(776) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173; **1993**, *34*, 5109.
(777) Roos, G. H. P.; McKervey, M. A. *Synth. Commun.* **1992**, *22*, 1751.
(778) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874.
(779) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397.
(780) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983.
(781) Pirrung, M. C.; Zhang, J. *Tetrahedron Lett.* **1992**, *33*, 5987.
(782) Kireger, P. E.; Landgrebe, J. A. *J. Org. Chem.* **1978**, *43*, 4447.
(783) Davies, H. M. L.; Cantrell, W. R., Jr. *Tetrahedron Lett.* **1991**, *32*, 6509.
(784) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468.
(785) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28.
(786) Kurth, M. J.; Tahir, S. H.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 2286.