

1.01

Aziridines and Azirines: Monocyclic

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1.01.1 Introduction – Monocyclic Aziridines

The aziridine functionality, occasionally referred to as an azaethylene or ethylenimine unit, is a valuable intermediate in organic chemistry <1994AGE599, B-2006M11>. In terms of its synthetic behavior, its utility comes from selective ring-opening reactions <2004T2701, 2000S1347>. Transformations of this stable but strain-loaded (27 kcal mol⁻¹) three-membered ring allows for regio- and stereoselective installation of a wide range of functional groups in a 1,2-relationship to nitrogen. Cycloadditions of N-protected aziridines with various substrates occur to furnish complex heterocyclic systems. Aziridines are useful intermediates in natural product synthesis as in the case of the kainoids, (–)-mesembrine, (–)-platynesine, sphingosines, actinomycin, (±)-epicapreomycin, and feldamycin. The aziridine functionality is also present in a small number of naturally occurring molecules. The biological properties of aziridine-containing compounds such as azinomycins, mitomycins, FR-900482, ficellomycin, miraziridine, maduropeptin, and azicemicins are of significant interest. The antibiotic and antitumor properties of several of these compounds are well known. It is impossible to comprehensively cover all of the numerous investigations dealing with monocyclic aziridines since 1995 in a chapter of this length. Consequently, only representative examples of aziridine reactivity and synthesis are highlighted. For further details, the reader is encouraged to consult the many review articles that have been published since the earlier CHEC-II(1996) review <1996CHEC-II(1A)1>.

1.01.2 Theoretical Methods

A number of the theoretical issues dealing with monocyclic aziridines were discussed in CHEC-II(1996) and CHEC(1984) <1996CHEC-II(1A)1, 1984CHEC(7)47>.

1.01.3 Experimental Structural Methods

Spectroscopic studies using X-ray, nuclear magnetic resonance (NMR), electron diffraction, microwave, and photoelectron methods have been used to determine the geometry and configurational stability of the monocyclic aziridine nitrogen atom <1996CHEC-II(1A)1>. These studies indicate that the barrier to pyramidal inversion of the nitrogen atom of aziridines is considerably higher than in acyclic amines, making it the dominant stereodynamic process for these heterocycles. The barrier for pyramidal inversion in aziridine itself is $19.5 \text{ kcal mol}^{-1}$. Aziridines are less basic than acyclic amines due to the increased s character of the nitrogen lone pair. The conjugate acid of aziridine has a pK_a value of 7.98, compared to a typical pK_a value of ca. 11 for the conjugate acid of an acyclic secondary amine <1996CHEC-II(1A)1>. The structural properties of aziridines, including spectroscopic features (NMR, mass spectrometry (MS), ultraviolet (UV), and infrared (IR)) were discussed in detail in CHEC-II(1996) and CHEC(1984) <1996CHEC-II(1A)1, 1984CHEC(7)47>.

1.01.4 Thermodynamic Aspects

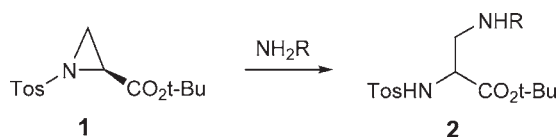
The ring-strain energy of aziridine is similar to that of cyclopropane (27 kcal mol^{-1}), reflecting high bond-angle strain <1996CHEC-II(1A)1>. Many of the reactions that aziridines undergo involve a nucleophilic opening of the three-membered ring and thus a release of strain energy. The lowering of the energy of activation in these strain-releasing reactions has been suggested not to be solely due to the release of strain. For further theoretical discussion of this issue, the reader is directed to Chapter 1.02.

1.01.5 Reactivity of Monocyclic Aziridines

Aziridines have attracted considerable attention as starting materials in numerous applications, and many papers and review articles dealing with the synthesis of aziridines <1994AGE599> as well as their use in synthetic applications have been published since 1995 <2004T2701, 2000S1347, 2002CSR247, 2004PRC220>. In ring-opening reactions, it is common either to perform the reactions employing Lewis acid catalysis <1996H(43)2473, 2001J(P1)1314> or to activate the aziridine by substitution on the nitrogen <2004T2701>, thus increasing the ability of the nitrogen atom to function as a leaving group. It has been shown by Stamm <1999JPR319> that in order to carry out the reaction on nonactivated aziridines and in the absence of a catalyst, it is imperative that the nucleophile supplies a proton in order to create a neutral leaving group. Aziridines are well-known carbon electrophiles capable of undergoing reactions with various nucleophiles; this ability of undergoing regioselective ring-opening reactions contributes largely to their synthetic value. They are useful precursors for the synthesis of many biologically interesting molecules such as amino acids <1994AGE599, 2000S1347>, heterocycles <1992T6079>, and alkaloids <1990JOC46837>. As a consequence, many methods have been reported for the regioselective ring opening of aziridines with nucleophiles such as organometallic reagents <1993SL676>, silyl nucleophiles <2000JOC1344>, Wittig reagents <1993TL7421>, amines <1994TL7395>, halides <1998TL2385>, and alkenes <2000AGE4615>.

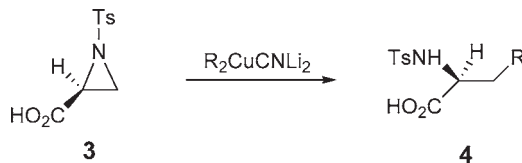
1.01.5.1 Nucleophilic Ring-Opening Reactions

Similar to the epoxides, the most frequently encountered synthetic transformation for aziridines is nucleophilic ring opening, whereby heteroatom- and carbon-based nucleophiles are comparably important. The marked reactivity of aziridines toward ring opening and expansion relates to their extremely strained ring structures. There is, of course, no paucity of examples using heteroatom-based nucleophiles. For example, aziridine-2-*t*-butyl carboxylate **1** reacts with primary amines to give the dialkylated diamino-propionic acid derivatives **2**, which are interesting precursors for the synthesis of cyclosporin analogs. Attack occurs overwhelmingly at the least-hindered β -carbon (Scheme 1) <1995TL4955>.



Scheme 1

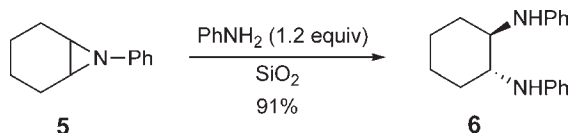
As an example of a ring opening using a carbon-based nucleophile, aziridine-2-carboxylate **3** can be ring-opened with higher-order cuprates to give the protected amino acid derivatives **4**, corresponding to attack at the less-substituted aziridine carbon (Scheme 2) <1995TL151>.



Scheme 2

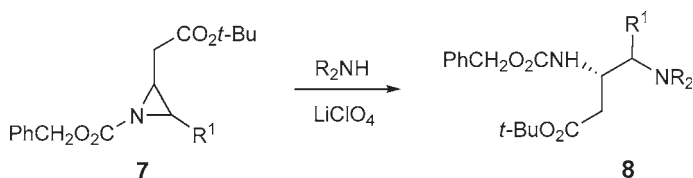
1.01.5.1.1 Ring-opening reactions by amines

Amines are probably the most frequently encountered nucleophiles in this type of reaction. A recent report described the ring opening of aziridines using silica gel under solvent-free conditions. Thus, aziridine **5** was combined with a slight excess of aniline in the presence of silica gel to give the diaminocyclohexane **6** in 91% yield (Scheme 3) <2002TL3975>.



Scheme 3

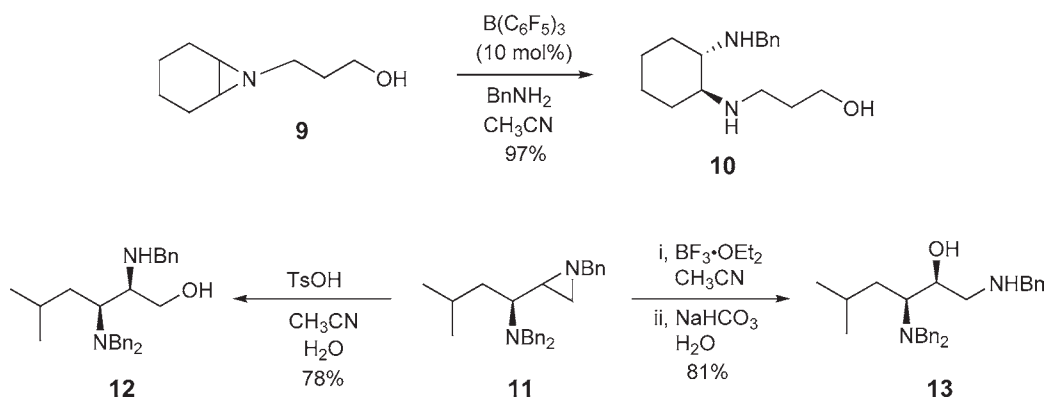
Benzylloxycarbamate-protected aziridines such as **7**, although less activated than tosylaziridines, are sufficiently reactive to be easily and regioselectively opened by N-nucleophiles producing 1,2-diamino compounds **8** suitably protected for further transformations. The opening of aziridine **7** with the methyl ester of H-Lys(BOC)-OMe provided the methyleneaminopseudopeptide with a good yield and excellent regioselectivity, thereby affording a new route to this kind of compound (BOC = *t*-butoxycarbonyl, Scheme 4) <2006T3509>.



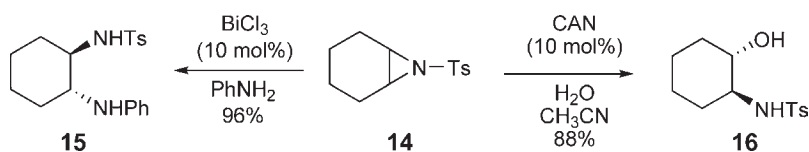
Scheme 4

Nonactivated aziridines can be prompted to undergo ring-opening reactions under the influence of tris(pentafluorophenyl)borane as a catalyst, as shown by the reaction of hydroxypropylaziridine **9** with benzylamine to give the diaminoalcohol **10**. Mechanistic studies suggest the intermediacy of $[(C_6F_5)_3B(H_2O)] \cdot H_2O$ formed *in situ* as a Brønsted acid catalyst <2003JOC5160>. In the case of amino aziridines **11**, the regioselectivity of the nucleophilic attack can be controlled by the reaction conditions. Thus, the use of a protic acid, such as *p*-toluenesulfonic acid (*p*-TsOH), leads to the attack of water at the less-hindered C-3 position, whereas the aprotic Lewis acid catalyst boron trifluoride etherate leads to a C-2 mode of ring opening. Anchimeric assistance from the amino substituent has been invoked as a rationale for the regiochemical changeover (Scheme 5) <2003JOC6407>.

Similarly, the *N*-tosylaziridine **14** is smoothly cleaved by aniline in the presence of bismuth trichloride acting as the Lewis acid to give the diamine **15** <2003SC547>. Ceric ammonium nitrate (CAN) catalyzes the ring opening of **14** with water to afford the amino alcohol **16** in 88% yield (Scheme 6) <2003CL82>.

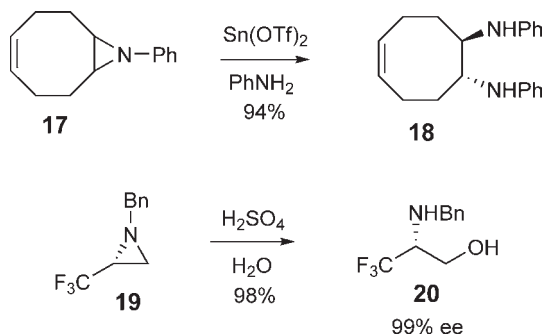


Scheme 5



Scheme 6

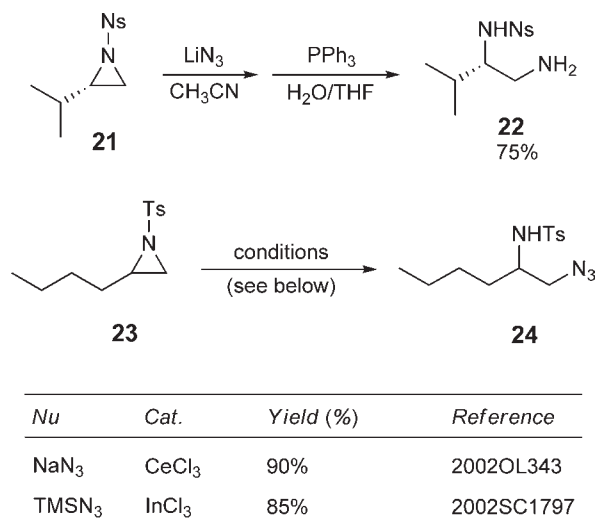
The bicyclic aziridine **17** was found to undergo smooth ring cleavage by aniline in the presence of $\text{Sn}(\text{OTf})_2$ to give the corresponding 1,2-diamino compound **18** <1999JOC2537>. The chiral trifluoromethyl aziridine of type **19** can be ring-opened even with relatively weak nucleophiles (in this example, water) to give optically active amines **20** in good yields with excellent retention of configuration (Scheme 7) <1999JOC7323>.



Scheme 7

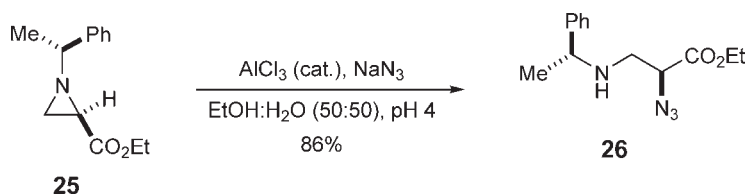
1.01.5.1.2 Ring-opening reactions by azides

For the simplest amine nucleophile, the azide anion is often used in preference to ammonia, since the course of the reaction is more controllable. For example, the valinol-derived nosyl aziridine **21** was converted to the primary amine **22** by treatment with lithium azide followed by triphenylphosphine <2002OL949>. Sometimes azidolysis is sluggish and accompanied by unwanted isomerization reactions, so catalytic methods continue to be of interest. Along these lines, cerium(III) chloride promotes the regioselective ring opening of unsymmetrical tosyl aziridines at the terminal carbon, as exemplified by the conversion of alkyl aziridine **23** to azido amine **24** in 90% yield <2002OL343>. Indium trichloride catalyzes the analogous reaction using the somewhat milder reagent trimethylsilyl azide (TMSN_3) (Scheme 8) <2002SC1797>.



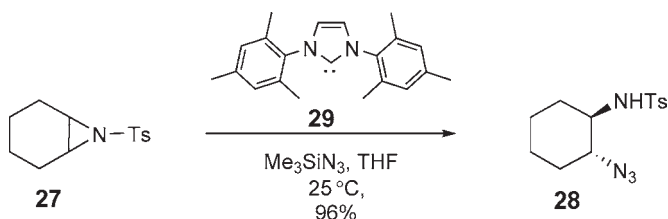
Scheme 8

The use of AlCl₃ to catalyze the ring opening of aziridine **25** by NaN₃ has proven surprisingly effective [\[2005TL4407\]](#). The authors report complete inversion at the carbon bearing the azide to give the ring-opened azide **26**. Given the acidic reaction conditions, it is also interesting to note that the reaction was carried out on a several hundred gram scale without any difficulties ([Scheme 9](#)).



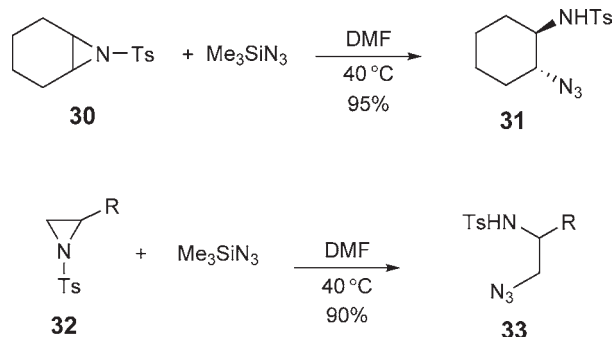
Scheme 9

Small organic molecules such as phosphines, amines, and nitriles have been utilized as catalysts to effect ring-opening reactions of aziridines. Recently, Wu *et al.* described the use of an N-heterocyclic carbene as an efficient catalyst in the ring-opening reaction of aziridines with trimethylsilyl (TMS) azide under mild reaction conditions. The advantages of this method include: (1) employing easily available N-heterocyclic carbene as the catalyst, (2) experimental ease of operation, (3) mild conditions, and (4) good substrate generality. A typical example involves the conversion of aziridine **27** into **28** at room temperature and in 96% yield using the N-heterocyclic carbene **29** ([Scheme 10](#)) [\[2006TL4813\]](#).



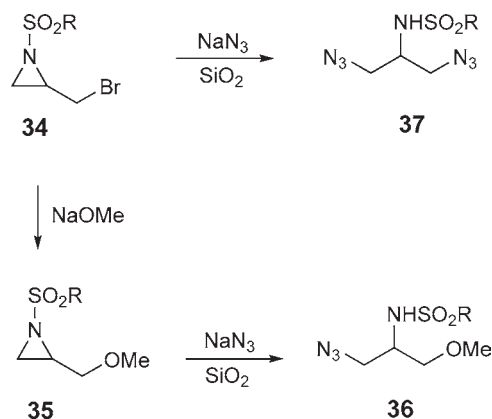
Scheme 10

Many ring-opening reactions of aziridines make use of silylated nucleophiles [<2000JOC1344>](#). The reactions of aziridines can be carried out with silylated nucleophiles and without any catalysts under neutral conditions and proceed with high efficiency to furnish a variety of 1,2-bifunctional compounds such as **31** and **33** (Scheme 11) [<2005EJO4769>](#).



Scheme 11

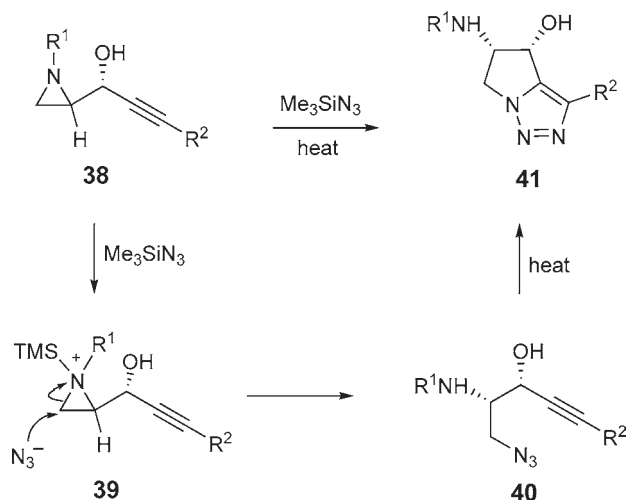
The versatility of 2-(bromomethyl)-1-sulfonyl-aziridines **34** as substrates in organic synthesis was demonstrated by allowing these substrates to react with water in the presence of silica gel to give 1,3-heteroatom-substituted 2-aminopropane derivatives. Monoazido **36** and diazidopropane derivatives **37** were prepared using sodium azide in water, as well as 1,3-diaryloxypropane sulfonamides using different potassium phenoxides as reagents. Since many methods are available for N-detosylation of sulfonamides, the methodology offers ready access to the synthesis of the corresponding amines (Scheme 12) [<2005T8746>](#).



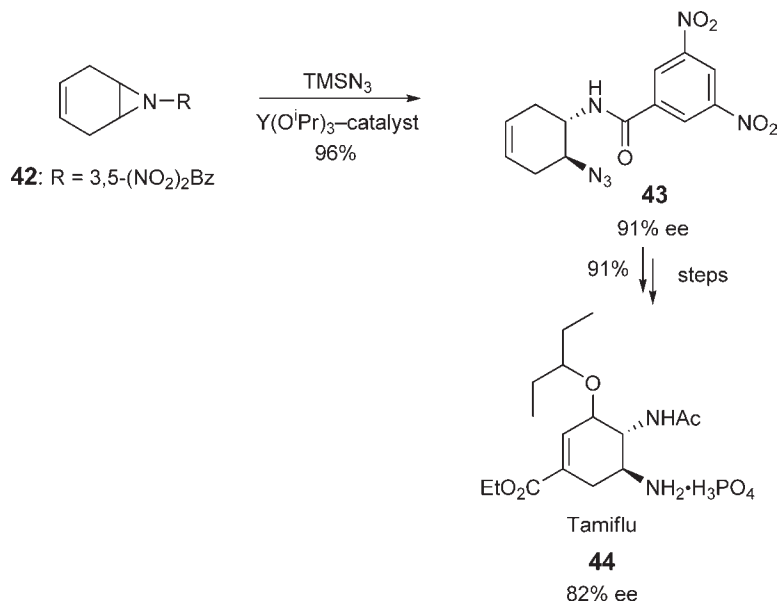
Scheme 12

Treatment of 1-aziridine-2-yl-propargylic alcohols **38** with trimethylsilyl azide followed by aqueous workup afforded azido amino alcohols of type **40**. The reaction was suggested to proceed via an activated aziridinium ion species **39** which is produced by the silylation of the aziridine nitrogen. A subsequent regioselective ring-opening reaction occurred by cleavage of the C(3)–N bond by the azide anion that was liberated from the trimethylazide reagents. Further heating of the azidoamino alcohol **40** gave the corresponding bicyclic triazoles **41** by an intramolecular 1,3-dipolar cycloaddition between the azide group and the adjacent alkyne (Scheme 13) [<2005SL2187>](#).

Recently, an asymmetric synthesis of Tamiflu **44**, an orally active anti-influenza drug, was carried out by Shibasaki and co-workers utilizing a general catalytic enantioselective ring opening of *meso*-aziridine **42** with TMSN₃ in the presence of a Lewis-acidic yttrium catalyst [<2006JA6312>](#). The enantiomerically enriched amidoazide **43** was obtained in 96% yield and 91% ee. This compound was subsequently converted to Tamiflu **44** using standard synthetic manipulations (Scheme 14).

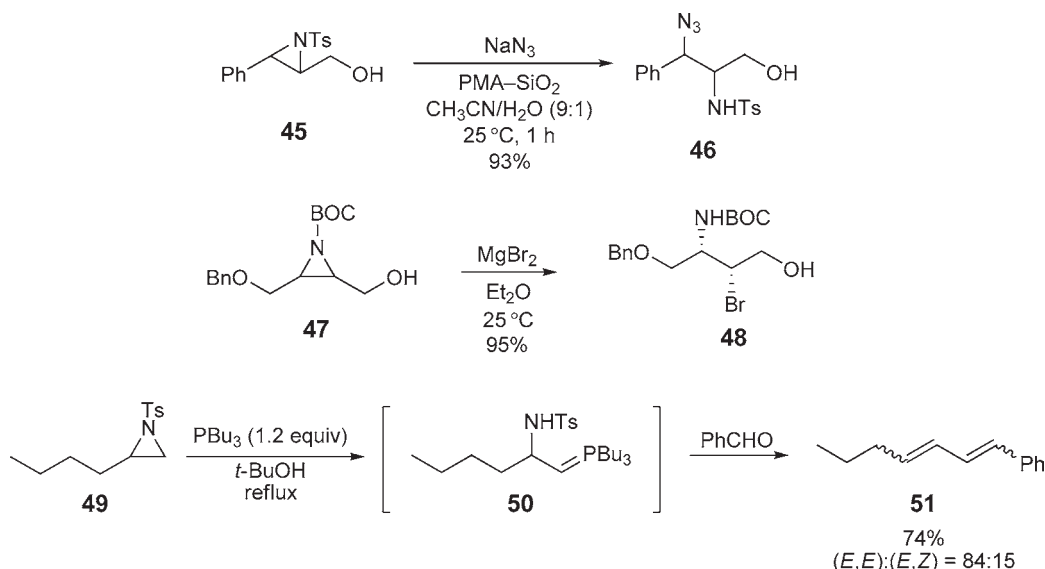


Scheme 13



Scheme 14

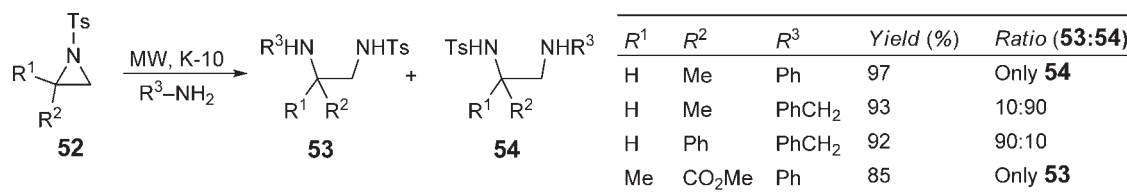
Silica-supported phosphomolybdic acid (PMA-SiO_2) has been found to be effective in promoting the ring cleavage of tosyl aziridines by a variety of nucleophiles. Thus, the azide anion preferentially attacks the benzylic position to provide the azidoaminoalcohol **46**, and the regioselectivity can be rationalized in terms of partial positive charge stabilization [\[2004SL1719\]](#). A different type of selectivity is observed in the magnesium bromide-mediated opening of hydroxymethyl aziridines. In these systems, the delivery of the nucleophile (i.e., bromide) is under chelation control, as demonstrated in the conversion of aziridine **47** to the bromo aminoalcohol **48** [\[2004SC85\]](#). In the absence of Lewis acid catalysts, heteroatomic nucleophiles tend to attack at the sterically least hindered center. Such is the case when the butylaziridine **49** is treated with tributylphosphine, a strong nonbasic nucleophile which smoothly opens the heterocyclic ring. The initial adduct undergoes rapid proton transfer to provide a betaine (**50**) which can serve as a Wittig reagent. The addition of benzaldehyde leads to an olefination/elimination sequence to afford the diene **51** as a mixture of (*E/Z*)-isomers (Scheme 15) [\[2004JOC689\]](#).



Scheme 15

1.01.5.1.3 Ring-opening reactions by other N-nucleophiles

1,2-Diamines are another highly useful class of molecules with potent biological activity and are used as synthetic intermediates and as metal ligands. The ring-opening reactions of aziridines with amines and azide provides a facile route for the synthesis of 1,2-diamines. The use of microwave-induced Montmorillonite K-10 clay-catalyzed opening of tosyl aziridines provides an environmentally friendly route to 1,2-diamines **53** and **54** <2005TL2083>. In general, these ring-opening reactions are regioselective with both arylamines and aliphatic amines participating equally well. Particularly interesting is the opening of aziridine **52** ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{CO}_2\text{Me}$) at the most-substituted carbon to provide diamino ester **53** (Scheme 16).



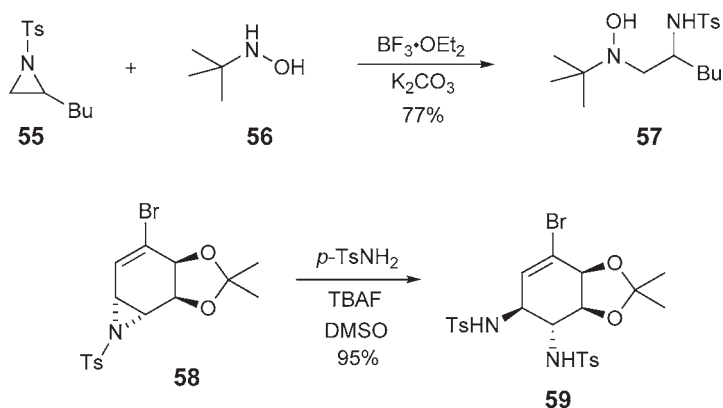
Scheme 16

Hydroxylamines also react with nonsymmetrical aziridines under Lewis-acidic conditions to give products of nucleophilic attack at the less-substituted site. Thus, treatment of methyl aziridine **55** with *N*-*t*-butylhydroxylamine **56** and 20 mol% boron trifluoride etherate provides the diamine derivative **57** in 77% yield <2001TL8243>. Fluoride ion is a powerful catalyst for the reaction of aziridines with the weakly nucleophilic *p*-toluenesulfonamide, a phenomenon which has been applied with advantage toward the preparation of protected diamino diol **59**, a precursor to the aminocyclitol substructure (Scheme 17) <2001TL6433>.

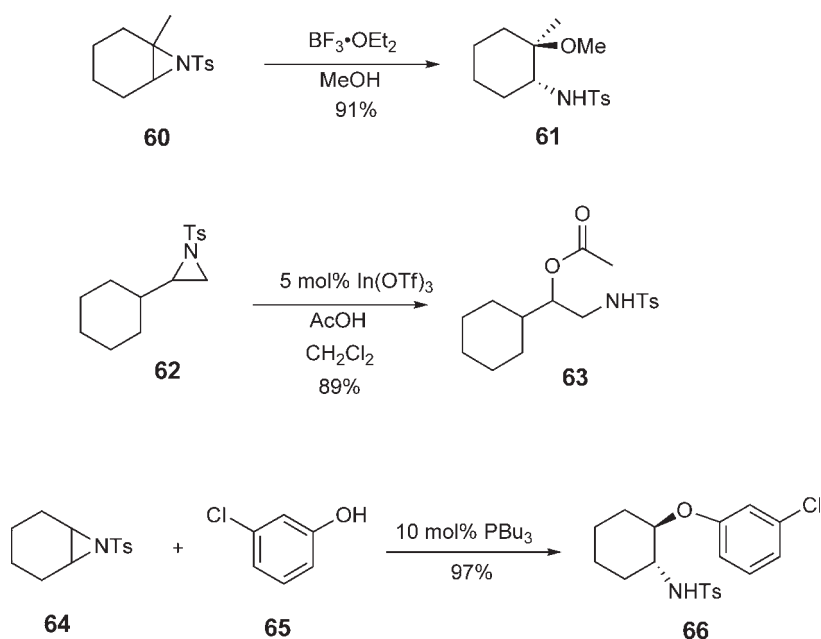
1.01.5.1.4 Ring-opening reactions by oxygen nucleophiles

The ring-opening reaction can also be induced by attack of oxygen-centered nucleophiles, as demonstrated by the facile ring cleavage of the unsymmetrical bicyclic aziridine **60** with methanol in the presence of boron trifluoride etherate to give the product of attack at the more-substituted aziridine carbon <2002T7355>. Indium triflate

catalyzes the opening of aziridines with carboxylic acids. For example, reaction of the cyclohexyl tosyl aziridine **62** with acetic acid and 5 mol% indium triflate resulted in the formation of amino acetate **63** in 89% yield, with a small amount of the regioisomer resulting from attack at the less-substituted position [<2002TL2099>](#). Phenol-based nucleophiles are also capable of this behavior, and adding tributylphosphine to the mix has been shown to facilitate the reaction. Thus, the cyclohexene aziridine **64** provided the corresponding aryl ether **66** in 97% isolated yield in the presence of *m*-chlorophenol **65** and tributylphosphine, but no reaction was observed in the absence of a phosphine additive (**Scheme 18**) [<2002JOC5295>](#).



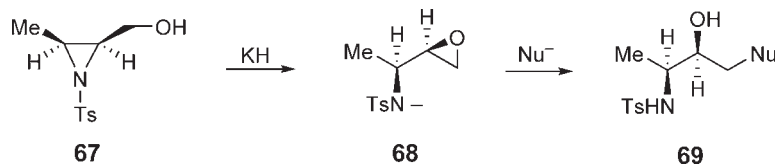
Scheme 17



Scheme 18

Hydroxymethylaziridine **67** undergoes ring opening in the presence of either carbon- or heteroatom-based nucleophiles upon treatment with 2 equiv of potassium hydride to provide the *vic*-aminoalcohol derivative **69**. The key step of the reaction is considered to be an aza-Payne rearrangement of the deprotonated aziridine methanol to the

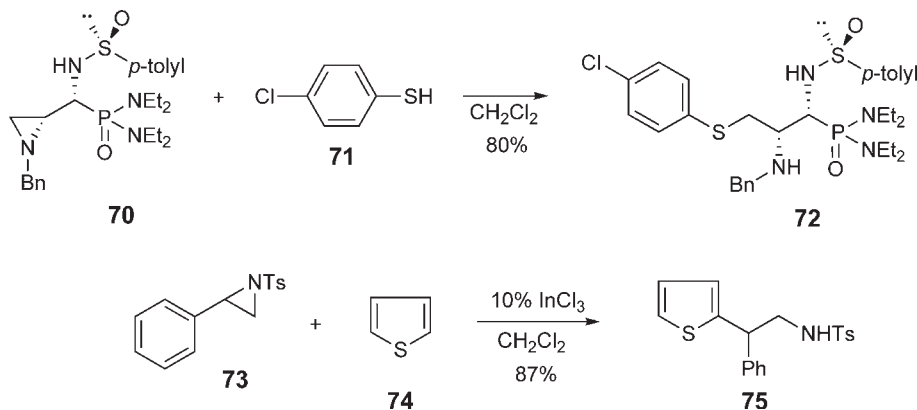
epoxide **68**, which then undergoes nucleophilic attack at the less-substituted oxirane carbon to give the observed product. The process is carried out in one pot, is amenable to various nucleophiles (e.g., thiols, TMS-cyanide, higher-order cuprates), and proceeds with very good de (Scheme 19) <1995TL6247, 1998CSR145>.



Scheme 19

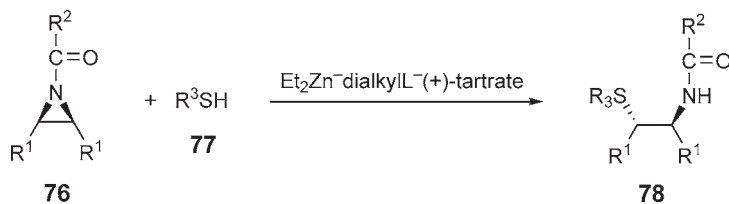
1.01.5.1.5 Ring-opening reactions by sulfur nucleophiles

Sulfur-containing nucleophiles are equally suitable nucleophilic partners, as shown by the reaction of *p*-chlorothiophenol **71** with the functionalized sulfynylaziridine **70** to give the corresponding sulfide **72** in 80% yield <2002JOC2902>. Even thiophene **74** can attack the ring in the presence of indium trichloride. The regioselectivity of this reaction prefers the 2-position of the heterocycle and the benzylic site of the aziridine, although ca. 10% of product formation derives from terminal attack (Scheme 20) <2002TL1565>.



Scheme 20

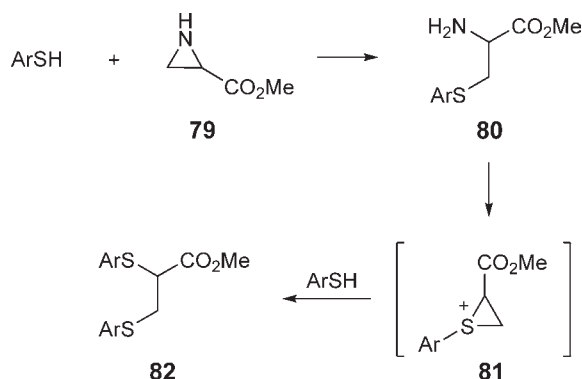
Chiral dialkyl tartrate–diethylzinc complexes catalyze the asymmetric ring opening of symmetrical *N*-acylaziridines (e.g., **76**) with thiols to give thioamides (e.g., **78**) with up to 93% ee. The enantioselectivity is dependent upon the stoichiometry of the reactants and the nature of the tartrate (Scheme 21) <1996T7817>.



Scheme 21

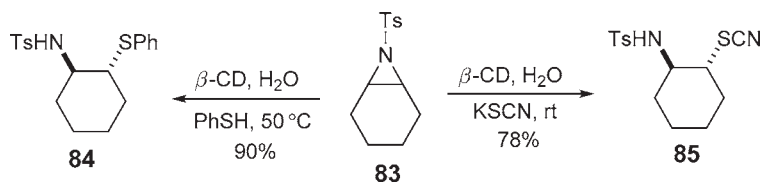
Interestingly, the ring opening of 2-aziridinecarboxylic acid methyl ester **79** by a number of aromatic thiols under solvent-free and noncatalytic conditions resulted in the formation of bis-arylsulfanyl propanoic acid esters **82**. Since only traces of the monosubstituted compound **80** were occasionally found in the crude reaction mixture, it would

appear that the product formed by initial attack by the thiol reacts much faster than the starting aziridine. This is probably due to anchimeric assistance from an intermediate episulfonium ion **81** (Scheme 22) <2006TL3949>.



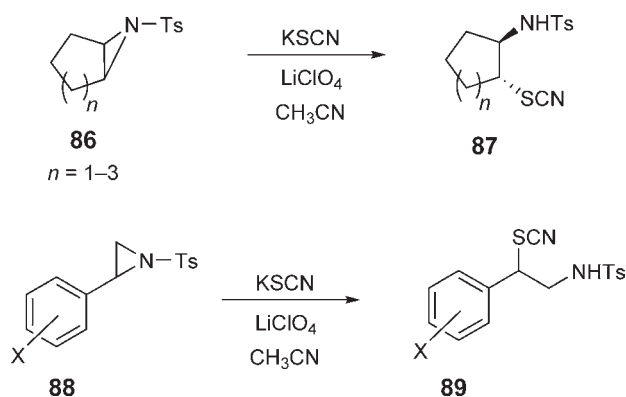
Scheme 22

β -Cyclodextrins (β -CDs) are very useful in creating microenvironments in which aziridines can be opened using mild conditions. The reaction of aziridines such as **83** with β -CD and sulfur nucleophiles such as thiocyanate <2005SL489> or thiophenols <2005TL6437> provides a mild route to ring-opened compounds **84** and **85** (Scheme 23).



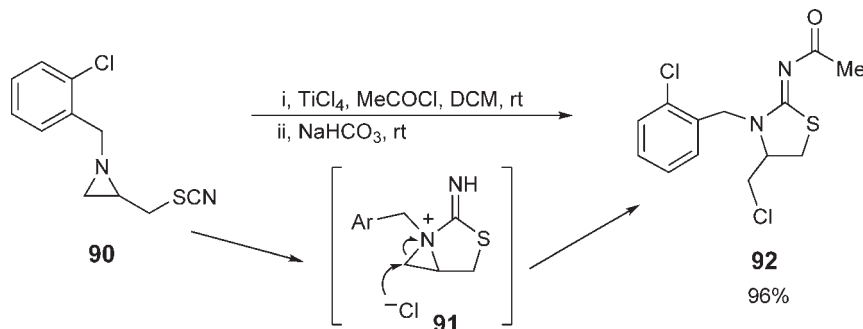
Scheme 23

Aziridines such as **86** react smoothly with potassium thiocyanate in the presence of a catalytic amount of lithium perchlorate in acetonitrile under mild reaction conditions to afford the corresponding β -aminothiocyanates **87** in high yields and with high regioselectivity. The combination of lithium perchlorate and acetonitrile provides a convenient catalytic medium to perform the reactions under neutral conditions (Scheme 24) <2005TL6385, 2006TL779>.



Scheme 24

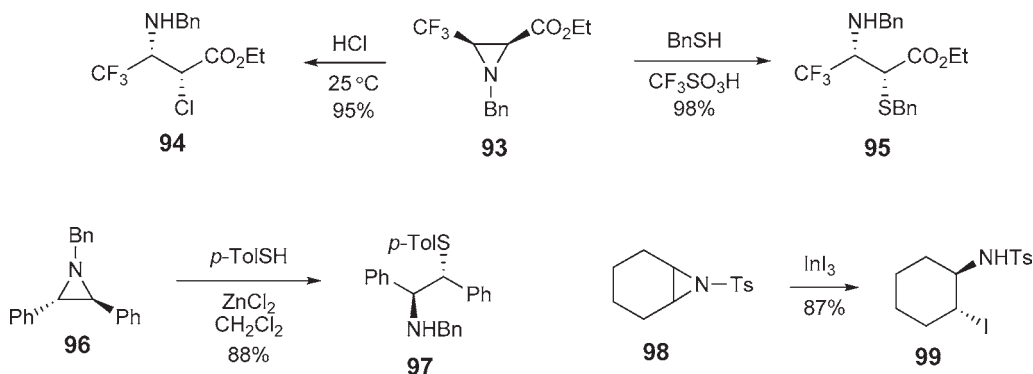
Several thiazolidines were synthesized via titanium tetrachloride catalytic cyclization [<2005JOC227>](#). The reaction proceeds via an intramolecular attack on the nitrile by the aziridine nitrogen to provide bicyclic aziridinium intermediate **91**. Subsequent ring opening by chloride yields thiazolidine **92** (Scheme 25).



Scheme 25

1.01.5.1.6 Ring-opening reactions by halides and other nucleophiles

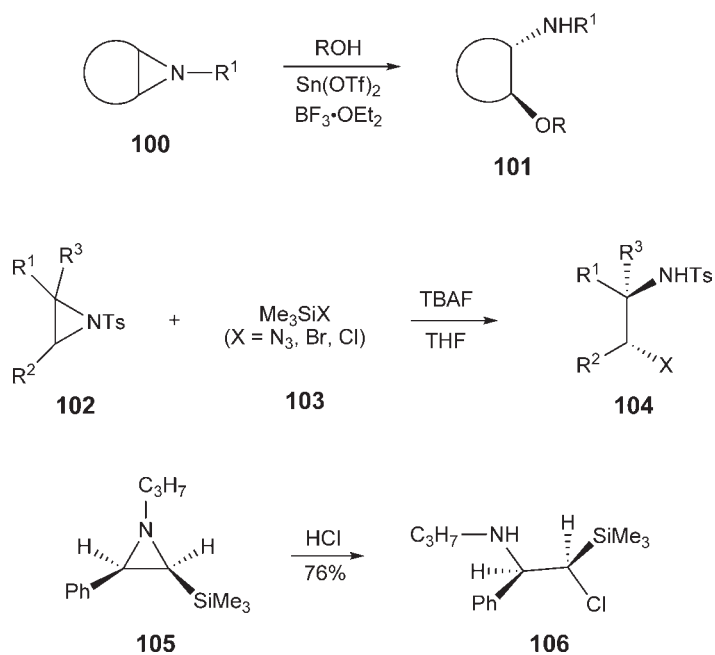
Aziridines engage in facile ring-opening reactions with many other types of nucleophiles, and this represents an entry into various functionalized amines. For example, the 3-trifluoromethylaziridine-2-carboxylate **93** undergoes efficient nucleophilic attack by chloride or thiols under acidic conditions to provide the protected amino esters **94** and **95**, respectively, in high yield and as a single diastereomer [<2001SL679>](#). The latter reaction can also be promoted by zinc chloride, as exemplified by the conversion of aziridine **96** to amino sulfide **97** [<2001\(P1\)1314>](#). As for halide-mediated ring opening, indium trihalides are competent reagents in promoting this transformation, as demonstrated by the clean conversion of *N*-tosyl aziridine **98** to the iodo amine derivative **99** (Scheme 26) [<2001SL1417>](#).



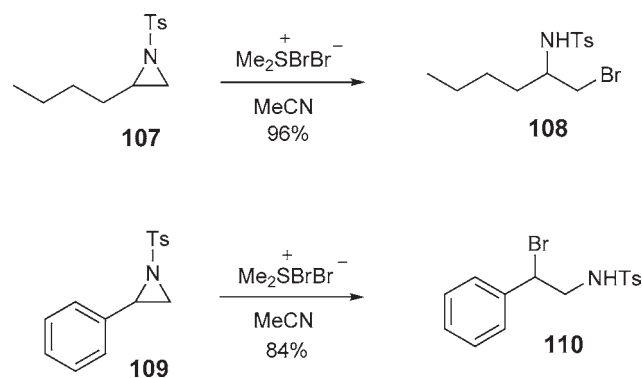
Scheme 26

A variety of *N*-activated aziridines **100** are efficiently cleaved by water, primary, allylic, and propargyl alcohols at room temperature in the presence of catalytic amounts of tin triflate and boron trifluoride etherate [<2000TL4677>](#). Aziridines can also be ring-opened by trimethylsilyl compounds **103** and tetrabutylammonium fluoride to give cyano-, azido-, and chloramines in simple and efficient fashion [<2000JOC1344>](#). Silyl-substituted aziridines **105** are attacked by hydrogen halides to furnish the corresponding haloamine compound **106** (Scheme 27) [<2000J\(P1\)439>](#).

N-Tosylaziridines **107** and **109** undergo ring opening efficiently with (bromo-dimethyl)sulfonium bromide at room temperature to form the corresponding β -bromoamines **108** and **110**. The conversions are highly regioselective and furnish the products in excellent yields within a short period of time. The reaction uses an inexpensive reagent, is operationally simple, involves short reaction times, and proceeds in high yield and with excellent regioselectivity (Scheme 28) [<2006TL4457>](#).

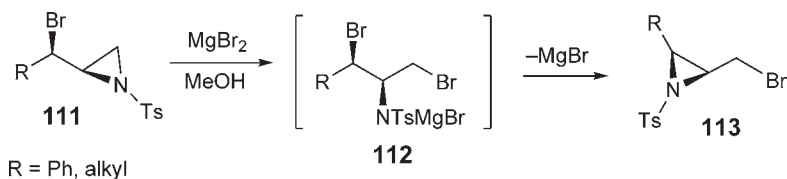


Scheme 27



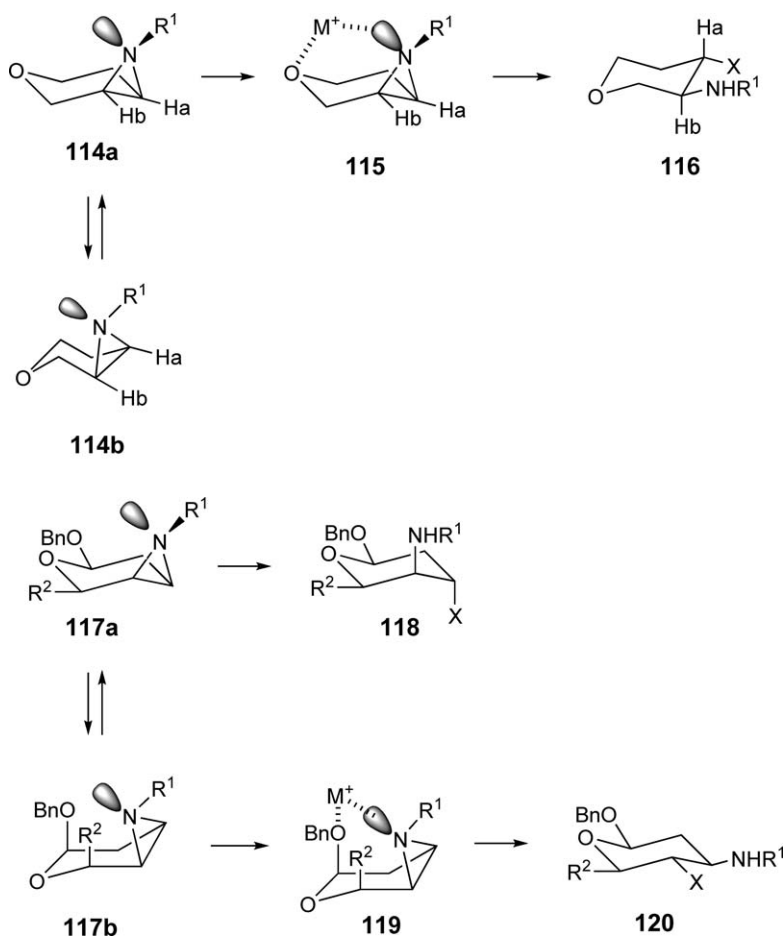
Scheme 28

A novel stereospecific isomerization of 2-(1-bromoalkyl)-1-sulfonylaziridines **111** into 2-(bromomethyl)-3-alkyl-1-sulfonylaziridines **113** was reported to occur by carrying out the reaction in the presence of MgBr_2 . The isomerization reaction was found to be considerably dependent on the nature of the solvent used. Polar solvents such as MeOH or dimethylformamide (DMF) are able to solvate the magnesium bromide and give **113** as the thermodynamically most stable regioisomer (Scheme 29) <2005TL6541>.



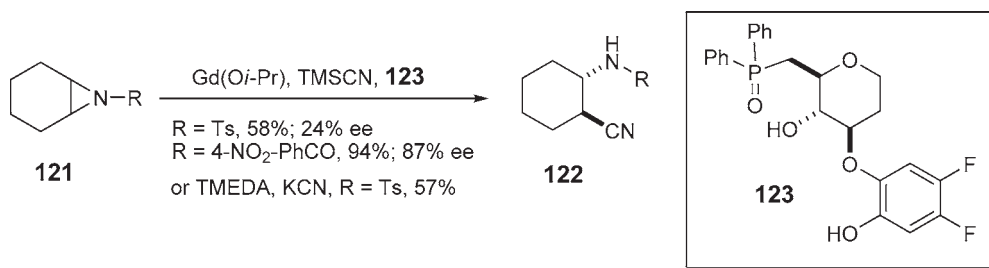
Scheme 29

Crotti *et al.* <1997T1417> have studied the ring-opening behavior of certain bicyclic aziridines under standard and chelating conditions; their findings are in keeping with those obtained from similar epoxide systems, namely that the course of the aziridine cleavage can be strongly influenced by the reaction conditions and the topography of the substrate. For example, when the two bicyclic aziridines **114** and **117** undergo nucleophilic attack under standard conditions, a strong C-1 preference is observed. In the former system, the C-2 position is believed to be deactivated toward nucleophilic attack due to the electronic effect of the pyransidic oxygen; in the latter, the observed selectivity is presumably due to the predominance of the more stable conformer **117a**, in which the benzylic group assumes an equatorial attitude. Introduction of a chelating metal into the reaction system causes an enhancement of C-1 selectivity in the case of **114**, yet a complete crossover is observed for the benzylic derivatives **117**. In both cases, the role of the metal is thought to be in the formation of a bidentate chelate structure (i.e., **115** and **119**) which further stabilizes the already low-energy intermediate **115** in the first series, but which coordinates with the benzylic oxygen in the latter case (i.e., **119**) to lock in an otherwise disfavored conformation, leading to C-2 products **120** (Scheme 30).



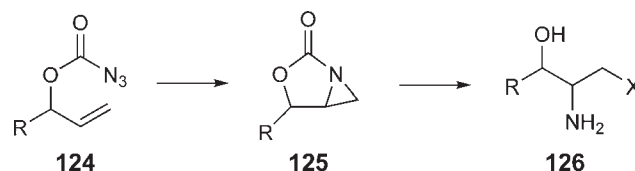
Scheme 30

The gadolinium•**123** complex was used to catalyze the enantioselective desymmetrization of an assortment of aziridines <2005JA11252>. The substitution on the nitrogen was critical to obtaining optimal yields and enantioselectivity. The use of *N*-tosyl aziridine gave **122** with only 24% ee while changing to the *p*-nitrobenzoyl gave **122** with an 87% ee. Aziridines have also been opened through the use of nucleophilic catalysis <2005OL3509>. Several nucleophilic catalysts were examined for the preparation of cyanoamides, **122**, and the optimal choice was tetramethylethylenediamine (TMEDA, 20 mol%). This represents a significant departure from the more typical acid catalysis used for aziridine ring opening (Scheme 31).



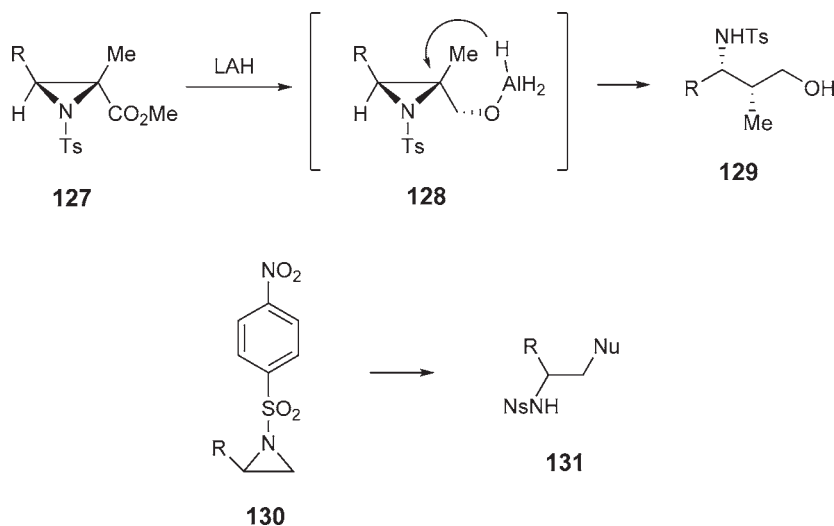
Scheme 31

The ring opening of a bicyclic aziridine is the key step in a novel synthesis of vicinal amino alcohols **126** from allylic alcohols. In this protocol, the thermolysis of an azidoformate **124** results in the formation of a nitrene which is captured intramolecularly to generate the strained bicyclic system **125**. The methylene carbon of the aziridine ring proved to be very susceptible to ring opening providing intermediate oxazolidinones, which on hydrolysis, yielded substituted amino alcohols (Scheme 32) <1997JOC4449>.



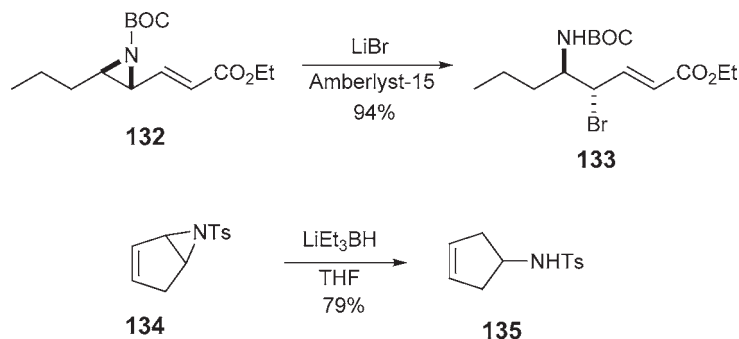
Scheme 32

The aziridine nucleus is frequently activated toward nucleophilic attack by attaching electron-withdrawing substituents to the nitrogen atom, as illustrated by the chiral *N*-tosylaziridine 2-carboxylate esters **127**, which undergo a highly stereoselective ring opening upon treatment with lithium aluminium hydride. In this case, the attack of hydride causes inversion of configuration and is directed by the hydroxyl group. This sequence is presented as an efficient asymmetric synthesis of α -alkyl- β -amino acids <1997TL5139>. In a similar vein, the *p*-nitrophenyl-sulfonyl (nosyl) group is also a useful activating group for ring-opening reactions. Nosyl aziridines **130** are highly reactive electrophiles toward a variety of nucleophiles and do not exhibit competing $\text{S}_{\text{N}}\text{Ar}$ reactivity; furthermore, the resultant nosylamide adducts **131** can be cleaved under mild conditions (Scheme 33) <1997TL5253>.



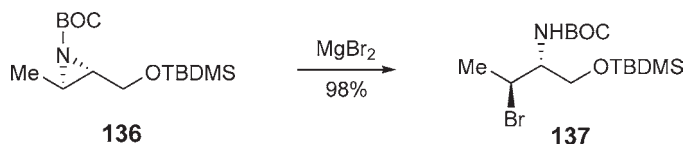
Scheme 33

Other useful nucleophiles for the ring opening of aziridines include bromide, as shown in the Amberlyst-15-catalyzed reaction of lithium bromide with vinyl aziridine **132** <2002TL5867> and hydride, which can be delivered by lithium triethylborohydride. This is illustrated by the conversion of tosyl azabicyclo[3.1.0]hexene **134** to the corresponding protected cyclopentenyl amine **135** in 79% yield (Scheme 34) <2002TL723>.



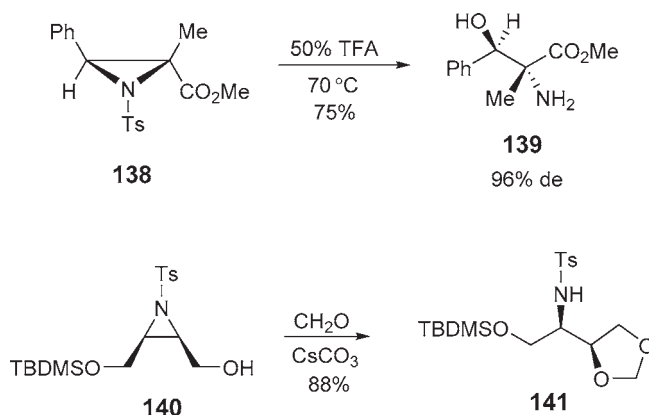
Scheme 34

N-BOC-2,3-aziridinoalcohol derivatives **136** undergo ring opening in a regio- and stereoselective fashion with magnesium bromide to give the corresponding 3-bromo-1,2-aminoalcohols **137**, thereby demonstrating a novel use of the BOC substituent as both a protecting and activating group. The products obtained can be deprotected under very mild conditions (Scheme 35) <1998TL2385>.



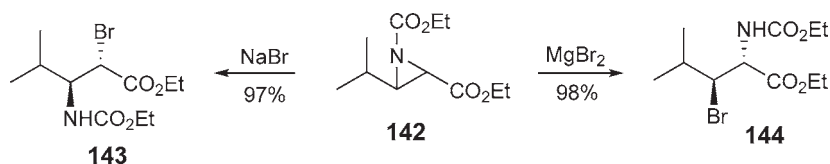
Scheme 35

If the starting aziridine is already optically pure, then it is desirable to preserve the ee during any subsequent ring openings. In this vein, 2-substituted aziridine **138** can be cleaved in a regio- and stereocontrolled manner upon heating to 70 °C in 50% trifluoroacetic acid (TFA) to give (2*R*,3*R*)-(+)- α -methyl- β -phenylserine **139** in 75% yield and 96% de <1996TL5473>. In an interesting intramolecular example of this process, aziridinylmethanol **140** reacts with formaldehyde in the presence of cesium carbonate to form a hemiacetal intermediate, which cyclizes with concomitant aziridine ring opening to furnish acetal **141**, which was then used to synthesize a key synthetic intermediate for bestatin (Scheme 36) <1996H(42)701>.



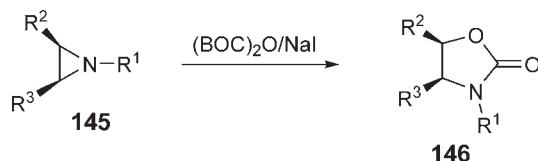
Scheme 36

The regioselectivity of such nucleophilic ring-opening reactions can sometimes be controlled by the reaction conditions. A striking example of such reaction steering is given by the cleavage of 3-substituted *N*-ethoxycarbonyl aziridine-2-carboxylates (e.g., **142**) with metal halides. Thus, treatment of **142** with sodium bromide leads to exclusive C-2 attack, providing amino acid derivative **143** as the sole product. On the other hand, use of magnesium bromide results in a complete crossover of reactivity to give isomer **144** via C-3 attack, presumably due to chelation effects (Scheme 37) <1996TL6893>.



Scheme 37

Certain reagents promote ring opening and subsequent cyclization to give other heterocycles. For example, di-*tert*-butyl dicarbonate induces the stereoselective ring transformation of *N*-alkyl aziridines **145** into oxazolidin-2-ones **146** (Scheme 38) <1996T2097>.



Scheme 38

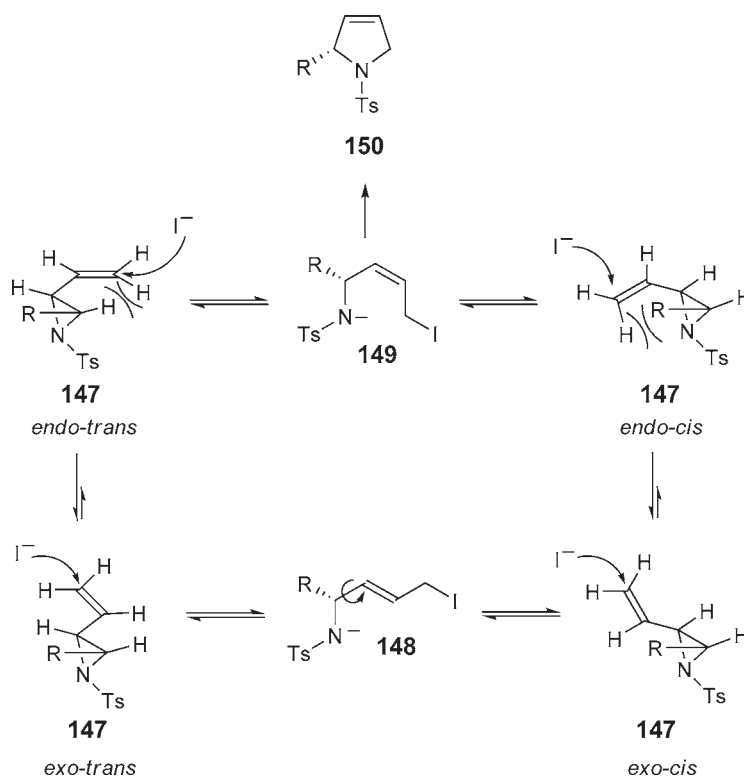
A convenient protocol for the formation of synthetically important 3-pyrrolines (i.e., **150**) involving a microwave-assisted rearrangement of 2-vinylaziridines **147** has been developed. The rearrangement proceeds in good to excellent yields and is mediated by NaI or LiI in MeCN at elevated temperatures. The proposed mechanism for the rearrangement starts with an $\text{S}_{\text{N}}2'$ ring opening of *trans*-**147**. Opening in the *exo-trans*-**147** conformation leads to intermediate **148** with (*E*)-configuration, whereas the thermodynamically less favored *endo-trans*-**147** conformation will give the (*Z*)-configured intermediate **149**. Only the latter intermediate can ring-close to the desired pyrroline **150**. Intermediates **148** and **149** only result in the reformation of the aziridine moiety (Scheme 39) <2005SL3099>.

1.01.5.1.7 Ring-opening by carbon-centered nucleophiles

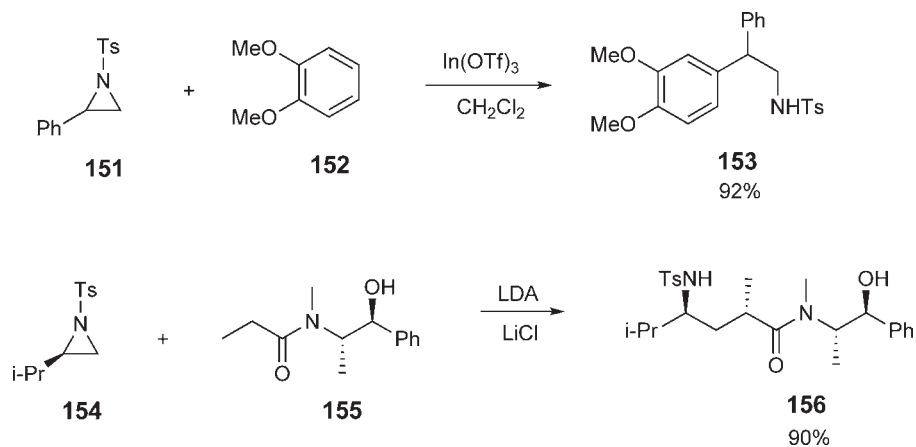
Some interesting advances have also been made in the area of ring opening by carbon-centered nucleophiles, an area of obvious practical impact. For example, aziridines react smoothly with arenes in the presence of a catalytic amount of indium triflate at ambient temperature to give the corresponding β -aryl amines (e.g., **153**) in good to excellent yields <2001TL8067>. The aziridine **154** was opened up in a stereocontrolled fashion by the chiral enolate prepared by deprotonation of **155**, itself derived from (*S,S*)-(+)-pseudoephedrine, and provides the γ -aminoamide **156** in 90% yield (Scheme 40) <2001JOC5801>.

Indole derivatives **157** also serve as carbon-centered nucleophiles in the scandium-mediated opening of aziridine carboxylates **158**. The overall process represents a facile synthesis of aryl-substituted tryptophans **159** (Scheme 41) <1998SL754>.

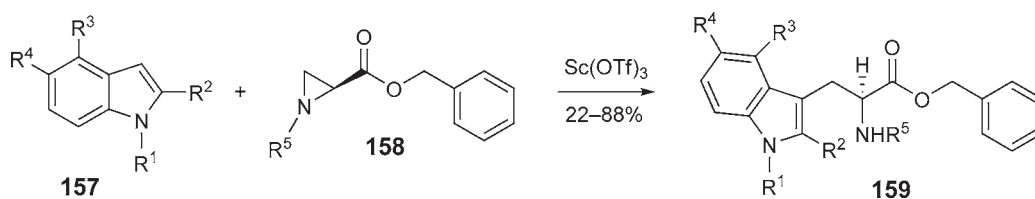
Alkynylation of aziridines can be effected through the copper-catalyzed ring opening with acetylides. For example, lithium phenylacetylide engages in smooth nucleophilic attack of *N*-tosyl-7-azabicyclo[4.1.0]heptane **160** in the presence of copper(I) triflate to provide the cyclohexyl alkyne **161** in excellent yield (Scheme 42) <2004SL1691>.



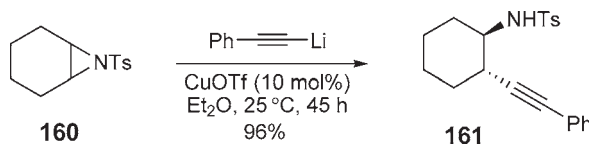
Scheme 39



Scheme 40

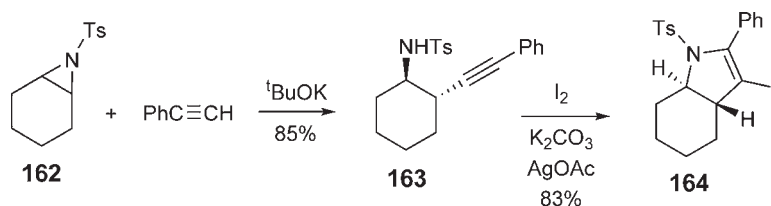


Scheme 41



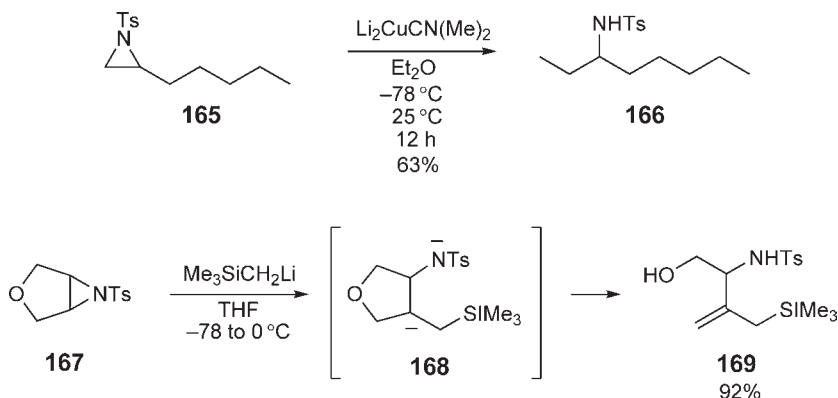
Scheme 42

In the presence of *t*-BuOK, the reaction of acetylenes with *N*-tosyl-substituted aziridines derived from both cyclic and acyclic alkenes at room temperature gave rise to homopropargylamines in high yield and high regioselectivity. Not only phenyl- and Me₃Si-substituted acetylenes but also acetylene itself were suitable reagents. Treatment of the ring-opening product **163** with I₂ and AgOAc in the presence of K₂CO₃ provided dihydropyrrole **164** in high yields (Scheme 43) <2005T9586>.



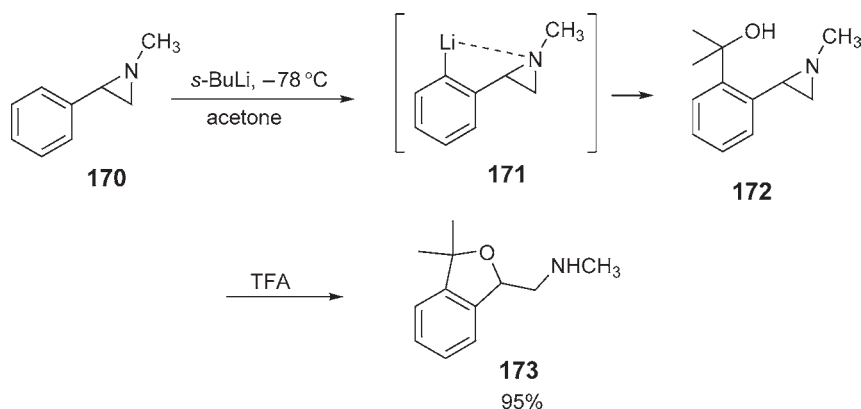
Scheme 43

Lithium dimethyl cyanocuprate can also be engaged in nucleophilic attack and this occurs on the less-substituted carbon with 1-pentyl-*N*-tosylaziridine **165** to give *N*-tosyloctane-3-amine **166**. In this system, the use of alkyllithium reagents led to eliminative pathways <2004T3637>. However, there are other reports of productive ring opening by lithiates. Treatment of 6-aza-3-oxabicyclo[3.1.0]hexane **167** with (trimethylsilyl)methyl lithium led to the formation of an intermediate ring-opened dianion **168**, which subsequently underwent elimination to form the functionalized allylic amine **169** <2004CC2234>. Key to the success of this protocol is the formation of the aziridinyl anion, which has considerable carbenoid character (Scheme 44).



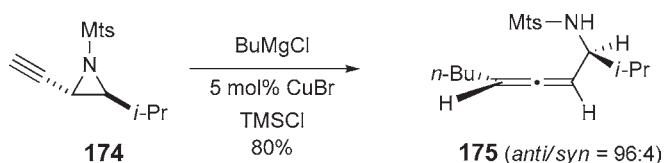
Scheme 44

In a very clever reaction sequence, *N*-methylaziridines have been shown to be useful directing groups for *ortho*-metallation <2005OL3749>. Reaction of **170** with *s*-BuLi followed by trapping with a carbonyl compound provides alcohol **172**. Subsequent intramolecular aziridine ring opening provides isobenzofuran derivative **173** (Scheme 45).



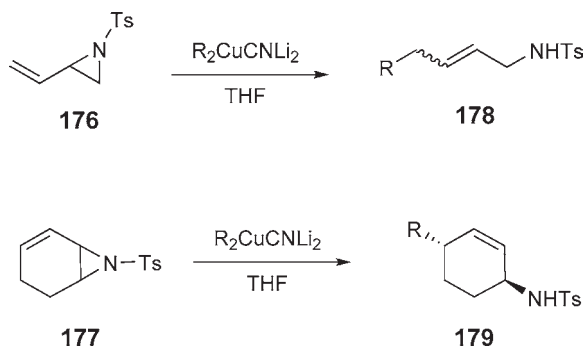
Scheme 45

The synthetically important subclass of alkynyl aziridines was included in a relatively recent review <2002COR539>, specifically from the standpoint of preparation and ring-opening reactions with carbon nucleophiles. Such substrates (e.g., **174**) tend to suffer S_N2' attack from Grignard reagents to give aminoallenes (e.g., **175**) (Scheme 46).



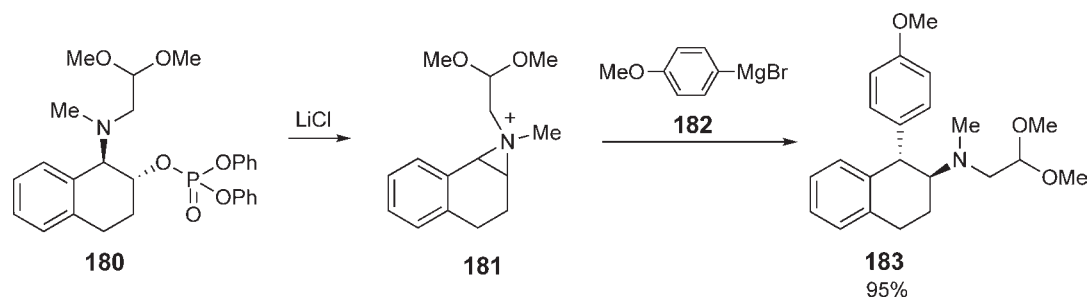
Scheme 46

Two structurally simple 2-alkenyl aziridines corresponding to the acyclic **176** and cyclic **177** were treated with routinely used organometallic reagents. With these systems, the lithium or magnesium cyanocuprates reacted cleanly with **176** and gave **178** with very high S_N2' selectivity. The reaction of the cuprate with **177** was also S_N2' -regioselective, furnishing the *trans*-3,6-disubstituted cyclohexene **179** as the major product of the reaction (Scheme 47) <2005TL2539>.



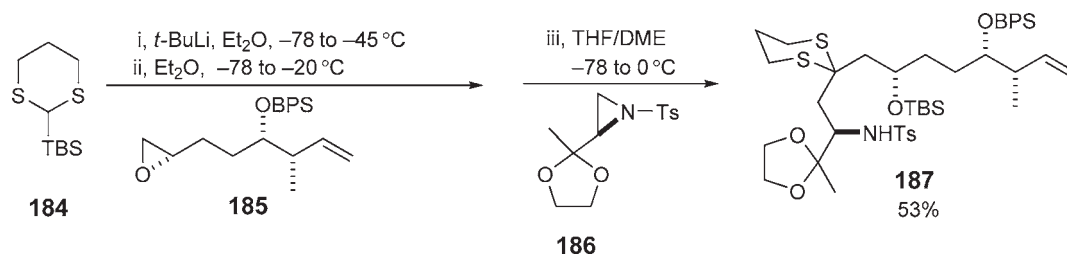
Scheme 47

An organometallic reagent has been used to ring-open an aziridinium ion **181**, formed *in situ* by the treatment of the amino alcohol derivative **180** with lithium chloride. Subsequent addition of the aryl magnesium bromide **182** led to the formation of amine **183** in 95% overall yield (Scheme 48) <2002TL6121>.



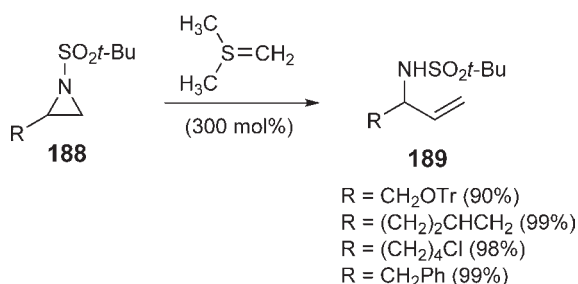
Scheme 48

In the synthesis of poison frog alkaloid (–)-205B, a three-component linchpin coupling was used to form a complex intermediate, **187**, in a single step [<2005OL3247>](#). Lithiation of **184** followed by addition of epoxide **185**, warming, and then addition of aziridine in tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) to trigger the Brook rearrangement leads to **187**. This tactic, in conjunction with a one-flask sequential cyclization, constitutes an effective general strategy for the construction of indolizidine and related alkaloids ([Scheme 49](#)) [<2006JOC2547>](#).



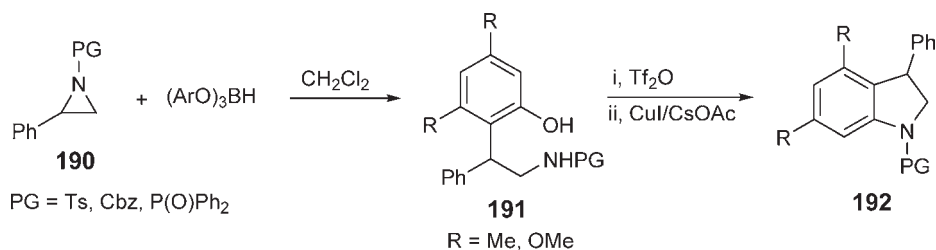
Scheme 49

The homologation of aziridines to give allylic amines is an attractive process to a very useful class of molecules. Thus, the reaction of N-protected aziridines with excess dimethylsulfonium methylide provides the homologated allylic amines in excellent yields ([Scheme 50](#)) [<2005OL3295>](#).



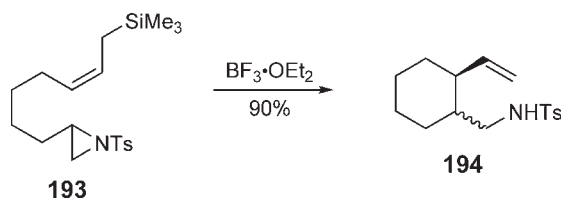
Scheme 50

A new carbon–carbon coupling reaction of phenol derivatives with aryl aziridines has been reported to occur with high regioselectivity and high *syn*-selectivity, without the need for any external transition metal catalyst or Lewis acids. Thus, reaction of electron-rich borates with optically active aziridines of type **190** in CH_2Cl_2 at -78°C provided the unsymmetrical 2,2-diaryl ethylamines **191**, which can be further used to produce stereodefined substituted 3-aryl indolines [<2006OL2627>](#). Conversion of the phenolic OH group to the corresponding triflate followed by a CuI/CsOAc-mediated intramolecular amination was the route used to synthesize the substituted 3-aryl indoline **192** ([Scheme 51](#)).



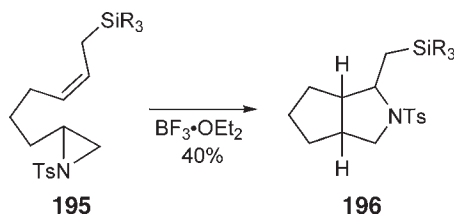
Scheme 51

The aziridine ring may also be opened in an electrophilic fashion using an intramolecular carbon nucleophile. For example, the aziridine nucleus of the functionalized allyl silane **193** undergoes intramolecular ring opening in the presence of boron trifluoride etherate to give the aminomethyl vinyl cyclohexane **194** in 90% yield as a 2.7:1 mixture of *cis*- and *trans*-isomers (Scheme 52) <1995TL3793>.



Scheme 52

When the related aziridine **195** was used containing one less carbon in the tether, an unusual cyclization occurred which corresponds to a formal [3+2] aziridine allylsilane cycloaddition to give the bicyclic pyrrolidine **196**. This substrate was used for the preparation of other fused ring systems (Scheme 53) <1999T8025>.



Scheme 53

1.01.5.2 Reactions of N-Unsubstituted Aziridines

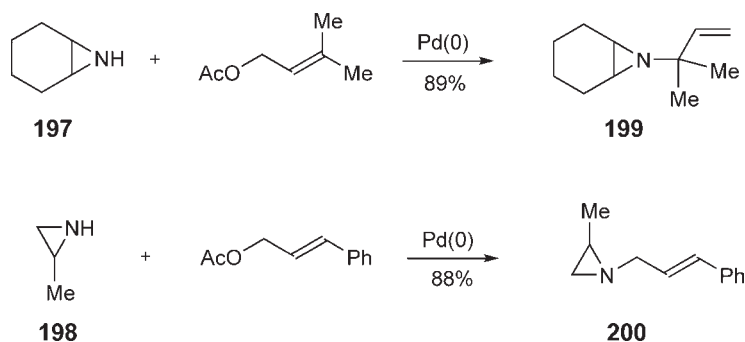
1.01.5.2.1 Palladium-catalyzed allylic amination

N-Allylation of aziridines is often complicated by side reactions. The classical solution to this problem, reductive amination, can also be problematic due to the increased strain energy of the aziridinium intermediate. A way to avoid this difficulty was developed by Yudin and co-workers <2005JA17516, 2004JA5086>. The results obtained showed that NH-aziridines such as **197** or **198** underwent a palladium-catalyzed allylic amination with various allyl acetates affording the desired allylated product **199** and **200** with high levels of regioselectivity and in high isolated yields (Scheme 54).

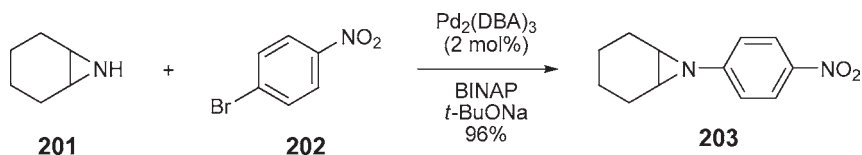
1.01.5.2.2 Palladium-catalyzed alkenylation and arylation

N-Unsubstituted aziridines can be elaborated by taking advantage of the nucleophilicity of the nitrogen center. One noteworthy example is the palladium-catalyzed arylation of aziridine **201** with *p*-bromonitrobenzene **202** using a

$\text{Pd}_2(\text{DBA})_3/\text{BINAP}$ system (DBA = dibenzylideneacetone; BINAP = 2,2-bis(diphenyl-phosphanyl)-1,1'-binaphthyl). Best results were obtained using electron-deficient aryl bromides. Aryl chlorides of any type, however, failed to react under these conditions. The aryl–aziridine coupling reaction could also be carried out with arylboronic acids using a copper catalyst (**Scheme 55**) <2003JOC2045>.

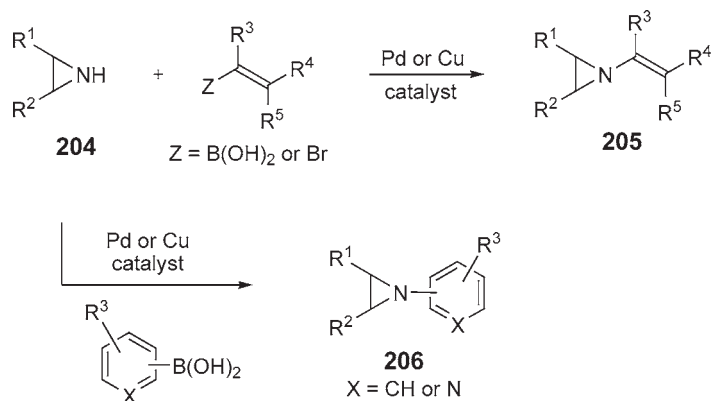


Scheme 54



Scheme 55

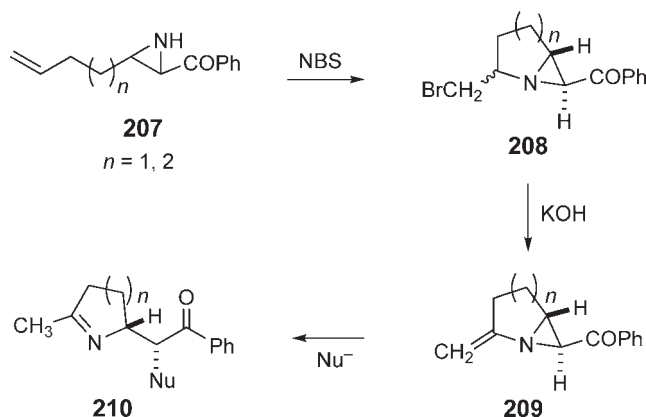
A range of *N*-aryl- and *N*-alkenylaziridines have been prepared by the palladium- or copper-catalyzed reaction between unsubstituted aziridines and aryl or alkenyl bromides or boronic acids without opening of the strained aziridine ring <2003JOC2045>. The $\text{Pd}_2(\text{DBA})_3/\text{BINAP}$ combination in toluene at 70 °C with *t*-BuONa as base serves as an effective catalyst for the amination of unsubstituted aziridines. Using this methodology, one can synthesize *N*-arylated products in 35–96% yield (**Scheme 56**). The insertion of palladium into the nitrogen carbon bond was not observed in any of these cases, although oxidative addition of Ni to *N*-tosylaziridines has been reported <2002JA2890> and oxidative addition of transition metals to aziridines has been invoked in catalytic carbonylation of aziridines to give β -lactams <1989JA931>.



Scheme 56

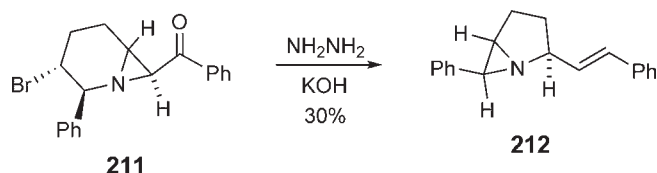
1.01.5.2.3 Intramolecular oxidative cycloamination

Synthetically versatile [3.1.0] and [4.1.0] bicyclic enamines have been prepared by intramolecular oxidative cycloamination of *N*-unsubstituted aziridine-containing tethered alkenes <2006JOC6067, 2006ACR194, 2003JA14242>. This process is initiated by *N*-bromosuccinimide (NBS) followed by base-mediated elimination of HBr to afford highly strained exo-bicyclic enamines (Scheme 57).



Scheme 57

The ring-opening reactions of **209** were found to proceed well with different nucleophiles (i.e., TMSN_3 , MeOH, Br^- , OAc, etc.) to afford high yields of **210** with excellent diastereoselectivity. The reactions are regioselective and preferentially give the corresponding pyrrolidine or piperidine precursors by ring opening at the α -position. The resulting enamines are tautomerized into the thermodynamically more stable cyclic imines **210**. Aziridine ring opening can also be triggered by hydrazinolysis with hydrazine. In the case of bicyclic aziridine **211**, this reaction afforded the novel rearranged aziridine **212** (Scheme 58) <2003JA14242>.



Scheme 58

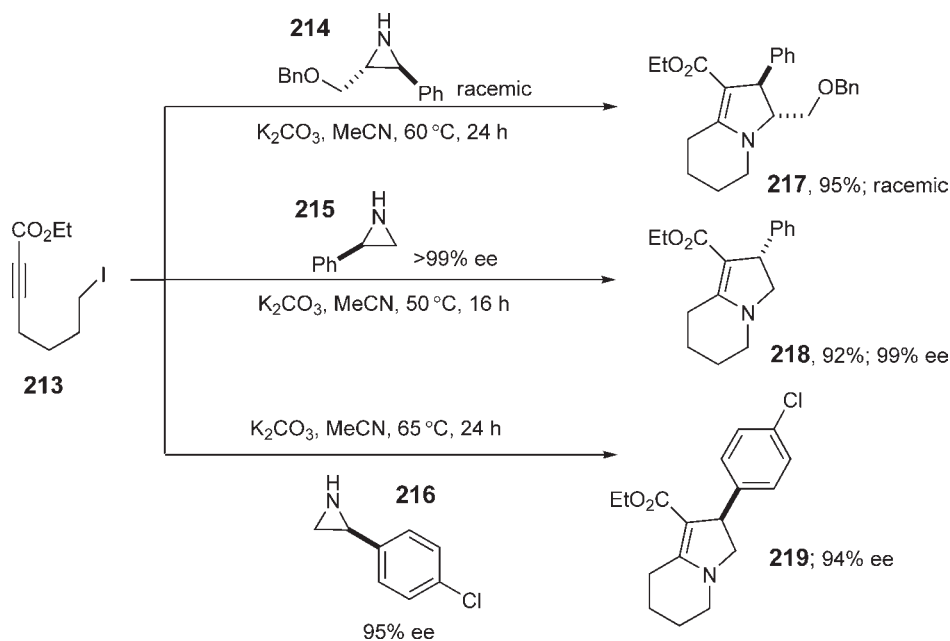
1.01.5.2.4 $\text{S}_{\text{N}}2$ /Formal [3+2] cycloaddition route

An interesting formal $\text{S}_{\text{N}}2$ /[3+2] cycloaddition route for the synthesis of substituted indolizidines has been reported <2005OL5545>. This reaction requires both an electron-withdrawing group on the alkyne and an aromatic ring on the aziridine. The reaction goes through an initial *N*-alkylation of the aziridine with iodide **213** followed by a Michael addition/rearrangement to generate indolizidines **217–219** (Scheme 59).

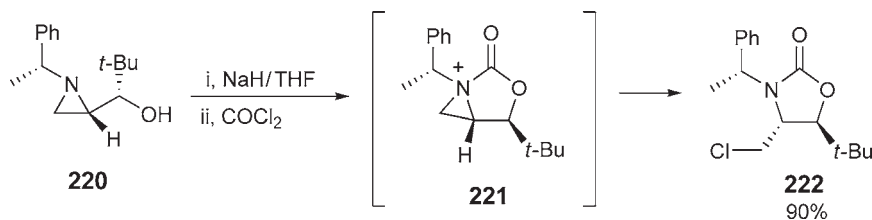
1.01.5.3 Rearrangement Chemistry

1.01.5.3.1 Nonthermal rearrangements

N-Substituted hydroxymethylaziridines undergo an interesting ring expansion in the presence of phosgene, which involves initial nucleophilic behavior of the nitrogen center. Thus, treatment of aziridine **220** leads to the formation of a short-lived bicyclic intermediate **221**, which suffers nucleophilic ring opening by chloride to give the chloromethyloxazolidinone **222** with retention of stereochemistry at both chiral centers. The use of 1 equiv of sodium hydride is necessary to prevent the buildup of hydrochloric acid during the reaction, which tends to cause an unwanted ring opening of unreacted aziridine (Scheme 60) <2003JOC43>. A similar rearrangement to oxazolidinones is known to occur upon treatment of aziridines with di-*tert*-butyl dicarbonate ($(t\text{-BOC})_2\text{O}$) <2003T677>.

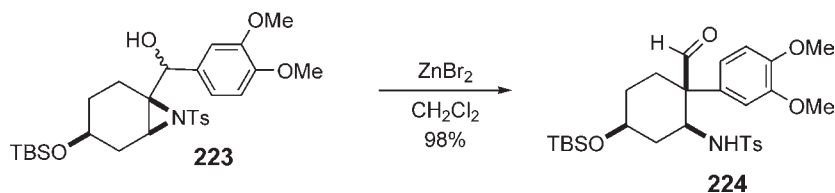


Scheme 59



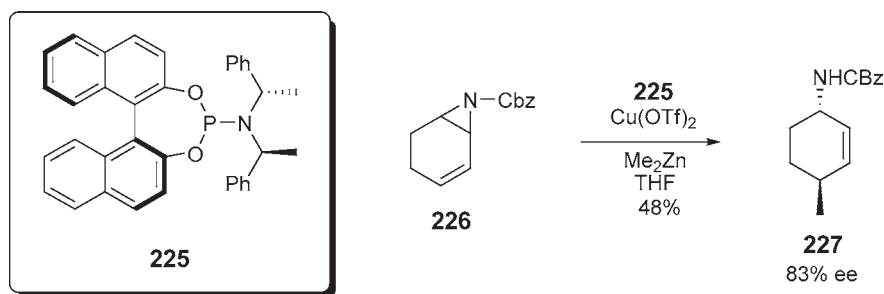
Scheme 60

Hydroxymethylaziridines of this type can also be induced to engage in a Lewis acid-mediated rearrangement to the corresponding aminocarbonyl compound. Thus, the bicyclic tosylaziridine **223** provided **224** in near-quantitative yield when treated with zinc bromide in methylene chloride. The rearrangement involves a stereospecific 1,2-migration of the aryl group. The latter compound was used as a key intermediate in the synthesis of mesembrine (Scheme 61) <2003OL2319>.



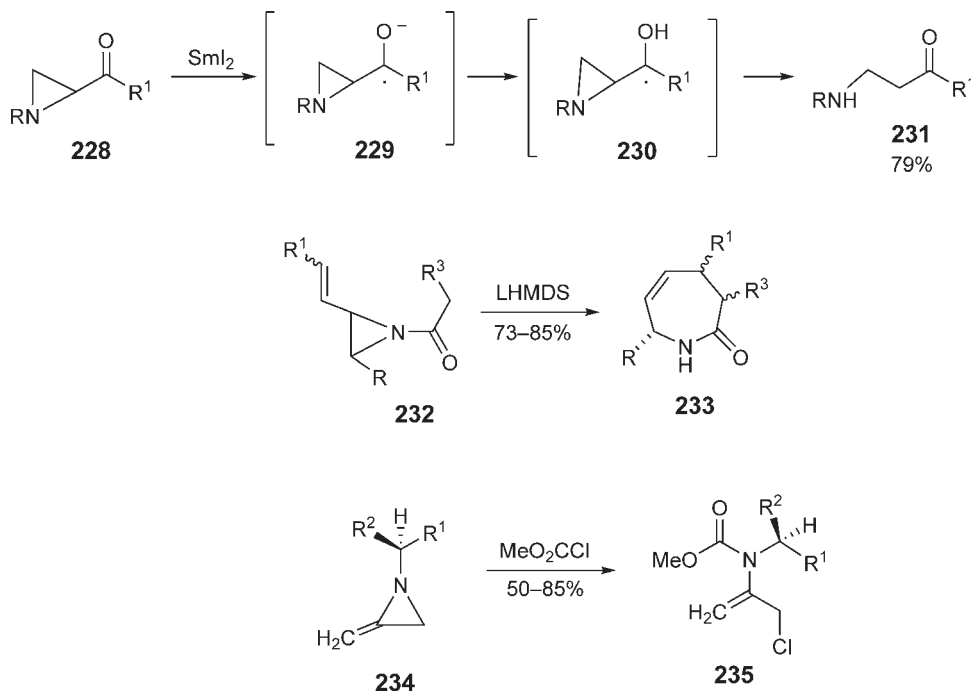
Scheme 61

When aziridines bear a 2-alkenyl substituent, they can engage in an $\text{S}_{\text{N}}2'$ reaction with dialkylzinc reagents using copper catalysts. Enantioselectivity can also be induced by including a chiral ligand, such as the binaphthyl phosphoramidite **225**. For example, the aziridinyl cyclohexane **226** provided exclusively the *trans*-1,4-adduct with 83% ee upon treatment with dimethylzinc in the presence of copper(II) triflate and ligand **225** (Scheme 62) <2003TL8559>.



Scheme 62

Various functionalized aziridines can undergo some interesting rearrangement chemistry. For example, α -carbonyl aziridines **228** can be smoothly ring-opened upon treatment with samarium iodide. This reaction proceeds via familiar radical anion formation **229** followed by rearrangement to give the β -amino carbonyl **231** <1997T8887>. Vinylaziridines **232** undergo a highly stereoselective aza-[3,3]-Claisen rearrangement to give seven-membered lactams **233** <1995JOC6660, 1997JA8385>. The reaction is rapid and is tolerant of many nitrogen protecting groups. Methyleneaziridines **234** provide enamines **235** when treated with methyl chloroformate in dichloromethane at room temperature (Scheme 63) <1997TL5887>.



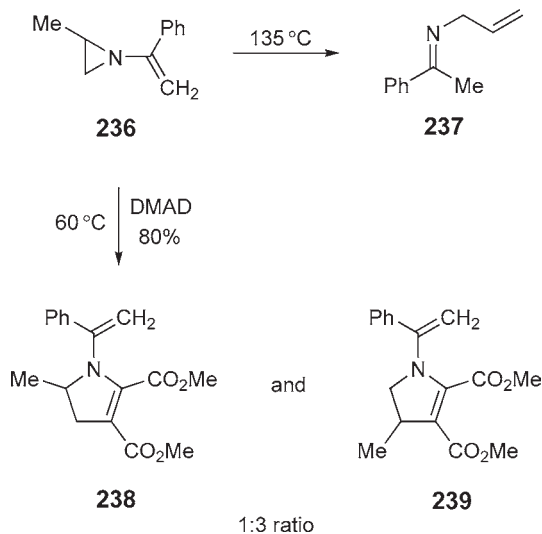
Scheme 63

1.01.5.3.2 Thermal rearrangements

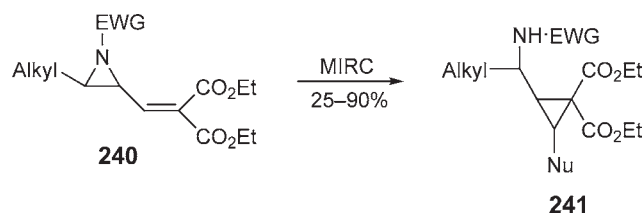
Heating an *N*-alkenyl-substituted aziridine such as **236** at 135 °C afforded **237**, the product derived from a thermal 1,5-hydrogen shift <2005OL1161>. When the thermolysis was carried out in the presence of dimethyl acetylenedicarboxylate, formal [3+2] cycloaddition products were obtained in yields ranging from 65% to 80%. The products were obtained as a mixture of two regioisomers depending on which carbon center of the aziridine ring participated in the cyclization (Scheme 64).

Rearrangements of complex aziridines can also result in interesting cyclic structures. For example, Zwanenburg and co-workers <1996T12253> have applied the Michael reaction-induced ring-closure (MIRC) reaction to aziridinyl

methylenemalonates **240**. Interestingly, this produces *cis*-cyclopropane derivatives **241** preferentially, in contrast to the analogous epoxide reactions. The results suggest that steric interactions between the nucleophilic reagent and the substituents of the aziridine ring direct the stereochemistry of the process (Scheme 65).



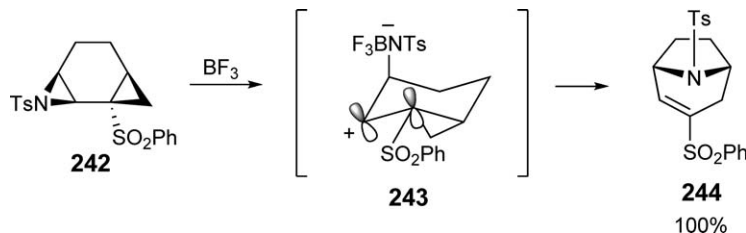
Scheme 64



Scheme 65

1.01.5.3.3 Acid–base rearrangements

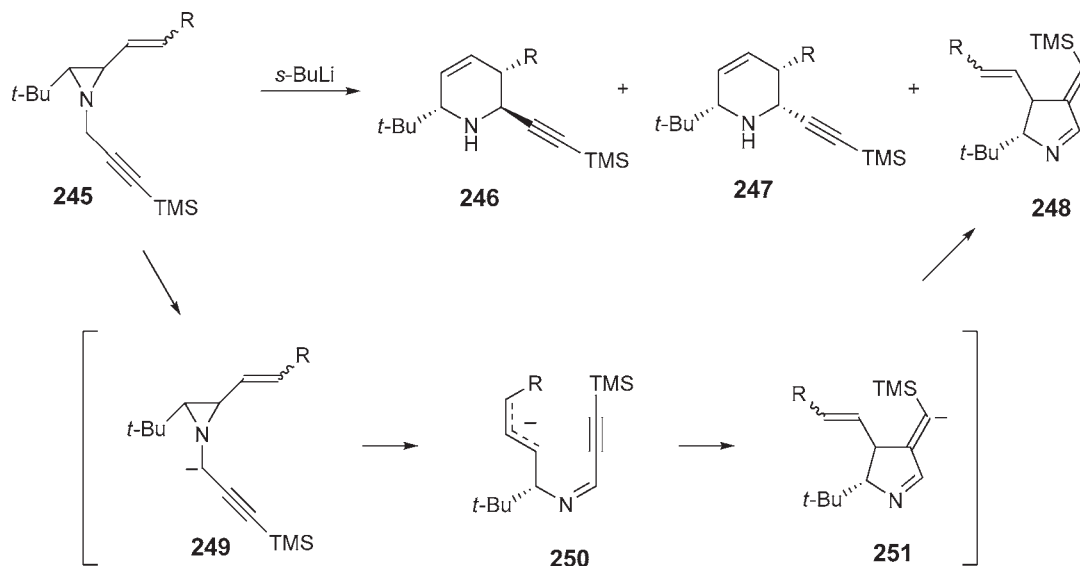
Aziridinocyclopropanes **242** derived from 2-phenylsulfonyl-1,3-dienes undergo BF₃-induced rearrangement to bicyclic amines **244**, which feature the skeleton of the tropane alkaloids. The reaction proceeds via cyclopropyl carbinyl cation **243**, an intermediate also invoked in the analogous epoxide rearrangements. Trapping by fluoride ion is a competing pathway (Scheme 66) <1996TL3371>.



Scheme 66

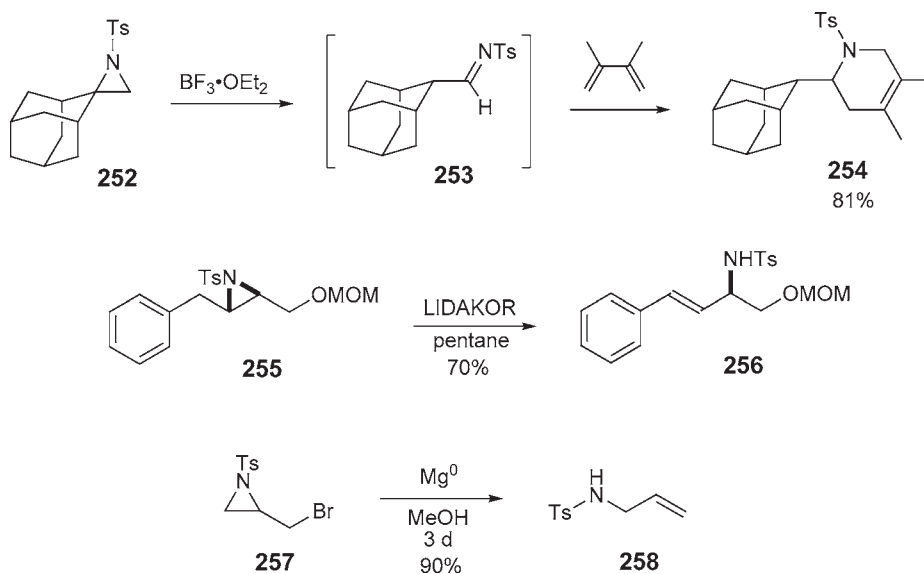
A novel rearrangement of *N*-propargyl vinylaziridines **245** under Wittig rearrangement conditions has been reported. Thus, treatment of **245** with *s*-BuLi led to the formation of the expected tetrahydropyridines **246** and **247**, products of an aza-[2,3]-Wittig rearrangement, along with significant amounts of pyrroline **248**. The formation of this latter product was surprising, and studies were carried out to elucidate the reaction pathway. Deuterium labeling

experiments indicate that the mechanism involves opening of the aziridine ring by an initially formed propargylic anion (cf. **249**) to give the corresponding allylic anion (cf. **250**), which then undergoes a 5-*exo-dig*-cyclization to form a vinylic anion (cf. **251**) (Scheme 67) <1996TL2495>.



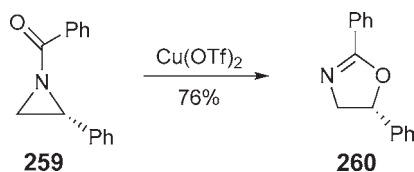
Scheme 67

The same ring strain that lends aziridines reactivity toward nucleophiles also makes them prone to ring-opening isomerizations and rearrangements. For example, the tetracyclic aziridine **252** underwent aza-pinacol rearrangement in the presence of boron trifluoride to give the tosyl imine **253**, which in turn could be trapped as the Diels–Alder adduct **254** <2002CC134>. Alternatively, base-catalyzed eliminative ring opening can be promoted with superbasic mixtures such as lithium diisopropylamide/potassium *t*-butoxide (LIDAKOR), as illustrated by the conversion of the protected aziridinyl alcohol **255** to the allyl amine derivative **256** <2002T7153, 2002CC778>. In the case of α -bromo aziridines (e.g., **257**), this elimination to allylamines can be promoted by electron transfer from magnesium metal in methanol (Scheme 68) <2002T7145>.



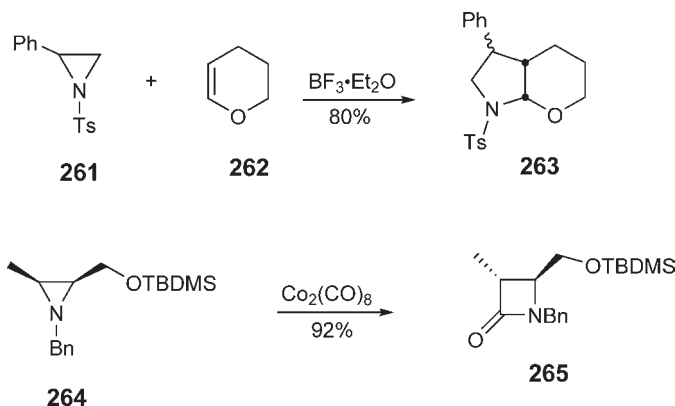
Scheme 68

Acylaziridines have been stereospecifically rearranged to give oxazolines, as illustrated by the copper(II) triflate-catalyzed conversion of the chiral aziridine **259** into (*R*)-oxytriphine **260**. Mechanistically, this transformation is believed to proceed via initial coordination of the amide nitrogen with the ‘azaphilic’ Lewis acid. This leads to the formation of an intermediate carbocation that exists as a tight ion pair in order to preserve the stereochemistry of the rearrangement (Scheme 69) <1998JOC4568>.



Scheme 69

Certain aziridines have been shown to engage in some interesting ring-expansion reactions. For example, phenylaziridine **261** behaved as a 1,3-dipole toward dihydropyran **262** in the presence of boron trifluoride etherate to give the bicyclic species **263**, which can be subsequently converted to substituted pyrrolidines <1999TL5315>. The silylated hydroxymethyl aziridine **264** undergoes carbonylative ring expansion promoted by dicobalt octacarbonyl to provide the functionalized β -lactam **265**, a process which proceeds with inversion of configuration (Scheme 70) <1999JOC518>.

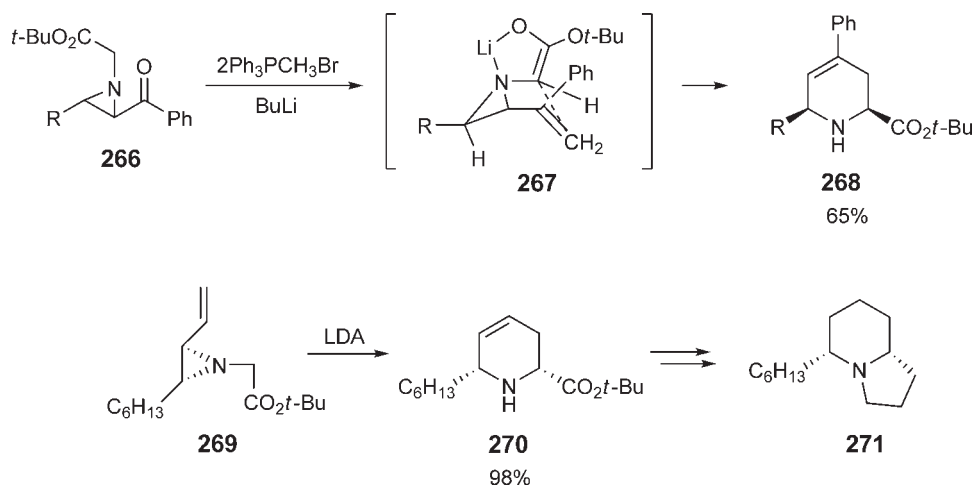


Scheme 70

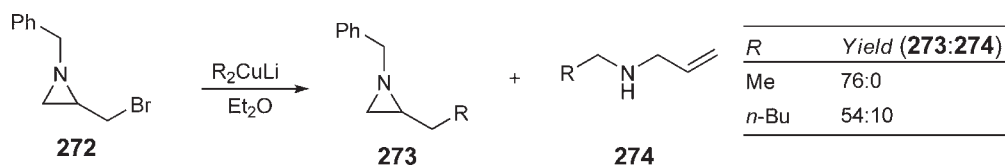
Coldham *et al.* <1995TL3557> and Somfai <1994CC2785, 1995TL1953> have independently investigated the ring expansion of vinyl aziridines to piperidines. Thus, Coldham *et al.* have prepared the unsaturated *cis*-piperidines **268** as single diastereoisomers in fair to good yield from the keto-aziridines **266** using a one-pot, two-step procedure. The stereochemical outcome is rationalized on the basis of the chelated intermediate **267**. In a related manner, Somfai has used this protocol for the enantioselective total synthesis of indolizidine 209D **271**, starting from aziridine **269** (Scheme 71).

De Kimpe and co-workers have found that (2-bromomethyl)-*N*-alkyl aziridines react with organocuprate reagents to provide largely the product of bromide displacement, **273** <2005SL931>. Most aliphatic organocuprates (e.g., R = Me, *n*-Bu) provide good yields of the displacement product **273**. When R = allyl, the sole product is **274** (40%), presumably via a competing electron-transfer or metal-halogen exchange reaction which then leads to ring opening (Scheme 72).

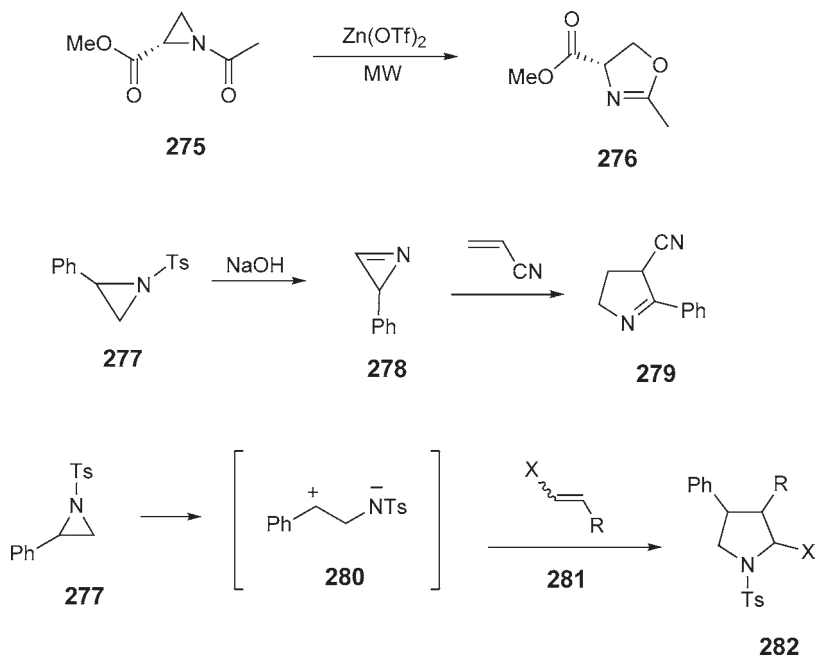
Aziridines can undergo a variety of synthetically useful rearrangement reactions which provide new heterocyclic species, as exemplified by the microwave-assisted ring expansion of *N*-acetyl 3'-aziridines **275** to oxazolines **276** <2001T2807, 2001EJO3545>, the formation of pyrrolines **279** in the presence of acrylonitrile and solid sodium hydroxide <2001T6993>, and thermal ring opening to a 1,3-dipole followed by capture with electron-rich alkenes to provide substituted pyrrolidines **282** (Scheme 73) <2001TL6087>.



Scheme 71



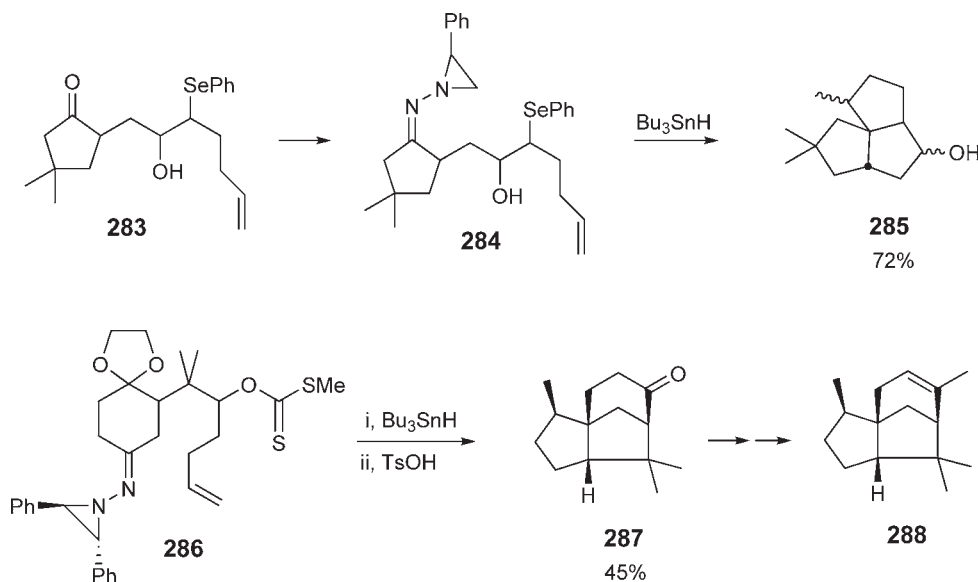
Scheme 72



Scheme 73

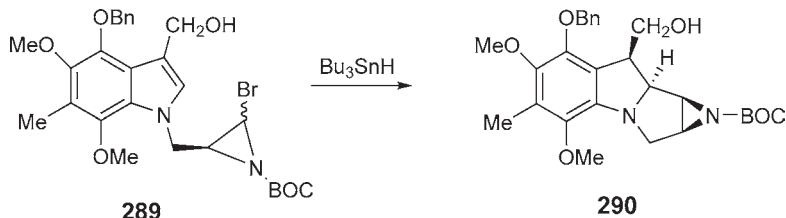
1.01.5.4 Radical Reactions

The aziridine functionality can also be synthetically useful in radical-based reactions. For example, the aziridinylamine group in the phenylselenane **284** serves as a convenient precursor for the generation of a radical center. The resulting carbon-based radical undergoes sequential cyclization to provide the tricyclic alcohol **285** in 72% yield [\(<1998SL981>\)](#). A similar sequence, using a chiral aziridine, was employed as a key reaction in a novel synthesis of α -cedrene **288** ([Scheme 74](#)) [\(<1998TL7713>\)](#).



Scheme 74

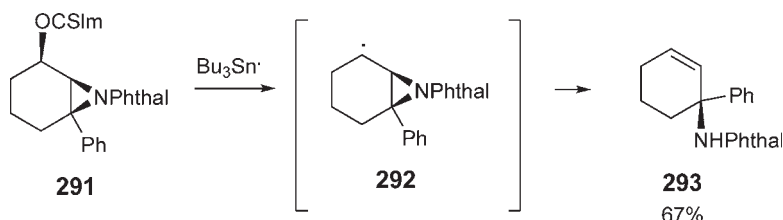
Radical centers can also be generated on the aziridine ring itself, which can then take part in further reaction with preservation of the heterocyclic entity. This process is demonstrated by the radical cyclization of the highly functionalized indole **289** to give the tetracyclic aziridine **290** in fair overall yield ([Scheme 75](#)) [\(<1998TL2455>\)](#).



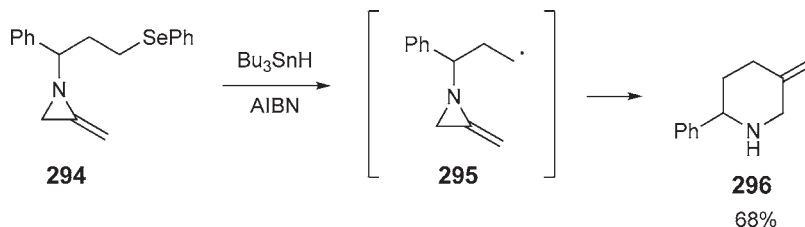
Scheme 75

Aziridinylcarbinyl radicals (e.g., **292**) are interesting reactive intermediates and were shown to undergo β -cleavage to form aminoalkenes (e.g., **293**), which are the products of C–N bond cleavage. The selectivity of the ring opening was rationalized on the basis of more effective overlap of the singly occupied π -orbital on the radical center with the C–N bond ([Scheme 76](#)) [\(<1999TL4873>\)](#).

An interesting radical variant involves the intramolecular 5-*endo*-cyclization of 3-(2-methyleneaziridin-1-yl)propyl radicals **295** to methylenepiperidine derivatives **296** ([Scheme 77](#)) [\(<2001OL2383>\)](#).



Scheme 76



Scheme 77

1.01.5.5 [3+2] Cycloaddition Chemistry

1.01.5.5.1 Azomethine ylide generation

Another interesting and synthetically useful reaction of aziridines is their tendency to open thermally to azomethine ylides, a process which can also be facilitated by Lewis acid catalysts. These reactive intermediates can be trapped by a variety of dipolarophiles to give new heterocyclic species. Methyl vinyl ethers convert aziridines such as **298** into a pyrrolidine derivative (i.e., **300**) in the presence of a zinc(salen) Lewis acid catalyst **297** (Salen = *N,N'*-bis(salicylaldehyde)ethylenediamine) <2004JA2294>. Similarly, nitriles (e.g., **302**) lead to the formation of 2,4-disubstituted-1*H*-imidazolines (e.g., **303**) under the catalysis of boron triethyloxonium tetrafluoroborate <2004TL1137>. Under almost-identical conditions, the aziridine–Lewis acid complex can be trapped with π -nucleophiles, such as a tethered olefin, to provide fused bicyclic pyrrolidines (e.g., **305**) <2004TL5011>. The reader is directed to a recent review dealing with the intramolecular dipolar cycloaddition reactions of azomethine ylides derived from substituted aziridines (Scheme 78) <2005CRV2765>.

1.01.5.6 [3+3] Annulation of Aziridines

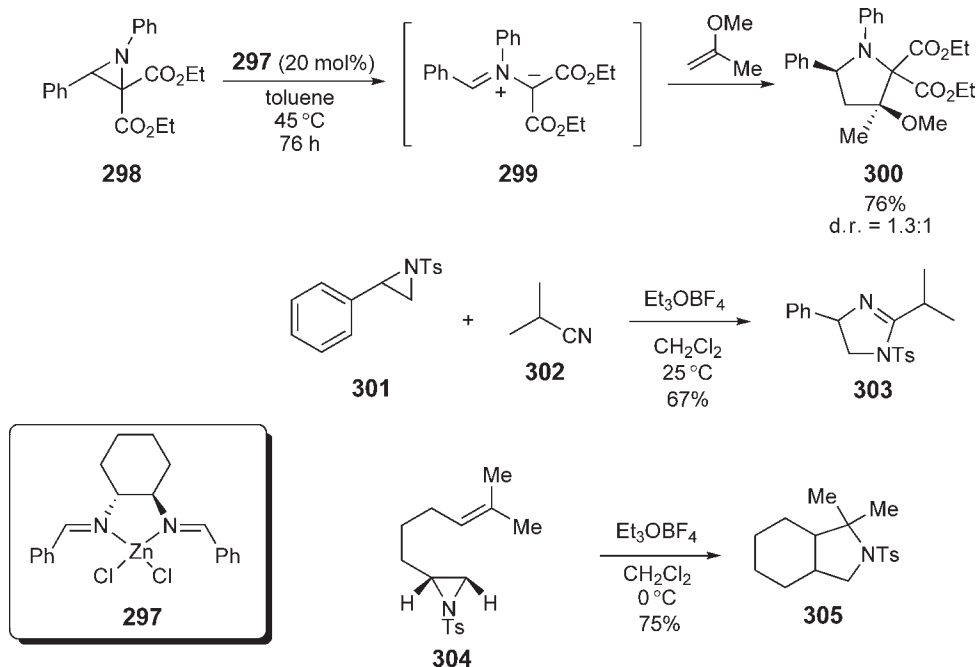
1.01.5.6.1 Stereoselective synthesis of functionalized piperidines

Work in the Harrity labs has focused on exploiting aziridines for the stereoselective synthesis of functionalized piperidines through a [3+3] annulation strategy. The initial studies centered on the employment of Trost's conjunctive reagent **306** in tandem with a palladium catalyst to deliver a series of enantiopure 2-alkyl piperidines with an exomethylene moiety at C-5 <2001SL1596, 2003JOC4286, 2003OL3427>. *N*-Tosyl-protected 2-substituted aziridines **307** underwent regioselective addition of the Pd–TMM complex at the least-hindered site and furnished the functionalized piperidines **308** (TMM = trimethylenemethane). This technique provides an expedient route to enantiopure 2-piperidines because the precursor aziridines are readily prepared in enantiomerically pure from the corresponding amino acids (Scheme 79) <1992SL41>.

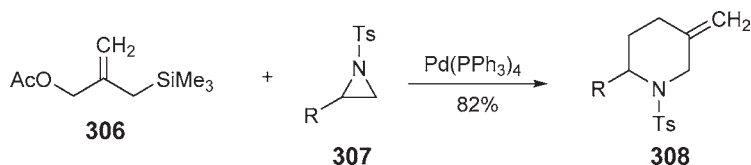
1.01.5.6.2 Grignard addition–cyclization reaction for piperidine synthesis

More recently, a stepwise formal [3+3] cycloaddition sequence via a Grignard addition–cyclization reaction leads to a much improved piperidine synthesis <2005OL2993>. This methodology provides improved flexibility in both the aziridine substrate and TMM equivalent. Double deprotonation of methallyl alcohol, transmetalation with MgBr_2 , and addition to aziridine **309** gave the corresponding adduct **310** in excellent yield. The Mitsunobu reaction of **310** provided the trisubstituted piperidine **311** in high yield but as an equal mixture of diastereomers at C-6 (Scheme 80). In a similar vein, a stepwise [3+3] annulation sequence was carried out by addition of the Büchi Grignard reagent **312** to aziridines. The initially formed ring-opened intermediate **313** was subjected to an acid-catalyzed deprotection–cyclization protocol

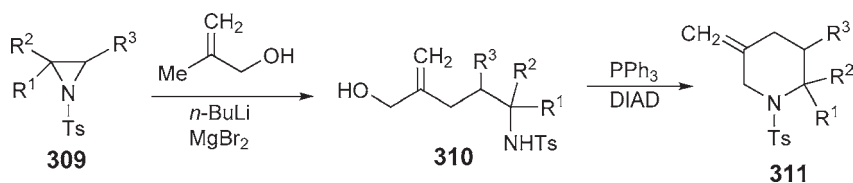
to produce tetrahydropyridine **314**, without loss of enantiopurity over the two steps. The methodology was used in the stereoselective synthesis of the alkaloid (–)-dihydropiridine. A similar [3+3] strategy was used by the Harrity group for the synthesis of several *Nuphar* alkaloids <2005JOC207> as well as for a formal synthesis of (±)-perhydrohistrionicotoxin (Scheme 81) <2006TL331>.



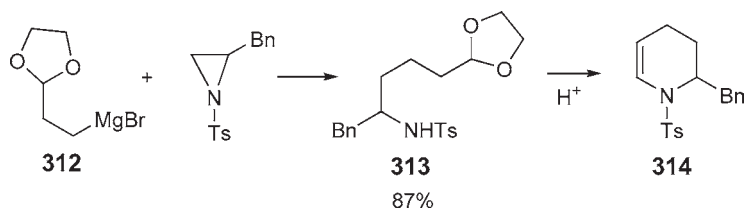
Scheme 78



Scheme 79



Scheme 80

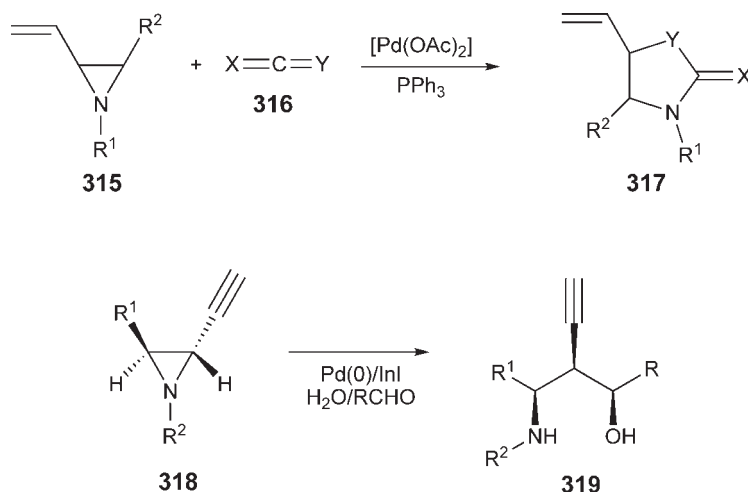


Scheme 81

1.01.5.7 Ring-Expansion Reactions

1.01.5.7.1 Ring expansion with heterocumulenes

Vinyl and alkynyl aziridines exhibit particularly interesting chemistry in the presence of palladium catalysts. Thus, 2-vinylaziridines undergo cycloaddition reactions with various heterocumulenes in the presence of $\text{Pd}(\text{OAc})_2$ and triphenylphosphine to give new five-membered heterocycles **317** in moderate to high yields. The mechanism is believed to involve an $\eta^3\text{-}\eta^1\text{-}\eta^3$ -interconversion of a $(\pi\text{-allyl})\text{palladium}$ intermediate <2000JOC5887>. Conversely, treatment of 3-alkyl-2-ethynyl-aziridines **318** with indium iodide in the presence of $\text{Pd}(\text{PPh}_3)_4$ and water gives intermediate allenylindium reagents which can undergo *in situ* addition onto aldehydes to afford 2-ethynyl-1,3-amino alcohols **319** bearing three chiral centers (Scheme 82) <2000OL2161>.



Scheme 82

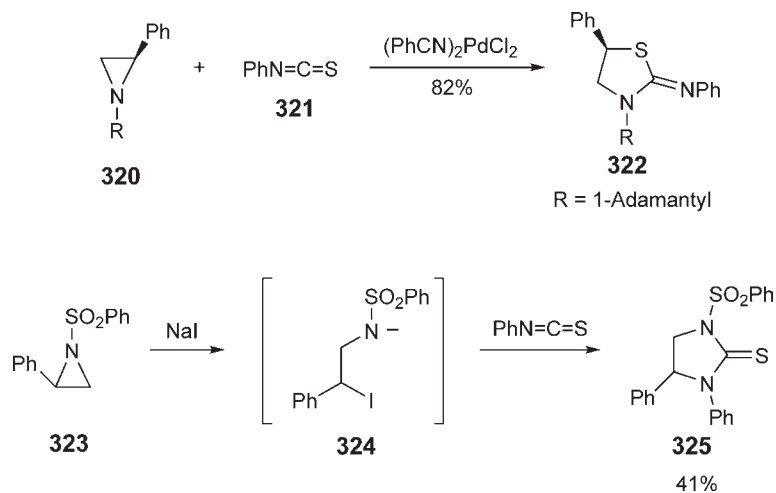
Alper and co-workers have reported the first enantiospecific palladium-catalyzed cycloaddition of aziridines with heterocumulenes. Thus, *N*-butyl phenylaziridine **320** reacts with phenyl isothiocyanate in the presence of $(\text{PhCN})_2\text{PdCl}_2$ to form thiazolidinimine **322** in good yield. This reaction proceeds with retention of configuration at the aziridine carbon center <1995JA4700>. Nadir and Basu have reported a very similar reaction involving the aziridine sulfonamide **323** and using sodium iodide as a catalyst. Based on spectroscopic evidence, these conditions provide the isomeric 2-imidazolidine-thione **325** rather than the thiazolidinimine. The reaction is believed to proceed via initial attack of iodide at the benzylic position to give an intermediate iodoamide **324**, which then condenses with the heterocumulene (Scheme 83) <1995JOC1458>.

1.01.5.7.2 Ring expansion with isocyanates

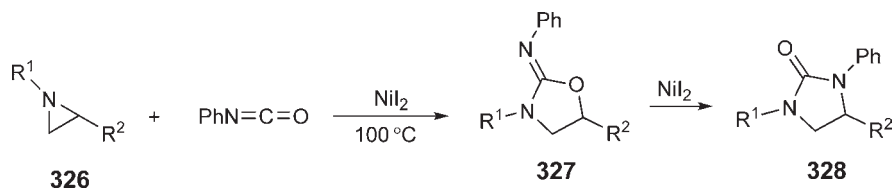
Cycloaddition of aziridines **326** with isocyanates proceeds smoothly in the presence of nickel catalysts and five-membered heterocycles **327** were isolated in good to high yields <2006OL379>. The best result was obtained when the reaction was carried out in the presence of NiI_2 . A longer reaction time resulted in the isomerization to the corresponding imidazolidinone derivative **328**. The mechanism suggested for the reaction involves cleavage of the aziridine ring by nucleophilic attack of iodide derived from NiI_2 . The resulting ring-opened nickel amine is a strong nucleophile and subsequently attacks the isocyanate to give the iminoxazolidine **327**. The subsequent isomerization proceeds to give the thermodynamically more stable isomer **328** (Scheme 84).

Enantiomerically pure *N,N*-disubstituted imidazolidine-2-one-4-carboxylates **332** can also be obtained in a one-step, simple, and highly efficient manner using a Lewis acid-catalyzed ring-expansion reaction of commercially available chiral aziridines with isocyanates. These reactions proceed both regio- and stereospecifically with retention of the configuration at the C-2 carbon of the chiral aziridines <2005CC3062>. The C(2)–N bond of the aziridine

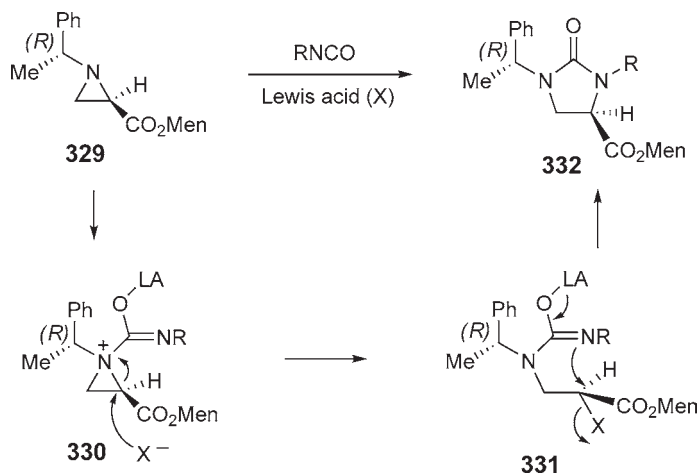
is regiospecifically cleaved by the bromide ion from MgBr_2 or the chloride ion from TMSCl via an $\text{S}_{\text{N}}2$ process as in **330**, and then an intramolecular cyclization by the urea amide nitrogen of **331** gives the corresponding imidazolidinone **332** which corresponds to overall retention of the configuration at C-2 of the original aziridine **329** (Scheme 85).



Scheme 83



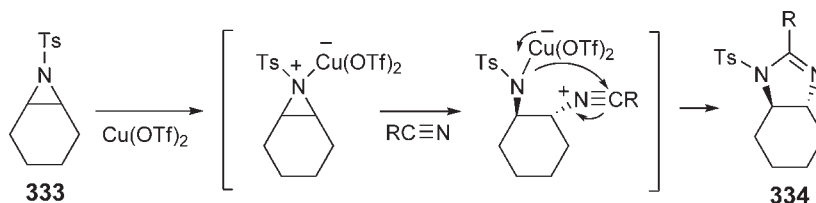
Scheme 84



Scheme 85

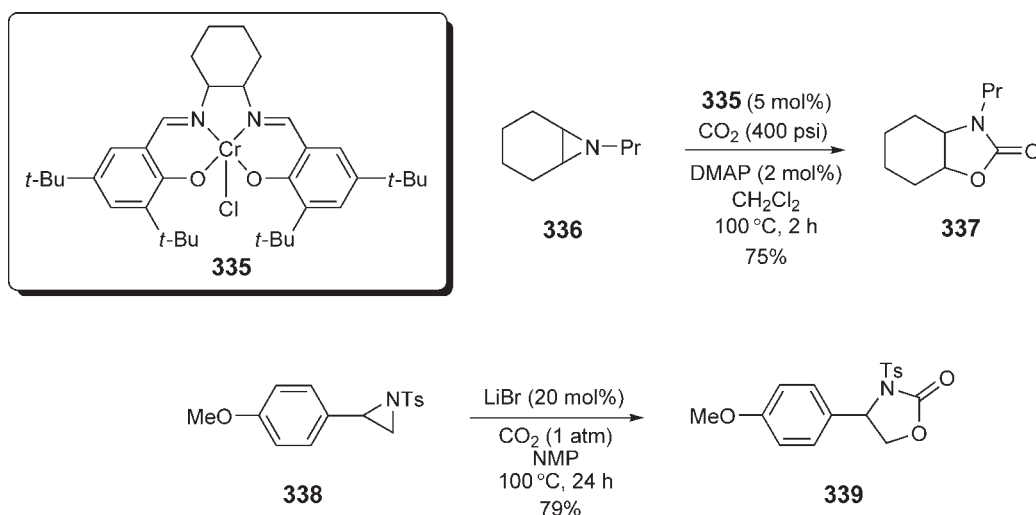
1.01.5.7.3 Ring expansion with nitriles

A direct and efficient route to imidazoline and pyrrolidine derivatives using copper(II) triflate-mediated [3+2] cycloaddition of various aryl, alkyl, and cycloalkyl *N*-tosylaziridines with nitriles and olefins as dipolarophiles has been reported <2006TL5399>. Formation of bicyclic imidazoline **334** with a *trans*-ring junction as a single product from aziridine **333** suggested that the reaction proceeded through an S_N2-type pathway (Scheme 86).



Scheme 86

The (salen)chromium complex **335** was shown to promote the insertion of carbon dioxide into aziridines (e.g., **336**) to yield the corresponding oxazolidinones (e.g., **337**), whereby the substrate is treated with CO₂ under high pressure (Parr reactor) in the presence of catalytic quantities of **335** and dimethylaminopyridine (DMAP) <2004OL2301>. Considerably milder conditions have been reported independently, in which lithium bromide serves as catalyst in a medium of *N*-methylpyrrolidone (NMP). For example, aryl aziridine **338** was converted to oxazolidinone **339** in 79% yield over 24 h. Use of the more-polar and higher-boiling solvent allows for delivery of CO₂ using a balloon at atmospheric pressure. Electron-donating substituents tend to accelerate the reaction (Scheme 87) <2004TL1363>.

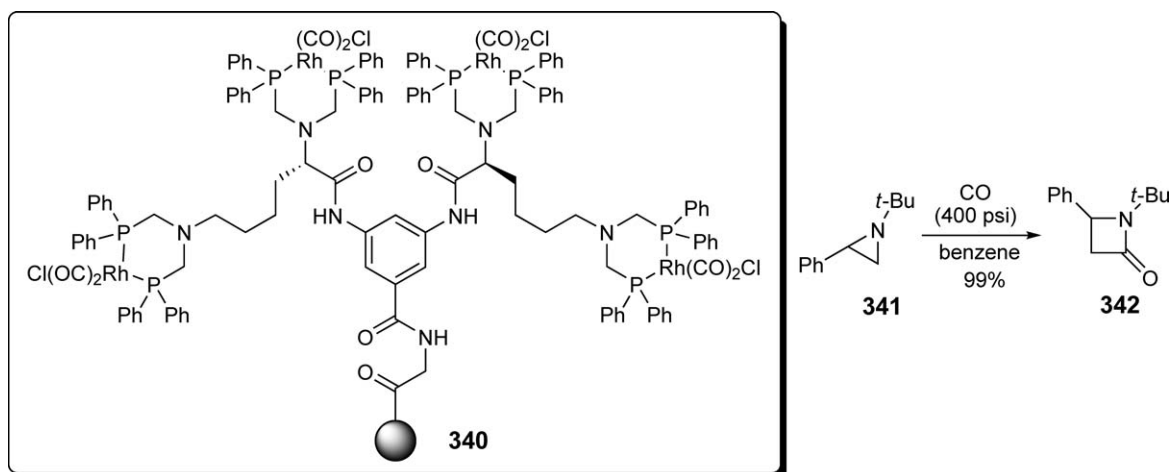


Scheme 87

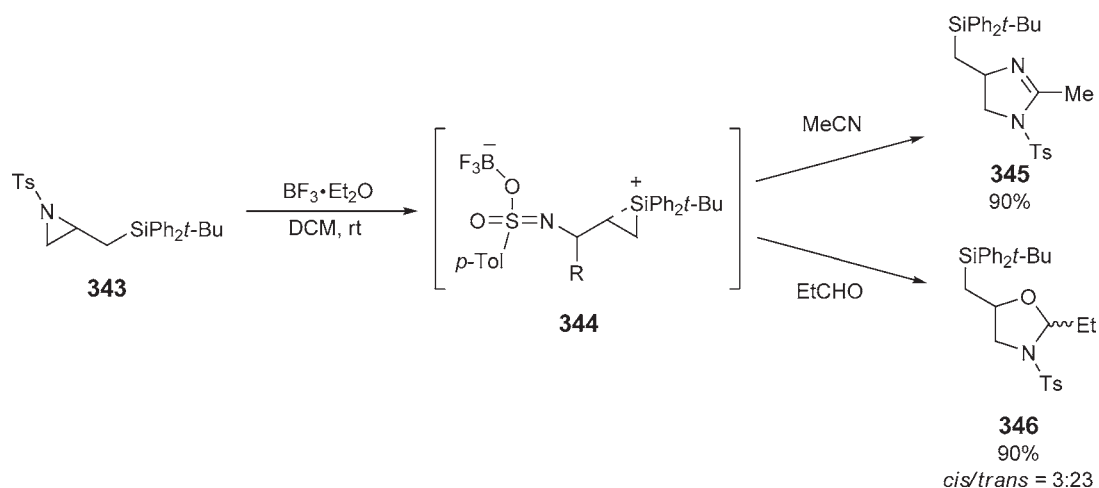
1.01.5.7.4 Carbonylative ring expansion

In a similar vein, a resin-supported rhodium-complexed dendrimer **340** has been shown to promote the carbonylative ring expansion of aziridines to β -lactams <1988CC710, 2006JHC11>, as illustrated by the conversion of the *N*-*t*-butyl aziridine **341** to the corresponding lactam **342** in almost quantitative yield. The supported catalyst, which shows reactivity comparable to the solution-phase variety, is easily recovered by filtration and exhibits no significant loss of activity upon recycling (Scheme 88).

The silicon β -effect has been exploited to convert aziridines to 2-imidazolines and oxazolidines <2005JA16366>. This reaction presumably goes through siliranium ion **344**, which can then react with an electrophile to form **345** or **346**. It has also been shown that zinc dihalides are effective in catalyzing the formation of **345**, but require elevated temperatures (Scheme 89) <2005TL4103>.



Scheme 88



Scheme 89

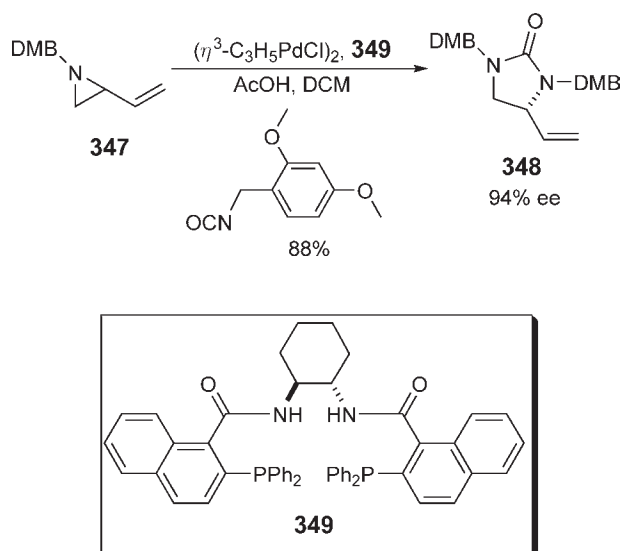
A dynamic kinetic asymmetric transformation (DYKAT) of racemic vinyl aziridine **347** yielded the enantiopure imidazolidinone **348** (Scheme 90) <2005OL823>. This transformation was the initial step in a total synthesis of (+)-pseudodistomin D.

1.01.5.8 Aziridinyl Carbanion Chemistry

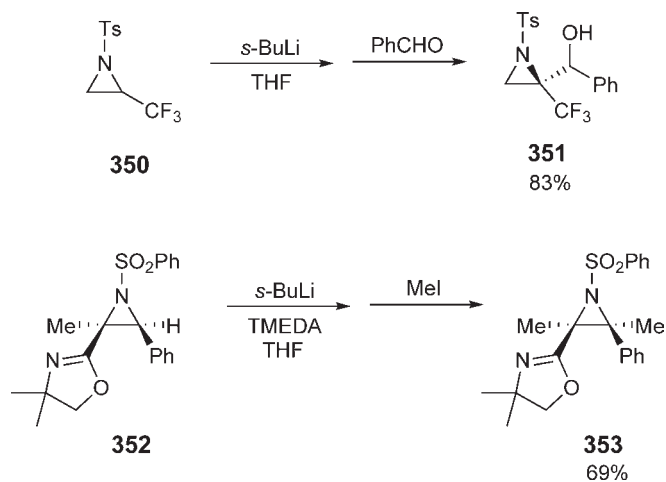
1.01.5.8.1 Aziridinyl carbanion with electron-withdrawing substituent

When one of the carbon atoms in the aziridine ring is equipped with an electron-withdrawing substituent, these substrates can often be cleanly deprotonated and used for subsequent carbanion chemistry. For example, the anion derived from the trifluoromethyl aziridine **350** engages in nucleophilic addition onto benzaldehyde to give the aziridinyl alcohol **351** in 83% yield <2003TL6319>. Similarly, deprotonation of the oxazolinylaziridine **352** followed by treatment with methyl iodide gave mainly the methylated product **353** (Scheme 91) <2003TL2677>.

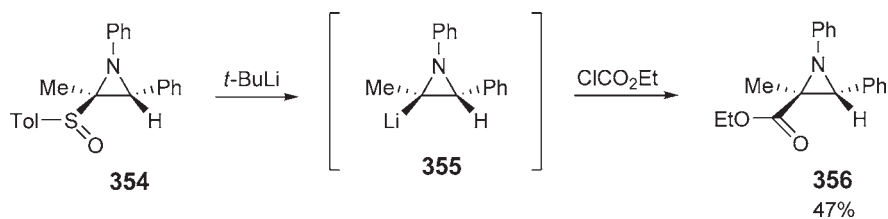
Sulfinylaziridines **354** can be converted to the corresponding carbanion **355** upon treatment with *t*-butyllithium. This anion has been captured with various electrophiles to give substituted aziridines **356** (Scheme 92) <1998TL2345>.



Scheme 90

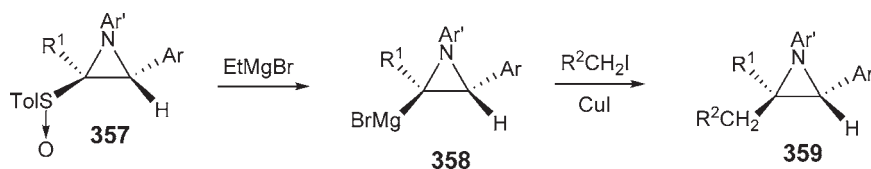


Scheme 91



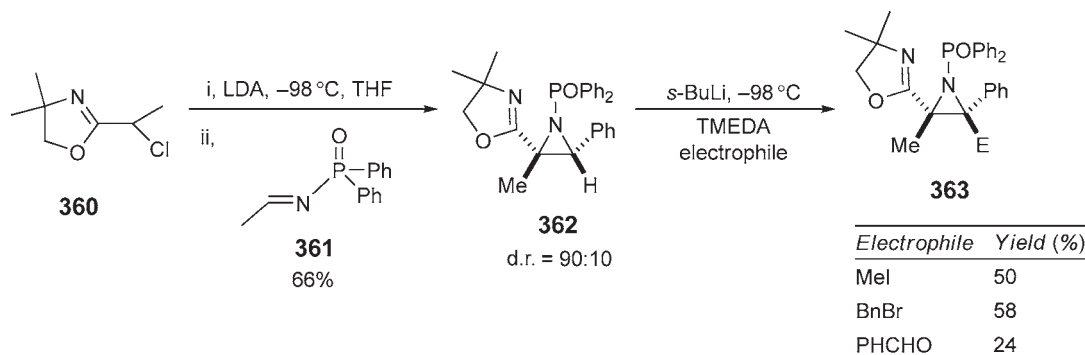
Scheme 92

Sulfonylaziridines of type **357** were found to undergo a clean metallation by ethyl Grignard with loss of the sulfoxide moiety to give the aziridinyl anions **358**, which in turn can be alkylated in the presence of copper(I) iodide to give new elaborated products **359** with the heterocyclic nucleus intact (Scheme 93) <2000TL6495>.



Scheme 93

The Darzens reaction of the oxazoline **360** with a series of aldimines has been shown to form aziridine **362** in good yields and with high diastereoselectivity <2005T3251>. Deprotonation of the aziridine to form the aziridinyl anion and subsequent reaction with an electrophile provide the highly substituted aziridines **363** in moderate yields. The diphenylphosphinyl group on the nitrogen provides optimal yields in the lithiation reaction (Scheme 94).



Scheme 94

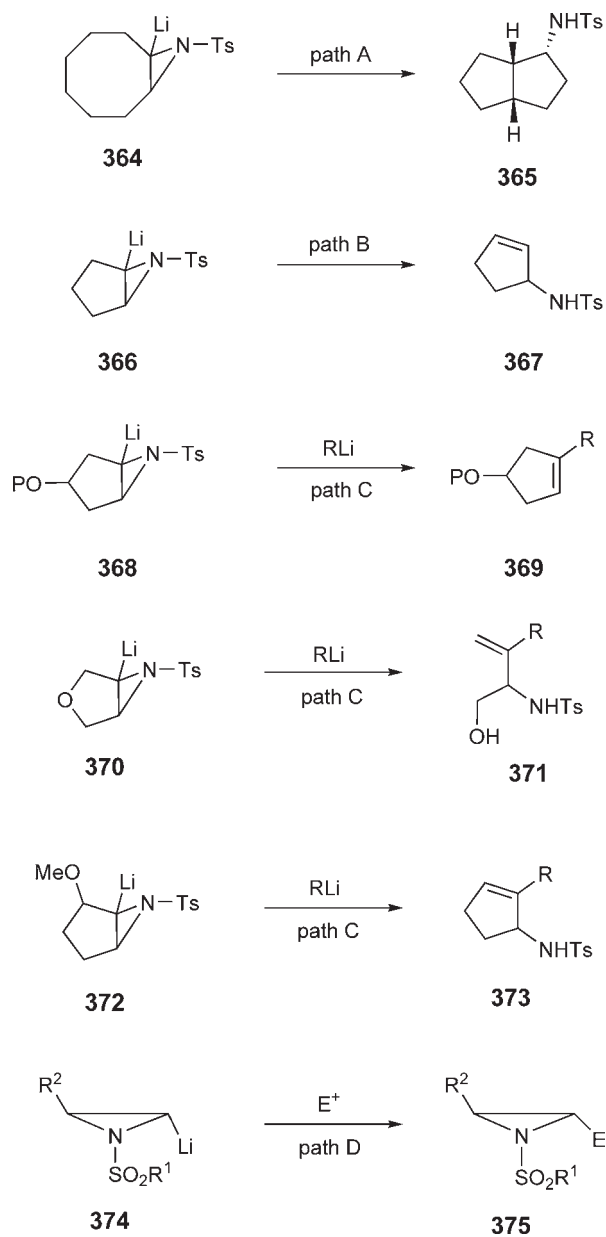
1.01.5.8.2 Reactions of lithiated *N*-sulfonylaziridines

In recent years, there has been significant interest in the development of novel synthetic transformations of lithiated *N*-sulfonylaziridines <2005CC5696, 2006OL995, 2001HCA662, 2004HCA227, 2003TL6613>. For lithiated aziridines generated by aziridine deprotonation using strong bases, at least four different reaction modes are known. Path A corresponds to an insertion into a CH bond. A typical example involves the transannular CH insertion reaction of **364** to give **365**. Path B involves insertion into an adjacent β -CH bond to produce an allylic amine (i.e., **366** $\rightarrow$ **367**). Path C proceeds by insertion into an organolithium reagent. This process has been referred to as a 'reductive alkylation' reaction and can occur with loss of the amino group to give alkenes <2003T9779>. The amino group can also be retained with the generation of a substituted allylic amine if there is a β -alkoxy group present (i.e., **370** $\rightarrow$ **371** and **372** $\rightarrow$ **373**) <2004CC2234, 2004OL4817>. Finally, path D involves the electrophilic trapping of lithiated terminal aziridines (i.e., **374** $\rightarrow$ **375**) (Scheme 95).

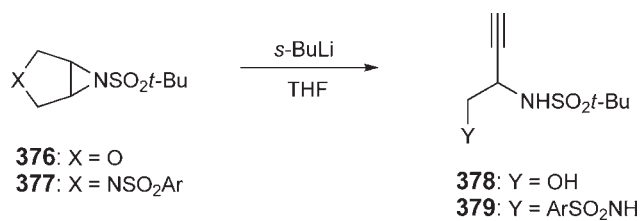
Recently, the O'Brien group has disclosed a new organolithium-mediated transformation of aziridines that had not been previously encountered <2005CC5696>. Thus, dihydrofuran **376** and dihydropyrrole *N*-benzenesulfonyl aziridine **377** were converted into alkynyl amino alcohols **378** and diamines **379**, respectively, using *sec*-butyllithium–PMDETA in THF (PMDETA = pentamethyldiethylenetriamine). The methodology provides an alternate and more direct route to protected alkynyl amino alcohols which are normally prepared in four to six steps from serine and have proved to be useful in the synthesis of natural and unnatural amino acids containing alkynyl, alkenyl, and cyclopropyl functionality (Scheme 96) <2003EJO3219>.

1.01.5.8.3 Trapping of lithiated *N*-sulfonylaziridines with electrophiles

Regio and stereoselective deprotonation of *N*-Bus (Bus = *t*-butylsulfonyl)-protected terminal aziridines **380** with lithium 2,2,6,6-tetramethylpiperidine proceeds smoothly to generate a nonstabilized aziridinyl anion **381** that undergoes *in situ* or external electrophile trapping to give *trans*-disubstituted aziridine **382** in good to excellent yields. No significant degradation of ee was observed during the deprotonation–*in situ* silylation of an enantio-enriched terminal aziridine <2005OL1153>. Anion trapping could be carried out with enolizable and nonenolizable carbonyl compounds, DMF, benzenesulfonyl fluoride, and carbon dioxide. While there are other indirect methods for aziridinyl

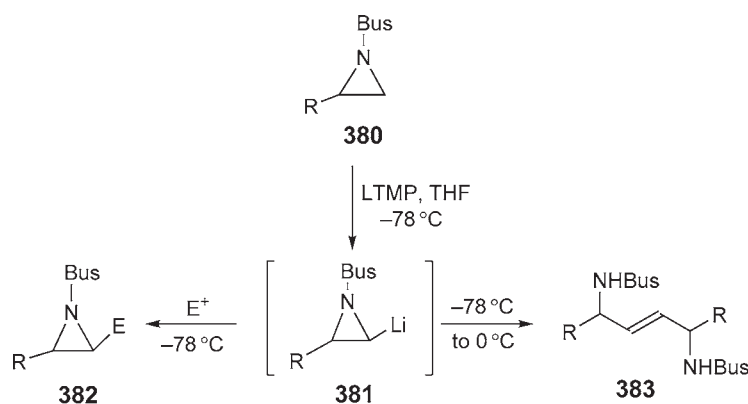


Scheme 95



Scheme 96

anion generation and electrophile trapping <1996CR3303, 1993JA1607, 2003T9803, 2003T9849, 2005AGE6169>, this procedure is attractive because it proceeds directly from simple terminal aziridines to give *trans*-disubstituted aziridines of type **382**. The latter retain a useful nitrogen protecting group to enable further synthetic transformations. Interestingly, when the temperature used for the deprotonation reaction was allowed to warm to 0 °C, the dimeric 2-ene-1,4-diamine **383** was isolated as the major product. The formation of this product clearly established the carbenoid reactivity of the α -lithiated aziridinyl anion **381** (Scheme 97) <2006AGE935>.

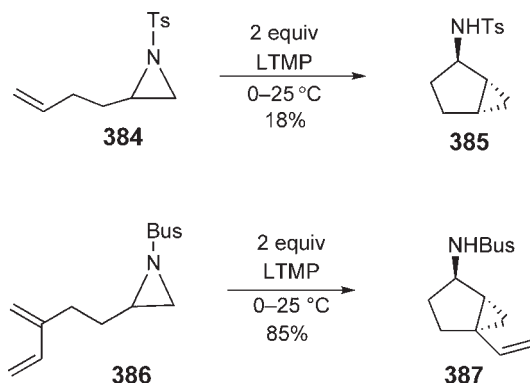


Electrophile	R	Yield (%)
TMSCl	SiMe ₃	86
PhCHO	CHOHPh	38
DMF	CHO	63
CO ₂	CO ₂ Me	63

Scheme 97

1.01.5.8.4 Intramolecular cyclopropanation of lithiated *N*-sulfonylaziridines

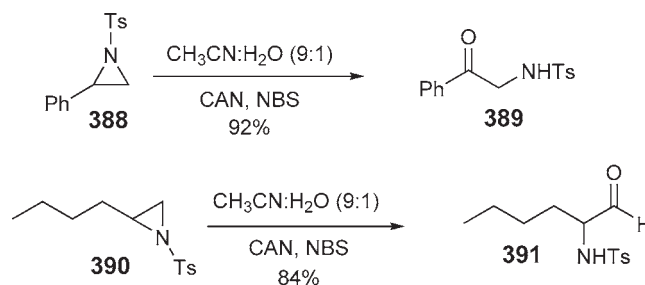
More recently, Hodgson *et al.* have found that aziridinyl anions can also undergo a diastereoselective intramolecular cyclopropanation reaction to give 2-aminobicyclo[3.1.0]hexenes in good yield <2006OL995>. Reversing the addition order so that the aziridine was added dropwise to the base led to increased yields of the bicyclic amine. When the dienyl-substituted aziridine **386** was used, an 85% yield of the 2-amino bicyclo[3.1.0]hexane **387** was obtained, which contains the potentially useful vinyl cyclopropane moiety (Scheme 98).



Scheme 98

1.01.5.9 Miscellaneous Reactions

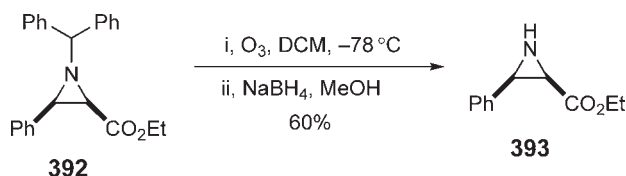
The regioselective oxidation of aziridines to α -tosylamino ketones has been accomplished via NBS and cerium(IV) ammonium nitrate (CAN) <2005TL4111>. Both styryl aziridines, **388**, and aliphatic aziridines, **390**, have been oxidized. A related report uses β -CDs in addition to NBS to catalyze the same transformation <2005TL1299>. These reaction conditions also work well for epoxides to provide the corresponding α -hydroxy ketones (Scheme 99).



Scheme 99

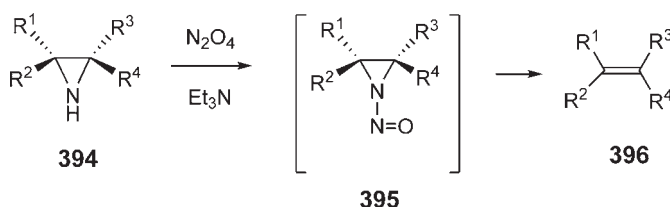
The transformation of aziridines that do not involve ring opening are rare due to the reactivity of the aziridine ring. Considering the somewhat more difficult synthesis of aziridines (relative to epoxides), the ability to convert one aziridine into another represents a significant expansion of the scope of any aziridine synthesis.

The deprotection of N-protected aziridines continues to be a problematic process. Many methods used to deprotect N-protected aziridines result in cleavage of the aziridine ring. The use of ozone to deprotect *N*-benzhydryl aziridines, **392**, has been reported <2005OL2201>. While the yields of this method were modest, this is an important new method for such deprotections (Scheme 100).



Scheme 100

An interesting deamination reaction of aziridines was reported, in which treatment of N-unsubstituted aziridines **394** with dinitrogen tetroxide (2 equiv) in the presence of Et₃N results in clean deamination to provide the corresponding alkenes **396** with remarkably high yields (>90%). The reaction is believed to proceed via the *N*-nitroso intermediate **395**, so that the driving force for the reaction is liberation of N₂O (Scheme 101) <1999SC1241>.



Scheme 101

1.01.6 Synthesis of Monocyclic Aziridines

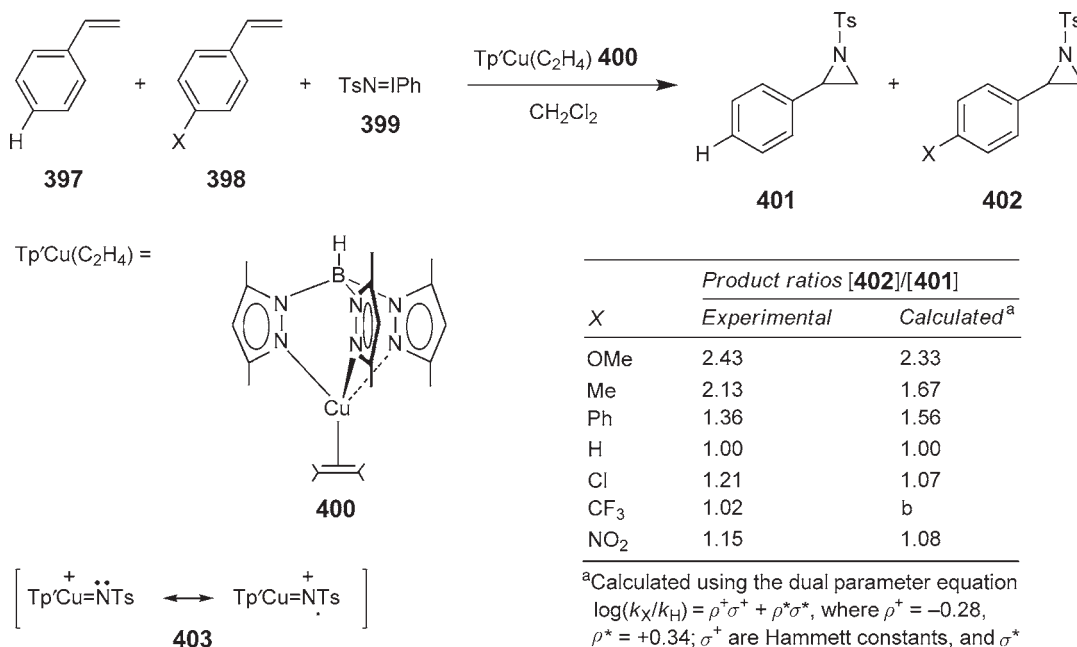
The synthesis of aziridines has been covered earlier in several major review chapters prior to 2007 <2003CRV29057, 2004T2701, B-2006MI1>. Murphree and Padwa have reviewed the literature of aziridine synthesis on a yearly basis, covering the period 1995–2005 <1995PHC43, 1996PHC43, 2000PHC52, 2001PHC52, 2002PHC75, 2003PHC54,

2004PHC55, 2005PHC81>. The synthetic scope of aziridine chemistry has blossomed in recent years, which is evident in a literature search by the term ‘aziridine review’ resulting in more than 140 hits of review articles in the last four decades. Among them, 40 reviews were published since the year 2000, averaging over six reviews per year. The many reviews on aziridine chemistry all contain sections on their synthesis. Representative examples of all the useful methods for monocyclic aziridine synthesis are presented below. Synthetic methodologies for the preparation of aziridines include nitrenation of alkenes [N+C=C], methylenation of imines [C+C=N], and cyclization of 1,2-amino alcohols, 1,2-amino halides, and 1,2-azido alcohols. In addition to coverage of new methods published since CHEC-II(1996), later examples of older methods are reported.

1.01.6.1 Metal-Catalyzed Reactions Using Aryliodanes

Olefin-aziridination reactions are typically accomplished by using a nitrene-transfer reagent. The nitrogen source for this reaction, a nitrene or nitrenoid, can be generated in various ways: (1) thermolytic or photolytic decomposition of organyl azides; (2) base-induced α -elimination of metal halides from metal *N*-arenesulfonyl-*N*-haloamides; (3) α -elimination of HX from an amine or amide with an electronegative atom X (X = halogen, O) attached to the NH group; (4) metal-catalyzed reaction of [*N*-(alkane/arenesulfonyl)imino]aryliodanes; (5) oxidation of a primary amine; and (6) thermally induced cycloreversion. Over the past decade, the metal-catalyzed conversion of [*N*-(alkane/arenesulfonyl)imino]aryliodanes with the formation of a metal-stabilized nitrene intermediate has been widely exploited and investigated with respect to the effect of varying (1) the olefinic substrate; (2) the nature of the nitrene source; (3) the alkane- or arenesulfonylimino group or the aryl iodide moiety in [*N*-(alkane/arenesulfonyl)imino]aryliodanes; (4) the transition metal catalyst; (5) the ligand for the complexation of the metal, in particular, the chiral ligand for asymmetric aziridination reactions; and (6) the solvent and other conditions for optimizing the aziridination reaction <2006ACR194, 2005COR657>.

Relative rates of the aziridination of styrene **397** versus a series of *para*-substituted styrenes **398** furnishing the respective aziridines **401** and **402** have been determined using $\text{Tp}^*\text{Cu}(\text{C}_2\text{H}_4)$ (Tp^* = hydridotris(3,5-dimethyl-1-pyr-azoly)borate) **400** as the copper precatalyst in combination with $\text{PhI}=\text{NTs}$ **399** as the nitrene source. The experimental data of the aziridination reaction can be fit with a two-term equation of the type $\log(k_X/k_H) = \rho^+ \sigma^+ + \rho^* \sigma^*$ (σ^+ are Jackson's radical substituent constants) leading to the values $\rho^+ = -0.28 \pm 0.06$ (polar contribution) and $\rho^* = +0.34 \pm 0.13$ (radical contribution). A paramagnetic copper nitrene species **403**, which behaves as an electrophilic nitrogen-centered radical, has been proposed as the intermediate for the aziridination reaction (Scheme 102) <1997OM4399>.



^aCalculated using the dual parameter equation $\log(k_X/k_H) = \rho^+ \sigma^+ + \rho^* \sigma^*$, where $\rho^+ = -0.28$, $\rho^* = +0.34$; σ^+ are Hammett constants, and σ^* are Jackson's constants.

^bNo σ^* available.

Scheme 102

A detailed study of the aziridination of styrene contrasting the use of $\text{PhI}=\text{NTs}$ and $\text{PhI}=\text{NNs}$ as nitrene donors with both the homogeneous catalyst, $\text{Cu}(\text{OTf})_2$, and the heterogeneous catalyst, copper-exchanged zeolite Y (CuHY), has been carried out in order to find optimal conditions. The ratio of styrene/nitrene donor significantly affects the yield of the aziridine formed and the enantioselection when a chiral bis(oxazoline) ligand is added to the reaction. In general, a slight excess of the nitrene donor gives the best results (styrene/nitrene donor 1:1.5), and high ee's ($\geq 85\%$) can be achieved with the heterogeneous catalyst, particularly when $\text{PhI}=\text{NNs}$ is used as the nitrene donor. Coordinating solvents (acetonitrile, nitromethane) give the highest yields of the aziridine, but with CuHY , high ee's are only obtained with acetonitrile. With respect to the requirements of the structure of the chiral modifier, the heterogeneous catalyst can give high enantioselection for many ligands such as **404** (Figure 1).

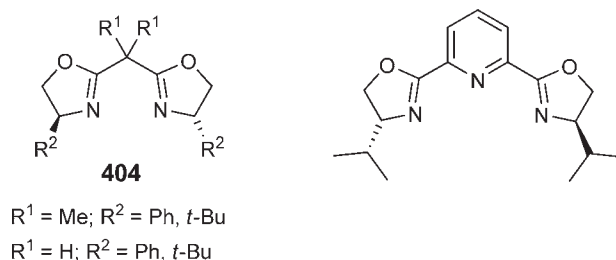
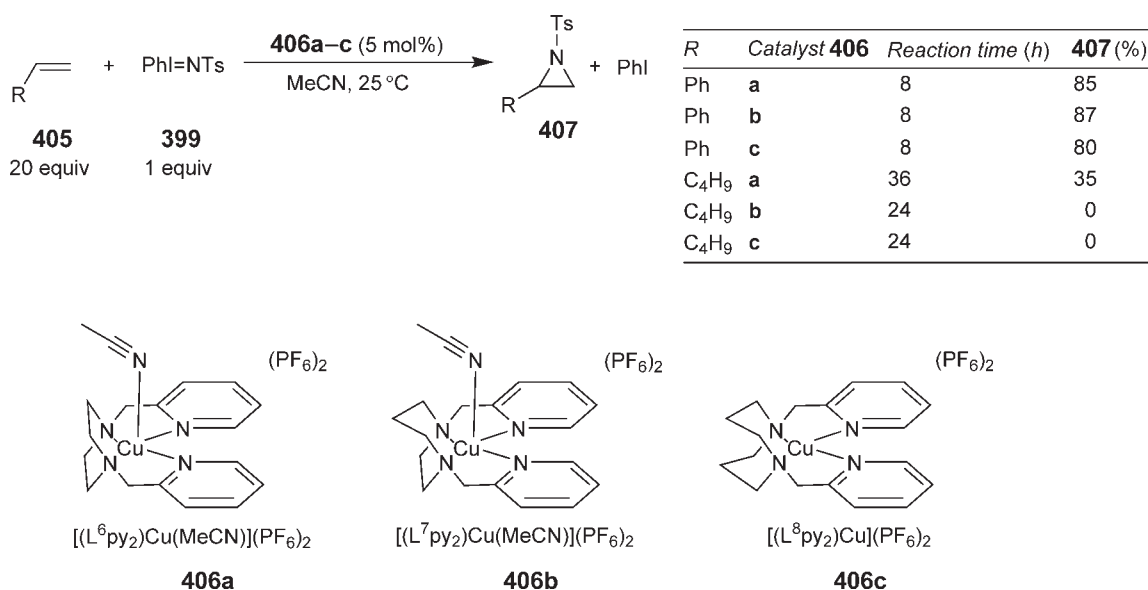


Figure 1

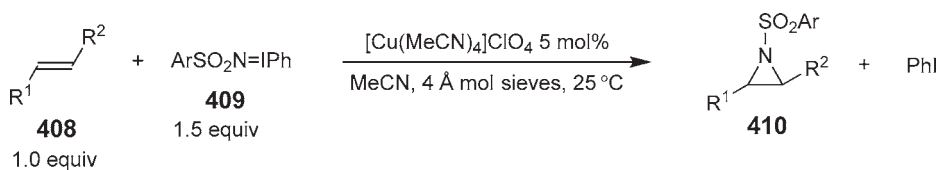
Copper(II) complexes of 2-pyridylmethyl-appended diazacycloalkane ligands **406a–c** are efficient catalysts for the aziridination of alkene **405a** with $\text{PhI}=\text{NTs}$ **399** (forming aziridine **407**), while only **406a** exhibits significant catalytic nitrene-transfer reactivity with 1-hexene (Scheme 103) <2000IC4903>.



Scheme 103

A series of [*N*-(arenesulfonyl)imino]phenyliodanes **409** have been evaluated for their utility as nitrene precursors for the copper-catalyzed $[\text{Cu}(\text{MeCN})_4\text{ClO}_4]$ aziridination of various olefins **408**. Best results were obtained with

4-nitro- and 4-methoxy-substituted [*N*-(benzenesulfonyl)imino]phenyliodanes (**409**; Ar = 4-O₂NC₆H₄, 4-MeOC₆H₄, respectively), both of which were found superior to [*N*-(benzenesulfonyl)imino]phenyliodane (Ar = Ph). Using 1.0 equiv of olefin **408** and 1.5 equiv of the nitrene precursor **409**, the corresponding aziridine products **410** were obtained in good to excellent yields (60–99%) (Scheme 104) <1997TL6897>.



<i>R</i> ¹	<i>R</i> ²	<i>Ar</i>	Conditions ^a	410 (%)
Ph	H	4-O ₂ NC ₆ H ₄	A	99
C ₈ H ₁₇	H	4-O ₂ NC ₆ H ₄	B	70
Bn	H	4-MeC ₆ H ₄	B	48
Bn	H	4-O ₂ NC ₆ H ₄	B	71 ^b
Ph	Me	4-O ₂ NC ₆ H ₄	A	97
Ph	CO ₂ Me	4-MeC ₆ H ₄	A	40
Ph	CO ₂ Me	4-O ₂ NC ₆ H ₄	A	62
Ph	CO ₂ Me	4-MeOC ₆ H ₄	A	60 ^b

^aMethod A: slow addition (3 h) of 1.5 equiv **409**;
method B: 1.5 equiv **409** added at once.

^bReaction at 0 °C.

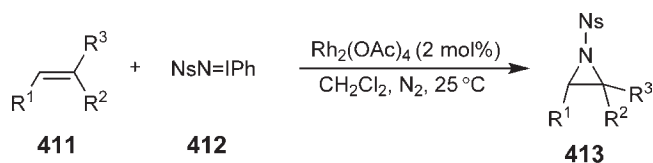
Scheme 104

Rhodium(II)-based catalysts such as Rh₂(OAc)₄ have been found to be less efficient in the reaction of styrene with [*N*-(4-toluenesulfonyl)imino]phenyliodane (59% yield), but the reaction proceeds well with [*N*-(4-nitrobenzenesulfonyl)imino]phenyliodane (NsN=IPh **412**) at room temperature <1996T1543>. The aziridination of (*E*)- and (*Z*)-alkenes with NsN=IPh **412** occurs stereospecifically in some cases as with (*E*)- and (*Z*)-1-propenylbenzene, (*E*)- and (*Z*)-2-hexene affording the corresponding *cis*- and *trans*-2,3-disubstituted *N*-(4-nitrobenzenesulfonyl)aziridines. A mixture of *cis*- and *trans*-aziridines **413** results from the reaction of *cis*-stilbene; the *trans*-aziridine isomer derived from *trans*-stilbene suffers phenyl migration induced by Rh₂(OAc)₄ and rearranges to give rise to *N*-(2,2-diphenylvinyl)-4-nitrobenzenesulfonamide (Scheme 105) <1996T1543>.

Aziridination of olefins of type **414** using PhI=NTs **399** is efficiently catalyzed by copper(II) acetylacetonate immobilized in ionic liquids such as bmimBF₄ or bmimPF₆, providing good yields of aziridines **415** at a faster rate than the earlier reported methods and with the additional benefit of easy catalyst/solvent recycling (bmim = 1-butyl-3-methylimidazolium, Scheme 106) <2004SL525>.

Nitrene or nitrene precursors such as [*N*-(*p*-toluenesulfonyl)imino]phenyliodane **399** can add to an alkene **416** forming an aziridine **417** and/or can insert into the allylic C–H bond forming an allylamine derivative **418**. Depending on the transition metal catalyst used (in combination with a complexing ligand), the reaction of nonactivated alkenes with [*N*-(*p*-toluenesulfonyl)imino]phenyliodane **399** as the nitrene source results predominantly in allylic amination with aziridination as a side reaction <2005JOM(690)2142>. The reaction has been extensively studied with cyclohexene **416b**, using Co(II) catalysts Co(II) (2*Z*,4*E*,8*E*,10*Z*)-4,9-dimethyl-5,8-diaza-2,4,8,10-dodecatetraene-2,11-diolate (Co(acacen), **420**) and Co(II) tetraphenylporphyrin dianions (Co(TPP), **421**). The reaction conditions (solvent, reaction time, and the ratio TsN=IPh **399**/catalyst) determine the ratio between aziridine **417** and the allylic amination product **418**, which is also formed (Scheme 107).

Experimental observations of the aziridination of styrene-type alkenes, catalyzed by CuPF₆ in the presence of chiral diimine ligands (such as (1*R*,2*R*,*N*¹*E*,*N*²*E*)-*N*¹,*N*²-bis(2,6-dichlorobenzylidene)cyclohexane-1,2-diamine **425**), have been taken as evidence of the intermediacy of a discrete, monomeric Cu(III)–nitrene complex, (diimine)Cu=NTs **423**. Variation of the steric properties of the aryl group in the oxidant TsN=IAr (Ar = Ph, 2-*t*-Bu-4,5,6-Me₃C₆H) has no effect on the enantioselectivities in forming the aziridination products **424** (Scheme 108) <1995JA5889>.



R^1	R^2	R^3	Time (h)	413 (%)
Ph	H	H	2.3	85 ^a
4-MeC ₆ H ₄	H	H	0.5	76 ^a
4-AcOC ₆ H ₄	H	H	0.75	82 ^a
3-O ₂ NC ₆ H ₄	H	H	0.5	46
C ₄ H ₉	H	H	1.0	63
AcO	H	H	4.0	47
Ph	H	Me	18	68
Ph	Me	H	0.25	82
C ₃ H ₇	H	Me	0.5	27
C ₃ H ₇	Me	H	0.5	54
Ph	H	Ph	36	41 ^b
Ph	Ph	H	19	18 ^c
H	Ph	Ph	0.2	59 ^d

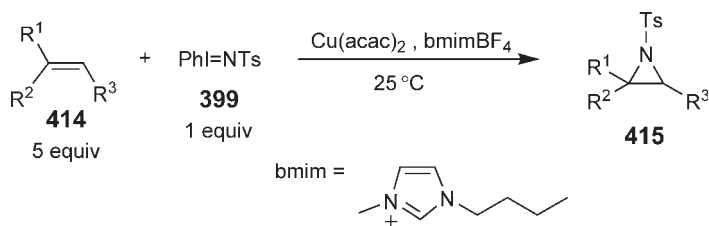
^a5 mmol **412**.

^bRearrangement to *N*-(2,2-diphenylvinyl)-4-nitrobenzenesulfonamide in 36 h, 11%.

^c(*E/Z*)-ratio 23:77.

^d10 mmol **412**.

Scheme 105

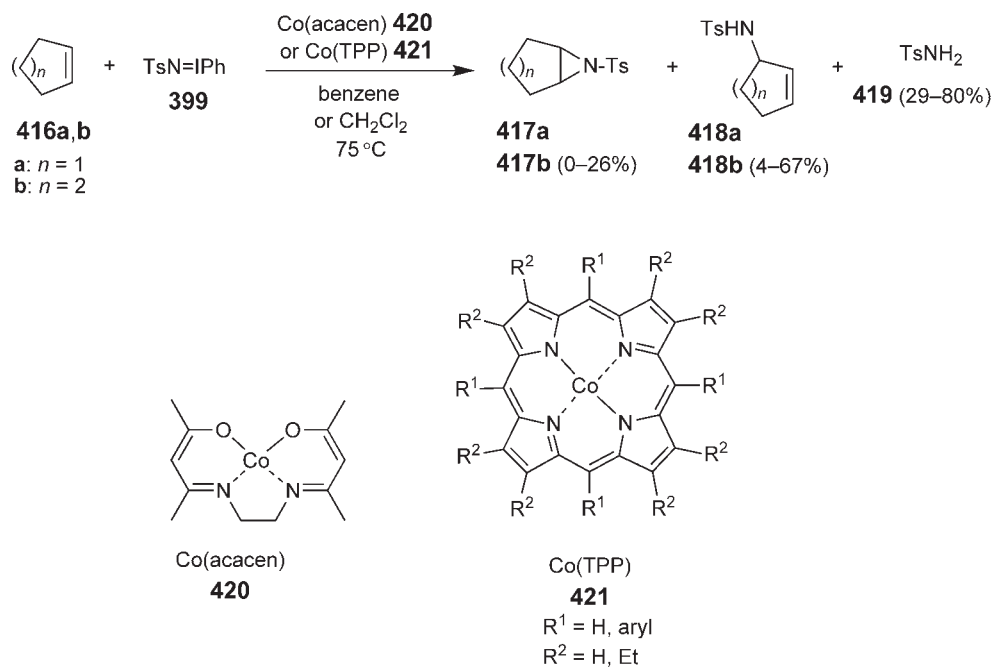


R^1	R^2	R^3	Reaction time (min)	415 (%)
Ph	H	H	25	88
Ph	H	H	25	84 ^a
Ph	H	H	60	95 ^b
Ph	H	Me	10	87
Ph	Me	H	15	78
C ₆ H ₁₃	H	H	10	65
Ph	H	CO ₂ Me	10	78

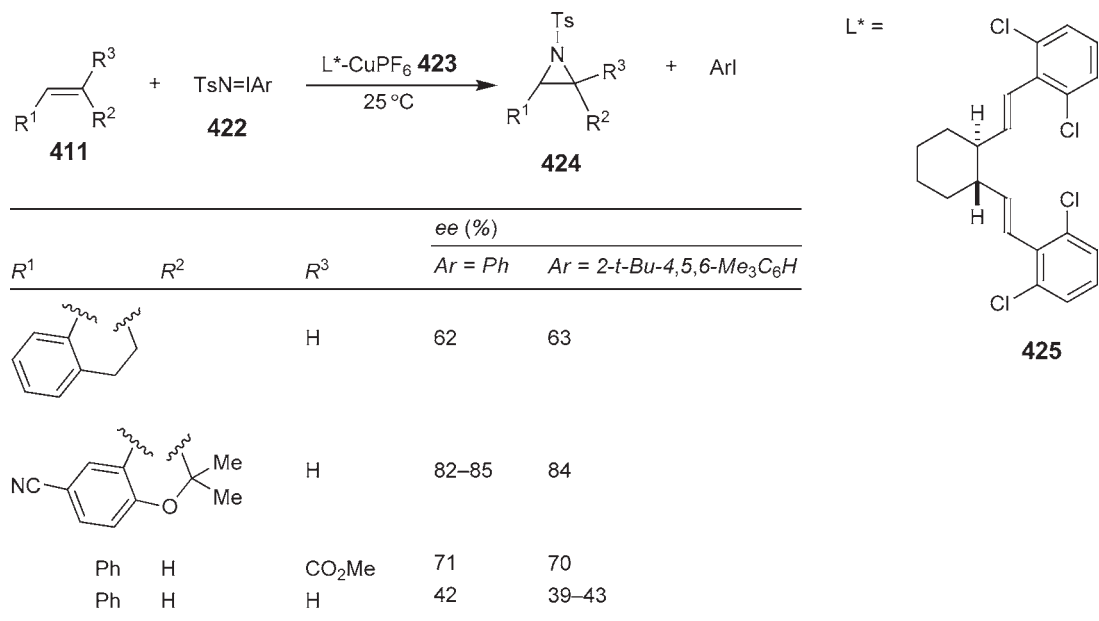
^aWith bmimPF₆.

^bMeCN as solvent.

Scheme 106

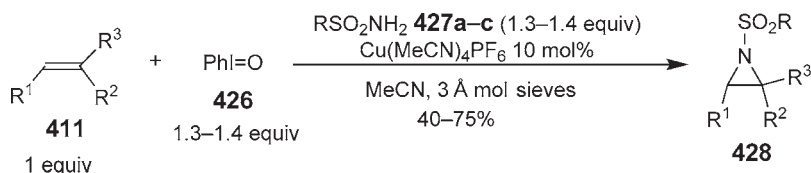


Scheme 107



Scheme 108

A major drawback of the aziridination reaction of olefins is the preparation and isolation of iminoiodanes, some of which have been reported to be unstable and explosive <1997TL6897, 1996CRV1123>. The nitrogen transfer from sulfonamides such as *p*-toluenesulfonamide **427a**, 4-methoxybenzenesulfonamide **427b**, and 2-(trimethylsilyl)ethanesulfonamide (SesNH₂, **427c**) has been shown to be mediated by the primary oxygen source iodosylbenzene (PhI=O, **426**); thus, alkenes **411** are converted into aziridines **428** in a one-pot reaction (Scheme 109) <2001JA7707>.

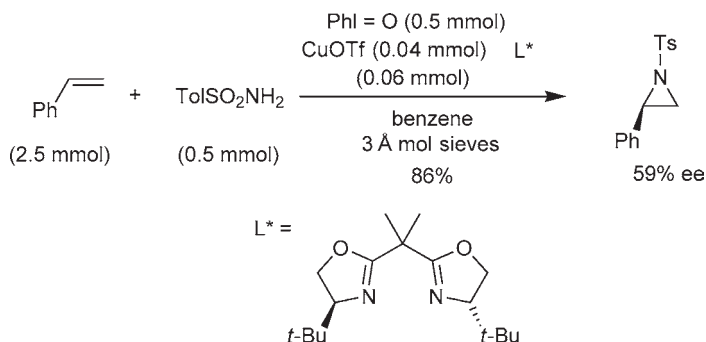


411: R¹, R², R³ = Ph, H, H; H, Me, CO₂Me; Ph, H, CO₂Me; H, H, CO₂Me; Me, Me, CO₂Me; cyclohexene, norbornene, 1,2-dihydronaphthalene

427a: R = 4-MeC₆H₄; **427b**: 4-MeOC₆H₄; **427c**: Me₃SiCH₂CH₂ (Ses)

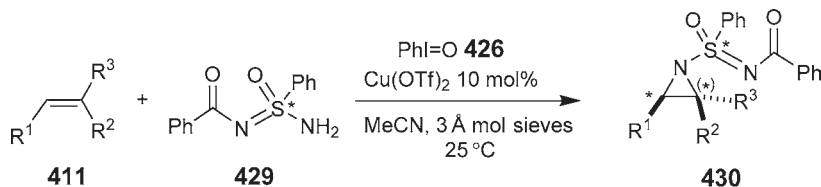
Scheme 109

The asymmetric copper-catalyzed aziridination of styrene with *p*-toluenesulfonamide, iodosylbenzene, and 2,2-bis[(4*S*)-*t*-butyl-1,3-oxazolin-2-yl]propane catalyst (Evans catalyst) provided the aziridine product with an ee comparable with that previously obtained (Scheme 110) <2001JA7707>.



Scheme 110

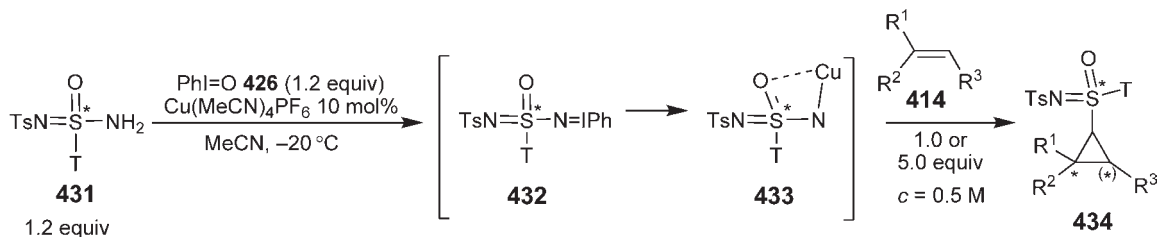
The reaction of *N*-[*S*-(benzoylimino)-*S*-phenylsulfonyl]amide **429** with iodosylbenzene **426** leads efficiently to nitrene intermediates that convert olefins **411** into aziridines **430** in good yields, through a copper(II)-mediated (Cu(OTf)₂) reaction. Owing to the stereogenic sulfur atom present in the molecules, the reactions proceed with some degree of diastereoselectivity (Scheme 111) <2004OL3573>.



R ¹	R ²	R ³	430 (%)	d.s.
Ph	H	H	78	52:48
2-BrC ₆ H ₄	H	H	64	60:40
H	CO ₂ Me	Me	43	58:42
Me	Me	Me	59	55:45

Scheme 111

The chiral sulfur(vi) reagent, *N*-[[*S*-(*p*-toluenesulfonimido)-*S*-(*p*-tolyl)]sulfonyl]amide **431** upon reaction with iodosylbenzene **426** affords *in situ* the chiral iminoiodane **432**. In the presence of Cu(MeCN)₄PF₆ as catalyst, iminoiodane **432** forms the complex **433** that very efficiently transfers the nitrene moiety together with the stereogenic information under stoichiometric conditions to a variety of alkenes **414**: the corresponding aziridines **434** were obtained with diastereoselectivities up to 60% (Scheme 112) <2004OL4503>.



T = 4-MeC₆H₄

Ts = 4-MeC₆H₄SO₂

R ¹	R ²	R ³	434^a		434^b	
			(%)	de (%)	(%)	de (%)
CO ₂ Me	H	H	81	50	93	55
CO ₂ Me	Me	H	96	41	97	38
CO ₂ Me	H	Me	35	50	63	60
CO ₂ Me	Me	Me	92	38	90	40
C ₅ H ₁₁	H	H	60	10	78	10
C ₃ H ₇	H	Me	40	<10	73	<10
H	C ₃ H ₇	Me	57	<10	79	<10
Ph	H	H	63	20	96	<10

^aWith 1.0 equiv of **431**.

^bWith 5.0 equiv of **431**.

Scheme 112

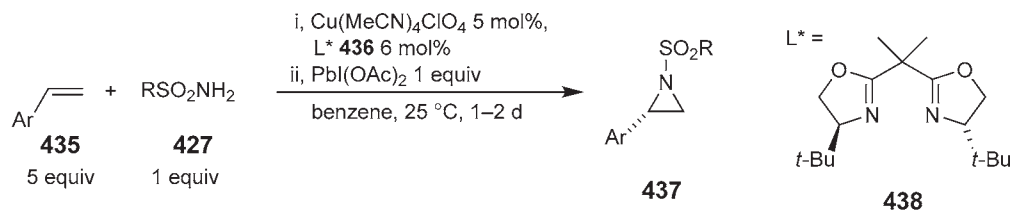
A one-pot procedure designed for the aziridination of a series of styrene derivatives employs commercially available iodobenzene diacetate [PhI(OAc)₂] and sulfonamides (**427**, RSO₂NH₂) to generate the nitrene precursors [*N*-(arene/methanesulfonyl)imino]phenyliodanes (RSO₂N=IPh) *in situ*. The reaction is carried out in the presence of the chiral catalyst Cu(MeCN)₄ClO₄-L* (**436**; L* = 2,2-bis[2-[(4*S*)-*t*-butyl-1,3-oxazolynyl]]propane) to give aziridine **437** (Scheme 113) <2004TL3965>.

[*N*-[(Trimethylsilyl)ethanesulfonyl]imino]phenyliodane (SesN=IPh **439**) proved useful for the copper-catalyzed aziridination of alkenes of type **411**. In comparison to TsN=IPh, its isolation is much easier, while their reactivities, that is, yields of aziridine products **440**, are comparable (Scheme 114) <1999JOC5304>.

The classical methods for the aziridination of alkenes involve the use of [*N*-(arylsulfonyl)imino]phenyliodanes (e.g., **442**) as nitrenoid donors, which can be solubilized in organic media by the addition of organic *N*-oxides such as 4-methylmorpholine *N*-oxide or trimethylamine *N*-oxide <1998TL191>. Müller *et al.* <1998JPO597, 1998CJC738> have reported on the rhodium(II)-catalyzed aziridination of olefins using phenyliodonium ylides. The reaction is stereospecific, although yields tend to be modest and a large excess of substrate is usually required. When the chiral rhodium catalyst **444** was used, enantioenriched (~50% ee) products were observed (Scheme 115).

1.01.6.2 Transition Metal-Mediated Nitrenoid-Transfer Approach

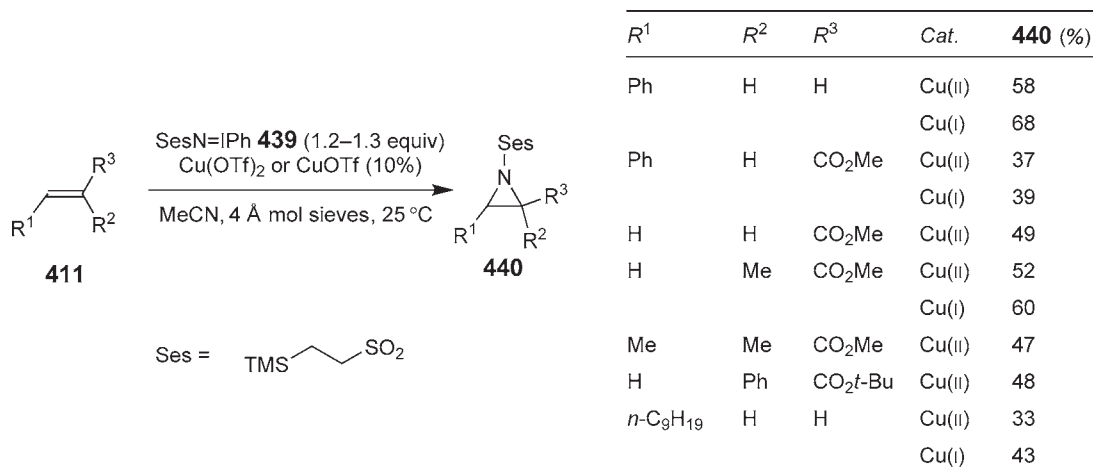
The transition metal-mediated nitrenoid transfer to olefins represents a very concise route to the aziridine structure; very often, however, an excess of the olefinic substrate is required for preparatively useful yields. In this arena, Andersson and co-workers <1997TL6897> have studied the copper-catalyzed aziridination of olefins using [*N*-(arenesulfonyl)imino]phenyliodanes **446** as nitrene precursors, and have reported on conditions which give good to excellent yields of aziridines **447** without the constraint of having to use an excess of alkene (Scheme 116).



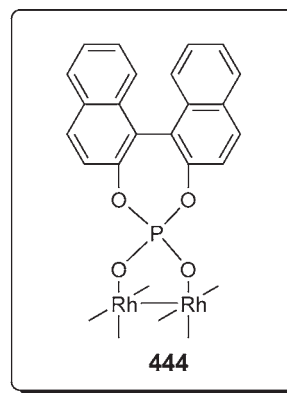
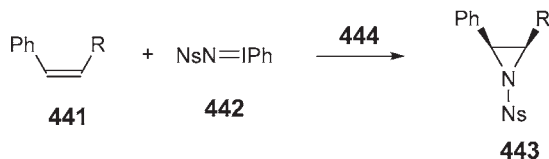
		437	
Ar	R	(%)	ee (%)
Ph	4-MeC ₆ H ₄	75	48
	4-O ₂ NC ₆ H ₄	94 (91) ^a	75 (66) ^a
	4-ClC ₆ H ₄	90	52
	Ph	82	50
	4- <i>t</i> -BuC ₆ H ₄	75	48
	4-MeOC ₆ H ₄	55 (73) ^a	33 (78) ^a
	2-O ₂ NC ₆ H ₄	66	22
	Me	86	36
4-FC ₆ H ₄	4-O ₂ NC ₆ H ₄	95	72
	4-ClC ₆ H ₄	95	51
	4-MeC ₆ H ₄	84	40
4-F ₃ CC ₆ H ₄	4-O ₂ NC ₆ H ₄	64	51
	4-ClC ₆ H ₄	68	43
	4-MeC ₆ H ₄	43	38
4-MeC ₆ H ₄	4-O ₂ NC ₆ H ₄	78	45
	4-ClC ₆ H ₄	80	43
	4-MeC ₆ H ₄	61	32
3-O ₂ NC ₆ H ₄	4-O ₂ NC ₆ H ₄	82	52
	4-ClC ₆ H ₄	89	48
	4-MeC ₆ H ₄	77	45
3-MeC ₆ H ₄	4-O ₂ NC ₆ H ₄	68	57
	4-ClC ₆ H ₄	78	42
	4-MeC ₆ H ₄	76	37

^aIn parentheses: Yield resulting from the two-step procedure employing isolated RSO₂N=IPh with CuOTf as catalyst at 0 °C.

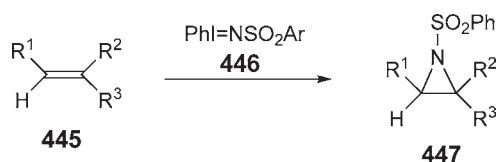
Scheme 113



Scheme 114



Scheme 115



Scheme 116

Jacobsen has studied the asymmetric aziridination of alkenes using (diimine)-copper(I) catalysts **448** (Figure 2). The results support the intermediacy of a discrete Cu(III)-nitrene intermediate and thus suggests mechanistic similarity (particularly regarding transition state geometry) to asymmetric cyclopropanation [<1995JA5889>](#).

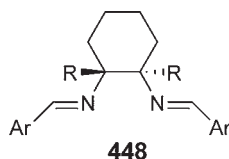
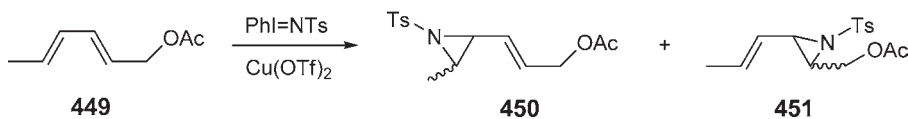


Figure 2

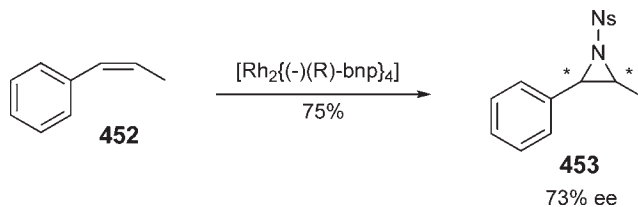
This nitrene-addition approach was used by Knight to synthesize vinyl aziridines from 1,3-dienes using PhI=NTs and a copper catalyst. The more-electron-rich double bond is selectively transformed in most cases. When the electronic difference is negligible, the regioselectivity is then determined by steric hindrance. A mixture of *cis*- and *trans*-isomers is usually obtained (Scheme 117) [<1995SL949>](#).



Scheme 117

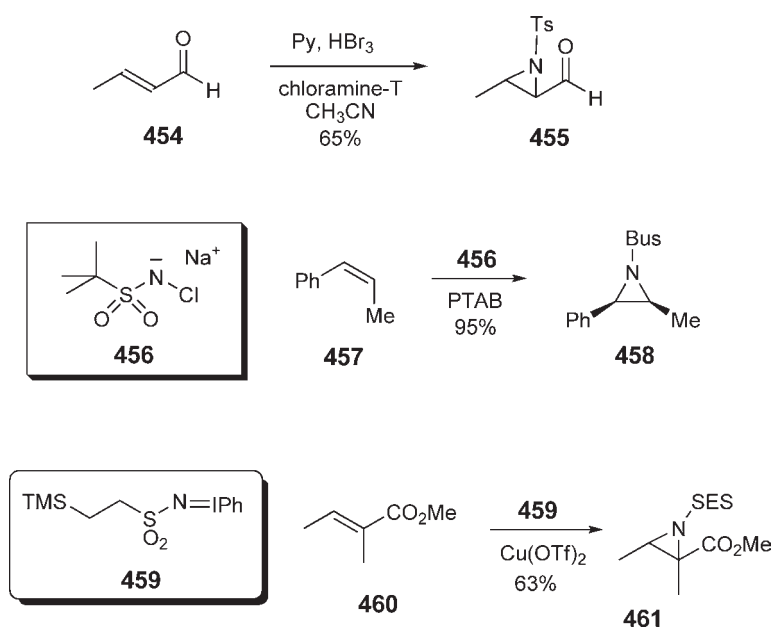
New variants of the (N+C=C) approach continue to be reported. Müller *et al.*, who recently reviewed the field of rhodium(II)-catalyzed aziridinations with [*N*-(*p*-nitrobenzenesulfonyl)imino]phenyliodinane [<1996JPO341>](#), have

explored the application of this technology to asymmetric synthesis. Thus, treatment of *cis*- β -methylstyrene **452** with $\text{PhI}=\text{NNs}$ and Pirrung's catalyst $[\text{Rh}_2\{(-)(\text{R})\text{-bnp}\}_4]$ (bnp = 1,1'-binaphthyl-2-2'-diyl phosphate) in methylene chloride medium afforded the corresponding aziridine **453** in 75% yield and 73% ee (**Scheme 118**) <1996T1543>.



Scheme 118

Alkenes can be aziridinated using a variety of nitrogen sources. Among the recently reported systems are chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) with pyridinium hydrobromide perbromide catalyst (e.g., **454** $\rightarrow$ **455**) <1999OL705>, the *N*-chloramine salt of *t*-butylsulfonamide **456**, which serves as both nitrogen source and terminal oxidant, in the presence of phenyltrimethylammonium tribromide (PTAB) <1999OL783>, and *N*-[2-(trimethylsilyl)ethanesulfonyl]iminophenylidiodane **459** (**Scheme 119**) <1999JOC5304>. The last example is particularly interesting, in as much as it represents the first *N*-alkylsulfonyl derivative used for such purposes. The trimethylsilylthanesulfonyl (SES) group has the advantage of being easily removed under conditions which are amenable to substrates with sensitive functionality.

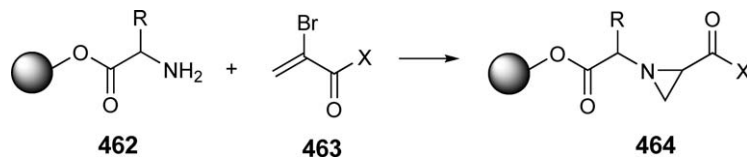


Scheme 119

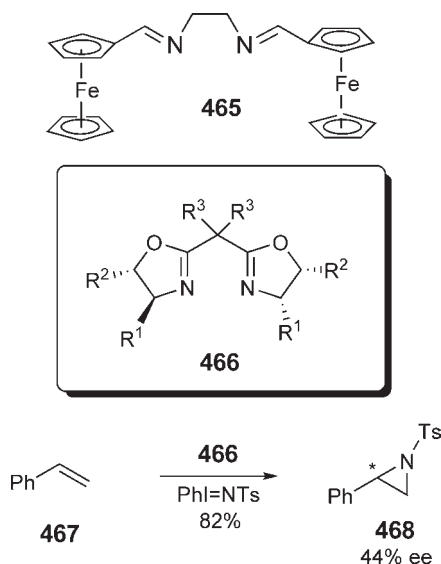
In the realm of heterogeneous catalysis, a copper-exchanged zeolite (CuHY) modified with bis-oxazoline was found to exhibit modest asymmetric induction in the aziridination of alkenes using $[\text{N}-(p\text{-tolylsulfonyl})\text{imino}]\text{phenyliodine}$ ($\text{PhI}=\text{NTs}$) as the nitrene donor <1999J(P2)1043>. Oligopeptides and amino acids containing an aziridine 2-carboxylate group have been prepared using a solid-phase version of the Gabriel–Cromwell reaction (i.e., **462** $\rightarrow$ **464**) (**Scheme 120**) <1999TL6503>.

There are reports on the use of a Cu(I) complex of ferrocenyldiimine **465** to facilitate nitrene transfer to olefins <1998SL617>. Of particular interest for industrial applications, these reactions can also be efficiently catalyzed by

copper-exchanged zeolite (CuHY) in acetonitrile. Some degree of asymmetric induction has been observed under these conditions using chiral bis(oxazoline) modifiers (e.g., **466**). For example, styrene **467** was converted to the corresponding aziridine **468** in 82% yield and 44% ee. The solid-supported catalysts can be easily removed from the reaction mixture, washed, and reused without detrimental effect to catalytic or enantioinductive activity (Scheme 121) <1998CC1601>.

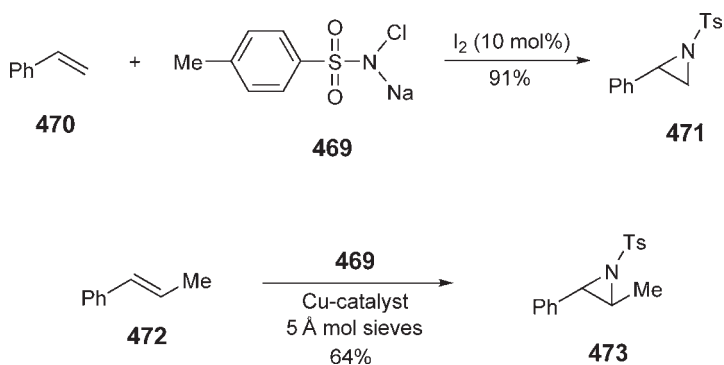


Scheme 120



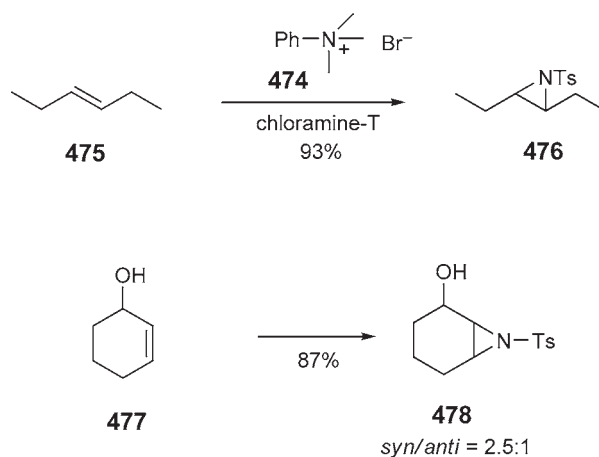
Scheme 121

In the arena of alternative nitrene sources, a flurry of activity has centered around the use of the readily available chloramine-T **469**. Komatsu and co-workers have reported on the successful aziridination of alkenes using **469**, catalyzed either by substoichiometric amounts of iodine (e.g., **470** $\rightarrow$ **471**) <1998T13485> or a combination of 5% cuprous chloride and 5 Å powdered molecular sieves (e.g., **472** $\rightarrow$ **473**) <1998TL309>. In certain cases, better yields are obtained using the bromo analog, presumably due to the more facile formation of the copper nitrenoid complex (Scheme 122) <1998TL4715>.



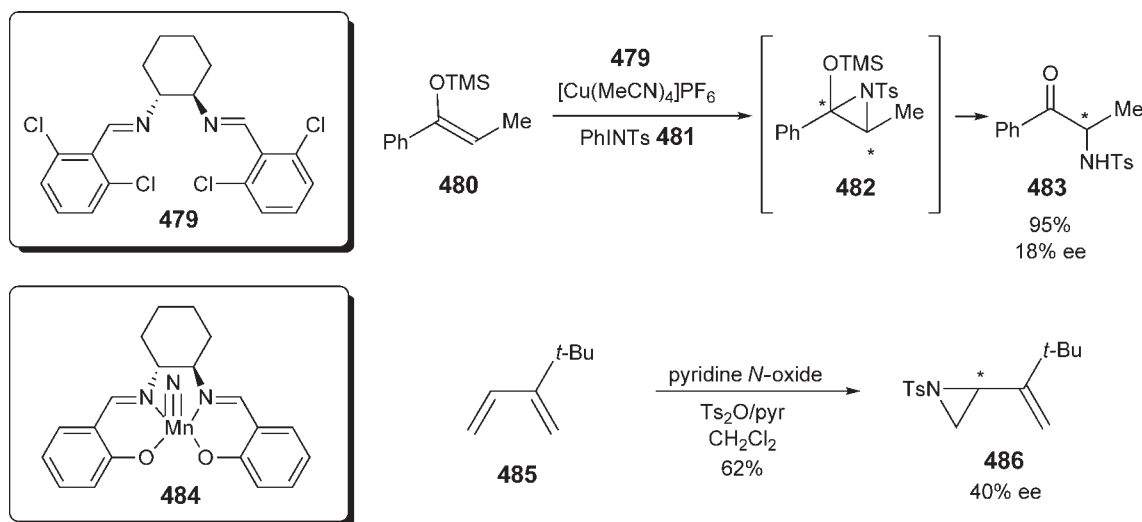
Scheme 122

Sharpless and co-workers <1998JA6844> developed a remarkably efficient aziridination system using chloramine-T with PTAB **474** as the catalyst. This combination provides good to excellent yields of aziridines across a wide range of olefin classes, from simple internal alkenes (e.g., **475** → **476**, 93% yield) to cyclic allylic alcohols (e.g., **477** → **478**, 87% yield) (Scheme 123). In the latter case, a slight *syn*-preference (2.5:1) was observed, presumably due to coordination of the aziridinating agent with the hydroxyl group in the transition state.



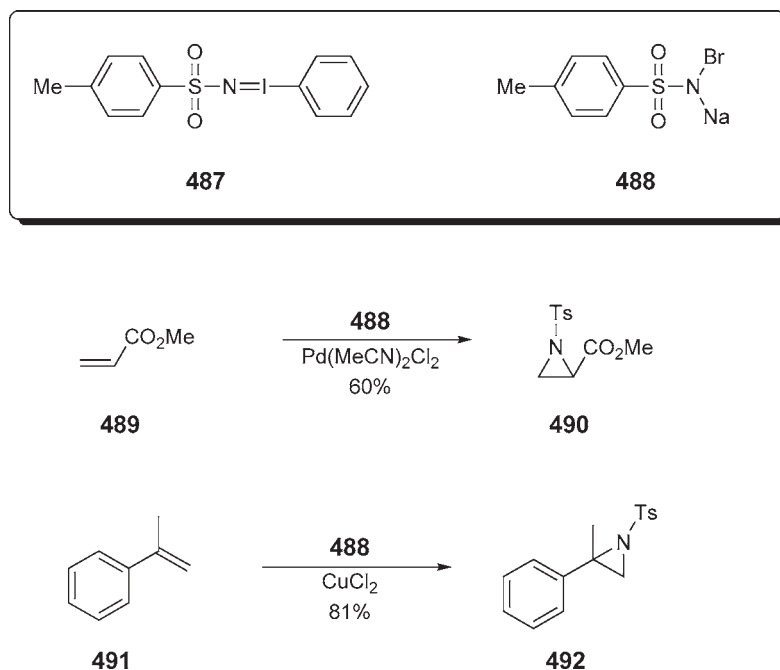
Scheme 123

Cyclic and acyclic enol derivatives **480** can be asymmetrically aziridinated with (*N*-tosylimino)iodobenzene **481** using a chiral copper catalyst prepared *in situ* from [Cu(MeCN)₄]PF₆ and the optically active ligand **479**. Collapse of the amination (i.e., **482**) leads to the formation of enantiomerically enriched α-amino carbonyl compounds **483**, although ee's to date are modest <2000EJO557>. Similarly, dienes can be selectively aziridinated using the chiral Mn–salen complex **484** to give vinyl aziridines **486** in scalemic form (Scheme 124) <2000TL7089>.



Scheme 124

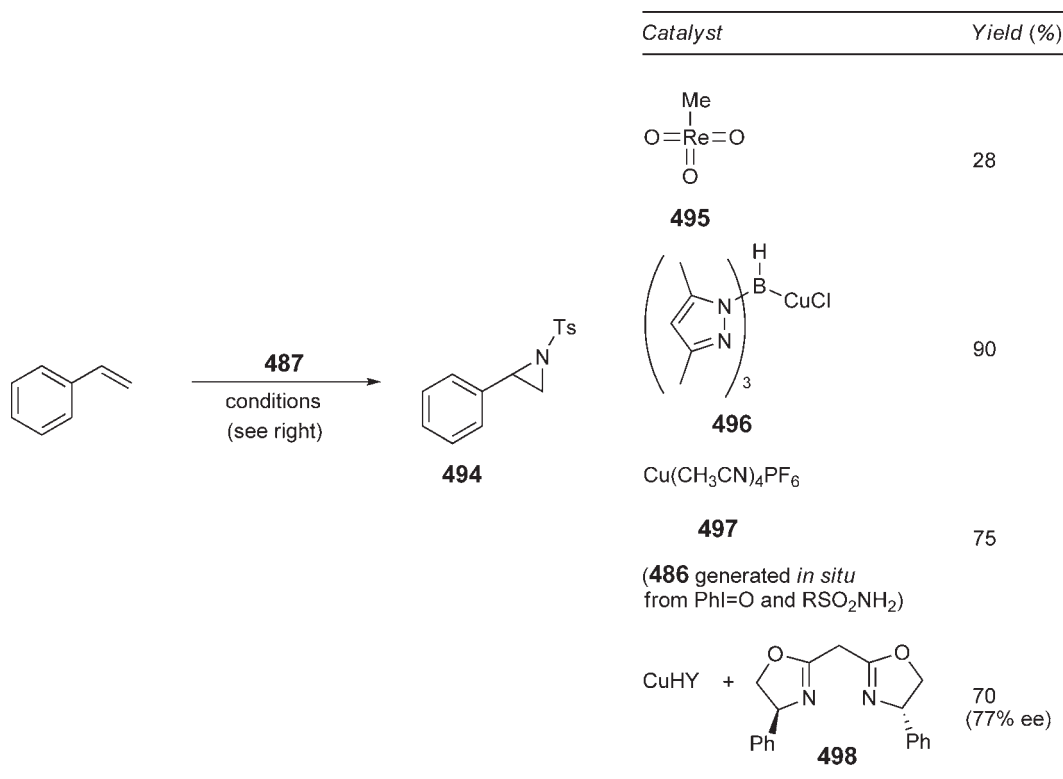
Two of the more frequently employed nitrene donors correspond to [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (PhI=Ts, **487**) and bromamine-T **488**. The latter reactions can be catalyzed by palladium(II) reagents (i.e., **489** → **490**) <2001CC405>, or with a variety of more common transition metals with the assistance of microwave radiation (i.e., **491** → **492**) <2001JOC30>. Similarly, the nitrene-transfer reaction from **487** is facilitated by a variety of catalysts, including methyltrioxorhenium (MTO) <2001CC235>, the tri(pyrazolyl)borate-copper(I) complex <2001OL1423>, and tetrakis(acetonitrile)copper(I) hexafluorophosphate (**Scheme 125**) <2001JA7705>. In the latter case, the reaction can be carried out using a sulfonamide and the primary oxidant, iodosylbenzene, whereby the actual nitrene-transfer reagent is presumed to be formed *in situ*. In all cases, acetonitrile appears to be the solvent of choice.



Scheme 125

An interesting asymmetric variant of this methodology has been reported, which employs an immobilized catalyst of Cu²⁺ ion exchanged into zeolite H-Y (CuHY) modified by the chiral bis(oxazoline) **498**. Using nitrene donor **487**, this catalyst system led to the chiral aziridination of styrene in 70% yield and 77% ee, a marked improvement of enantioselectivity compared to the same reaction using the homogeneous catalyst Cu(OTf)₂ (28% ee). The optical yield could be further increased by using the *p*-nitrophenyl variant of the nitrene donor, PhI=NNs (82% ee) (**Scheme 126**) <2001J(P2)1714>.

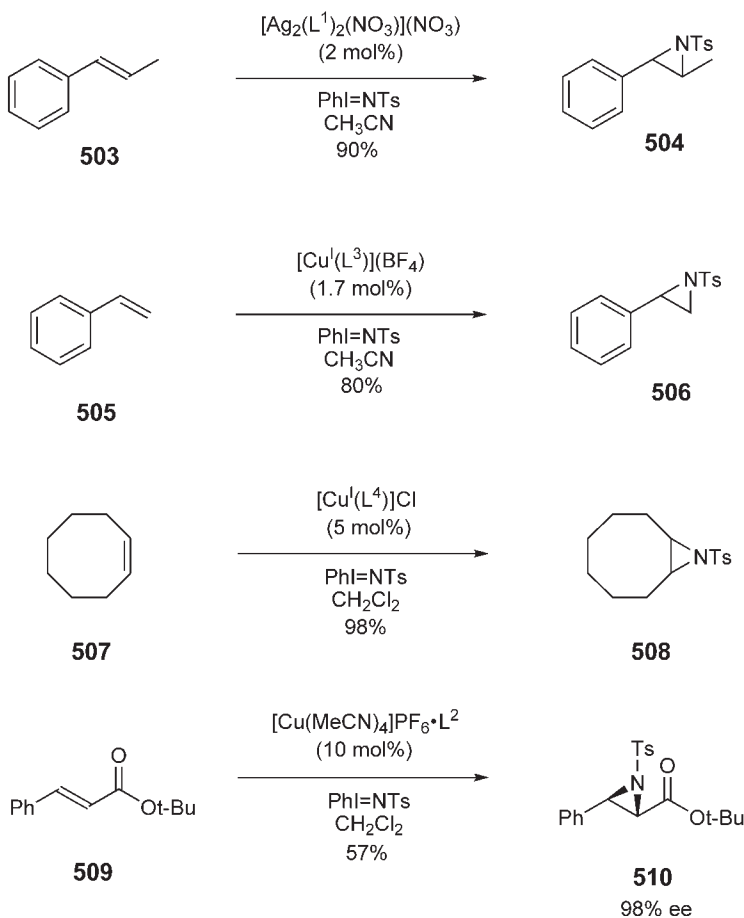
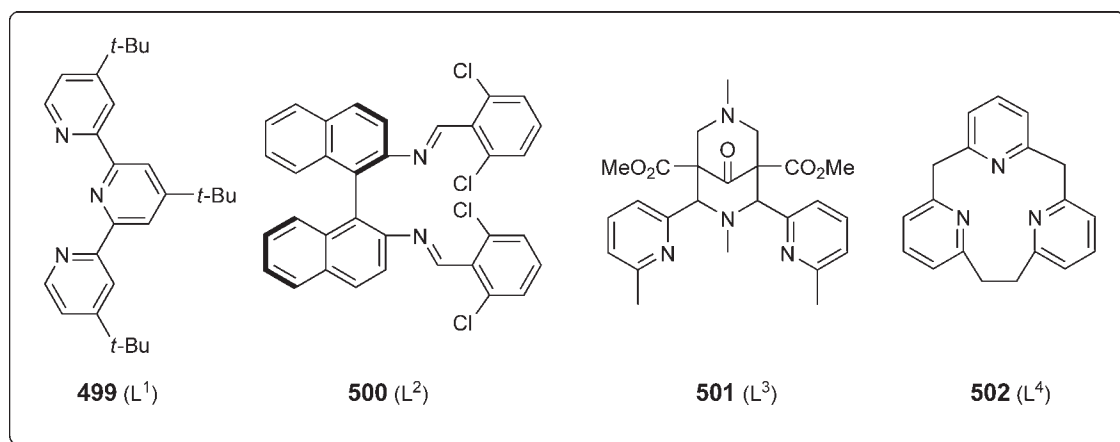
[*N*-(*p*-Tosyl)imino]phenyliodinane (PhI=NTs), in the presence of some transition metal catalyst, is frequently used as a nitrenoid carrier. Effective catalysts show remarkable diversity, both in structure of the ligands and the metal centers to which they are coordinated. For example, the tridentate *t*-Bu₃tpy ligand **498** forms a 2:2 complex with silver(I) to provide a novel soluble disilver catalyst which exhibits well-controlled oxidation reactivity as seen in the aziridination of *trans*-methylstyrene **503** <2003JA16202>. The tetradentate pyridyl ligand **501** was found to provide the most efficient catalyst with copper(I) ion in the aziridination of styrene **505**, but subtle changes to the ligand structure resulted in striking differences in the properties of the resultant catalyst <2003EJ11711>. The macrocyclic pyridinophane **502** gives rise to an interesting conformationally strained 'capped' catalyst that is particularly reactive, converting cyclooctene **507** to the corresponding aziridine **508** in near-quantitative yield <2003OL2591>. The chiral copper(I) complexes derived from binaphthylidimine **500** (BINIM-TC) are effective in the asymmetric aziridination of 3-aryl-2-propen-1-ones (e.g., **509**) with excellent ee (**Scheme 127**) <2003BCJ189>.



Scheme 126

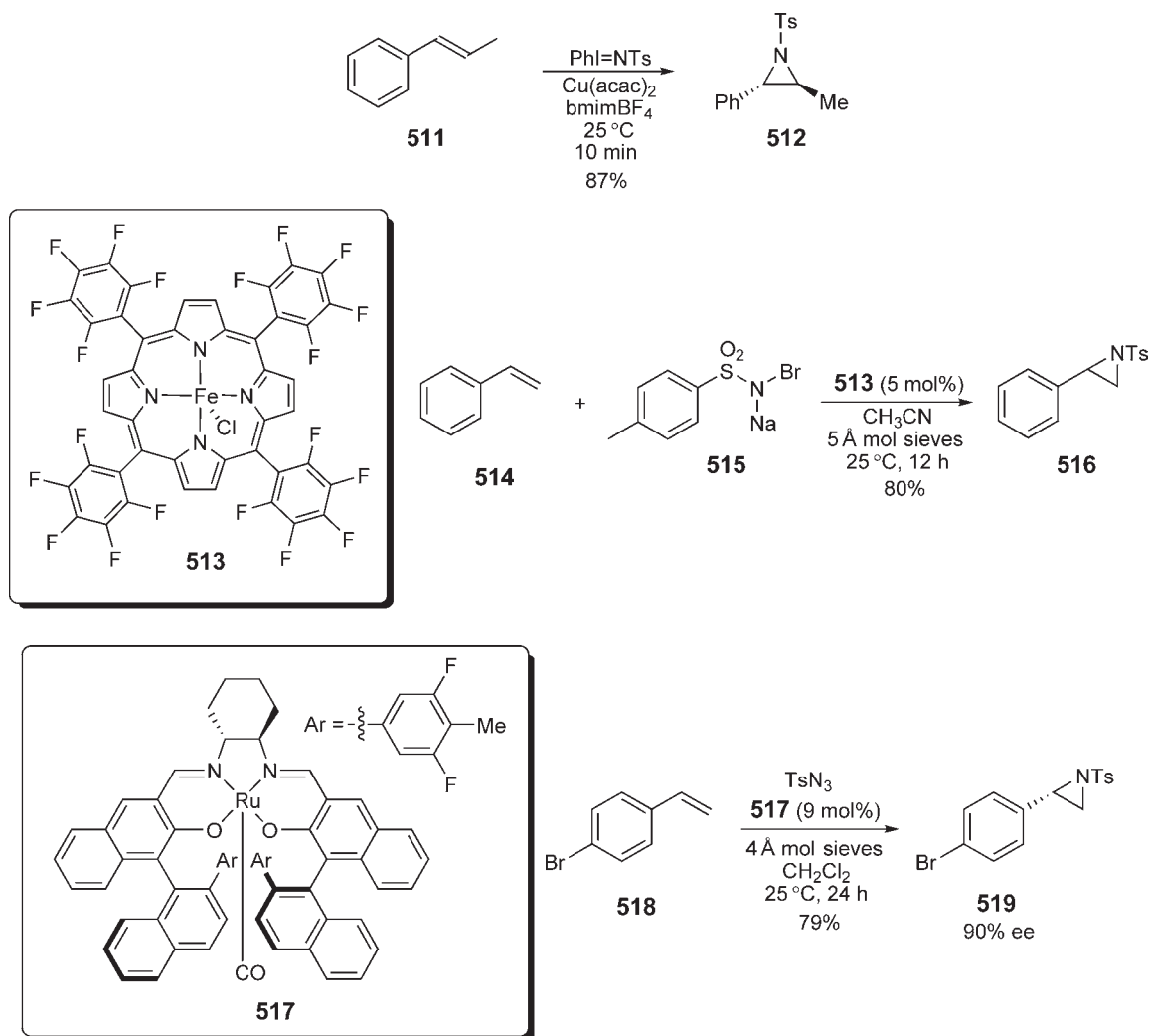
Other interesting catalyst systems include copper(II) acetylacetonate (acac) immobilized in ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (bmimBF₄), which facilitates catalyst recycling and also appears to accelerate the reaction. Thus, *trans*-methylstyrene **511** was converted to the corresponding tosyl aziridine **512** within 10 min using (tosylimino)phenyliodine as the nitrogen donor <2004SL525>. Bromamine T **515** is also a convenient, stable, and commercially available nitrene precursor. The perfluoroaryl iron porphyrin catalyst **513** is effective in promoting aziridination of a wide spectrum of alkenes in fair to good yields, as illustrated by the conversion of styrene to the corresponding *N*-tosyl aziridine **516**, which is believed to proceed through a mechanism involving an iron–nitrene intermediate <2004OL1907>. A fluorinated aryl ligand is also at the heart of a chiral ruthenium(salen) catalyst **517** designed for the purpose of effecting enantioselective aziridination of olefins using sulfonyl azides as nitrene precursors. Thus, *p*-bromostyrene **518** provides the corresponding aziridine **519** in the presence of tosyl azide and catalyst **517**. Enantioselectivities can reach as high as 99%, and the protocol also works well when tosyl azide is substituted with nosyl azide (Scheme 128) <2004CC2060>.

The use of the rhodium catalyst, Rh₂(cap)₄, TsNH₂, and NBS provides a number of aziridines in good to excellent yields <2005OL2787>. Another rhodium catalyst, Rh₂(pfm)₄ (pfm = perfluorobutyramide), has been shown to catalyze the aziridination of olefins using TsNH₂ and PhI(OAc)₂ (Scheme 129) <2005TL4031>. An advantage of the Rh₂(pfm)₄ catalyst system is the reported ability to use a variety of sulfonamides (e.g., nosyl, trichloroethoxy-sulfonyl) in the aziridination reaction. A cobalt porphyrin catalyst system that uses bromamine-T as the nitrogen source provides excellent yields of aziridines <2005OL3191>. A simple copper complex has been shown to catalyze aziridination as well <2005JOC4833>. This reaction system uses PhINTs as the nitrogen source and requires a borate, NaBAR^F₄, to remove the anionic ligands creating a coordinatively unsaturated cationic copper species. A key feature of all of these methods is that the olefinic substrate is the limiting reagent. This is an important feature of being able to use these methods in synthetically significant settings.

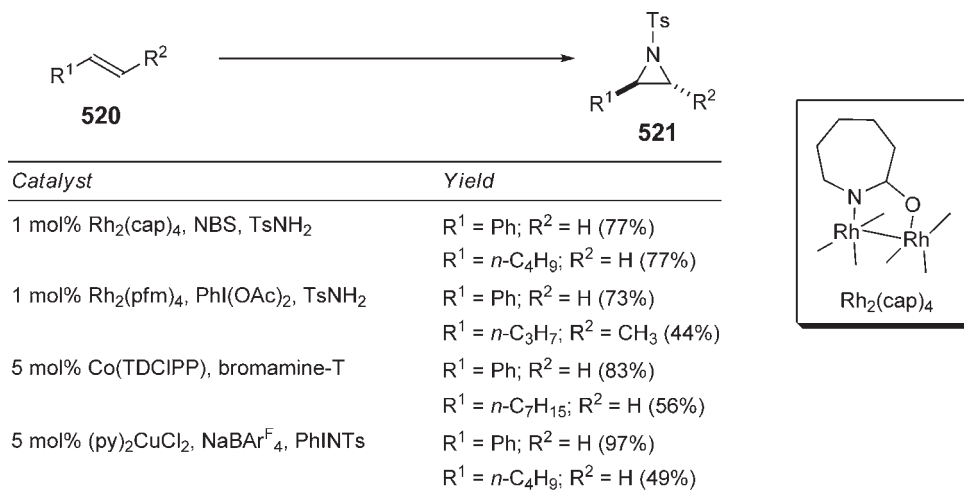


Scheme 127

Other reagents are also employed as nitrene precursors, primarily in an effort to avoid the practical problems associated with $PhI=NTs$ <2001TL8089>, such as expense of the reagent and the generation of iodobenzene as a by-product. For example, tosyl azide has been used in combination with the chiral ruthenium(salen) catalyst **522** to effect the enantioselective aziridination of terminal alkynes with very good ee's <2003CL354>. Another

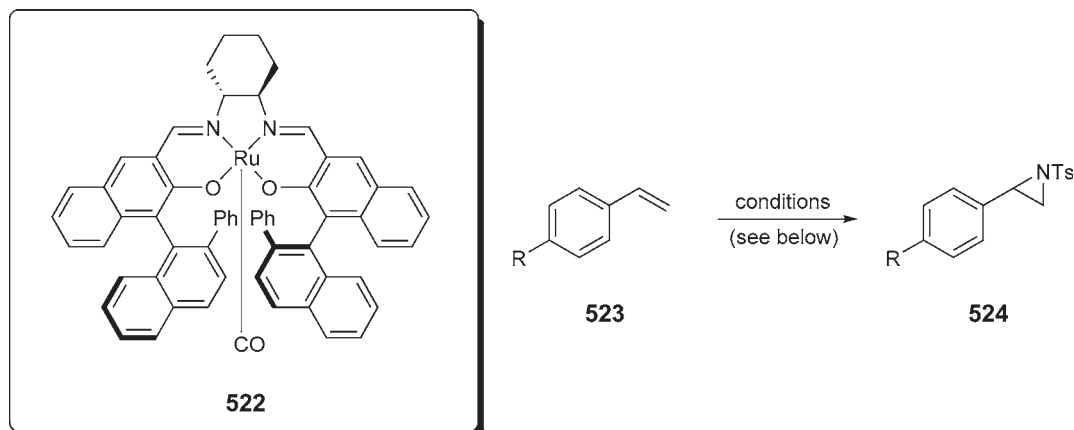


Scheme 128



Scheme 129

alternative source of latent nitrene is *N*-iodo-*N*-potassio-*p*-toluenesulfonamide (TsN•KI), a stable crystalline solid obtained from the treatment of toluenesulfonamide with iodine in the presence of potassium hydroxide. When used in combination with copper(I) chloride as a catalyst, simple alkenes undergo aziridination in fair to good yields <2003TL575>. Chloramine-T can also be used as a source of nitrogen in the presence of NBS; however, here the mechanism is not believed to proceed through a nitrene species, but rather by initial bromonium ion formation from the alkene, which undergoes subsequent nucleophilic attack by chloramine-T (Scheme 130) <2003TL989>.



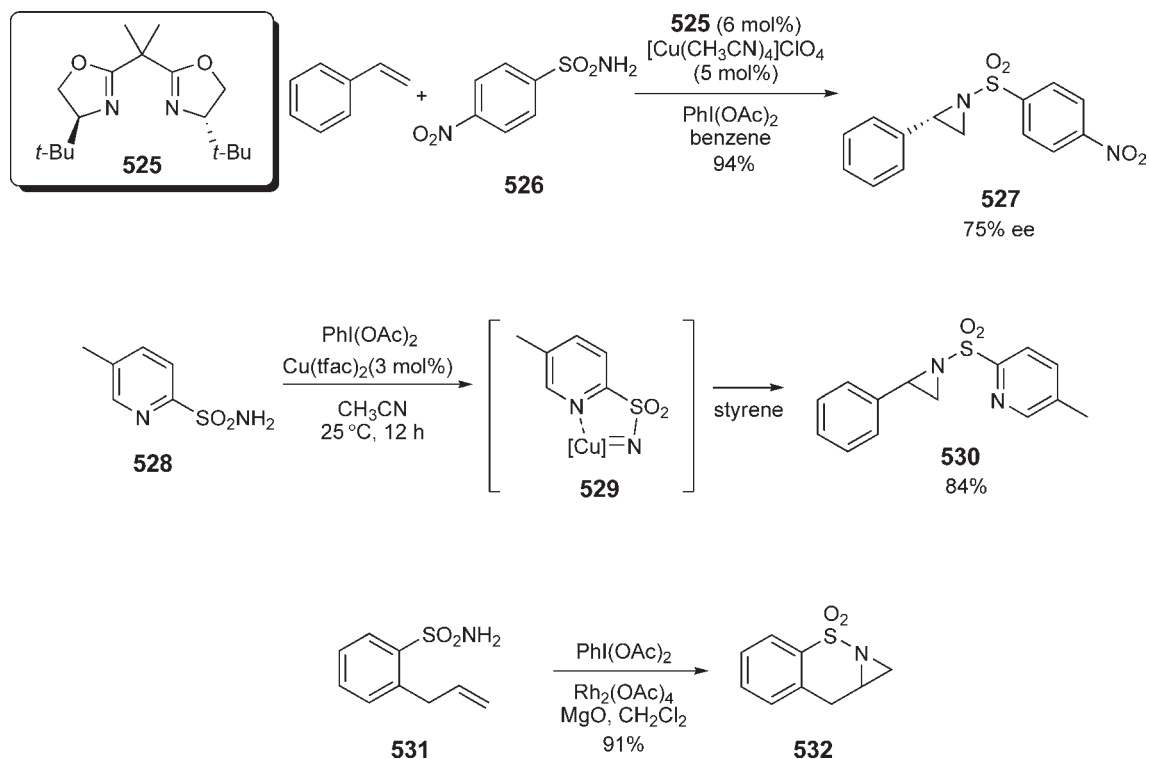
<i>R</i>	Catalyst	Conditions	Yield (%)	ee (%)
H	134 (2 mol%)	TsN ₃ , CH ₂ Cl ₂	71	87
Me	CuCl (5 mol%)	TsN•KI, CH ₃ CN	75	<i>rac</i>
ClCH ₂ -	NBS (20 mol%)	Chloramine-T, CH ₃ CN	67	<i>rac</i>

Scheme 130

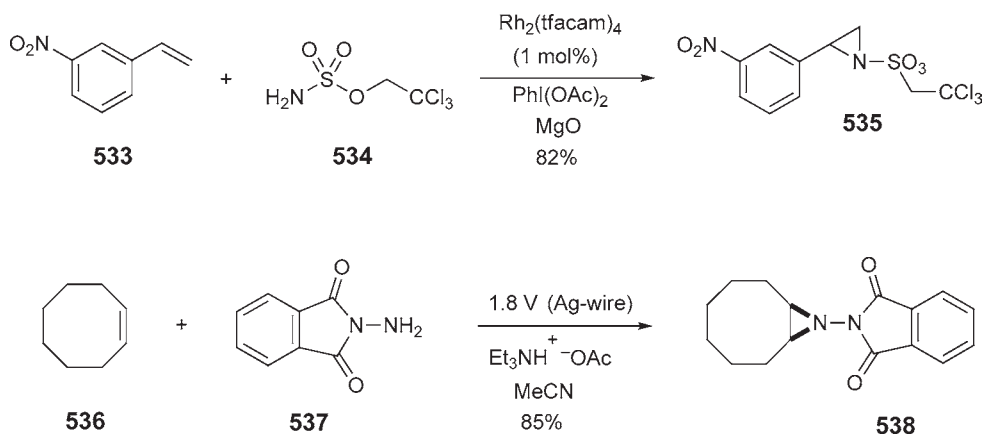
Sulfonamides have been found to be convenient nitrene precursors, which can be converted using commercially available iodobenzene diacetate in the presence of various transition metal catalysts. A copper(I) catalyst derived from the Evans chiral bis(oxazoline) ligand **525** was found to promote the high-yielding aziridination of styrene with good enantioselectivity <2004TL3965>. Chang and co-workers have developed a copper-catalyzed variant that requires no external ligand. Instead, a pyridyl nitrogen onboard the sulfonamide moiety serves as an internal ligand (i.e., **529**), which in turn increases the efficiency of the aziridination <2004OL4109>. Several unsaturated sulfonamides (e.g., **531**) were shown to undergo a very facile intramolecular aziridination in the presence of a rhodium catalyst to provide tricyclic aziridines (e.g., **532**) (Scheme 131) <2004JOC6377>.

DuBois and Guthikonda have developed a broadly applicable aziridination of alkenes using a sulfamate ester (e.g., **534**), a rhodium carboxamide catalyst, and iodosylbenzene as a terminal oxidant <2002JA13672>. An intriguing electrochemical approach has also been reported using *N*-aminophthalimide **537** as the nitrogen donor (Scheme 132) <2002JA530>.

N-Aminophthalimide **537** can also be added to olefins in an asymmetric fashion. Thus, reaction of *N*-enoyl oxazolidinone **541** with **537** and lead tetraacetate in the presence of the camphor-derived chiral ligand **539** provides aziridine **542** in 83% yield and 95% ee <2002OL1107>. Other useful chiral ligands include imine **540**, derived from the condensation of 2,2'-diamino-6,6'-dimethylbiphenyl with 2,6-dichlorobenzaldehyde. The corresponding



Scheme 131

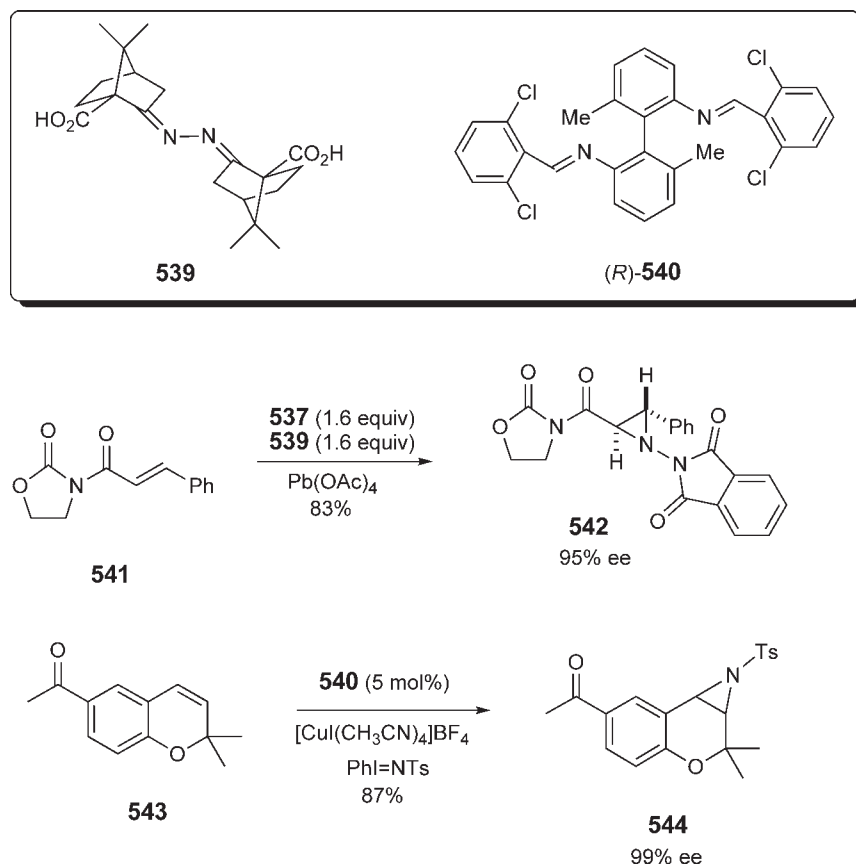


Scheme 132

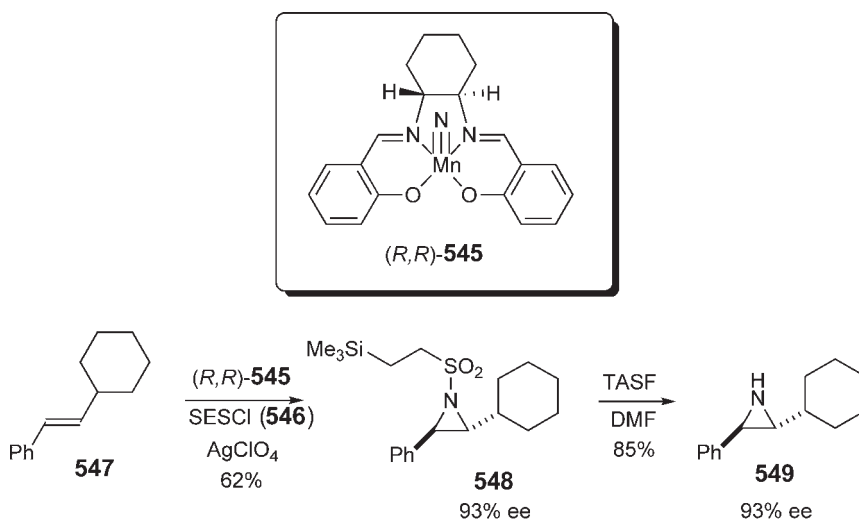
monometallic Cu(I) complex was found to be very efficient in chiral nitrogen transfer onto chromene derivative **543** using (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane ($\text{PhI}=\text{NTs}$) to provide aziridine **544** in 87% yield and 99% ee (Scheme 133) <2002JOC3450>.

The chiral nitridomanganese complex **545** represents a novel self-contained asymmetric nitrogen-transfer reagent which has been used to convert alkenes to scalemic aziridines directly, although a stoichiometric amount of transfer reagent is required. This protocol makes use of *N*-2-(trimethylsilyl)ethanesulfonyl chloride (SESCl) (**546**) as an activator, providing *N*-SES-aziridines **547** that are easily deprotected under mild conditions using

tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) to give NH-aziridines in good yield. The enantioselectivity can be quite high, especially with *trans*-olefins bearing sterically bulky substituents, as is the case with the cyclohexyl stilbene derivative **547**. However, terminal and *cis*-alkenes tend to be less amenable to chiral induction (**Scheme 134**) <2002JOC2101>.

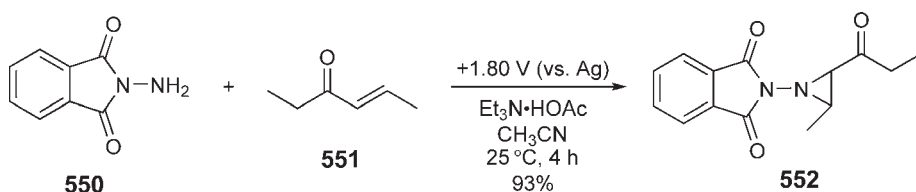


Scheme 133



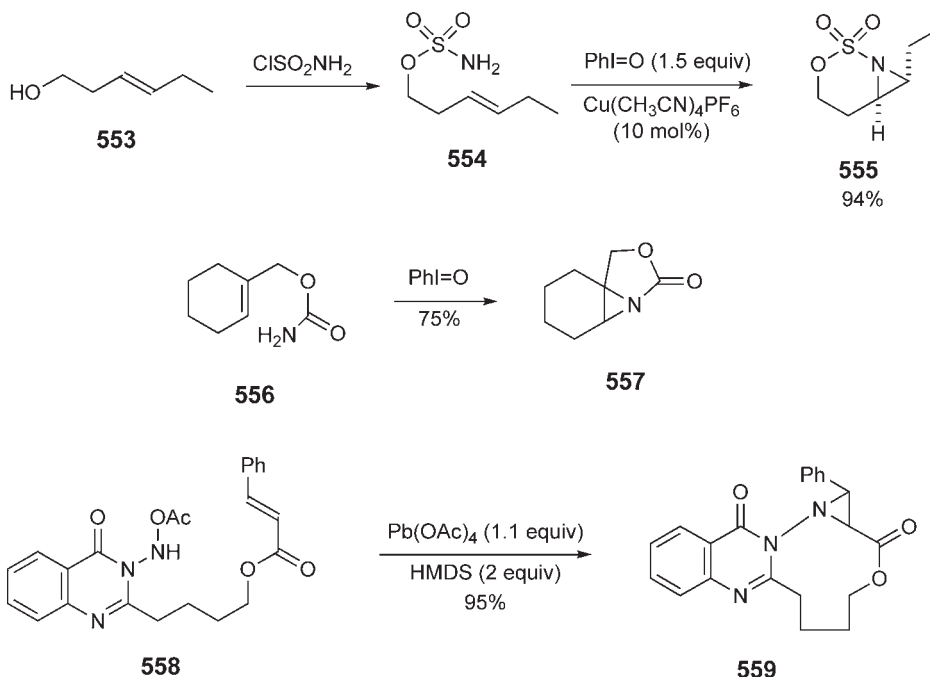
Scheme 134

An intriguing electrochemical aziridination is based on the selective anodic oxidation of *N*-aminophthalimide (**550**, oxidation potential +1.60 V) in the presence of olefins. Thus, *trans*-hex-4-en-3-one **551** is converted to the corresponding aziridine **552** in acetonitrile solution using a platinum electrode at a constant potential of +1.80 V (**Scheme 135**). The reaction mixture is buffered using triethylammonium acetate, since the cathodic process reduces proton to hydrogen gas. The use of platinum at the anode is critical, as graphite electrodes yielded no aziridination products <2004PAC603>.



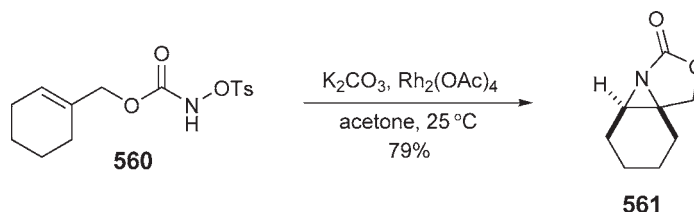
Scheme 135

Some interesting intramolecular variants have been reported. For example, homoallylic alcohols (e.g., **553**) can be treated with sulfamoyl chloride to form the corresponding sulfamates **554**, which then engage in a direct intramolecular copper-catalyzed aziridination mediated by iodosylbenzene <2002OL2481>. A carbamate tether is also effective in delivering the nitrene center to the olefin, as is the case with the cyclohexenyl derivative **556**, which spontaneously cyclizes in the presence of iodosylbenzene <2002OL2137>. The acetoxyaminoquinazolinone **558** is converted to the lactone **559** via intramolecular aziridination upon treatment with lead tetraacetate and hexamethyldisilazane (HMDS) (**Scheme 136**) <2002TL2083>.



Scheme 136

A rhodium-catalyzed route to bicyclic aziridines **561** from *N*-tosyloxycarbamates has been reported (**Scheme 137**) <2005JA14198>. Several olefins were tested in this intramolecular process with yields ranging between 62% and 79%.



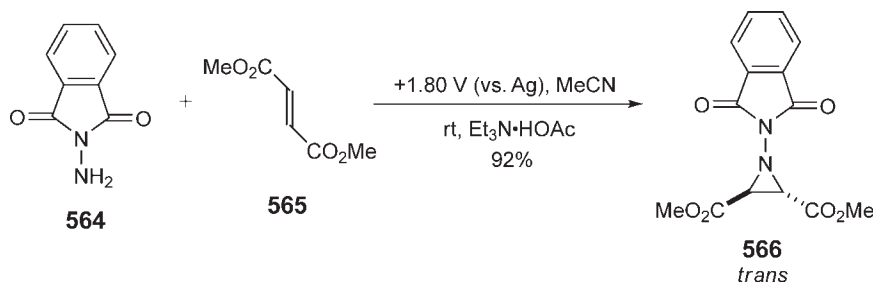
Scheme 137

In the realm of electron-deficient alkenes, 2-substituted acrylates and cinnamates such as **562** can be converted to aziridines **563** by the Evans aziridination procedure. This protocol involves using *N*-(*p*-tolylsulfonyl)iminophenyldinane in the presence of a catalytic amount of copper salt (Scheme 138). Yields are variable, but can be as high as 72% <1998TL5739>.



Scheme 138

The use of *N*-aminophthalimide as a nitrogen source in aziridination reactions has been examined in some detail. One of the problems associated with *N*-aminophthalimide as a nitrogen source is the need for a strong oxidant. The use of electrochemical catalysis with *N*-aminophthalimide has proven to be an effective and mild route for aziridination (Scheme 139) <2005JOC932>. Both electron-rich and electron-poor substrates worked well in this reaction.

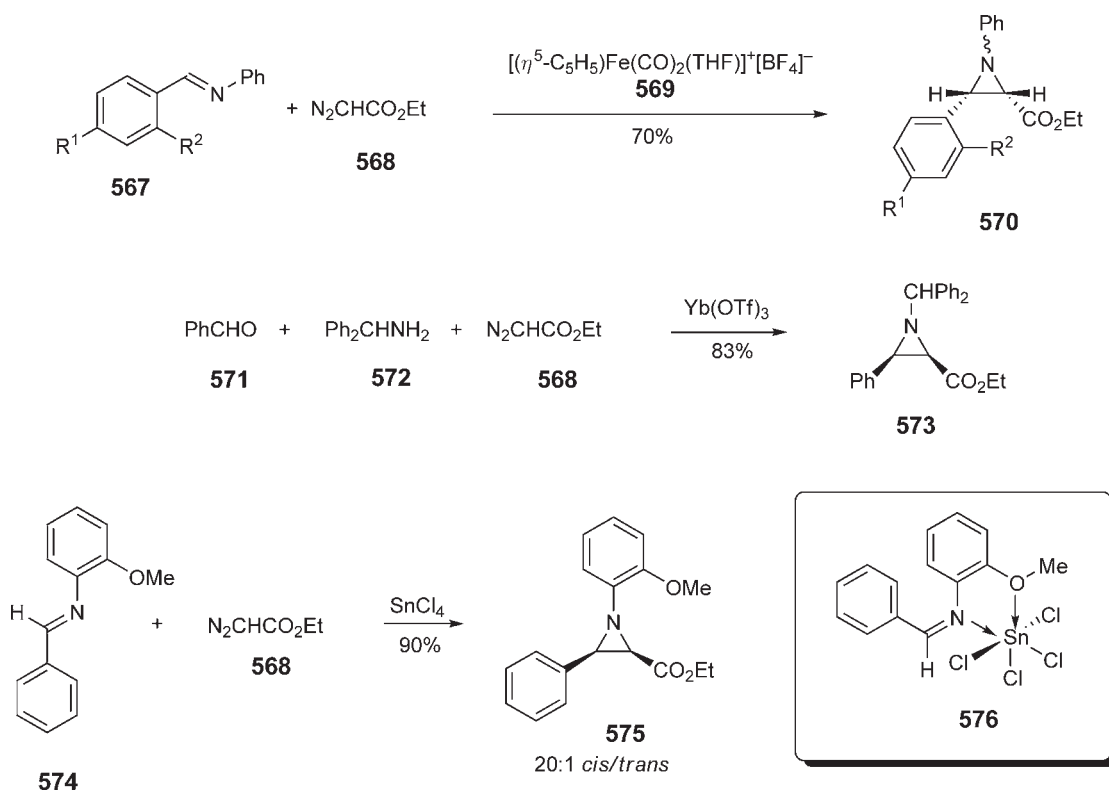


Scheme 139

1.01.6.3 Methylation of Imines

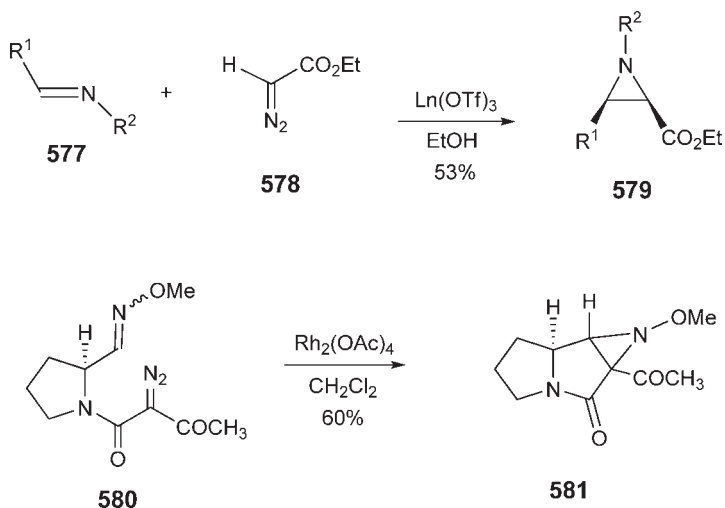
1.01.6.3.1 Preparation of aziridines by reaction of diazo compounds with imines

Another major route used for the preparation of aziridines is the formal addition of carbenoids across an imine π -bond $[\text{C}=\text{C}=\text{N}]$. The carbon fragment is typically provided by reagents such as ethyl diazoacetate **568**. The reaction can proceed under the influence of various catalysts, such as the iron Lewis acid **569**, which provides predominantly the *cis*-aziridine (e.g., **570**) <1998JOC6839>. It was also found that a mixture of ethyl diazoacetate and the appropriate aldehyde and primary amine (i.e., **571** and **572**) in the presence of catalytic ytterbium triflate leads to the efficient generation of *cis*-aziridines **573** in a one-pot process <1998CL685>. The analogous tin-catalyzed aziridination of imines (i.e., **574** $\rightarrow$ **575**) has also been investigated. The mechanistic pathway is believed to proceed by nucleophilic attack of ethyl diazoacetate onto the imine, whose π -bond is activated by coordination with the catalyst. This rationale is supported by the isolation of the imine–Lewis acid intermediate **576**, which has been fully characterized by X-ray diffraction studies (Scheme 140) <1998J(P2)1347>.



Scheme 140

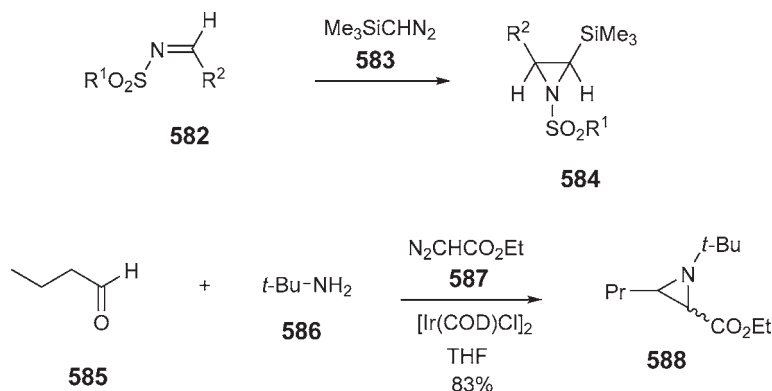
Carboxylate derivatives **579** can be prepared through the lanthanide-catalyzed reaction of imines with diazo compounds, such as ethyl diazoacetate (EDA). In this protocol, *N*-benzyl aryl aldimines and imines derived from aromatic amines and hindered aliphatic aldehydes are appropriate substrates [<1999T12929>](#). An intramolecular variant of this reaction (e.g., **580** $\rightarrow$ **581**) has also been reported (Scheme 141) [<1999OL667>](#).



Scheme 141

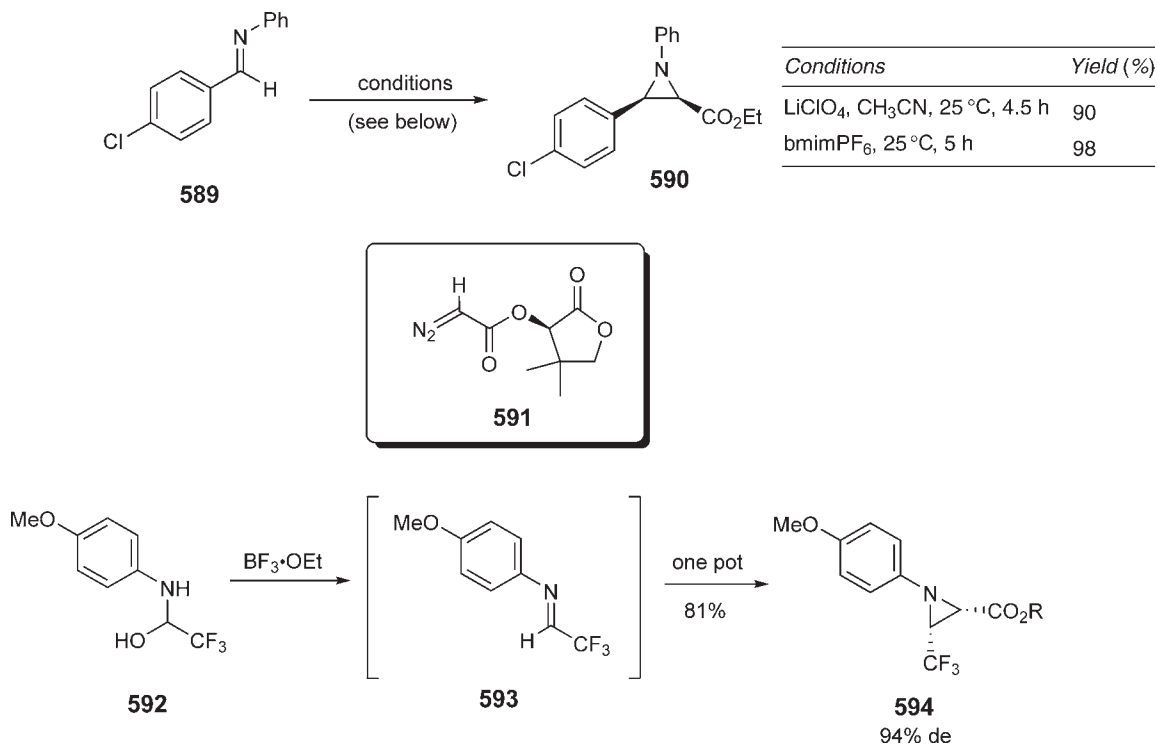
Trimethylsilyldiazomethane **583** smoothly reacts with *N*-sulfonylaldimines **582** to give 2-substituted *N*-sulfonyl-3-trimethylsilylaziridines **584** with high *cis*-selectivity [<2000TL9455>](#). The reaction of ethyl diazoacetate can be catalyzed

by InCl_3 <2000TL6245> or by iridium complexes. In the latter case, the aldimines can be generated *in situ* in a one-pot, three-component procedure to give ethoxycarbonyl aziridines **588** in generally good yield (Scheme 142) <2000CC625>.



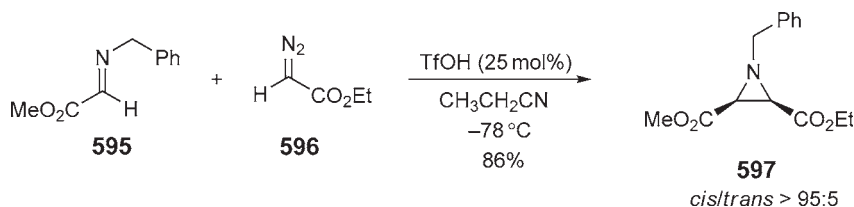
Scheme 142

Ethyl diazoacetate is a frequently encountered carbene donor for the methylenation of imines. For example, the imine derived from *p*-chlorobenzaldehyde **589** is converted to the *cis*-aziridinyl ester **590** upon treatment with ethyl diazoacetate in the presence of lithium perchlorate <2003TL5275>. These conditions have also been applied to a reaction medium of the ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate (bmimPF_6) with excellent results <2003TL2409>. An interesting enantioselective twist to this protocol has been reported, in which a diazoacetate derived from (*R*)-pantolactone **591** is used. This system was applied to the aziridination of trifluoromethyl-substituted aldimines **593**, which were prepared *in situ* from the corresponding alminals **592** under the catalysis of boron trifluoride etherate to give aziridines **594** (Scheme 143) <2003TL4011>.



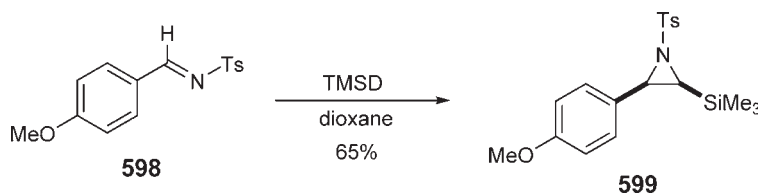
Scheme 143

Ethyl diazoacetate can also serve as an acetate enolate synthon under acidic conditions, engaging in [2+1] annulation with *N*-alkyl aldimines (e.g., **595**) to provide the corresponding aziridine (**597**) with very high *cis*-selectivity. The conditions are mild enough that acid-catalyzed ring opening of the products is not observed (Scheme 144) <2004JA1612>.



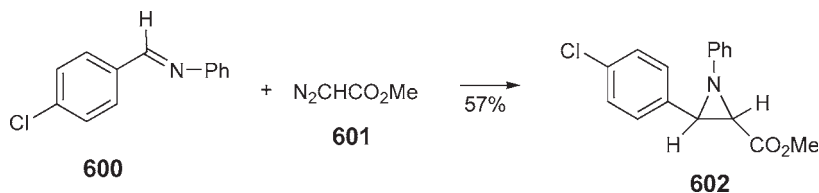
Scheme 144

Aggarwal *et al.* have reported a highly diastereoselective aziridination of imines with trimethylsilyldiazomethane (TMSD). Thus, tosylimine **598** was converted to the *cis*-aziridine **599** in 65% yield (Scheme 145) <2002JOC2335>.



Scheme 145

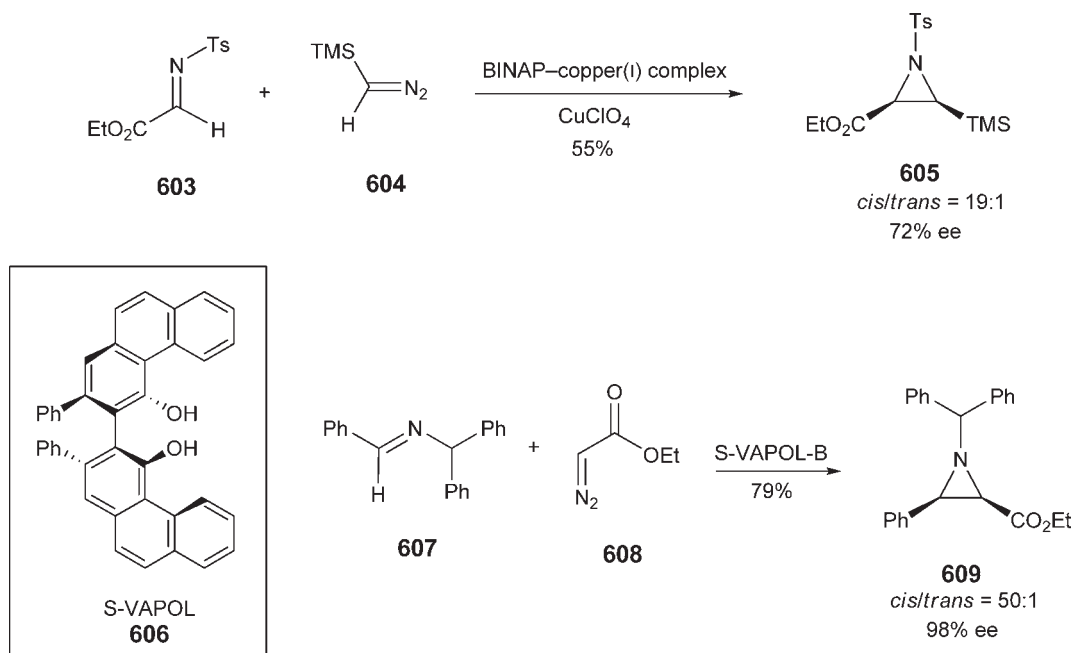
Two new heterogeneous catalysts have been prepared by exchanging a Montmorillonite K-10 clay with dilute solutions of RhCl_3 and $\text{Mn}(\text{NO}_3)_3$, respectively. These catalysts are effective for the synthesis of *trans*-aziridines (e.g., **602**) from imines (e.g., **600**) and methyl diazoacetate (Scheme 146) <1997CC1429>.



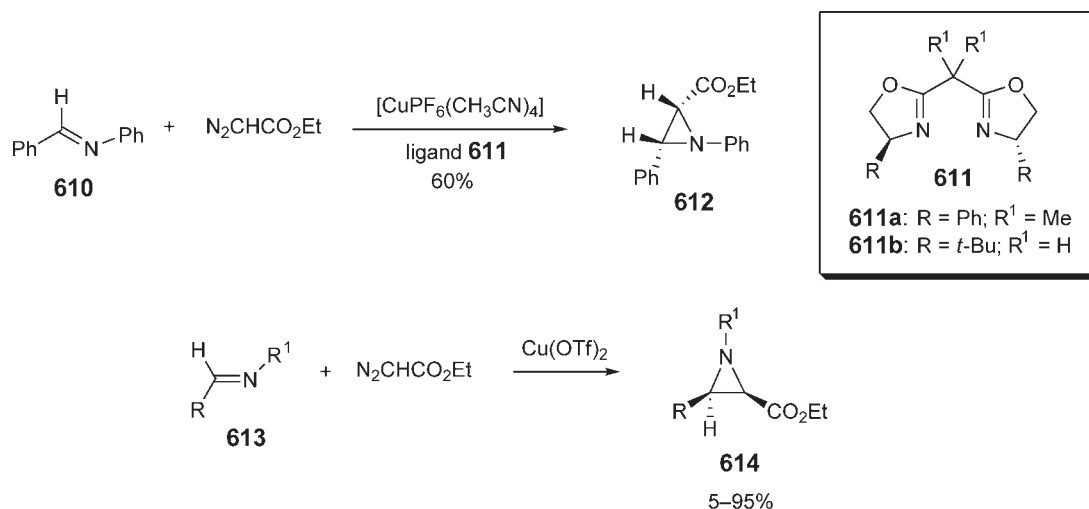
Scheme 146

As with epoxide synthesis, formation of optically pure aziridines is of ever-increasing interest. In this regard, the asymmetric aziridination of α -imino esters **603** can be promoted by copper(I) catalysts equipped with chiral BINAP or bis-oxazoline ligands. In this case, the asymmetric induction is believed to occur through a pre-coordination of the imino ester with the catalyst <1999J(P1)2293>. Simple imines, such as **607**, undergo aziridination under the influence of the chiral boron Lewis acid derived from S-VAPOL **606** to provide scalemic aziridines in excellent ee's in almost all cases (Scheme 147). Yields are fair to good <1999JA5099>.

The Jacobsen group has been active in the area of asymmetric synthesis of aziridines using the route of carbenoid transfer to imines and employing copper(I) salts in association with bis(dihydrooxazole) ligands **611** (Scheme 148), a process which yields modest ee's starting from imine **610** <1995AGE676>. Rasmussen and Jørgensen have also reported a similar racemic version of this protocol which features the copper(II) triflate-catalyzed group transfer from ethyl diazoacetate to various imines **613** to give the corresponding aziridines **614** as a mixture of *cis*- and *trans*-isomers; however, they report low ee's for the corresponding chiral approach using chiral ligand **611a** <1995CC1401>.



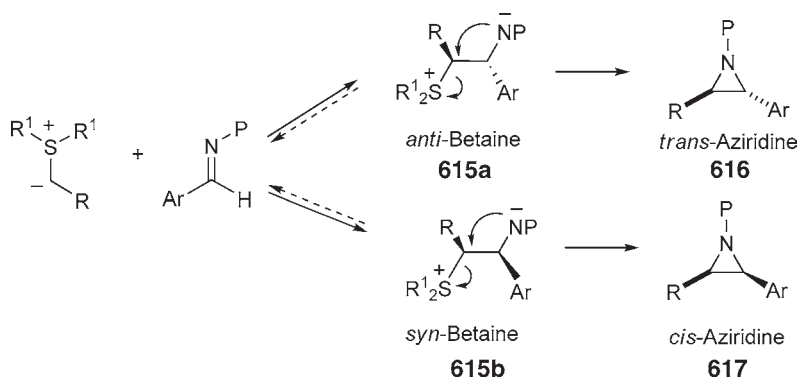
Scheme 147



Scheme 148

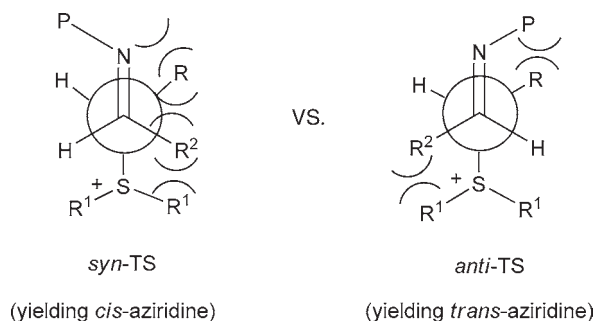
1.01.6.3.2 Preparation of aziridines using sulfur ylides and imines

Another variation of the [C+C=N] pathway involves the addition of sulfur ylides to imines and this method has been effectively used to access a wide range of substituted aziridines under mild reaction conditions. Although high ee's can be achieved by using a chiral sulfide (up to 98%), the *cis/trans*-diastereoselectivity in this process is, in most cases, poor. The generally accepted mechanism for aziridine formation from sulfur ylides and imines involves two key steps (Scheme 149) <2006JOC2726>. The first is addition of the ylide to the imine to form a betaine intermediate **615**. Two isomeric betaines (**615a** vs. **615b**) can be formed during this step: an *anti*- and a *syn*-diastereomer. The *transoid*-conformer (aza and sulfonium groups *anti*-periplanar to each other) of each of these betaines can then ring-close to yield a *trans*- **616** and a *cis*-aziridine **617**, respectively.



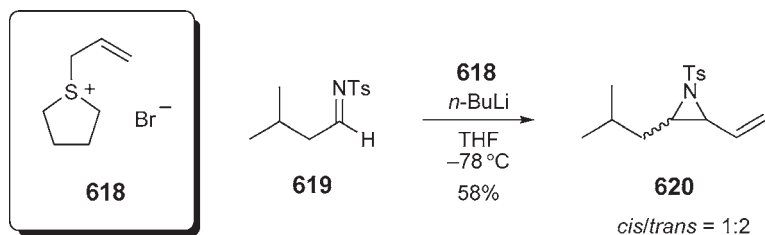
Scheme 149

Aggarwal *et al.* have suggested that the *anti*-betaine (leading to *trans*-aziridine) was formed preferentially in the reaction of *N*-sulfonylimines with semistabilized ylides (Scheme 150) <2001J(P1)3159>. This was attributed to steric strain in the transition state leading to the *syn*-betaine. In this model, ylides add to imines via transition states with a *transoid*-arrangement of the aza and sulfonium groups. Comparing the two diastereomeric transition states, *syn* and *anti*, it was suggested that the lesser steric encumbrance between the ylidic substituent (R) and the approaching imine in the *anti*-transition state accounts for the preferential formation of the *anti*-betaine and hence *trans*-aziridine with this system.



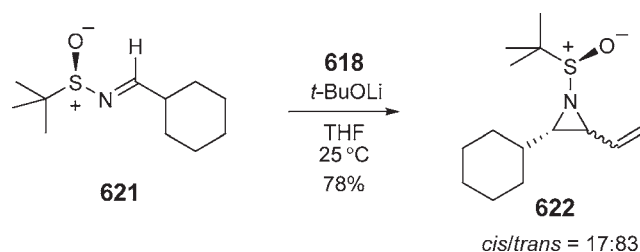
Scheme 150

In a typical example for aziridine synthesis, *S*-allyl tetrahydrothiophenium bromide **618** was smoothly deprotonated with strong base to provide an ylide which adds to a variety of *N*-protected imines. For the *N*-tosyl aldimine **619** derived from isovaleraldehyde, the corresponding vinyl aziridine **620** is formed in fair yield as a mixture of stereoisomers (Scheme 151) <2004TL1589>.



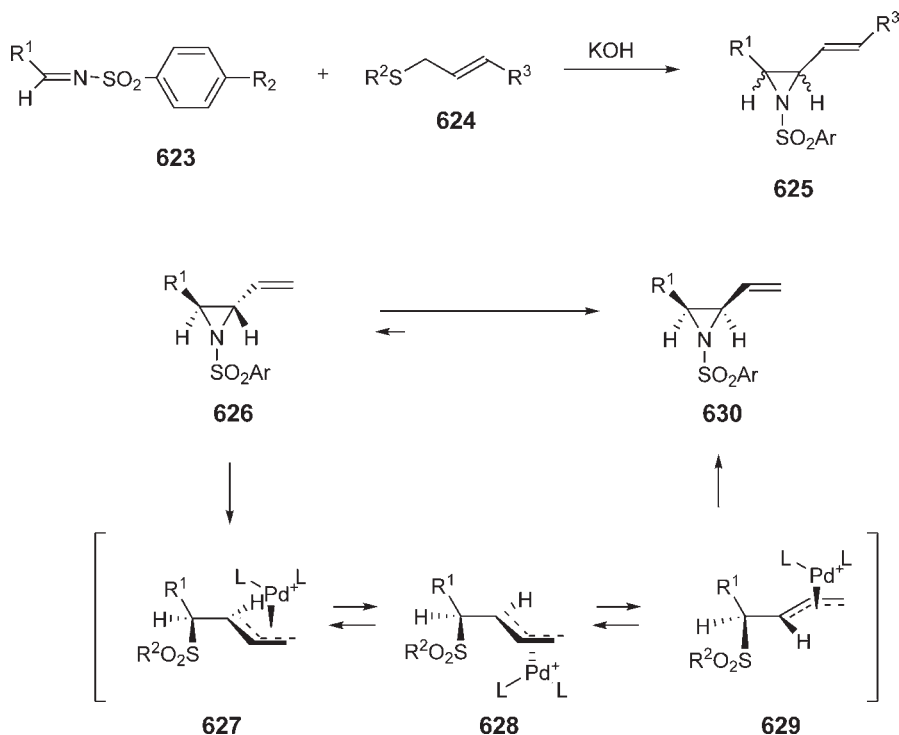
Scheme 151

When chiral *t*-butylsulfinylimine **621** is used as the substrate, a highly stereoselective aziridination ensues, providing the heterocycle **622** in good yield and good to excellent de (Scheme 152) <2004OL2377>.



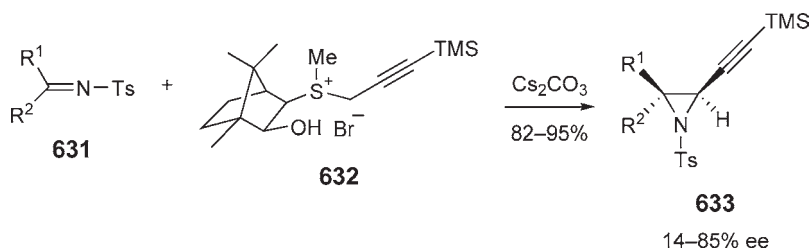
Scheme 152

Dai and co-workers [\[1996JOC4641, 1996CC491\]](#) have utilized the ylide–imine strategy in developing a direct route to *C*-vinylaziridines **625**. Thus, allylic sulfonium salts (i.e., **623**) react with aromatic, heteroaromatic, and α,β -unsaturated *N*-sulfonylimines (i.e., **624**) under solid–liquid phase-transfer conditions in the presence of KOH at room temperature to produce vinyl aziridines **625** (Scheme 153). Yields are excellent, but *cis/trans*-selectivity is modest. Interestingly, however, it has been demonstrated that the isomerization of such mixtures is feasible under palladium(0) catalysis. Under these conditions, *N*-arylsulfonyl-*trans*-3-alkyl-2-vinylaziridines are converted almost quantitatively to the corresponding *cis*-isomers through the intermediacy of a palladium–allyl complex. The observed apparent thermodynamic preference of the *cis*-isomer is in agreement with *ab initio* calculations [\[1996CC351\]](#).



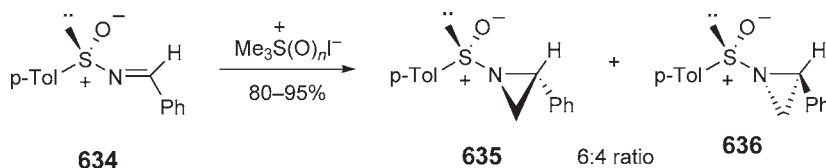
Scheme 153

The reaction of sulfur ylides with imines is an operationally straightforward procedure which is often carried out under phase-transfer conditions [\[1997TL7225\]](#). The use of a chiral auxiliary allows the preparation of enantiomerically enriched aziridines, as illustrated by the reaction of *N*-sulfonylimine **631** with chiral sulfonium propargylide **632** to give the chiral aziridine **633** (Scheme 154) [\[1997AGE1317, 1998JOC4338\]](#). *cis*-Selectivity is excellent, yields are good, and asymmetric induction, while generally modest, can also be quite high (up to 85%). The reader is directed to a recent review of the aziridination reaction via the ylide route [\[2006SL181\]](#).



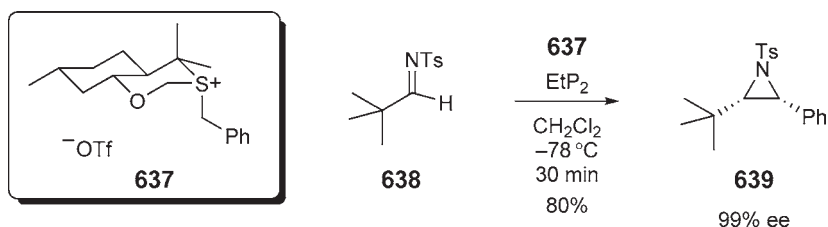
Scheme 154

The stereochemical outcome of the asymmetric aziridination route seems to be dependent upon the nature of the methylene-transfer reagent. Thus, dimethyloxosulfonium methylide provided predominantly isomer **635**, whereas the use of dimethylsulfonium methylide led to the formation of **636** as the major product (Scheme 155) <1995TL295>.



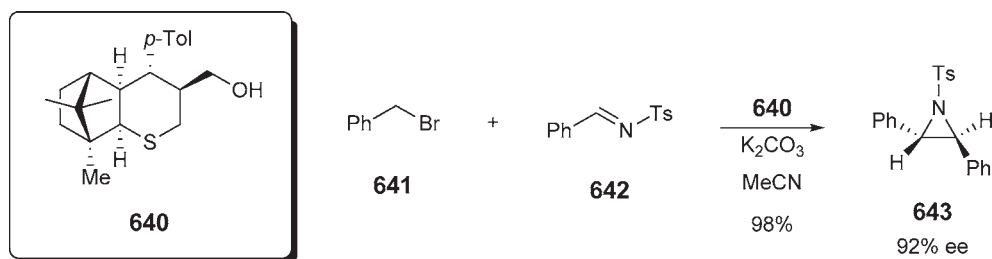
Scheme 155

Chiral induction can also be quite effective when the locus of asymmetry is attached to the sulfur ylide itself. The sulfonium salt **637**, derived from Eliel's oxathiane, can be used to deliver a benzylic center to tosylimines (e.g., **638**) and efficiently produces phenylaziridines with a very high degree of asymmetric induction. The method is amenable to gram-quantity synthesis, and the chiral auxiliary can be easily recovered. In general, *cis/trans*-mixtures are obtained, depending upon the steric bulk of the imine substituent (Scheme 156) <2004JOC1409>.



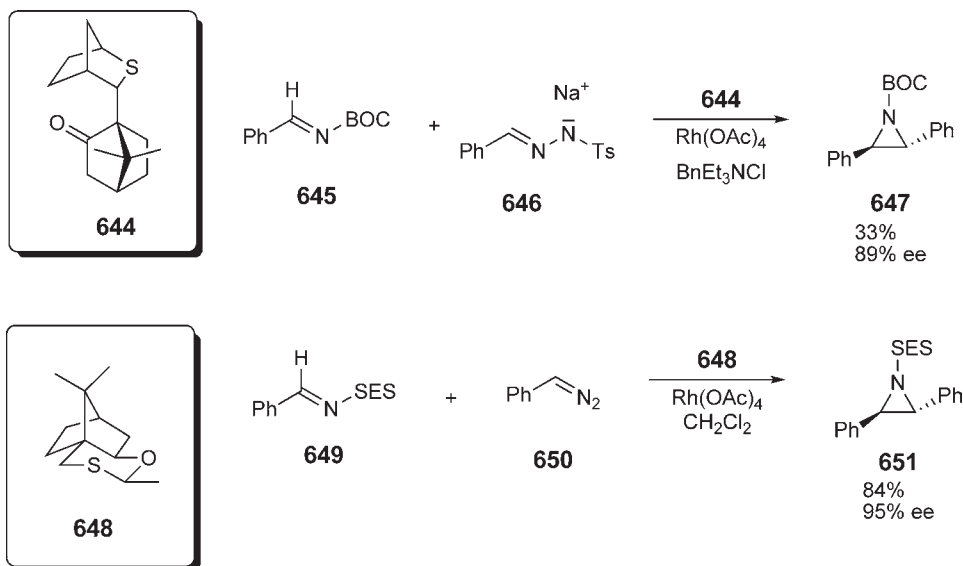
Scheme 156

Aziridines can also be synthesized enantioselectively from imines and alkyl halides using a camphor-derived chiral sulfide mediator **640** in a one-pot procedure via the imino Corey–Chaykovsky reaction. Thus, benzyl bromide **641** and tosyl imine **642** provide aziridine **643** in practically quantitative yield as a 3:1 mixture of (*E/Z*)-isomers and in 92% ee ((*E*)-isomer) (Scheme 157). An electron-withdrawing substituent on the imine nitrogen is necessary to activate the π -system for nucleophilic attack <2001TL5451>.



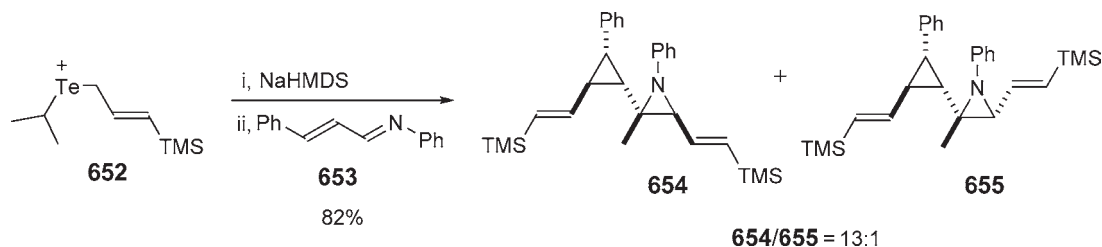
Scheme 157

Aggarwal *et al.* have applied their sulfur ylide methodology to the synthesis of aziridines with notable success. Thus, the ylides derived from chiral sulfide **644** and rhodium carbenoids (generated *in situ*) provide chiral aziridines (e.g., **647**) from imine precursors (e.g., **645**) (Scheme 158). The protecting group on the imine nitrogen plays a large role in yield and diastereomeric ratios, and to a lesser extent on the enantioselectivity. The BOC group gives the best *trans/cis*-ratio, but the lowest overall yield. The opposite is true for the SES group. Enantiomeric excesses range from 89% to 98% <2001AGE1433>. The SES group also turns out to be the best choice when the sulfide **648** is used as the chiral auxiliary. Solvent and substrate structure also influence the selectivity <2001J(P1)1635>.



Scheme 158

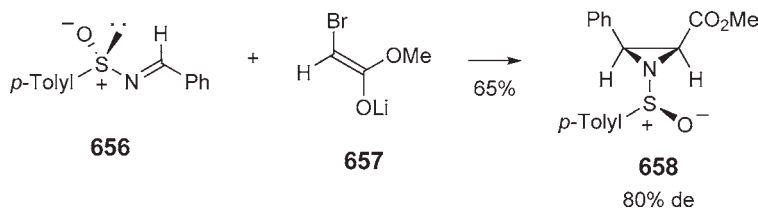
The related telluronium ylides also add to α,β -unsaturated imines through a Michael addition–elimination to the olefin followed by a second equivalent of telluronium ylide addition to the imine, which subsequently eliminates to form aziridines **654** and **655** in a ratio of 13:1 (Scheme 159) <2005JA12222>.



Scheme 159

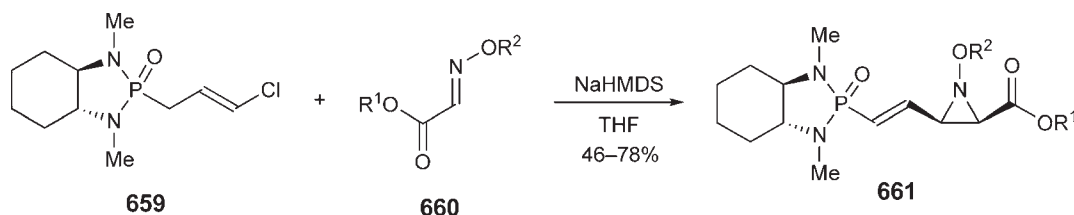
1.01.6.4 Anion Addition–Elimination Approach

The Gabriel–Cromwell approach proceeds through the intramolecular displacement of the halide in the cyclization step, and this end game can be approached from more than one starting point. Thus, Davis *et al.* <1999JOC7559> reported on a one-step aza-Darzens reaction of sulfinimines **656** with lithium α -bromoacetates **657** to give the corresponding aziridines **658** in fair to good yield and good to excellent de (Scheme 160). The *cis/trans*-isomer ratio is dependent upon the nature of the bromoacetate, with the anion of α -bromoacetate itself giving rise to predominantly the *cis*-isomer **658**, and substituted analogs producing mainly the *trans*-isomer. This selectivity was rationalized on the basis of a chair-like transition state.



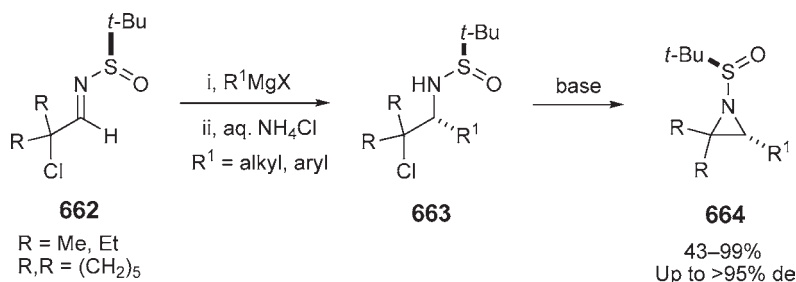
Scheme 160

In an anionic approach, the sodium salt of the chiral chloroallyl phosphonamide **659** engages in nucleophilic addition onto oximes and gives the optically pure *N*-alkoxy aziridines **661** (Scheme 161). The chiral auxiliary can be removed by oxidative cleavage of the double bond with ozone <2000TL787>.



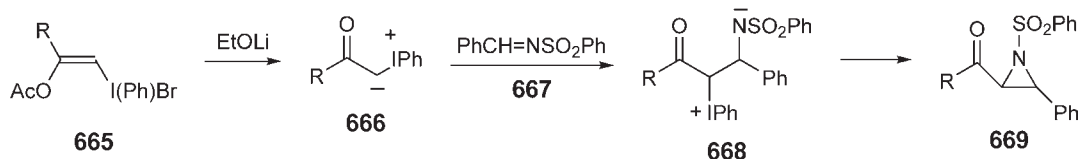
Scheme 161

Reaction of chiral α -chloro *tert*-butanesulfinyl aldimines **662** with Grignard reagents efficiently affords β -chloro-*N*-sulfinamides **663** with high de. These compounds were cyclized to give the corresponding chiral aziridines **664** in a high-yielding one-pot reaction or after separate treatment with base. The diastereoselectivity obtained in the newly synthesized β -chloro sulfinamides was explained via the coordinating ability of the α -chloro atom with magnesium which results in the opposite stereochemical outcome as generally observed for nonfunctionalized *N*-sulfinylimines (Scheme 162) <2006OL3129>.



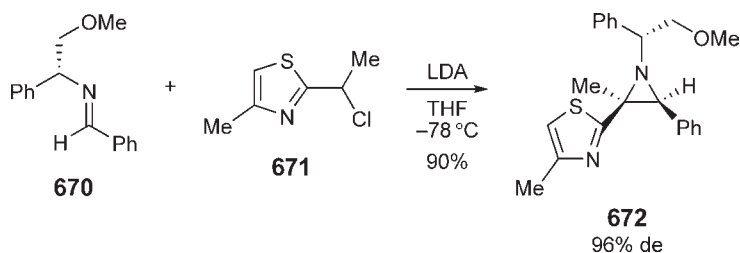
Scheme 162

Monocarbonyl iodonium ylides such as **666** have been generated *in situ* from iodoenol ester precursors **665**. These reagents undergo alkylidene-transfer reactions with activated imines (e.g., **667**) to give α,β -aziridino ketones, mainly as the *cis*-isomer. The selectivity of the aziridination was noted to be slightly increased by the presence of electron-donating substituents on the imine *C*-phenyl ring (Scheme 163) <1998TL5569>.



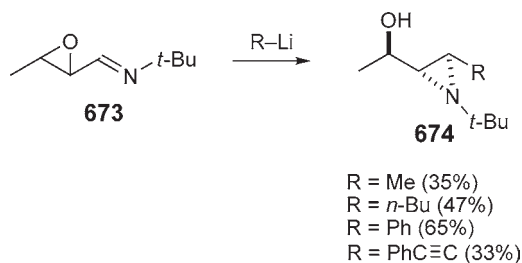
Scheme 163

The approach of leveraging chirality at the imine nitrogen to impart enantioselectivity has also been used to advantage in the preparation of chiral heterosubstituted aziridines. Thus, when 2-(1-chloroethyl)-4-methyl-thiazole **671** is deprotonated with lithium diisopropylamide (LDA) and treated with the chiral aldimine **670**, the aziridinyl thiazole derivative **672** is produced in excellent yield and diastereoselectivity (Scheme 164) <2004T1175>.



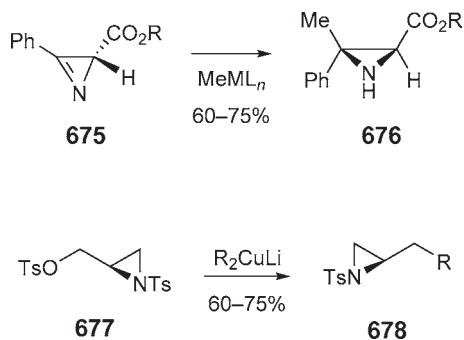
Scheme 164

A new example of the aza-Payne rearrangement has been used to prepare α -hydroxyaziridines <2005OL3267>. The epoxy imine **673** is prepared by a sequential epoxidation and imination. Reaction of **673** with a series of alkyl lithium reagents initially adds to the imine which then does an aza-Payne rearrangement to form the hydroxyaziridine **674** (Scheme 165). While the method generally suffers from poor yields, the one-step nature of the transformation lends greatly to its appeal.



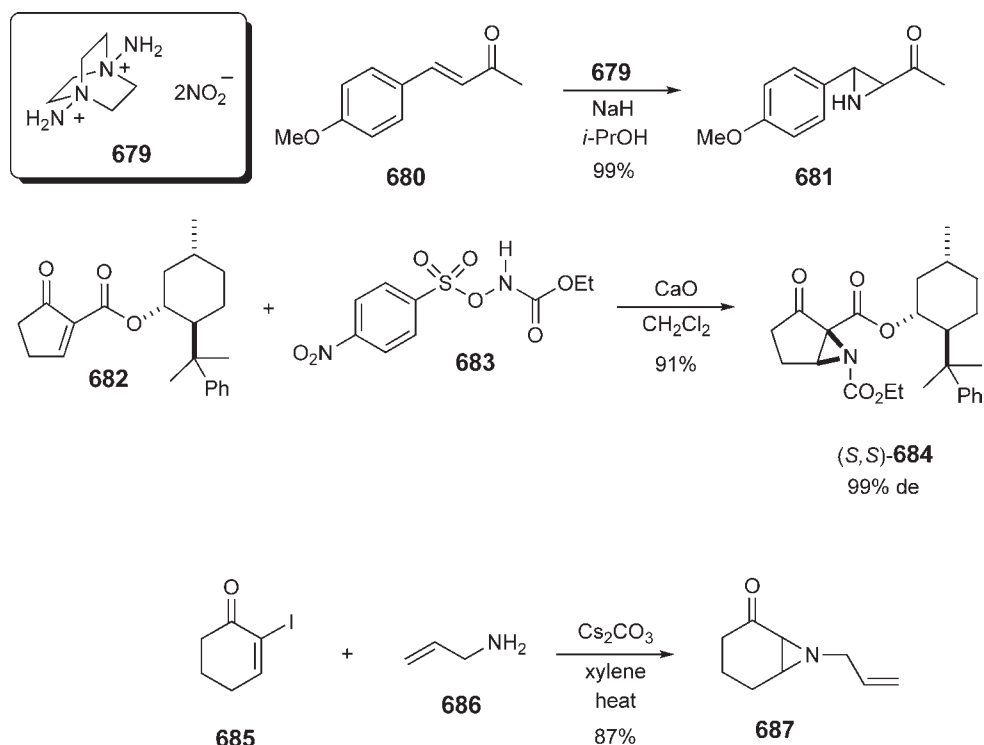
Scheme 165

The addition of Grignard reagents onto chiral azirenes (e.g., **675**) has been used for the highly stereoselective preparation of unsymmetrical 3,3-disubstituted-aziridine-2-carboxylate esters (e.g., **676**), themselves useful precursors for the synthesis of unnatural β -substituted α -amino acids <1997JOC3796>. Organometallic reagents can also engage in nucleophilic attack on the aziridine nucleus, which Bergmeier and Seth <1997JOC2671> use to advantage in their synthesis of monosubstituted alkyl aziridines **678** starting from the chiral tosylated derivative **677**, a reaction which occurs without the loss of optical purity (Scheme 166).



Scheme 166

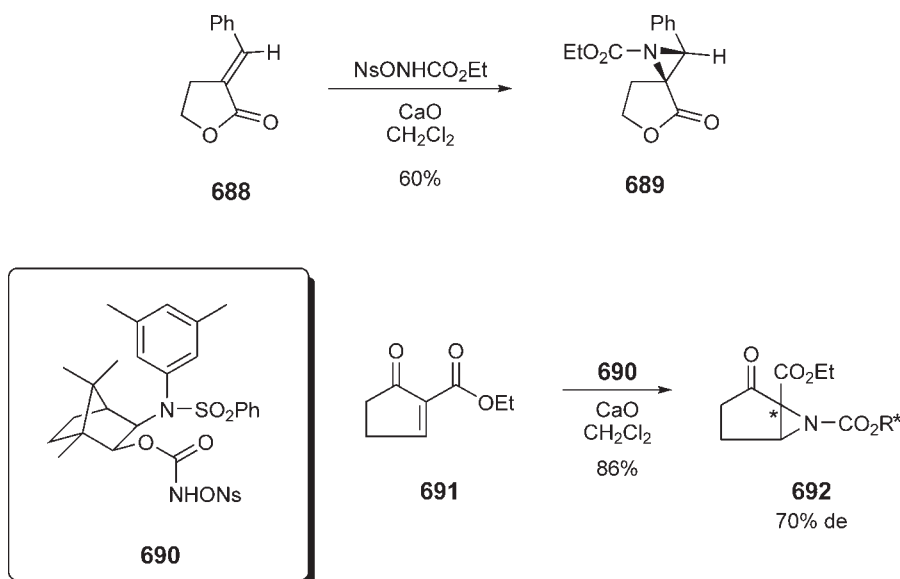
Electron-deficient alkenes can be converted to aziridines using nucleophilic nitrogen donors attached to good leaving groups. For example, *N,N'*-diazoniabicyclo[2.2.2]octane dinitrate **679** forms a nitrogen–nitrogen ylide in the presence of sodium hydride, which converts enones directly to the unprotected aziridines (e.g., **681**) by way of initial Michael addition and subsequent cyclization <2002J(P1)1491>. Another method employs the anion of nosyloxycarbamate **683** as the aziridinating agent and a diactivated substrate which is equipped with a phenylmenthol chiral auxiliary appended to the ester moiety. Thus, enone ester **682** is converted to the azabicyclo[3.1.0]hexanone derivative **684** in 91% yield and 99% de upon treatment with **683** and calcium oxide <2002JOC4972>. In the case of α -iodoenones (e.g., **685**), even simple primary amines can engage in aziridination, a process which is mediated by cesium carbonate (Scheme 167) <2002TL4329>.



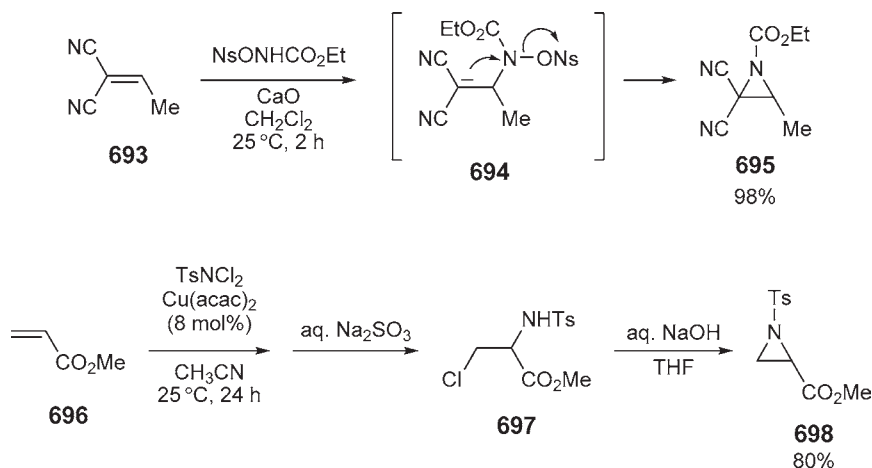
Scheme 167

Exocyclic α,β -unsaturated lactones (e.g., **688**) have been converted to the corresponding spiroaziridines **689** by treatment with ethyl *N*-[(4-nitrobenzene)sulfonyl]oxy]carbamate (NsONHCO₂Et) in the presence of calcium oxide <2003TL4953>. In a similar vein, a novel chiral carbamate **690** based on Helmchen's alcohol has been applied to the same conditions with moderately good diastereoselectivities, as shown in the aziridination of carboethoxy-cyclopentenone **691** (Scheme 168) <2003TL3031>.

In the case of electron-deficient olefins, other methodologies are also available. For example, the dicyanoalkene **693** (derived from the Knoevenagel condensation of malononitrile with acetaldehyde) undergoes a facile aza-Michael addition of ethyl nosyloxycarbamate in the presence of calcium oxide to give a β -aminocarbanion intermediate **131**, which quickly cyclizes to the corresponding dicyanoaziridine **695** in excellent yield <2004SL1083>. When trifluoro-methylacrylates are used as substrates, the intermediate Michael adducts can be isolated in >95% yield <2004OL197>. Some degree of enantioselectivity has been observed when *Cinchona* alkaloids are used as catalysts in the reaction <2004T8073>. An electrophilic variant is represented by the copper-catalyzed addition of *N,N*-dichloroarylsulfonamide across electron-deficient olefins such as methyl acrylate **696**. The resulting β -chloroamines, which exhibit stereochemistry resulting from net *anti*-addition, can be cyclized by treatment with sodium hydroxide to provide tosyl aziridines (e.g., **698**) in good overall yield (Scheme 169) <2004SC1337>.



Scheme 168



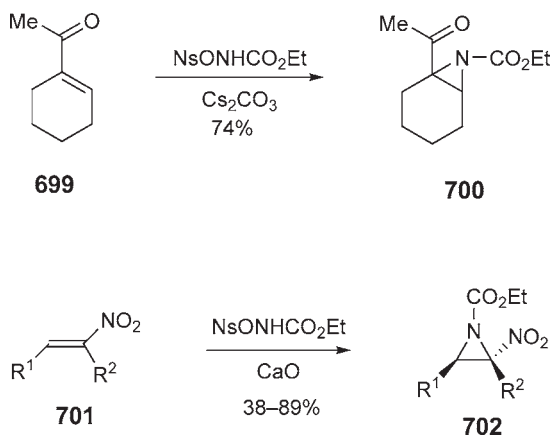
Scheme 169

Pellacani and co-workers have reported on the aziridination of α,β -unsaturated ketones (e.g., **699**) <1998T14105> and α -nitroalkenes (e.g., **701**) <1998T6169> using a system of ethyl [(4-nitrobenzenesulfonyl)oxy]carbamate (NsONHCO₂Et) as the nitrene donor and calcium oxide as the base (Scheme 170). The reaction can be carried out in the absence of auxiliary solvent and is suspected to proceed via an aza-Michael route, rather than by a true nitrene-addition pathway.

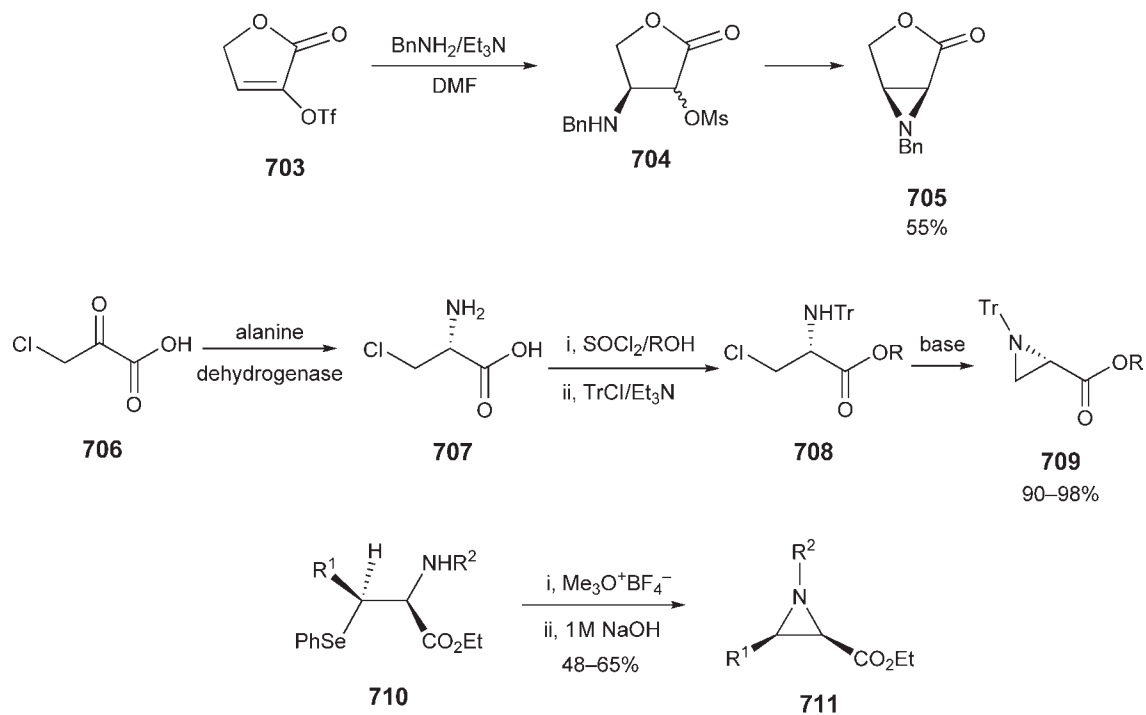
Aziridination of electron-deficient olefins usually proceeds by a conjugate addition pathway. Thus, benzylamine adds to 2-(5*H*)-furanon-3-yl methanesulfonate **703** to give a Michael adduct **704**, which ring-closes to form the corresponding aziridine **705** <2000TL3061, 2000TL6393>. Ring-closure strategies have also been used in other systems not constructed directly from electron-deficient olefins. For example, the chloroamino ester **708**, derived from the action of alanine dehydrogenase on keto acid **706**, undergoes base-catalyzed ring closure to form an aziridine <2000CC245>, as does the β -alkylamino phenylselenide **710**, which is prepared from an α -phenylselenanyl imine (Scheme 171) <2000TL663>.

Similarly, chiral aziridinoalcohols **714** are readily obtained from the reaction of racemic methyl 2,3-dibromopropionate **712** and optically pure 2-phenylglycinol **713** (Scheme 172) <2000SC1303>.

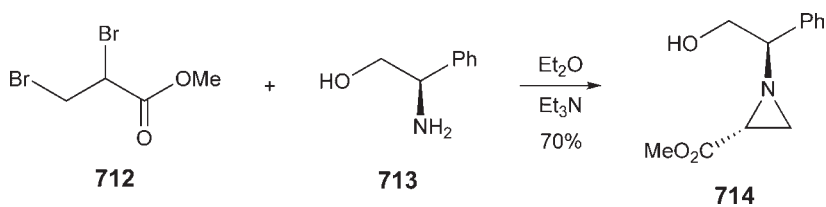
Alkenes undergo diastereoselective aziridination in the presence of chiral 3-acetoxyaminoquinazolinones (e.g., **715**), prepared *in situ* by acetoxylation of the corresponding 3-aminoquinazolinones. Thus, trimethylsilyl styrene **716**



Scheme 170

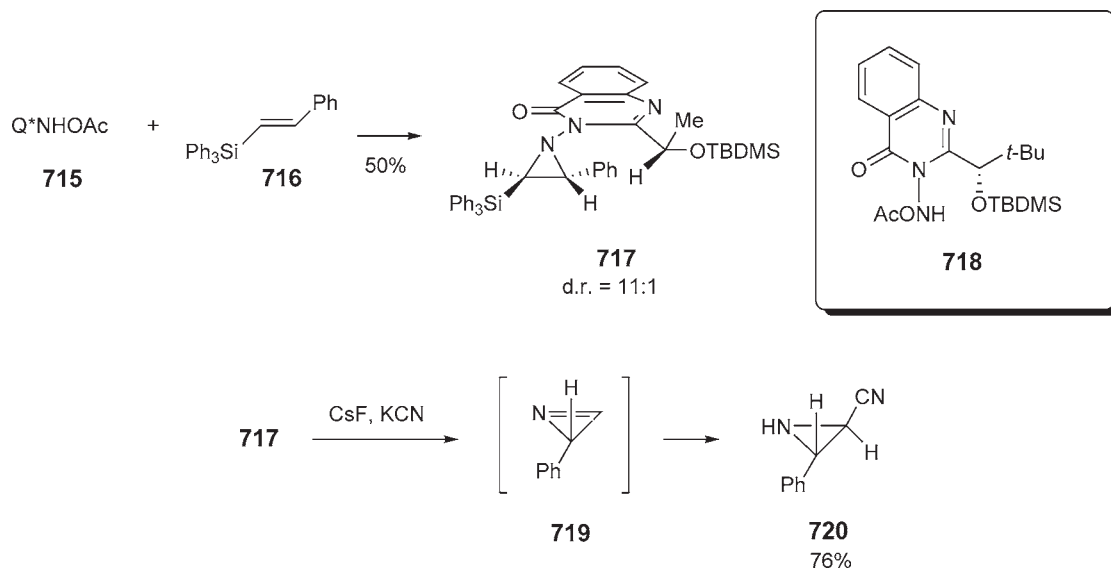


Scheme 171



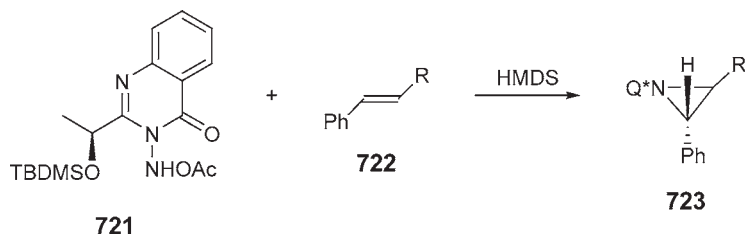
Scheme 172

is converted to the aziridine **717** with a diastereomeric ratio of 11:1. The diastereoselectivity is rationalized by a transition state which maximizes *endo*-overlap of the substrate phenyl ring with the reagent π -system, while minimizing nonbonded interactions, a factor largely dominated by the relative steric volumes of the two substituents on the chiral carbon center. This is illustrated by a sharp drop in the diastereoselectivity of this reaction (4:1) when the bulkier *t*-butyl group is substituted for the methyl group (i.e., **718**) <1996TL5179>. After aziridination, the chiral auxiliary can be removed by desilylative elimination to give an intermediate azirine **719**, which can be trapped *in situ* by the addition of cyanide, providing the NH-aziridine **720** with 83% ee (Scheme 173) <1996CC789>.



Scheme 173

3-Acetoxyaminoquinazolinones **721** have been found to function as chiral aziridinating agents for alkenes. Aziridine formation proceeds with retention of alkene configuration via a mechanism analogous to the epoxidation of alkenes with peroxyacetic acid (Scheme 174). In the case of styrene derivatives (e.g., **722**), diastereoselectivity increases as the β -substituent (R) becomes more electronegative, with an observed diastereomeric ratio of 5:1 for the methyl derivative and 20:1 for the dichloromethyl analog. These results were rationalized on the basis of a tighter and more symmetrical transition state, as predicted by highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO–LUMO) considerations <1998TL5113, 1998J(P1)583>.

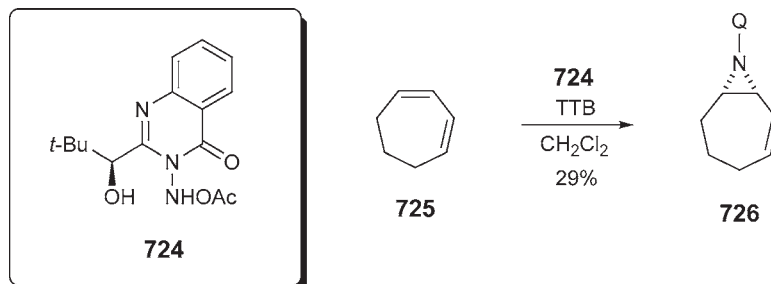


Scheme 174

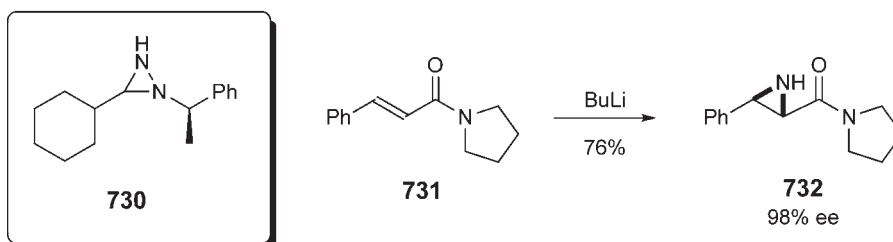
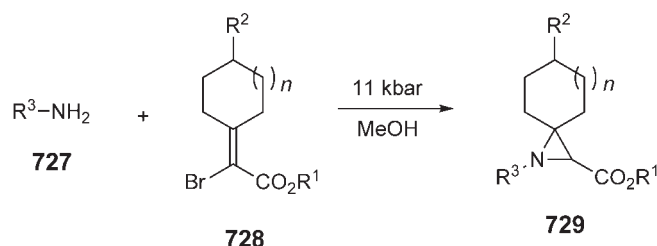
Other approaches to chiral aziridines have been reported. For example, treatment of cycloheptadiene **725** with the leucine-derived (*S*)-3-acetoxyamino-2-(3-hydroxy-2,2-dimethylpropyl)quinazolin-4(3*H*)-one **724** in the presence of titanium(IV) *t*-butoxide (TTB) in methylene chloride leads to formation of the chiral aziridine **726**, in which the chiral auxiliary (Q) is in the *exo*-position, as the only isolated product in 29% yield (Scheme 175) <2001J(P1)1518>.

The aziridination of electron-deficient alkenes can be carried out under slightly different conditions. The reaction between primary amines **727** and 2-bromo-2-(cycloalkylidene)acetates **728** in alcohol under high pressure provides spiroaziridines **729** in good yields and de's. The reaction is general for most primary amines, except for

those that are weakly nucleophilic or sterically bulky <2001EJO2569>. Enamides (e.g., **731**) can be converted to corresponding aziridinylamides **732** with excellent enantioselectivity using the chiral diaziridine **730** (Scheme 176) <2001CL984>.



Scheme 175

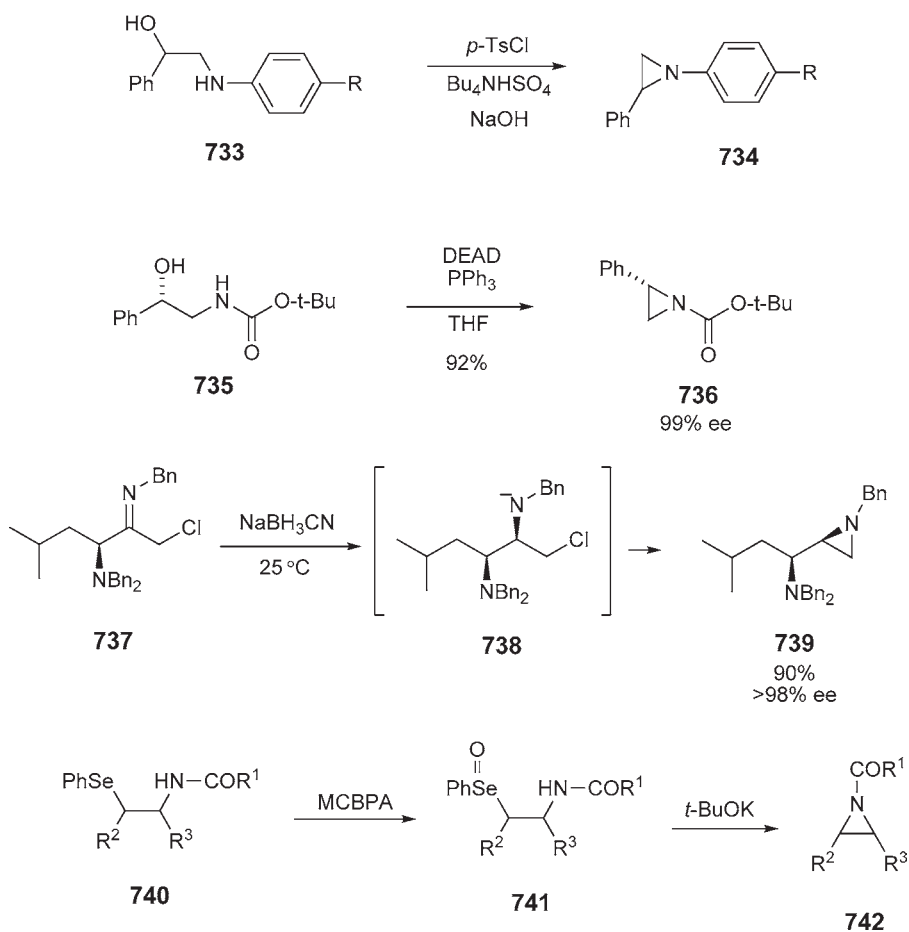


Scheme 176

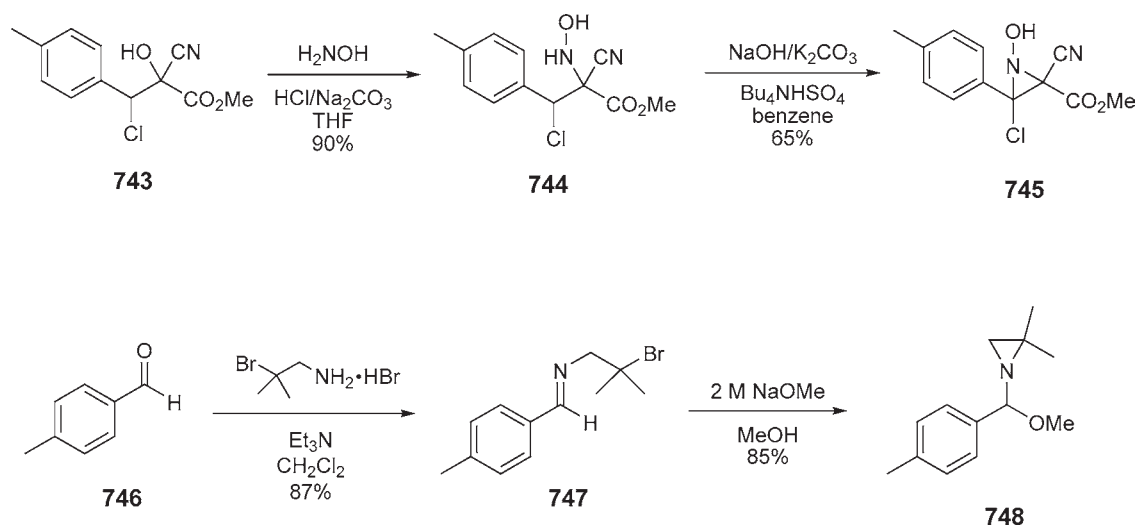
1.01.6.5 Cyclization of 1,2-Diamino Alcohols and Derivatives

Aziridines can also be formed by the ring closure of appropriately substituted amines. For example, treatment of *N*-aryl- β -amino alcohols **733** with *p*-toluenesulfonyl chloride under phase-transfer conditions provides *N*-aryl aziridines **734** in 80–90% yield <2001SC1105>. Enantiomerically pure aziridines can be prepared in a similar fashion, starting with optically pure amino alcohols derived from the enantioselective reduction of α -amino ketones. Thus, treatment of the amino alcohol **735** with diethyl azodicarboxylate (DEAD) and Ph₃P in THF led to the formation of aziridine **736** in 92% yield and 99% ee <2001J(P1)1916>. The chiral chloroimine **737** could be converted to the optically pure aziridine **739** via diastereoselective reduction with sodium cyanoborohydride to produce the intermediate amide anion, which cyclizes to form **739** in 90% yield and >98% ee <2001JOC2764>. Finally, the oxidation of β -amido selenides **740** with *m*-chloroperbenzoic acid (MCPBA), followed by treatment of the corresponding selenones with potassium *t*-butoxide, gives *N*-acylaziridines in good to excellent yields (Scheme 177) <2001J(P1)944>.

Of course, aziridines can also be synthesized by the ring-closing reactions of appropriately substituted amines <2003T2435>. For example, halohydrins of type **743** are converted to *N*-hydroxy aziridines **745** by treatment with hydroxylamine derivatives, followed by base-catalyzed intramolecular S_N2 reaction of the intermediate β -haloaminoesters **744** under phase-transfer conditions <2003TL3259>. *N*-Bromoethylamines **747**, formed from the reaction of benzaldehyde derivatives (e.g., **746**) and 2-bromo-2-methylpropylamine hydrobromide, undergo nucleophilic attack by methoxide, followed by intramolecular displacement of bromide to form *N*-(α -methoxybenzyl)aziridines **748** (Scheme 178) <2003TL1137>.

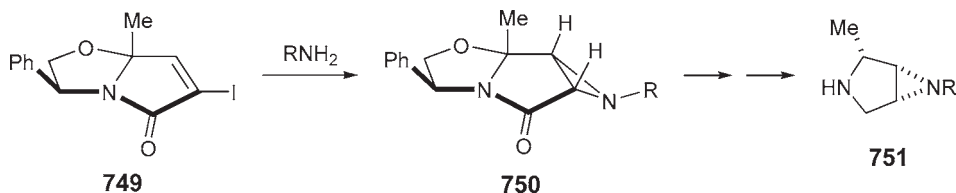


Scheme 177



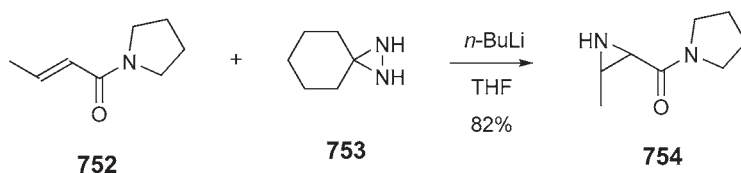
Scheme 178

A strictly nucleophilic approach can also be used for an $[N+C=C]$ protocol. Thus, the chiral iodo-unsaturated bicyclic lactam **749** undergoes stereoselective conjugate addition with primary amines to give the tricyclic aziridine **750**, which can be subsequently transformed into the chiral 3,4-aziridinopyrrolidine **751** by reductive cleavage. Yields of up to 90% can be achieved and facial selectivity is greater than 98:2 (**Scheme 179**) <1995TL3491>.



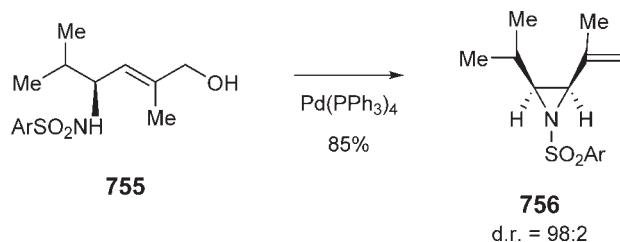
Scheme 179

An interesting anionic aziridination of α,β -unsaturated amides was reported <1999TL5207>, utilizing lithiated 3,3-pentamethylenediaziridine **753** as the nitrogen atom donor (**Scheme 180**). Formation of *cis*-aziridines was generally observed, regardless of the stereochemistry of the starting material, a phenomenon which is in keeping with a stepwise mechanism of conjugate addition and subsequent ring closure.



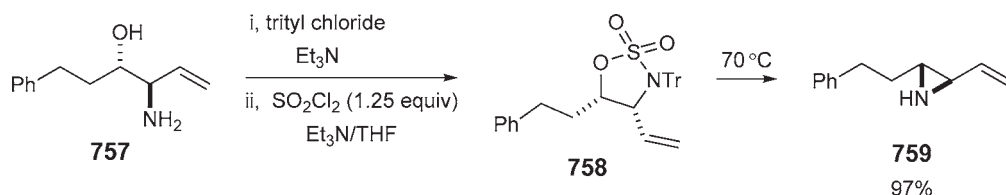
Scheme 180

Sterically congested *cis*-aziridines such as **756** were prepared from the derivatized amino allyl alcohol precursor **755** through a palladium-catalyzed cyclization reaction <1999TL1331>. This methodology has also been extended to the cyclization of amino allenes (**Scheme 181**) <1999JOC2992>.



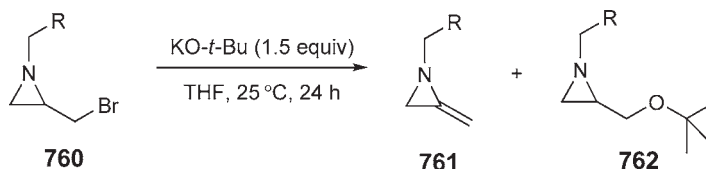
Scheme 181

One straightforward route to the aziridine ring system is available through the ring closure of vicinal amino alcohols, an approach which has been used to prepare vinyl NH-aziridines. Thus, 4-amino-1-phenylhex-5-en-3-ol **757** was treated with sulfuryl chloride to provide the sulfamate **758**, which underwent clean thermolysis at $70^\circ C$ to form the vinyl aziridine **759** in 97% overall yield (**Scheme 182**) <2002T5979>.



Scheme 182

Finally, some rather interesting but esoteric methyleneaziridines (e.g., **761**) have been prepared via the 1,2-dehydrobromination of 2-(bromomethyl)aziridines **760** under carefully controlled conditions (Scheme 183) <1997JOC2448>.



Scheme 183

1.01.7 Introduction – Monocyclic 2H-Azirines

2H-Azirines correspond to the smallest nitrogen unsaturated heterocyclic system, with two carbon atoms and one double bond in a three-membered ring. The theoretical and biological applications and the synthetic chemistry of these heterocycles have been extensively explored and a number of general reviews on 2H-azirines have appeared <1996CHEC-II(1A)1, 2001EJO2401, 2002OPP219>. Substituted 2H-azirines are versatile compounds and have been used for the preparation of functionalized aziridines. The chemistry of 2H-azirines is dominated by processes in which the strain of the three-ring system is relieved. They readily participate in cycloaddition reactions as 2 π -components and undergo ring cleavage on photochemical excitation to give nitrile ylides. These dipoles then undergo a subsequent 1,3-dipolar cycloaddition reaction with a variety of π -bonds. Thermal ring cleavage produces vinyl nitrenes by cleavage of the N–C₂ bond, which then undergo ring-expansion reactions.

1.01.8 2H-Azirines

1.01.8.1 Theoretical Methods

A number of the theoretical issues dealing with 2H-azirines were discussed in CHEC-II(1996) and CHEC(1984) <1996CHEC-II(1A)1, 1984CHEC(7)47>.

1.01.8.2 Experimental Structural Methods

The structures of 2H-azirines, their complexes with H⁺ and Li⁺, and the relative basicities of 2H-azirines have been calculated by semi-empirical and *ab initio* methods <1993JA11074, 1999PCA3330, 1998PCA7074>. The spectroscopic properties of 2H-azirines were discussed in detail in CHEC-II(1996) <1996CHEC-II(1A)1>. Polarization toward the more electronegative nitrogen atom of the 2H-azirine ring results in a shorter C–N bond and a longer C–C bond, consistent with the dimensions of 2H-azirines found by single crystal X-ray data <1997CEJ1757>.

1.01.8.3 Thermodynamic Aspects

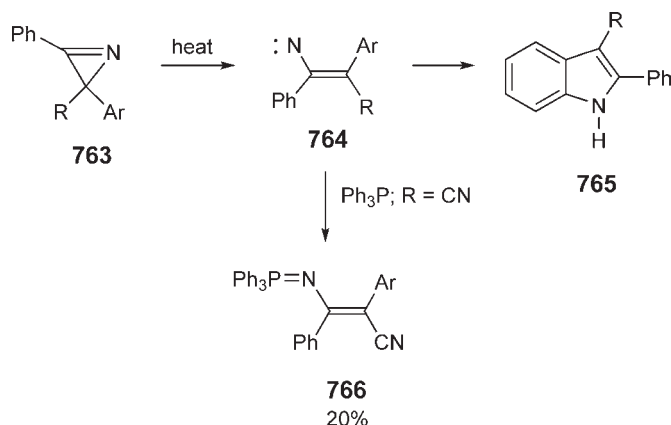
The stability of the 2H-azirine ring can be attributed not only to the combined effects of bond shortening and angle compression, but also to the presence of the electron-rich nitrogen atom. The strain energy associated with these heterocycles is principally due to deformation of the normal bond angles between the atoms of the ring. The total ring-strain energy of 2H-azirine has been estimated at 48 kcal mol^{−1} <1991AGE238, 2002EJO1750>, although lower values of 44.6 and 46.7 kcal mol^{−1} have been reported using *ab initio* calculations at the MP2/6-31G* and B3LYP/6-31G* levels of theory <1998JCC912>.

1.01.9 Reactivity of Monocyclic 2H-Azirines

The chemical reactivity of 2H-azirines is quite high as a consequence of their ring strain, reactive π -bond, and ability to undergo regioselective ring cleavage. 2H-Azirines not only are capable of acting as nucleophiles and electrophiles in organic reactions, but also can act as dienophiles and dipolarophiles in cycloaddition reactions. Consequently, they are useful precursors for the synthesis of a variety of nitrogen-containing heterocyclic systems.

1.01.9.1 Thermal Reactions of 2*H*-Azirines

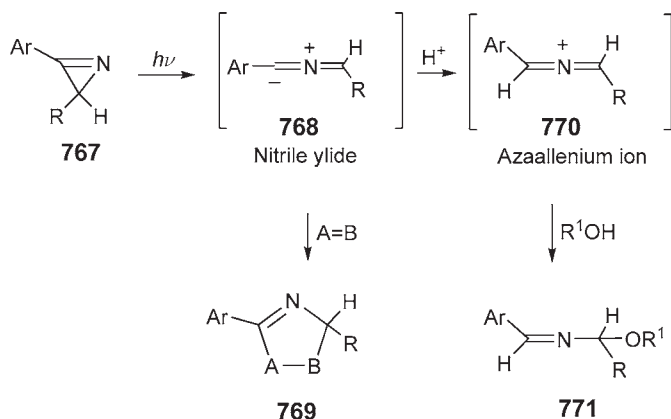
The major thermal reaction of 2*H*-azirines involves C(2)–N bond cleavage to form vinyl nitrene intermediates <1984CHEC(7)47, 1996CHEC-II(1A)1, 1998H(48)2551>. In a typical example, the thermolysis of aryl-substituted 2*H*-azirines **763** results in the formation of indoles **765** by intramolecular electrocyclicization of the intermediate vinyl nitrene **764** with the aromatic ring <1996CHEC-II(1A)1>. In the case where a cyano group is present in the 2-position of the azirine ring, the vinyl nitrene intermediate can be trapped with triphenyl phosphine to give the conjugated phosphazene **766** (Scheme 184) <1999JOC6239, 1996T4857>.



Scheme 184

1.01.9.2 Photochemical Reactions of 2*H*-Azirines

2*H*-Azirines are photochemically highly active substances. Upon irradiation into their $n\text{--}\pi^*$ -absorption bands, the strained three-membered azirine ring **767** opens selectively at the C–C bond in a heterocyclic fashion leading to the formation of a nitrile ylide intermediate (i.e., **768**) <1973JA1954>. The nitrile ylide can be trapped by reactive dipolarophiles ($\text{A}=\text{B}$) to give five-membered rings **769**. A recent example of the 1,3-dipolar cycloaddition is the facile synthesis of exohedrally functionalized fullerenes <1996T5407>. In alcohols as solvents, the nitrile ylides are protonated to yield azallenium cations **770** which are then trapped by the alcohol to furnish alkoxyimines **771**. The protonation rate of the ylide in alcohol increases with the acidity of the alcohol. On the basis of a large kinetic isotope effect ($K_{\text{H}}/K_{\text{D}}=5.5$) for protonation of the ylide, the transition state for the nitrile ylide protonation was concluded to be linear <1997JA11605>. Ring expansion of the 2*H*-azirine to pentagonal heterocycles by photochemical isomerization was also reported to occur (Scheme 185) <1995HCA935>.

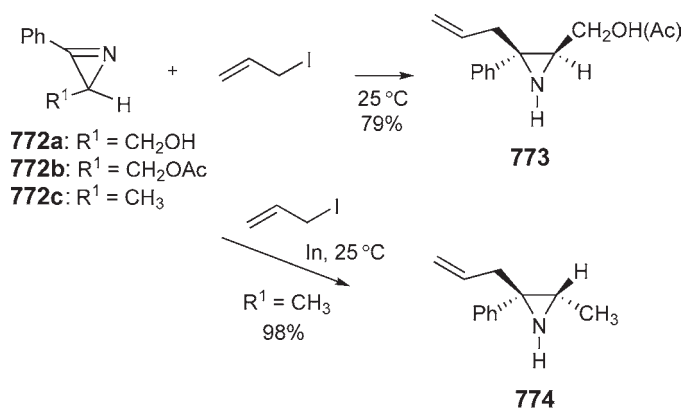


Scheme 185

More recently, the photochemistry of 3-methyl-2-(1-naphthyl)-2*H*-azirine has been investigated by the direct observation of reactive intermediates in Ar-matrices and by the characterization of reaction products in solution <2005JA2628>. Interestingly, the irradiation of this particular 2*H*-azirine with long-wavelength light resulted in selective cleavage of the C–N bond. On the other hand, products derived from C–C bond cleavage were obtained when the irradiation was carried out with short-wavelength light. On the basis of molecular orbital (MO) calculations using the intermediate neglect of differential overlap/screened approximation (INDO/S) method, it was proposed that C–N bond cleavage occurs from an excited triplet state having an electronic character of a localized π – π^* -excitation on the naphthyl moiety.

1.01.9.3 Reaction of 2*H*-Azirines with Nucleophiles

A very common reaction of 2*H*-azirines involves the addition of various nucleophiles to the ring carbon atom to produce substituted aziridines, which may undergo further reaction by a subsequent ring opening. For example, allylindium reagents react with 2*H*-azirines of type **772** to give allyl aziridines **773** in good yield. A *cis*-allylation with respect to the substituent on the ring was realized with 2*H*-azirines bearing a hydroxymethyl **772a** or an acetoxymethyl **772b** group due to chelation with the allylindium reagent <2006TL1613>. In contrast, only *trans*-allylation occurred to give **774** with 2*H*-azirines **772c** substituted with a methyl, phenyl, or ester group owing to steric repulsion (Scheme 186).



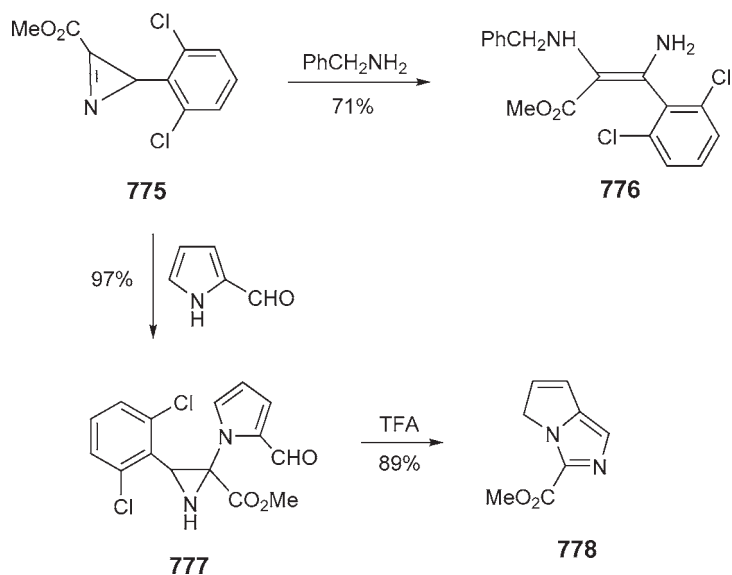
Scheme 186

2*H*-Azirines are more susceptible to nucleophilic attack than other imines as a consequence of the strained nature of the C=N bond. When this ring strain is combined with the presence of an activating group on the carbon atom, nucleophilic addition reactions occur very easily. For example, when methyl 2-aryl-2*H*-azirine-3-carboxylate **775** was used as the substrate, reaction with benzyl amine induced a ring opening by addition of the amino group onto the C=N bond followed by cleavage to provide enediamine **776** <1999J(P1)1305>. The intermediate amino-substituted aziridine adduct could not be isolated with primary or secondary amines since the amino aziridine is easily cleaved. However, when pyrrole-2-carboxaldehyde was used as the nucleophile, it was possible to isolate the pyrroloaziridine **777**. Aziridine **777** was found to undergo a further transformation when treated with TFA at room temperature to give the 5*H*-pyrrolo[1,2-*c*]imidazole **778** in good yield (Scheme 187). A similar reaction occurred with other five-membered aromatic heterocycles <2000TL4991>.

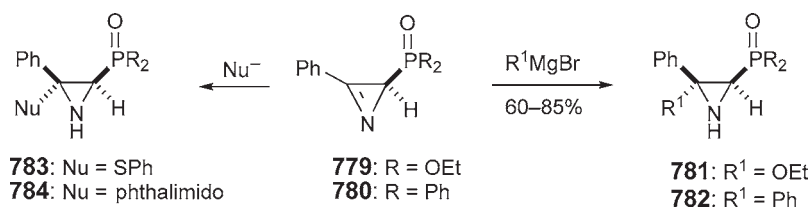
A simple and efficient stereoselective synthesis of aziridine-2-phosphonate **781** and phosphine oxide **782** was achieved by diastereoselective addition of Grignard reagents to 2*H*-azirine phosphonate **779** and phosphine oxide **780**. Addition of benzenethiol and heterocyclic amines proceeded in an analogous manner to yield functionalized aziridines **783** and **784** (Scheme 188).

In contrast, treatment of the related 2*H*-azirine-3-methylacrylate **785** with imidazoles and pyrazoles gave 2-aza-1,3-dienes **786** derived from a transient addition product (Scheme 189) <1999JOC49>. These dienes are useful in hetero-Diels–Alder reactions with electron-deficient dienophiles.

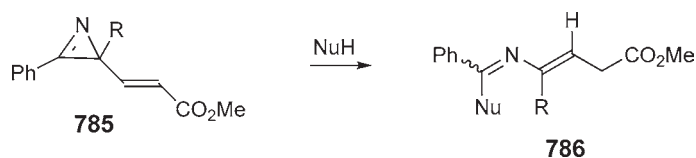
The chiral enriched ethyl 3-methyl-2*H*-azirine-2-carboxylate **787** was found to act as an efficient alkylating agent for the preparation of a variety of five-membered aromatic nitrogen heterocycles **788** (Scheme 190) <2003TL6277>.



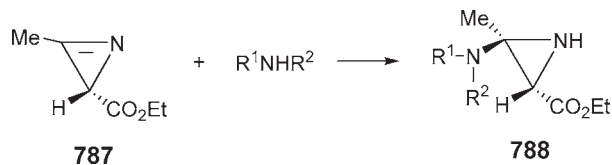
Scheme 187



Scheme 188

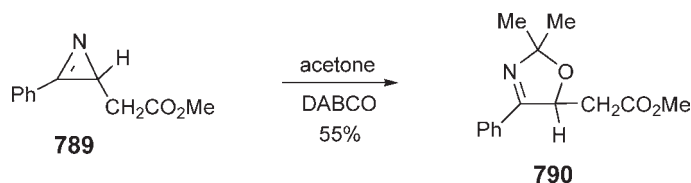


Scheme 189



Scheme 190

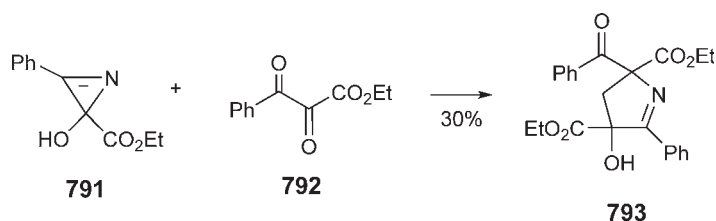
Azirines which have pendant electron-withdrawing functionality undergo an interesting reaction with aldehydes and acetone via a so-called ‘3-X mode’, a reactivity arising from the pushing effect on the 2*H*-azirine ring by the active methylene center. Thus, 2*H*-azirine ester **789** reacts with acetone in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to give the 3-oxazoline **790** (Scheme 191) <1996JOC3749>.



Scheme 191

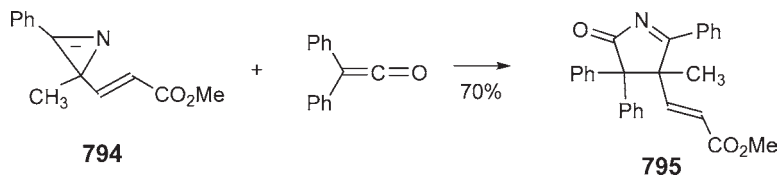
1.01.9.4 Reaction of 2H-Azirines with Electrophiles and Metal-Induced Reactions

Although the basicity of the nitrogen atom in the 2H-azirine ring is less than in simple aliphatic imines, the imino π -bond can still function as a nucleophilic reagent and react with different electrophilic compounds. For example, the reaction of 2-hydroxy-2H-azirine **791** with the dioxo ester **792** gives rise to a 3-oxazoline **793** (Scheme 192) <2000TL7217>. The reaction probably involves a nucleophilic attack of the 2H-azirine onto the reactive carbonyl oxygen of **792** followed by ring opening and a subsequent intramolecular nucleophilic addition with formation of the five-membered heterocycle.



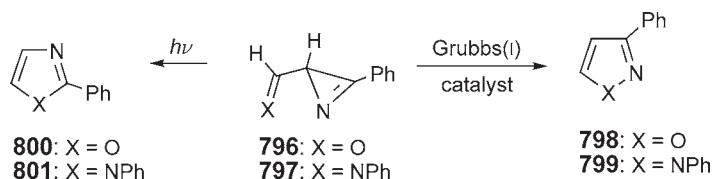
Scheme 192

The reaction of simple 2H-azirines with heterocumulenes proceeds to give a wide range of heterocyclic adducts. For example, treating 2H-azirine-3-methylacrylate **794** with diphenylketene afforded 5-pyrrolin-2-one **795** in 70% yield (Scheme 193) <1997T7089>. A related reaction occurred using *N*-sulfonylimines to give 1,2,5-thiodiazoles <1996J(P1)1629>.



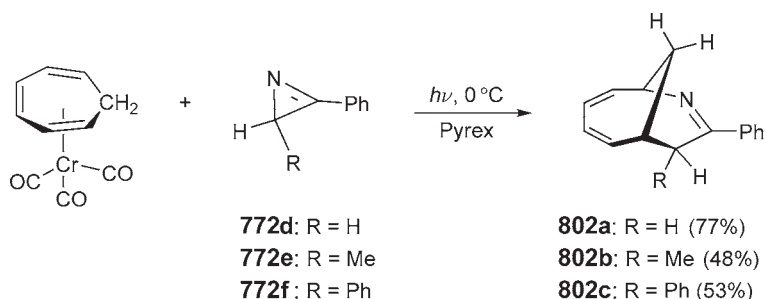
Scheme 193

By comparison with the extensive studies carried out on the thermal and photochemical behavior of the 2H-azirine ring system, its behavior toward organometallic reagents has been relatively unexplored. Reaction of 2H-azirines **796** and **797** with the commonly employed Grubbs(I) catalyst was found to induce a clean rearrangement, producing isoxazole **798** and pyrazole **799** in good yield. These results stand in marked contrast to the photochemical behavior of **796** and **797**, which afforded 2-phenyloxazole **800** and 1,2-diphenylimidazole **801** as the exclusive products <2004TL5991>. The isolation of isoxazole **798** and pyrazole **799** by use of the Grubbs(I) catalyst clearly indicates that these transition metal-catalyzed transformations occur by C–N bond fragmentation as opposed to C–C bond cleavage which occurs photochemically (Scheme 194).



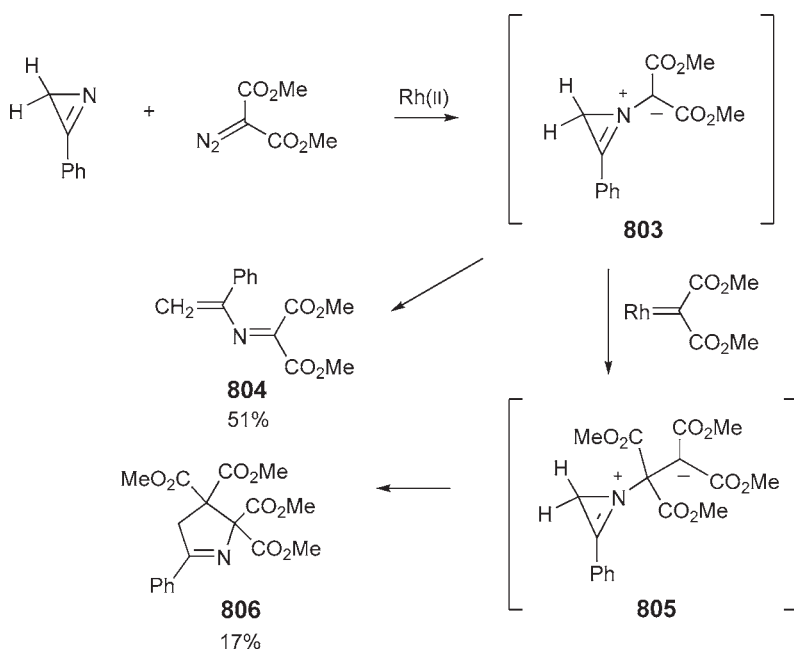
Scheme 194

UV irradiation of tricarbonyl(cycloheptatriene)chromium(0) and 2-phenyl-2*H*-azirines of type **772** through Pyrex at 0 °C leads to 7-aza-8-phenylbicyclo[4.3.1]deca-2,4,7-trienes **802** via a novel [6+3] cycloaddition of the azirine to the cycloheptatriene ring [<1995TL1577>](#). The bicyclic product **802** arises from addition of the 2*H*-azirine C=N bond across the 1- and 6-carbons of the cycloheptatriene ring. The observed N–C bond scission is somewhat surprising since 2*H*-azirines generally undergo C–C bond cleavage under photochemical conditions. Nevertheless, metal- and thermally mediated reactions of azirines cleave the C–N bond, and it was suggested by the authors that the role of light in the reaction is not to open the 2*H*-azirine ring but rather to open a coordination site at the metal by CO ejection or ring slippage. Coordination of the 2*H*-azirine nitrogen to this site then facilitates cleavage of the C–N bond and coupling of the coordinated groups in a [6+3] fashion. Noteworthy is that **772e** and **772f** gave single isomers of the 9-substituted species **802b** and **802c**. This stereocontrol may be due to the steric bulk of the metal and its ancillary ligands, which force the 2*H*-azirine to coordinate in a particular orientation prior to bond formation ([Scheme 195](#)).



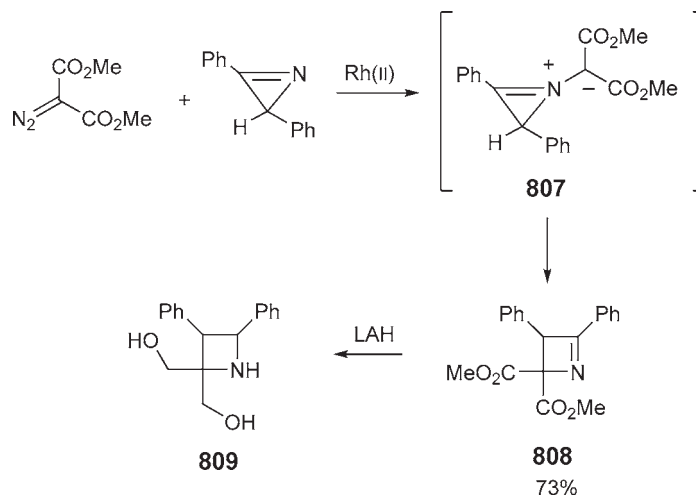
Scheme 195

The thermocatalytic Rh(II) decomposition of diazo malonate in the presence of 3-phenyl-2*H*-azirine **772d** was proposed to give rise to an azirinium ylide **803** [<2004TL6003>](#). This reactive ylide is preferentially transformed into 2-azabuta-1,3-diene derivative **804** or, with excess diazo compound, via reaction with the Rh-carbenoid, forms the 3,4-dihydro-2*H*-pyrrole derivative **806** via intermediate **805** ([Scheme 196](#)).



Scheme 196

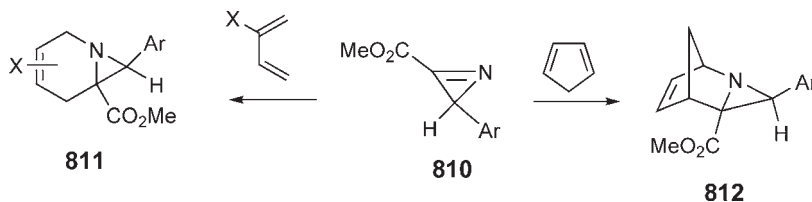
Interestingly, the reaction of the more heavily substituted diphenyl *2H*-azirine afforded azetine **808** in 73% yield when it was allowed to react with diazo malonate in the presence of $\text{Rh}_2(\text{OAc})_4$. The structure of azetine **808** was established by reduction to diol **809** under the action of LiAlH_4 (Scheme 197). It would appear as though the reactivity of the initially formed azirinium ylide is dependent on the degree of substitution about the *2H*-azirine ring.



Scheme 197

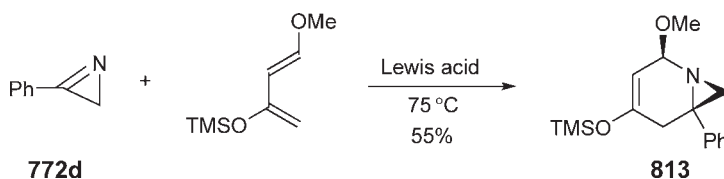
1.01.9.5 *2H*-Azirines as Dienophiles or Dipolarophiles in Cycloaddition Reactions

The strained, electron-rich carbon–nitrogen double bond present in the *2H*-azirine ring is more reactive than the corresponding double bond in an imine and, while *2H*-azirines participate in reverse electron-demand Diels–Alder reactions <1996CHEC-II(1A)1>, there are only a few publications describing the normal electron-demand Diels–Alder reactions of *2H*-azirines. Methyl 2-aryl-*2H*-azirine-3-carboxylates **810** are good dienophiles and they readily react with a variety of dienes to give bicyclic products such as **811** and **812** by cycloaddition across the C–N double bond (Scheme 198). The cycloadditions are *endo*-selective and the dienophile approach takes place from the less-hindered face of the *2H*-azirine <1997S271, 1998TL7579, 1998J(P1)299>. The Diels–Alder reactions of a chiral ester of *2H*-azirine-3-carboxylic acid with cyclopentadiene was observed to be highly diastereoselective <1999J(P1)1399>.



Scheme 198

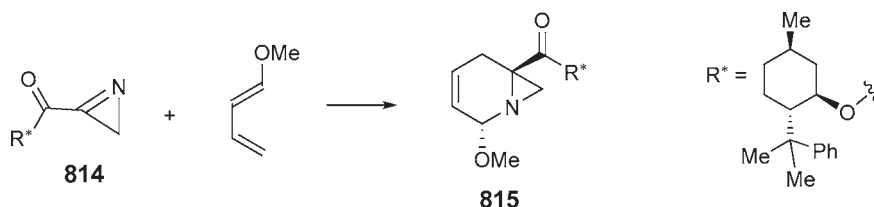
Activation by Lewis acids of 3-alkyl- and 3-phenyl-*2H* azirines also promotes their participation in hetero-Diels–Alder reactions with a variety of dienes. This methodology circumvents the previous requirement of needing an electron-withdrawing carboxyl moiety at the 3-position of the *2H*-azirine ring <2001TL9289>. Thus the reaction of *2H*-azirine **772d** with Danishefsky's diene gave the *endo*-cycloadduct **813** when the reaction was carried out using 0.3 equiv of a Lewis acid (i.e., ZnCl_2 , YbCl_3 , CuCl_2) at 75 °C (Scheme 199). Several other, less-activated dienes could also be used for the reaction.



Scheme 199

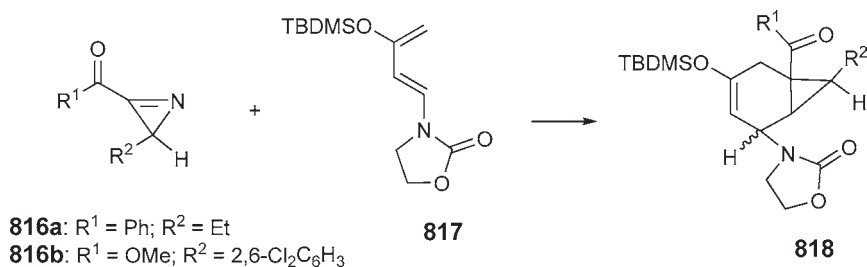
Highly diastereoselective Lewis acid-mediated aza-Diels–Alder reactions of chiral auxiliary derivatized 2*H*-azirines have been studied [\[2002T5983, 2003JOC9958, 2003CC1150\]](#). The cycloaddition proceeded with high diastereoselectivity (97% dc), with the absolute stereochemistry of the major product confirmed by X-ray crystallography. Without the presence of a Lewis acid, no diastereoselectivity was obtained at room temperature.

The dramatic effect observed on the reaction diastereoselectivity upon addition of a Lewis acid to 2*H*-azirine **814** could be explained by a bidentate coordination of the Lewis acid to the azirine nitrogen and the carbonyl group. This chelation would lead to hindered rotation around the azirine-carbonyl single bond and thus greater stereoselectivity. The increased reaction rate also indicates coordination of the Lewis acids to the 2*H*-azirine which leads to a lowering of the LUMO energy level and thus an increased reactivity toward the electron-rich diene ([Scheme 200](#)).



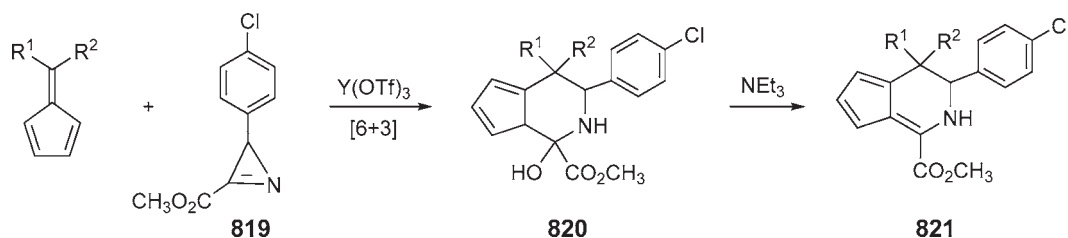
Scheme 200

2*H*-Azirines are excellent partners in aza-Diels–Alder reactions that occur at room temperature when the C=N bond is activated with a conjugated oxo, alkoxy, or heteroaromatic group [\[2005S555\]](#). For example, 3-(3-*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **817** reacted with several electrophilic 2*H*-azirines of type **816** to furnish the expected [4+2] cycloadducts **818** in moderate to good yield [\[2006T3095\]](#). The chiral oxazolidinone **817** was also allowed to react with the same electrophilic 2*H*-azirines but showed no diastereoselectivity for the cycloaddition. 2*H*-Azirine **816b** underwent smooth [4+2] cycloaddition with furan, diphenylisobenzofuran [\[2001J\(P1\)2969\]](#), and several electron-rich 2-azadienes ([Scheme 201](#)) [\[2003TL5079\]](#). All of the [4+2] cycloaddition reactions were found to be *endo* and regioselective with the 2*H*-azirine being added from its less-hindered face.



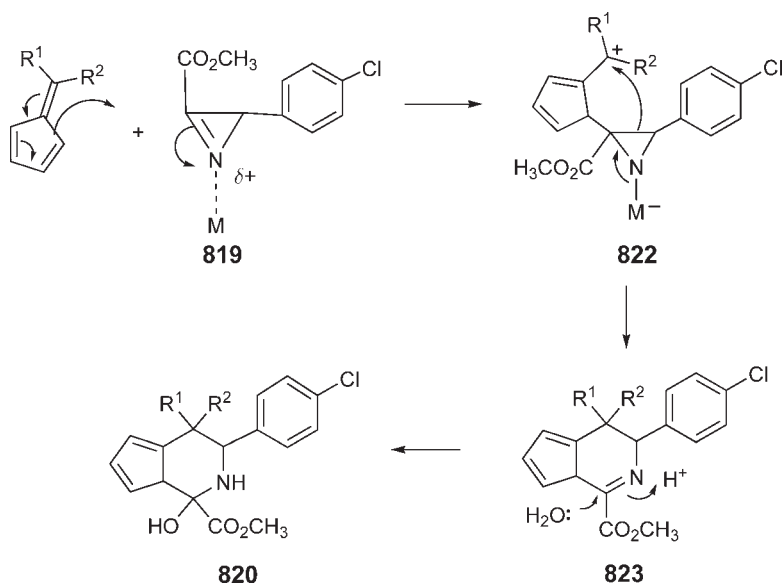
Scheme 201

2*H*-Azirine **819** also undergoes reaction with various fulvenes in THF at 25 °C to afford the corresponding [2]pyridine **820** in 19% yield as the only isolable product. The yield of the [6+3] cycloadduct **820** improved to 83% in the presence of 20 mol% $\text{Y}(\text{OTf})_3$ in THF [\[2004TL1663\]](#). [2]Pyridine **820** proved to be unstable and was gradually converted to **821** after standing for a few days in the refrigerator ([Scheme 202](#)).



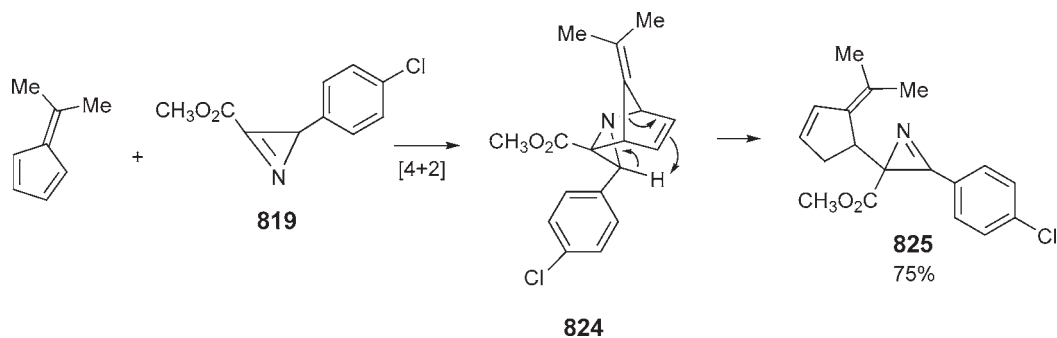
Scheme 202

The formation of **820** was rationalized by a stepwise mechanism. The initial addition of the fulvene to the activated 2H-azirine generates the zwitterionic intermediate **822** which then cyclizes to [2]pyridine **820** via intermediate **823** (Scheme 203).



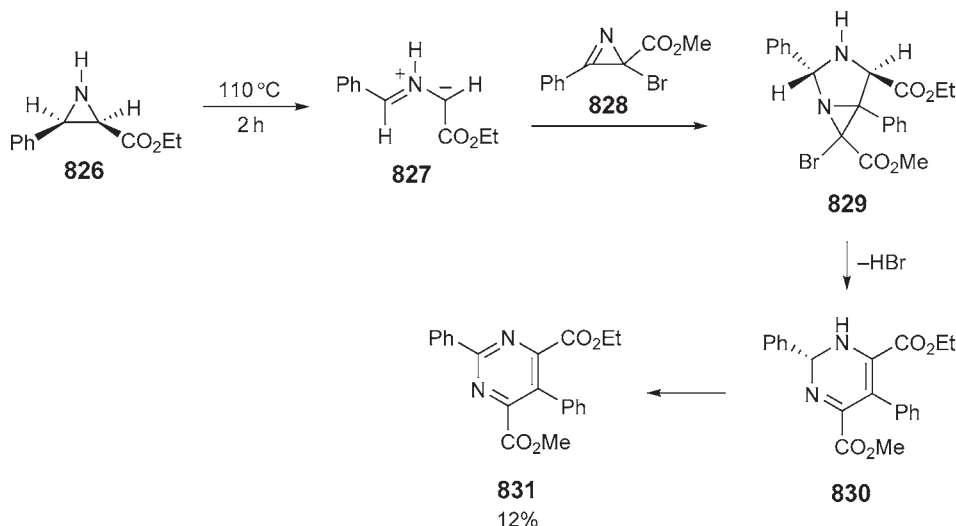
Scheme 203

Interestingly, the reaction of dimethyl fulvene ($R = Me$) with 2H-azirine **819** in an ultrasonic bath (neat) yielded the alkylation product **825**. The structure of **825** was unambiguously assigned by single crystal X-ray structure. A possible mechanism to account for the formation of **825** involves an initial [4+2] cycloaddition followed by a subsequent rearrangement of the initially formed Diels–Alder cycloadduct **824** (Scheme 204).



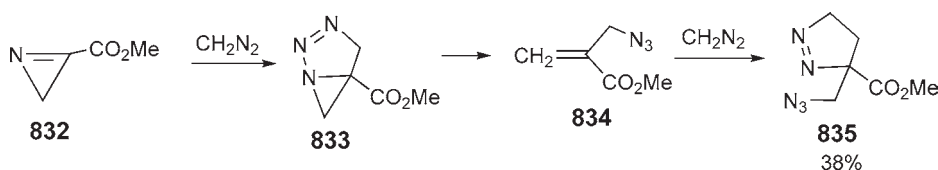
Scheme 204

The 2*H*-azirine ring can also be used as a dipolarophile. The formation of pyrimidine **831** from the reaction of aziridine **826** with 2*H*-azirine **828** in toluene was rationalized by a 1,3-dipolar cycloaddition across the 2*H*-azirine π -bond. Thus, thermal ring opening of aziridine **826** gave the expected azomethine ylide dipole **827** which reacted by way of a [3+2] cycloaddition with 2*H*-azirine **828** to afford cycloadduct **829**. This transient intermediate underwent a subsequent ring-opening reaction with elimination of HBr, leading to dihydropyrimidine **830**, and this was followed by aromatization to give the observed product **831** (Scheme 205) <2003TL6313>.



Scheme 205

The reaction of 2*H*-azirine-3-carboxylate **832** with diazomethane occurs to produce a 4,5-dihydro-3*H*-pyrazole derivative **835**. This reaction represents an interesting example of the imino group acting as a 2π -component in a 1,3-dipolar cycloaddition reaction <2003TL6319>. The process seemingly involves the reaction of 2*H*-azirine **832** with diazomethane to give cycloadduct **833** as a transient species which then undergoes a subsequent rearrangement to generate allyl azide **834**. This compound participates in a second 1,3-dipolar cycloaddition with diazomethane to give **835** (Scheme 206).



Scheme 206

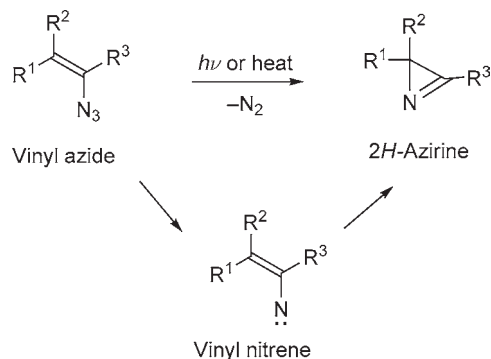
1.01.10 Synthesis of 2*H*-Azirines

1.01.10.1 Photo- or Thermal Extrusion of Nitrogen

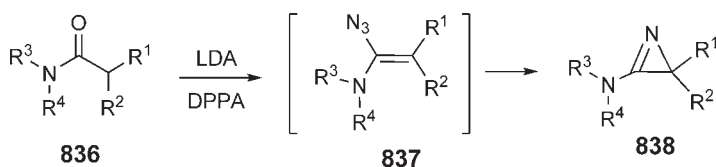
A number of synthetic methods are available for forming 2*H*-azirines such as intramolecular rearrangements of N-functionalized imines, vinyl azides, isoxazoles, and oxazaphospholes. 2*H*-Azirines have also been prepared by bimolecular reactions between nitriles and carbenes or nitrenes and acetylenes. A well-known method for preparing 2*H*-azirines involves the photo- or thermal extrusion of nitrogen from vinyl azides <2003TL5339>. This rearrangement can take place in a concerted manner or via a vinyl nitrene intermediate. An efficient and environmentally friendly method for preparing 2*H*-azirines was achieved by microwave irradiation of vinyl azides in solvent-free conditions (Scheme 207) <2003TL6763>.

The vinyl azide method has been employed to prepare heterospirocyclic 3-amino-2*H*-azirines, which represent useful synthons for heterocyclic amino acids <1997HCA1528>. Diphenyl phosphorazidate (DPPA) was used as the azide

source and, by substitution of the oxygen atom of amide enolates, 3-amino-2*H*-azirines **838** were obtained in ‘one pot’ and high yield [<1995HCA1983>](#). For the synthesis of optically active 3-amino-2*H*-azirines, a modification of this approach with a chiral substituent at the amino group of the thioamide has been used ([Scheme 208](#)) [<1996HCA1903>](#).

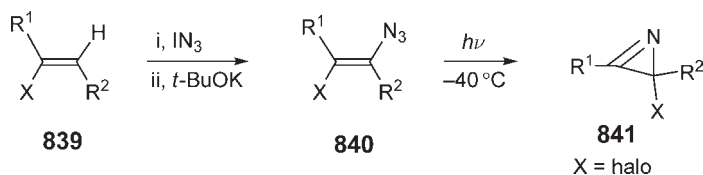


Scheme 207



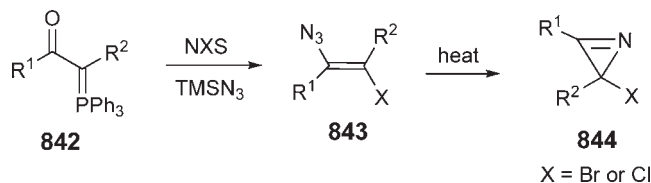
Scheme 208

The reaction of iodine azide with haloalkenes **839** followed by elimination of hydrogen halide by potassium *tert*-butoxide gives the corresponding halo vinyl azides **840**, which can be converted into haloazirines **841** by photolysis at -40°C ([Scheme 209](#)) [<2001T6203>](#).



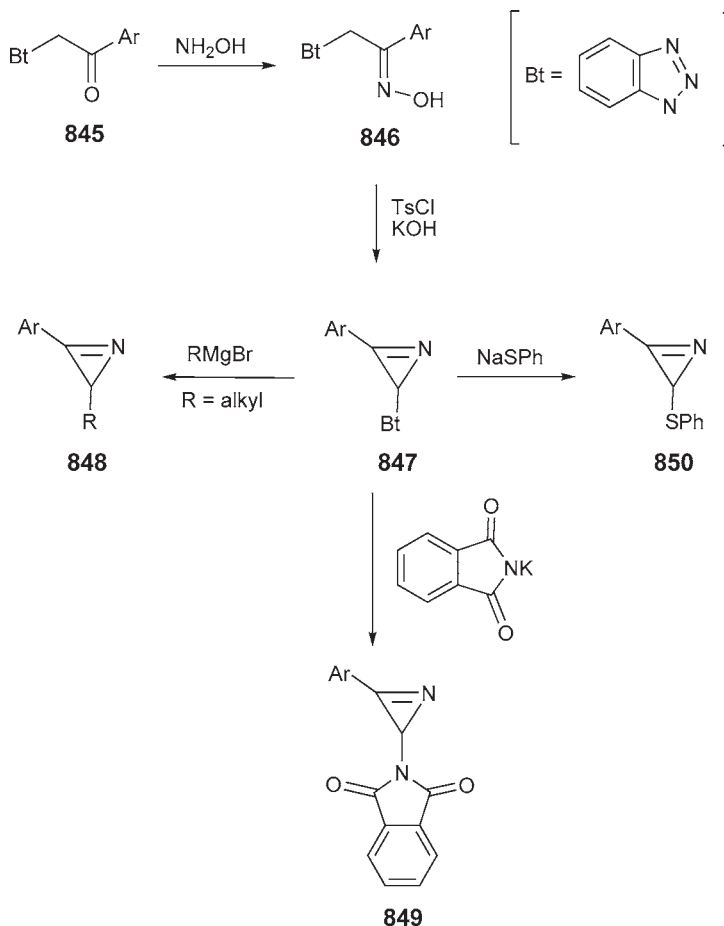
Scheme 209

An alternate route to the same halo 2*H*-azirine system starts from α -oxophosphorus ylides **842**. These ylides react with chlorine, bromine, and electrophilic halogen donor reagents in the presence of nucleophiles and give substituted alkenes of type **843** by elimination of triphenylphosphine oxide. When the reaction of **842** was carried out with an *N*-halosuccinimide in the presence of azidotrimethylsilane, haloazidoalkenes **843** were obtained in good yield ($\text{Y} = \text{N}_3$). These vinyl azides were easily converted into the corresponding 2-halo-2*H*-azirines **844** upon heating in heptane for 2–3 h ([Scheme 210](#)) [<1999TL789, 2000TL7217, 2001T6203>](#).



Scheme 210

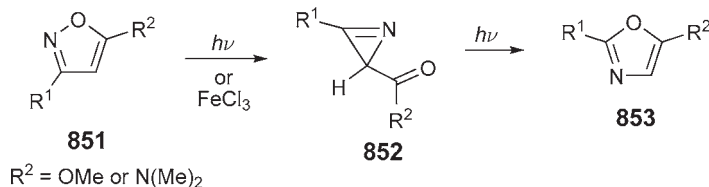
2-(Benzotriazol-1-yl)-2*H*-azirines **847**, obtained by treatment of oximes **846** with tosylchloride and aqueous KOH, were reacted with benzylmagnesium bromide or 4-methylbenzylmagnesium bromide in the presence of zinc chloride and gave 2-benzyl-2*H*-azirines **848**. Potassium phthalimide and the sodium salt of benzenethiol converted the 2-(benzotriazol-1-yl)-2*H*-azirines **847** into novel 2*H*-azirines **849** and **850** (Scheme 211) <2003JOC9105>.



Scheme 211

1.01.10.2 Ring Contraction of Isoxazoles

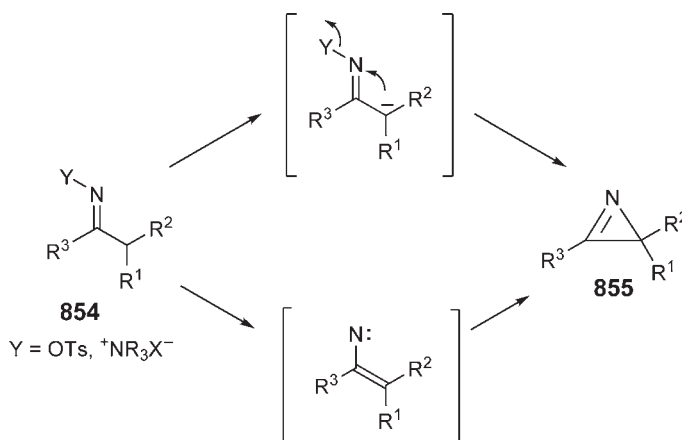
Thermal or photochemical treatment of isoxazoles **851** has been found to result in a ring-contraction reaction to produce acyl 2*H*-azirines **852**, which sometimes rearrange to form other heterocycles like oxazoles **853**. This ring-contraction reaction can also be promoted by iron(II) catalysts. Thus, 5-alkoxy- and 5-aminoisoxazoles isomerize to 2*H*-azirine-2-carboxylic esters and 2*H*-azirine-2-carboxamides, respectively, in nearly quantitative yield by reaction with catalytic FeCl_3 (Scheme 212) <1997T10911>.



Scheme 212

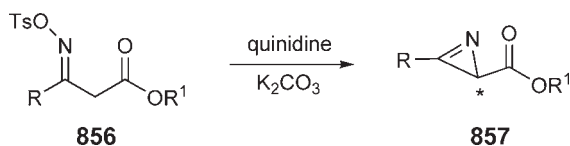
1.01.10.3 Neber Rearrangement of Oxime Sulfonates

Another significant preparative pathway to the *2H*-azirine system is the Neber rearrangement of oxime sulfonates. The presence of strong electron-withdrawing groups in the α -position to the oxime increases the acidity of those protons, and thus favors the cycloelimination reaction under mild conditions. The Neber reaction occurs either through an internal concerted nucleophilic displacement or via a vinyl nitrene (Scheme 213) <2001EJO2401>.



Scheme 213

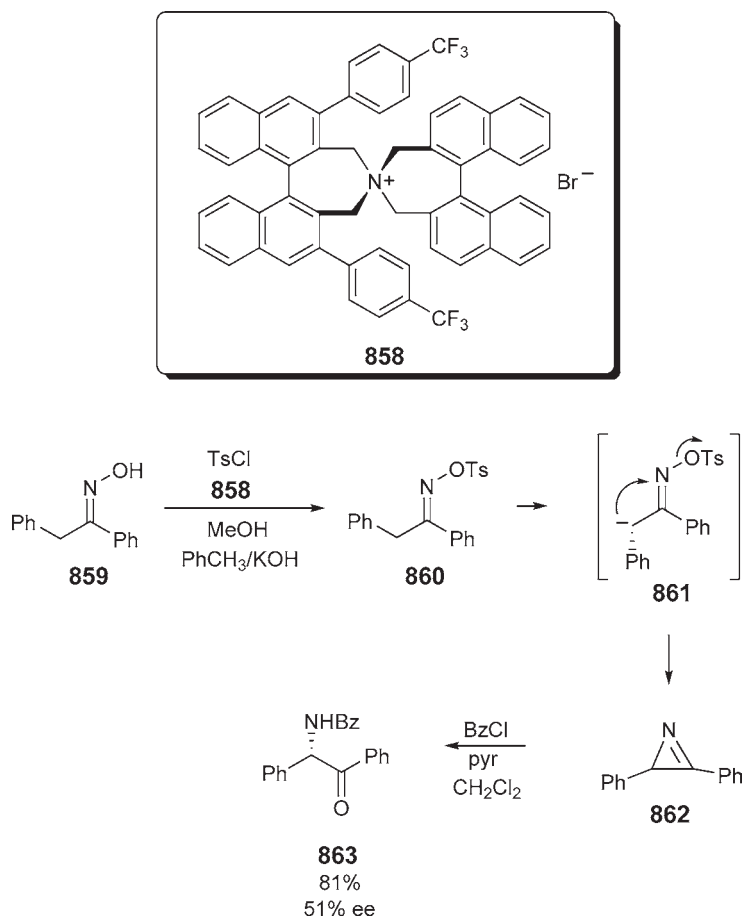
2H-Azirines can be prepared in optically enriched form by the asymmetric Neber reaction mediated by *Cinchona* alkaloids. Thus, ketoxime tosylates **856**, derived from 3-oxocarboxylic esters, are converted to the azirine carboxylic esters **857** in the presence of a large excess of potassium carbonate and a catalytic amount of quinidine. The asymmetric bias is believed to be conferred on the substrate by strong hydrogen bonding via the catalyst hydroxyl group <1996JA8491>. A similar strategy was used for the preparation of alkyl- and aryl-substituted *2H*-azirines with a phosphonate group in the 2-position of the ring (Scheme 214) <2000JOC3213, 2000TL5363, 1998T599>.



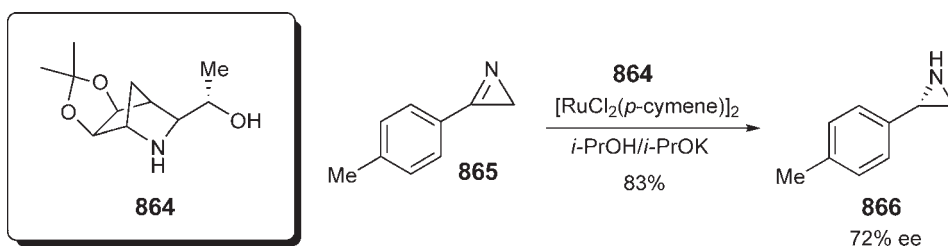
Scheme 214

The Neber route has been noted to be mildly influenced by the introduction of chiral auxiliaries. Thus, rearrangement of the tosyl oxime **860** (formed *in situ* from the oxime **859**) in the presence of catalytic amounts of the chiral quaternary ammonium bromide **858** led to the formation of enantiomerically enriched amino ketone **863**, which is presumed to arise from the preferential formation of the intermediate *2H*-azirine **862**. Association of the cationic chiral auxiliary with an anionic intermediate (i.e., **861**) has been invoked to rationalize the stereochemical outcome (Scheme 215) <2002JA7640>.

Preferential chirality can also be imposed on the sp^2 carbon of the *2H*-azirine through an asymmetric transfer hydrogenation protocol. Thus, *2H*-azirine **865** was converted to the scalemic aziridine **866** in 83% yield and 72% ee in the presence of a ruthenium catalyst and the chiral auxiliary **864** in an isopropanol medium (Scheme 216) <2002CC1752>.



Scheme 215



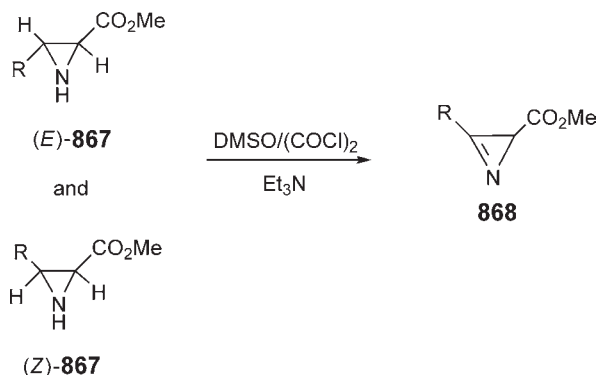
Scheme 216

1.01.10.4 Elimination from *N*-Sulfinylaziridines

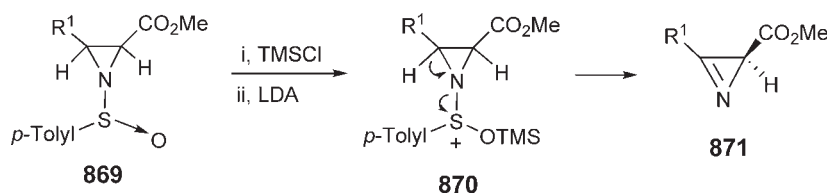
3-Alkyl-2*H*-aziridine-2-carboxylates **867** have been oxidized with the Swern reagent to afford 2*H*-azirine-2-carboxylates [<1995TL4665>](#). Oxidation of either the (*Z*)- or the (*E*)- isomers of **867** provides the same 2*H*-azirine-2-carboxylate **868**, where the integrity of the stereogenic center at C-2 is retained. This regioselectivity results from the unexpected removal of the apparently less acidic C-3 proton during the base-induced *syn*-elimination of the *N*-dimethylsulfonium intermediate (Scheme 217).

The closely related 2*H*-azirine-2-carboxylate esters **871** have been prepared in enantiomerically pure form via the base-induced elimination of sulfenic acid from nonracemic *N*-sulfinylaziridine 2-carboxylate esters **869** [<1997JOC3796>](#),

1999JOC8929>. For steric reasons, the *N*-sulfinylaziridine invertomers likely adopt structure **870** in which the bulky *p*-toluenesulfinyl group is *anti* to the aziridine ring substituents (Scheme 218). This *syn*-periplanar arrangement of leaving groups results in a *syn*-elimination of sulfenic acid to afford 2*H*-azirine **871**.

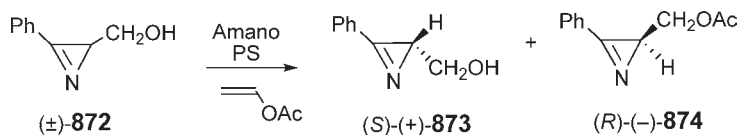


Scheme 217



Scheme 218

Finally, chemoenzymatic synthesis has been used for the preparation of enantiomerically pure 2*H*-azirines. Thus, (*S*)-(+)-phenyl-2*H*-azirine-2-methanol **873** and its (*R*)-(–)-acetate **874** were prepared by a lipase-catalyzed kinetic resolution of the racemic 2*H*-azirinemethanol **872**. The reaction was carried out at very low temperature (–40 °C) and therefore enhanced the enantioselectivity (Scheme 219) <1997JOC4906>.



Scheme 219

1.01.11 Important Compounds and Applications

Monocyclic aziridines and 2*H*-azirines have found broad application in the synthesis of complex natural products. The facility with which these small ring nitrogen-containing compounds can be converted to important pharmaceutical products under mild conditions with wide functional group compatibility makes these molecules quite useful for heterocyclic chemistry.

1.01.12 Conclusion

This chapter reviews the chemical literature of monocyclic aziridines and 2*H*-azirines from 1995 through 2007. It reveals that aziridines are well-behaved carbon electrophiles capable of reacting with various nucleophiles. The ability of aziridines to undergo regioselective ring-opening reactions contributes largely to their synthetic value.

In ring-opening reactions, it is common either to perform the reactions employing Lewis acid catalysis or to activate the aziridine by substitution on the nitrogen, thus increasing the ability of the nitrogen atom to function as a leaving group. Interesting advances have also been made in the area of ring opening by carbon-centered nucleophiles, an area of obvious practical impact. The same ring strain that lends aziridines reactivity toward nucleophiles also makes them prone to ring-opening isomerizations and rearrangements which can be used for the synthesis of interesting heterocyclic structures. The versatile aziridine functionality can be used in radical-based reactions, [3+2] cycloaddition chemistry, [3+3] annulations, and organolithium-mediated transformations. The chemistry of the related unsaturated 2*H*-azirine system is also quite versatile as a consequence of its high ring strain, reactive π -bond, and its ability to undergo regioselective ring-cleavage reactions. 2*H*-Azirines not only are capable of acting as nucleophiles and electrophiles in organic reactions, but can also act as dienophiles and dipolarophiles in cycloaddition chemistry. Thus, 2*H*-azirines represent very useful precursors for the synthesis of a variety of nitrogen-containing ring systems.

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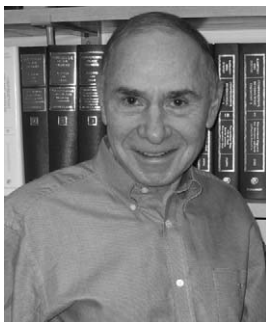
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Biographical Sketch



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1.02

Aziridines and Azirines: Fused-ring Derivatives

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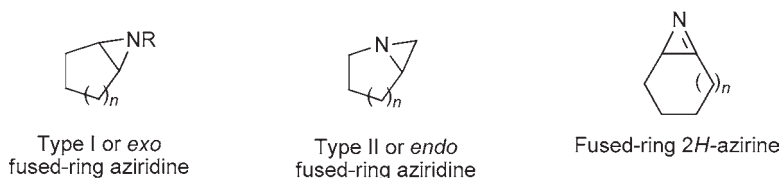
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1.02.1 Introduction

Aziridines and azirines are the simplest of the heterocyclic ring systems containing nitrogen, containing just two carbon atoms and one nitrogen. Aziridines are the fully saturated example of this heterocyclic ring system, while azirines contain a single double bond. Two types of azirine can be formed, the *1H*-azirine and the *2H*-azirine. Given this simplicity in terms of structure, aziridines combine a unique blend of reactivity and stability. This mixture of reactivity and stability makes aziridines and azirines singularly useful for the synthesis of more complex nitrogen containing molecules. The incorporation of an additional ring annulated onto the aziridine ring (i.e., a fused-ring aziridine) increases both the reactivity and complexity of this system



Fused-ring derivatives of aziridines can be divided into two general categories based on the position of the nitrogen with respect to the annulated ring. We will use the terminology type I or *exo* to describe fused-ring aziridines in which the nitrogen of the aziridine is exocyclic to the fused ring. We will call aziridines in which the nitrogen is in the bridgehead position, type II or *endo*. Fused-ring azirines are quite rare and fused-ring examples of only the 2*H*-azirine are known. While these bicyclic ring systems are often identified as a fused-ring aziridine or azirine, they are also identified as by their systematic bicyclic ring name. For example, a type II aziridine, where $n = 1$, is usually identified as a 1-azabicyclo[3.1.0] hexane.



There are numerous methods for the synthesis of aziridines and azirines. Similarly, there are a host of reactions that aziridines and azirines undergo. Many of these reactions are equally applicable to both monocyclic (Chapter 1.01) and fused-ring derivatives. This chapter focuses on reactions and synthetic methods that are unique for fused-ring derivatives of aziridines and azirines. The previous chapter in this series <1996CHEC-II(1A)61> provided coverage of the literature on fused-ring aziridines and azirines up to 1996. Since then a large number of reviews on the synthesis and reaction of aziridines and azirines (both monocyclic and fused-ring derivatives) have been published <2004PHC(16)54, 2006ACR194, 2005ARB103, 2005COR657, 2003MI206, 2004CSY275, 2004T2701, 2003PHC(15)75, 2003ALD57, 2003ALD39, 2003CRV2905, 2002PHC(14)52, 2002CSR247, 2002OPP219, 2001PHC(13)52, 2001TCC93, 2000S1347, 2000PHC(12)57, 2000COR727, 1999PHC(11)66, 1998PHC(10)49, 1997PHC(9)43, 1997CRV2341, 1997RCC(4)59, 1997TA1693, 1996CRV3303, 1996PHC(8)44>.

1.02.2 Structure

1.02.2.1 Theoretical Considerations

As might be expected, fused-ring derivatives of aziridines are generally more reactive than their monocyclic counterparts. Many of the reactions that aziridines participate in involve a nucleophilic opening of the three-membered ring and thus a release of strain energy. The lowering of the energy of activation in these strain-releasing reactions is not solely due to the release of strain. For example, the strain energy of cyclopropane and cyclobutane is roughly the same, yet cyclopropane rings generally open much faster. Two theories have been proposed to account for this. One suggests that an aromatic stabilization of the transition state is responsible for the faster ring openings <2000JMM158>. The other postulates that a change in hybridization at the reacting center, thus lowering the energy of the lowest unoccupied molecular orbital (LUMO), is responsible <1996JA416>. A quantification of the factors that contribute to the ring opening has been calculated recently <2001JOC915>.

The *ab initio* reaction energy (ΔE_0) and the activation energy (E_a) for each reaction were calculated at the *ab initio* level. Using the intrinsic barrier of the strain free reaction and the ΔE_0 , the Marcus equation was applied to determine the Marcus activation energy (E_a Marcus). The difference between the Marcus activation energy and the intrinsic barrier (strain free) is strain contribution to the lowering of the activation energy. The difference between E_a (Marcus) and E_a is considered to be the additional factor to the lowering of the transition state energy (Table 1). While a number of conclusions can be drawn from these studies, one can clearly see that the fused-ring aziridines have significantly higher levels of strain contributions as well as the additional contribution relative to the monocyclic aziridine.

The homolytic bond dissociation energies (BDEs) of the N–H bond of type I aziridines have been calculated (Table 2) <2004JOC3129>. It was found that there is generally smaller effect of ring strain in these heterocyclic systems relative to the parent hydrocarbon. This is attributed to fewer geometrical constraints in these heterocyclic systems as compared to the hydrocarbons. In addition to calculating the BDE for these systems, a natural bond orbital (NBO) analysis was carried out to determine the hybridization of the nitrogen. The NBO analysis of NH_3 , for example, finds that the %p is 0.748, indicating that NH_3 is mostly sp^3 hybridized. The NBO analysis of $\text{NH}_2\cdot$ provided a %p of 1.00 indicating that $\text{NH}_2\cdot$ is sp^2 hybridized.

Table 1 Contributions to aziridine ring-opening reactions

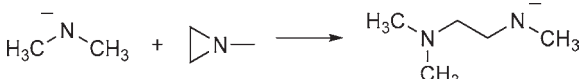
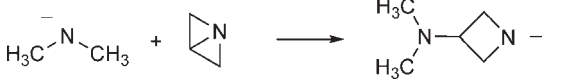
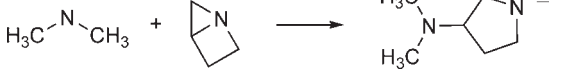
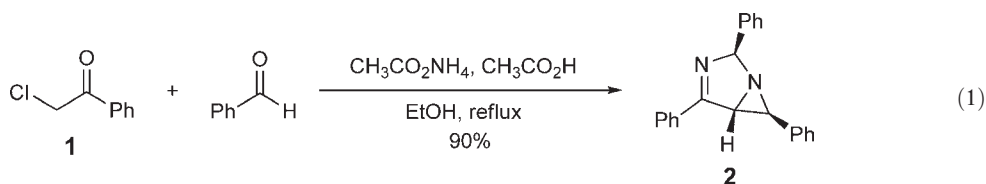
	ΔE_0	E_a	E_a Marcus	Strain contribution	Additional contribution
	-22.8	25.1	33.2	10.6	8.2
	-29.3	11.0	30.4	13.4	19.5
	-42.7	12.5	25.1	18.8	12.7

Table 2 Bond dissociation energies for select aziridines

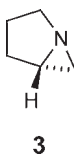
Structure	Theoretical BDE	%p parent	%p radical
$\text{H}_2\text{N}-\text{H}$	106.7	0.748	1.00
	93.7	0.780	1.00
	83.6	0.784	0.96
	93.0	0.773	0.96
	94.4	0.783	0.99

The condensation of **1** with 2 equiv of benzaldehyde and ammonium acetate provides **2** as a single diastereomer in excellent yield <2006HCA190>. These types of compounds are interesting both from a structural perspective as well as their potential utility in ring-opening reactions. The X-ray crystal structure of **2** was determined and the bond distances and angles were comparable to related structures. In addition, the structure of **2** was optimized using density functional theory (DFT) methods (B3LYP); the calculated structure was in good agreement with the diffraction data (Equation 1). Optimized structures obtained using HF methods (6-31+G(d,p)) gave poorer agreement with experiment. The calculated proton affinities for each nitrogen atom in **2** were obtained and found to be almost identical.



1.02.2.2 Infrared and Electron Absorption Spectroscopy

The ultraviolet (UV) absorption spectra of aryl-substituted aziridines can be quite useful in assigning stereochemistry for this group of heterocycles. While unsubstituted aziridines are transparent in the UV region above 200 nm, analysis of **3** demonstrates the use of UV spectroscopy for stereochemistry assignment. The (5*S*)-1-azabicyclo[3.1.0]hexane system **3** is a key fragment in the azinomycin family of anticancer agents. Previous attempts at studying the chiroptical properties of this compound were not possible since the maximum of the longest wavelength Cotton effect is below 200 nm. As the absorption was quite low, both absorption and CD spectra of **3** were obtained in the gaseous phase <1995JA4160>. The geometry of **3** was optimized using *ab initio* methods (RHF/6-31G^{*(0.3)}, B3LYP/6-31G^{*}, and MP2/6-31G^{*}) and indicated a boat-like conformation for this compound. The first band in the VUV at 188 nm is assigned to the $n_{\text{N}}-3s$ Rydberg transition while the second band at 169 nm is believed to be the result of overlapping of two $n_{\text{N}}-3p$ transitions.



1.02.2.3 NMR Spectroscopy

There have been few, if any, nuclear magnetic resonance (NMR) studies of fused-ring aziridines. Most of the NMR data for fused-ring aziridines parallel that of the monocyclic systems. A recent study on ^{13}C – ^{13}C coupling constants in fused-ring heterocycles provided some interesting data regarding the additivity of coupling constants [<2003RJ0698>](#). An important consideration in calculating coupling constants is the proper choice of procedure for optimization of the geometric constraints (e.g., MNDO (Modified Neglect of Differential Overlap), AM1 (Austin Method 1), PM3 (Parameterized Model 3)). Among semi-empirical methods, the PM3 method most accurately reproduces experimental results.

1.02.2.4 X-Ray Spectroscopy

X-Ray structures provide one of the best methods to obtain detailed information regarding bond angles and bond lengths for highly strained molecules such as fused-ring aziridines. A number of X-ray structures of fused-ring aziridines have been published in recent years. We have noted in the sections on the synthesis of various structural types of aziridines when an X-ray structure of an aziridine is available.

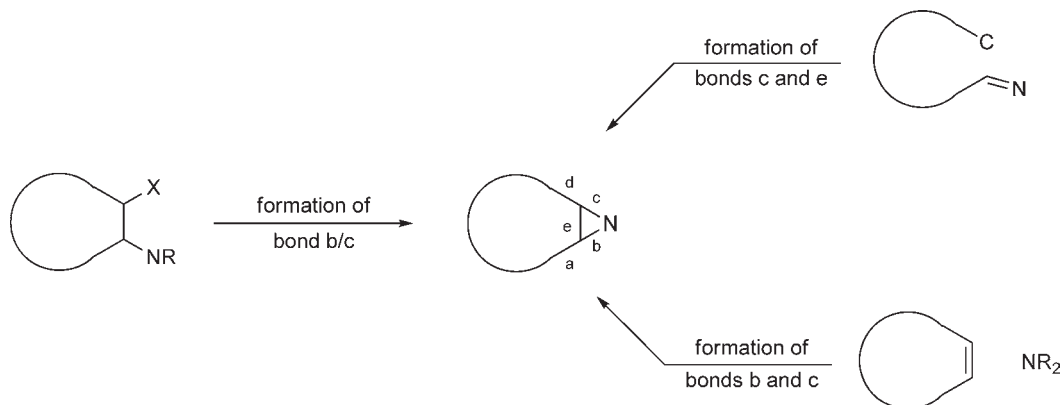
1.02.3 Synthesis of Aziridines

There are a number of limitations associated with the synthesis of fused-ring aziridines that are not observed in the synthesis of monocyclic aziridines. As a consequence of this, some methods that work well for monocyclic aziridines and azirines have not been reported for fused-ring derivatives.

1.02.3.1 Synthesis of Type I aziridines

Type I fused-ring aziridines are generally more stable than type II aziridines. Formation of the type I or exocyclic aziridine is limited to a very few types of bond constructions. The most useful synthetic methods for the synthesis of the exocyclic aziridines are limited to three major classes with some nongeneral alternative methods.

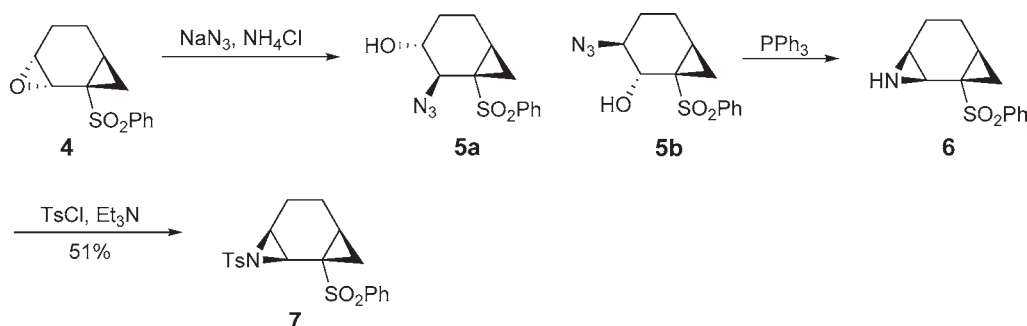
The most commonly used of these three bond classes is the formation of bond 'b'. Formation of bond 'b' typically occurs through an intramolecular alkylation of a nitrogen atom. A second highly prevalent method for the formation of the type I structure is the formation of bonds 'b' and 'c' from addition of a nitrogen across a carbon–carbon double bond. A final rarely used route is the formation of bonds 'c' and 'e' through the intramolecular addition of a carbene across and carbon–nitrogen double bond. Methods in which bond 'a' is formed are rare in terms of simple fused-ring aziridines but several examples can be found in [Section 1.02.7](#) in the discussion of the mitomycin family of alkaloids ([Scheme 1](#)).



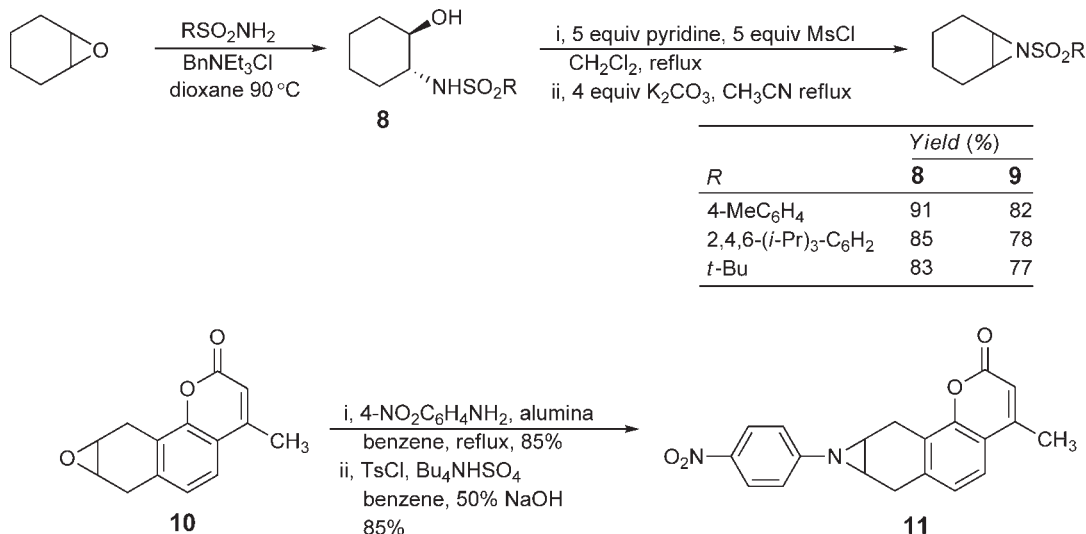
Scheme 1

1.02.3.1.1 Formation of aziridines via intramolecular cyclization

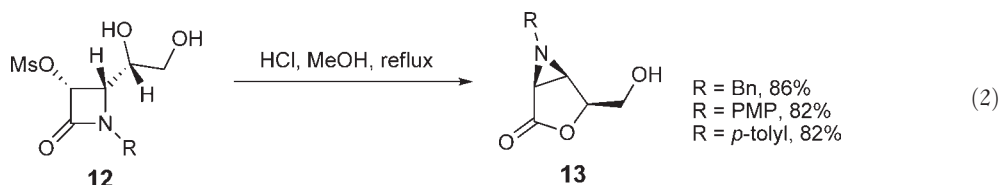
The intramolecular cyclization of a nitrogen nucleophile with a leaving group at the β -carbon is one of the most common methods for the synthesis of both monocyclic as well as fused-ring aziridines. The use of a ring-opening reaction of an epoxide by a nitrogen nucleophile (azide or an amine) is a common approach to generate the β -amino α -leaving group system. The general usefulness of this approach is due to the ready ability to prepare epoxides with high levels of stereocontrol. An example is shown in **Scheme 2** where Bäckvall prepared tosylaziridine **7** from epoxide **4** <1996TL3371>. Addition of azide to epoxide **4** provided an intermediate azido-alcohol, as a mixture of regioisomers **5a** and **5b**. The azido-alcohol was not isolated but reduced and cyclized with PPh_3 under Staudinger-like conditions to generate aziridine **6**. Finally, the unprotected aziridine was reacted with tosyl chloride and base to prepare the *N*-tosyl aziridine **7**. Similar procedures have been extensively used in the synthesis of 2,3-aziridino- γ -lactones <1999T7589, 1997JOC4277, 1996JOC2488>.

**Scheme 2**

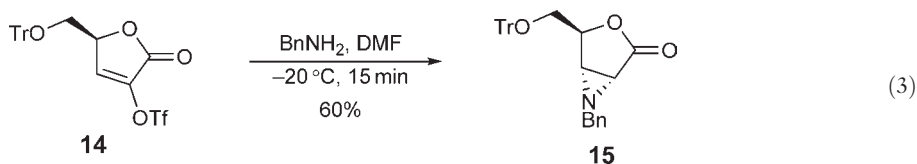
As shown in **Scheme 3**, both amines <2001SC1105> and arylsulfonamides <2006S425> have been used to open the cyclohexene epoxide and subsequently closed to form the aziridine ring. *N*-Sulfonamide aziridines are quite often prepared by the sulfonamidation of an *N*-H aziridine. This approach to *N*-sulfonamide aziridines has some limitations owing to the lower nucleophilicity of the aziridine nitrogen. A method has recently been reported which overcomes some of those limitations <2006S425>. The reaction of cyclohexene oxide with a sulfonamide is catalyzed by benzyltriethylammonium chloride to provide alcohol **8** in good overall yield. This sulfonamido alcohol was then cyclized to the aziridine **9**. A two-step process to prepare *N*-aryl aziridines is shown in **Scheme 3**. Treatment of an epoxide with an aniline derivative can be catalyzed by alumina to provide a 1:1 mixture of regioisomeric amino alcohols. Treatment of this mixture with TsCl and NaOH provides the *N*-aryl aziridine **11** in excellent yield.

**Scheme 3**

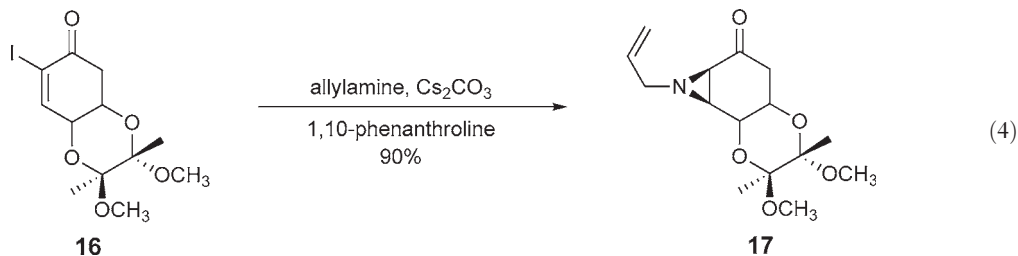
A rather intriguing route that both forms bond 'b' as well as the annulated ring in a single step is outlined in Equation (2) <2005SL2370>. The starting azetidinone **12** is prepared by a ketene–imine cycloaddition. Treatment of **12** with methanolic HCl at reflux provides the aziridino- γ -lactone **13** in excellent yield.



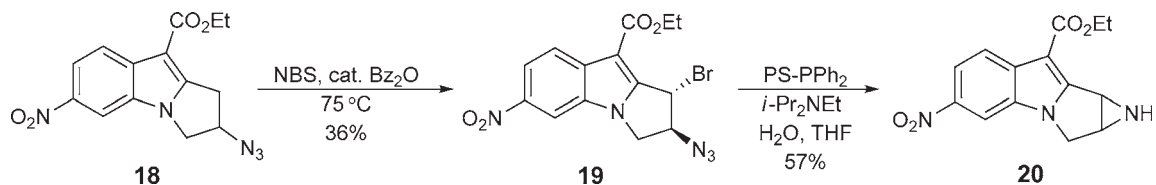
Enones with leaving groups bonded to the α -carbon of the enone provide a novel substrate for the formation of α -ketoaziridines. The Gabriel–Cromwell reaction (amine, α,β -dibromo acyclic esters and ketones) has been utilized for the construction of nonfused aziridines. One of the first examples of a cyclic system being utilized in a Gabriel-type synthesis is provided by Dodd *et al.* <2000TL6393, 2003JOC9521>. Addition of benzylamine to the enol triflate **14** provided aziridino lactone **15** in good yield (Equation 3). This reaction is quite sensitive to both solvent and time. DMF was the preferred solvent over other polar nonprotic solvents. The reaction had to be carefully monitored as longer reaction times led to lactone ring opening.



It has been found that α -iodoenones can also undergo this reaction <2002TL4329, 2003OL4321>. Normal conditions for this reaction require the leaving group α - to the amine group be *trans* to one another. This requires that the enolate must be protonated to form the α -halo- β -aminoketone. It was found that initial reaction of allylamine to iodoenone **16** under standard conditions provided only the recovery of starting material. It is likely that the intermediate enolate from this reaction collapsed prior to cyclization occurring. Addition of Cs_2CO_3 to the reaction followed by 1,10-phenanthroline provided an excellent yield of the *N*-allyl aziridine **17** (Equation 4). The addition of 1,10-phenanthroline appears to provide an increase in the reaction rate and act as a ligand for cesium ion in the reaction.

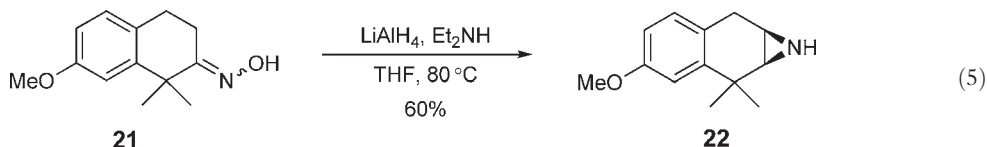


The methods used to prepare aziridines via this general approach rely upon the leaving group (or the group which will be transformed into a leaving group) be already present in the ring prior to the introduction of the nitrogen. An interesting method that introduces the leaving group after the introduction of the nitrogen is shown in Scheme 4 <2004T7367>. Treatment of indole **18** with *N*-bromosuccinimide (NBS) provides azido bromide **19** in 36% yield. The azide was reduced with polystyrene-supported diphenylphosphine (PS-PPh₂) and then cyclized to generate mitosene analog **20** in reasonable yield.



Scheme 4

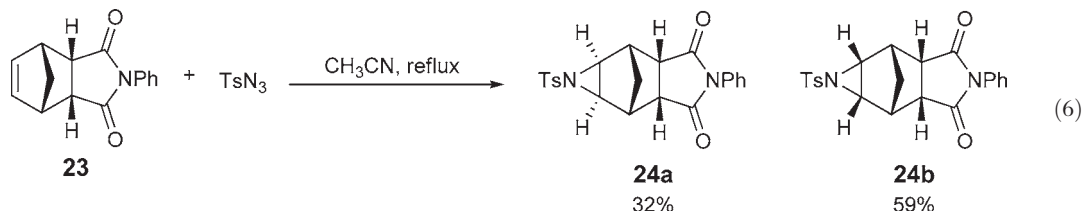
An interesting route to generate type I aziridines which is formally the formation of bond 'b' is shown in Equation (5) <2002BML3141>. Oxime **21** is prepared in high yield from the corresponding tetralone. Reduction of oxime **21** with LiAlH_4 and diethylamine in tetrahydrofuran (THF) provides the unprotected type I aziridine **22** in good yield.



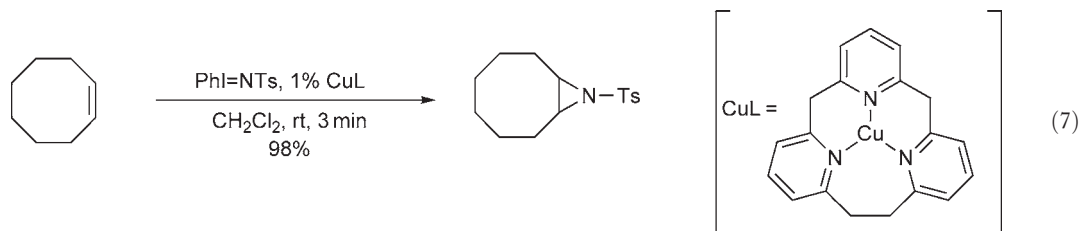
1.02.3.1.2 Formation of aziridines via N addition across a C=C

The classical methods utilized for the addition of nitrene to olefins generally suffer from several drawbacks including harsh conditions required to generate the nitrene and the lack of stereoselectivity in bond formation. Issues associated with triplet versus singlet nitrene generation have plagued this process and rendered it less useful than most epoxidation methods.

The reaction of olefins with azides to prepare an aziridine is one of the simplest methods to prepare a type I aziridine. Unfortunately, this method has not found particularly general use. There are however substrates (particularly bicyclic olefins) for which these types of reactions work quite well. One example is shown in Equation (6) <2004SC3073>. Reaction of tricyclic olefin **23** with tosylazide provides aziridines **24a** and **24b** in excellent yield.

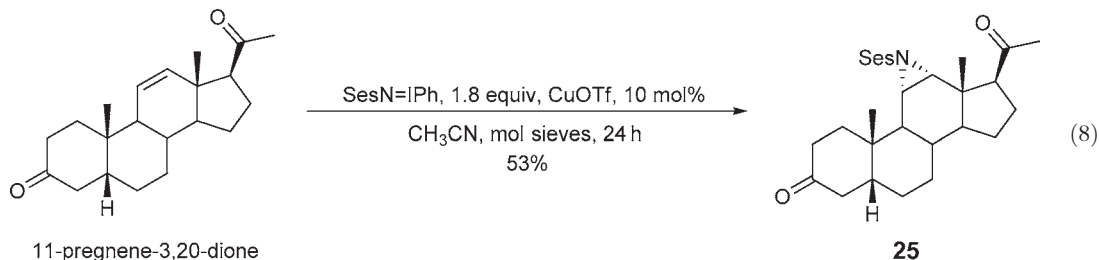


Nitrogen transfer with $\text{PhI}=\text{NTs}$ under copper catalysis with simple aliphatic olefins has been hampered by poor yields, high catalyst loading, and formation of many side products <2003CRV2905, 1997ACR364>. Recently, novel copper catalysts have been developed that have substantially different electronic and steric characteristics from catalysts such as pybox, α -diimines, and the tris-pyrazolylborates <2003OL2591>. In this reaction the authors assume that $\text{PhI}=\text{NTs}$ as a two electron oxidant will oxidize the closed $(\eta^3\text{-L})\text{Cu}^{\text{I}}$ to a copper(III) species. The constrained ligand will destabilize the $(\eta^3\text{-L})\text{Cu}^{\text{I}}$ to help produce the reactive $(\text{L})\text{Cu}^{\text{III}}(\text{NTs})$ and enhance reactivity toward $\text{PhI}=\text{NTs}$. Cyclooctene under the reaction conditions gives an exceptional yield of the aziridine. Both electron-rich and electron-poor olefins also provide outstanding chemical yields. It was found that the reaction would give very good yields of aziridine with merely stoichiometric amounts of the olefin rather than the 5–10 equiv that are usually required. Other substrates such as cyclopentene, cyclohexene, and ethylene give poor yields under these reaction conditions (Equation 7).

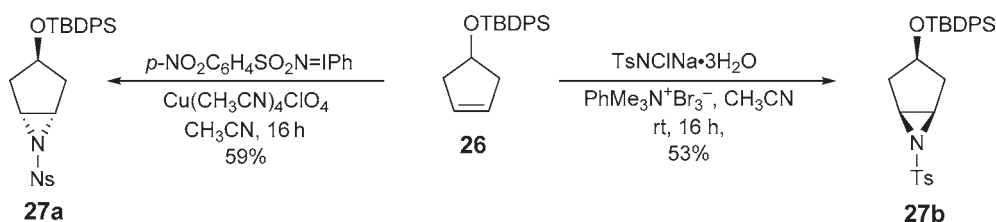


The synthesis of an aminosteroid such as Minaxolone is readily achievable from an unsaturated steroid core through an aziridination process mediated by $\text{PhI}=\text{NSes}$ as the nitrogen source <2003T1009>. One apparent drawback of the usual aziridination methodology is the preparation of an *N*-arylsulfonyl group, typically found difficult to remove after aziridination or ring opening. The trimethylsilyl ethanesulfonyl (Ses) nitrogen-protecting group alleviates many of the difficulties associated with the arylsulfonyl group. Removal of the Ses group with a fluoride source (such as tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)) usually results in good yield of the unprotected aziridine. Application of hypervalent Ses-substituted iodine reagent $\text{SesN}=\text{I}^+\text{Ph}$ in the presence of

10% CuOTf to 11-pregnene-3,20-dione provided the Ses-protected aziridinosteroid **25** in 53% yield (Equation 8). Deprotection of the Ses-aziridine resulted in a 77% yield of the deprotected aziridine. The aziridination reaction of 11-pregnene-3,20-dione provided only the 11,12- α aziridine analog of the steroid.



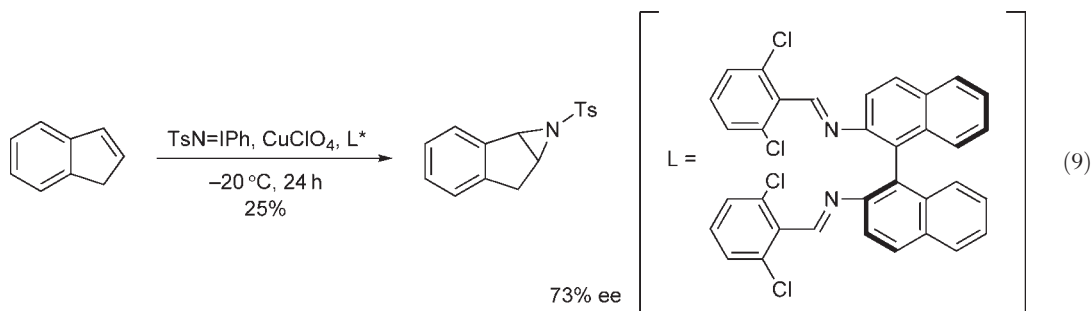
Caine *et al.* have found that utilizing two different methods for aziridination of the oxygen-substituted cyclopentene **26** would provide both the *trans*- and *cis*-substituted cyclopentylaziridines **27a** and **27b** as shown in Scheme 5 <2002OL1923>. An alternate nitrene-based method was used to achieve the synthesis of the *trans*-substituted aziridine exclusively. Usually, the olefin needs to be in large excess or run under very dilute conditions to achieve reasonable yields of aziridine. Use of NsN=IPh has been shown to increase yield, while providing a nitrogen protected with a *p*-nitrophenylsulfonyl group. The *p*-nitrophenylsulfonyl group also provides enhanced ring-opening capability of the resulting aziridine ring. Deprotection of the *p*-nitrosulfonyl group with thiols has been shown to be a very efficient process.



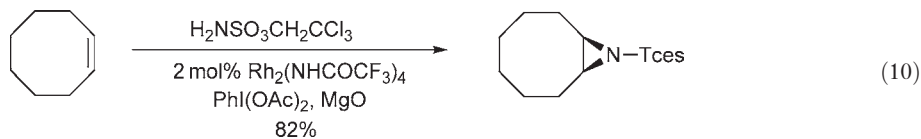
Scheme 5

The use of chloramine T and phenyltrimethylammonium bromide (PTAB) is expected to give the *cis*-product. Under these conditions, the bromonium ion forms initially, followed by the attack of the nitrogen source on the bromonium intermediate. It was assumed that the bromonium ion would form on the face opposite the OR group. Backside attack of the nitrogen (*cis* to the oxygen substituents) resulted in the formation of the *cis*-aziridine **27b**.

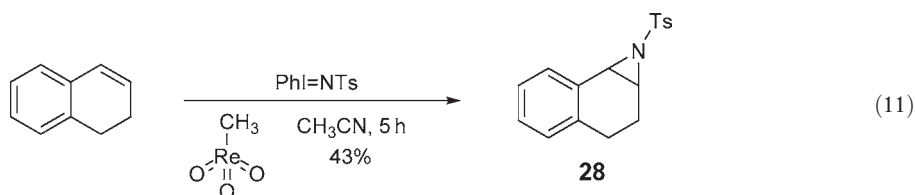
Asymmetric aziridination can also be accomplished via chiral salen ligands. Shi has synthesized a number of axially dissymmetric binaphthylidene salen complexes that have shown excellent facility in catalytic asymmetric aziridination reactions <2001TA3105>. Although yields were generally good with acyclic electron-deficient olefins, the chemical yield with electron-rich olefin indene was relatively low (25%). A reasonable enantiomeric excess of 73% was achieved at -20°C over a 24 h reaction period (Equation 9).



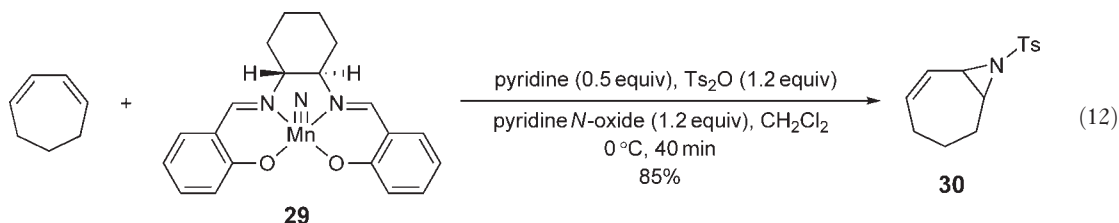
Du Bois has found that 2,2,2-trichloroethylsulfamate (TcesNH₂) readily aziridinates a variety of olefins <2006T11331>. TcesNH₂ was chosen for a number of reasons, including ease and cost of preparation from trichloroethanol, stability, and ease of cleavage of the nitrogen-protecting group. One major advance for this technology is the need for only 1 equiv of the olefin (Equation 10). Normally good yield in these reactions has required more than 5 equiv of olefin substrate to generate good chemical yield. The reaction is also selective for electron-rich olefins in preference to electron-deficient olefins. Of interest is that cyclopentene and cyclohexene do not aziridinate readily, but provide some of the allylic nitrogen insertion product.



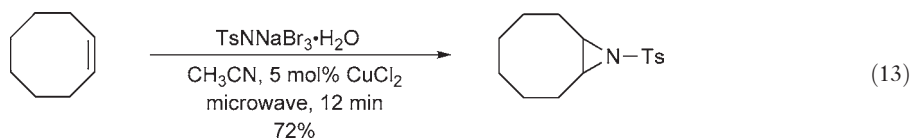
Methyltrioxorhenium has been found to be a universal catalyst for a number of [2+1] cycloaddition reactions, including nitrene, carbene, or oxo-atom addition to olefins <2001CC235>. Typically, to increase the chemical yield of the reaction, at least 5 equiv of an olefin is required. As with most nitrene transfer reactions, simple cyclic olefins such as cyclohexene produce a low chemical yield of aziridine. The authors assume that the intermediate of the reaction is a reactive rhenoxaziridine intermediate. 1,2-Dihydronaphthalene provides aziridine **28** in 43% chemical yield under these reaction conditions (Equation 11).



Komatsu and co-workers have prepared the simple monoaziridine **30** from 1,3-cycloheptadiene using the nitrido-manganese complex **29** as the nitrogen transfer reagent (Equation 12) <2000TL7089>. The nitridomanganese complex appears to have advantages over other transfer reagents such as the PhI=NTs, that tend to give a mixture of the alkenylaziridine and pyrroline derivatives. Other synthetic methods such as addition of azide combined with thermolysis or photolysis results in a variety of by-products with little of the azidoalkenes formed. The nitridomanganese reagent is also useful for asymmetric aziridination as the chiral complex.

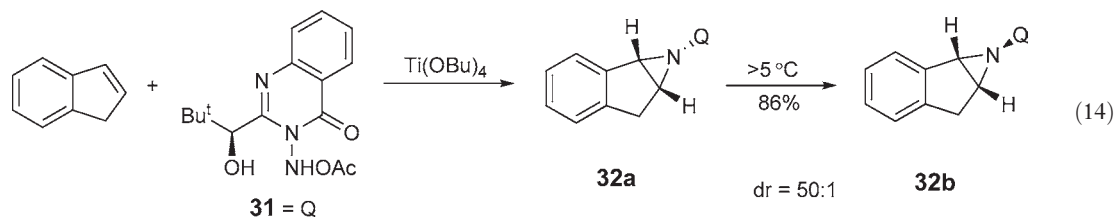


The use of Chloramine-T or Bromamine-T as the nitrogen source has been useful as the transfer reagent in the aziridination reaction. Bedekar and co-workers have found that simple cyclic olefins such as norbornene, cyclohexene, or cyclooctene produce low yields of aziridinated products. However, the same reaction run in a simple microwave oven increases the chemical yield dramatically <2001JOC30>. The reaction shown in Equation (13) was run without the assistance of microwave energy and provided approximately half of the chemical yield at 38%.

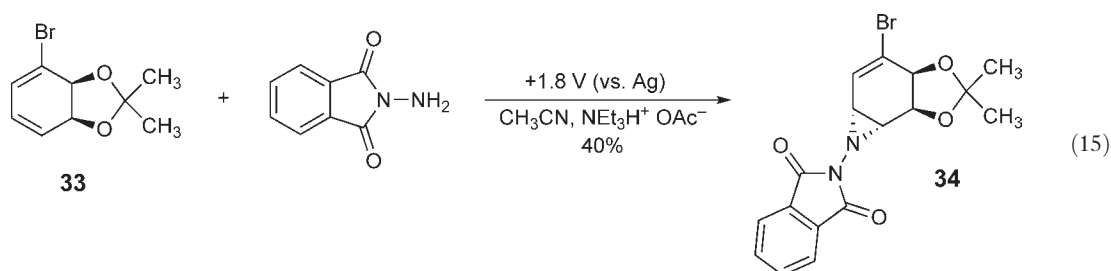


Atkinson has extended the initial work of Rees, utilizing substituted acetoxyaminoquinazolinone as the aziridinating species rather than the original family of *N*-aminoheterocycles <1996CC1935, 1998J(P1)2783>. Complete diastereoselectivity is obtained through titanium chelation of the pendent alcohol and N-1 of the quinazolinone **31**

when reacted with indene. The first product formed is the *cis*-*N*-invertomer **32a** which at greater than 5 °C slowly converts to the *trans*-*N*-invertomer **32b** (Equation 14). Diastereoselectivity comes from minimization of the steric interactions of the catalyst with the methylene unit of the indene molecule.



Cyclic voltammetry provided Yudin with information that oxidation of aminophthalimide at +1.8 V will provide an active nitrogen species capable of aziridinating both electron-rich and electron-poor olefins. The electron-rich olefin of the diene **33** was thus able to be selectively aziridinated to provide aziridine **34** (Equation 15) <2005JOC932>. Yudin found that addition of acetate anion was key in the aziridination process. Addition of acetate to the solution forms the *N*-acetoxyaminophthalimide, a compound previously prepared by oxidation of aminophthalimide with lead tetraacetate. The absence of acetate allows the aminophthalimide to dimerize, then oxidize further to lose nitrogen and provide phthalimide as the final product, without any reasonable concentration of aziridinating agent.



1.02.3.1.3 Formation of aziridines via C addition across a C=N

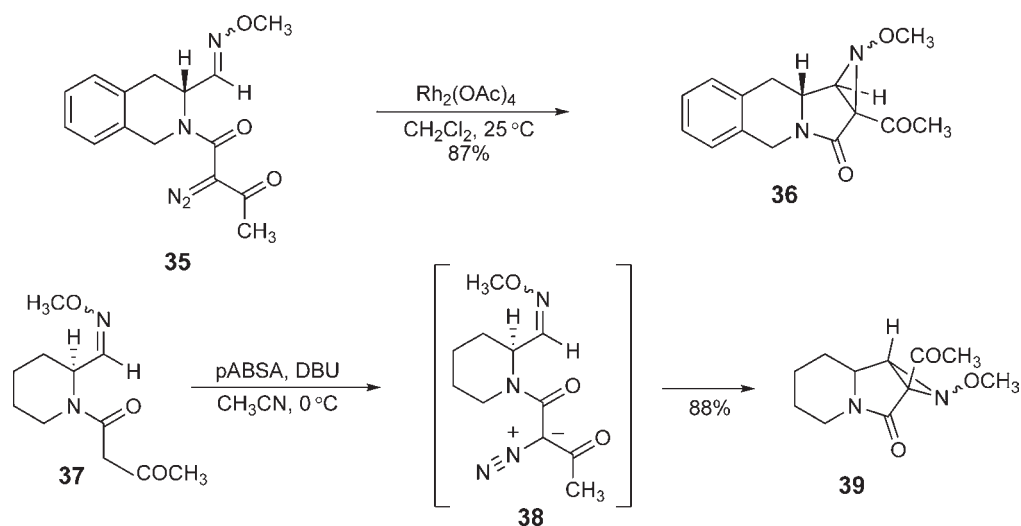
Alternatively, one can add a carbene source to some form of a C=N bond. This will generate bonds 'c' and 'b'. This model is limited by the availability of cyclic imine or imine-like structures. Several methods are available to prepare aziridines through the functionalization of a C=N bond, although formation of the fused rings will require an intramolecular addition to a pendent imido-bond. The Darzens process and ylide addition to C=N bond are generally not applicable in most cases owing to the structural requirements of the cyclic system. This requirement renders this process less useful overall than the addition to a C=C bond.

One of the few examples of an intramolecular carbene addition to an imino-bond is shown in Scheme 6 <1999OL667>. Isoquinoline diazoamide **35** was subjected to standard dirhodium catalysis. The resulting aziridino-isoquinoline **36** was isolated in an excellent 87% yield. The *N*-O invertomers could be isolated chromatographically. Several other cyclic and acyclic systems were also synthesized. A simple acyclic system provided an 86% yield of a bisazabicyclo[3.1.0]hexane system. A pyrrolizidine aziridine was prepared in 60% overall yield.

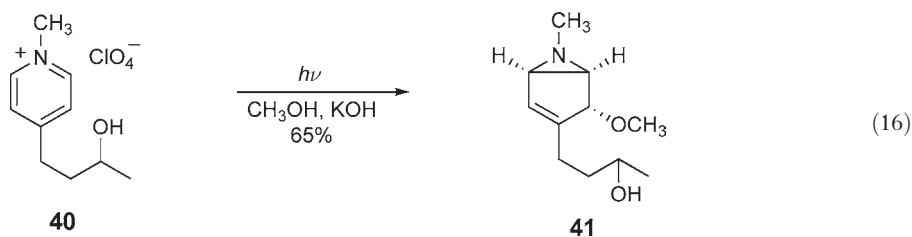
Surprisingly, the indolizidine aziridine **39** was synthesized in 88% yield, but was found to be an uncatalyzed reaction, providing the product upon diazo-transfer at 0 °C to oxime **37**. Two plausible mechanisms are invoked for this carbene reaction sequence: (1) a carbenoid insertion process or (2) collapse of the azomethine ylide formed upon addition of the diazoamide. The uncatalyzed process is likely due to a dipolar cycloaddition of the diazo and pendent oxime.

1.02.3.1.4 Formation of type I aziridines via other methods

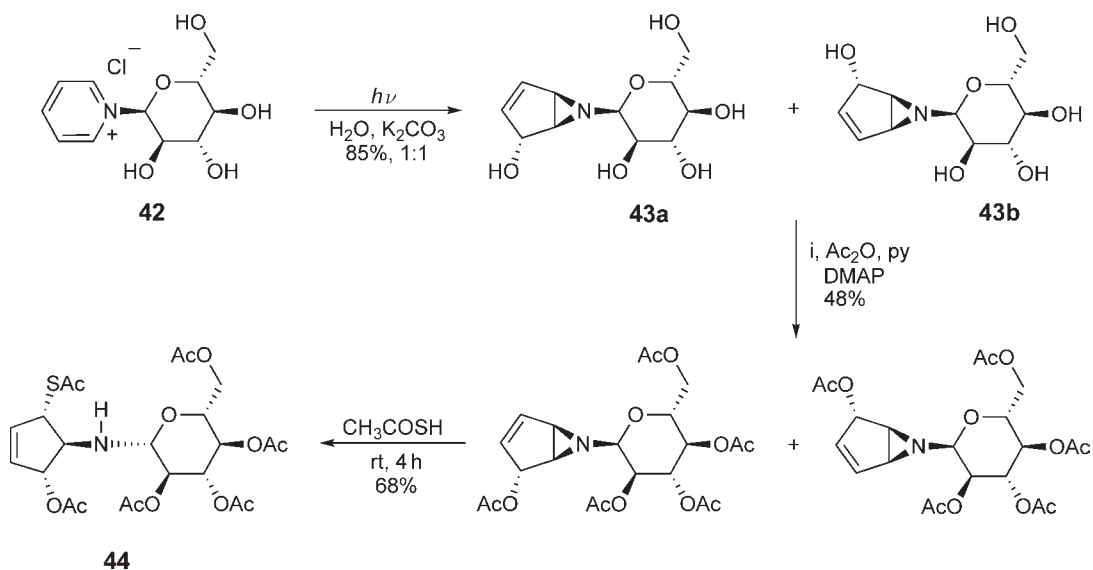
Type I aziridines can be prepared via photolysis of functionalized pyridinium ions. Mariano and co-workers have shown that irradiation of pyridinium ion **40** via a 450 W Hanovia lamp with Vycor filter will induce a ring contraction to produce a fused-bicyclic aziridine moiety **41** (Equation 16) <1996JOC4439>. The azabicyclo[3.1.0]hexane prepared through this method can rapidly experience nucleophilic opening to produce an amine-substituted cyclopentene.



Scheme 6

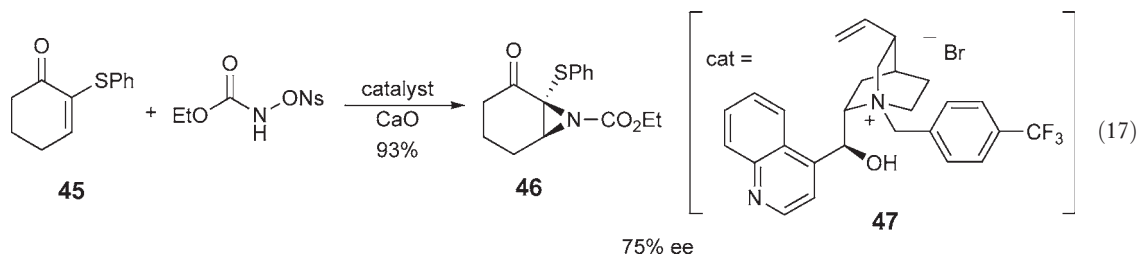


This photolysis methodology was utilized by Burger *et al.* to prepare novel β -glucosylamines [<2000T4311>](#). Pyridinium salt **42** was prepared from pyridine and a glucopyranosyl bromide. Irradiation of pyridinium salt **42** gave a 1:1 mix of the diastereomeric aziridines **43a** and **43b**. The unstable diastereomers were acetylated and then treated with thioacetic acid to provide glucosylamine **44** as a single diastereomer from the separated aziridines **43a** and **43b** (Scheme 7).

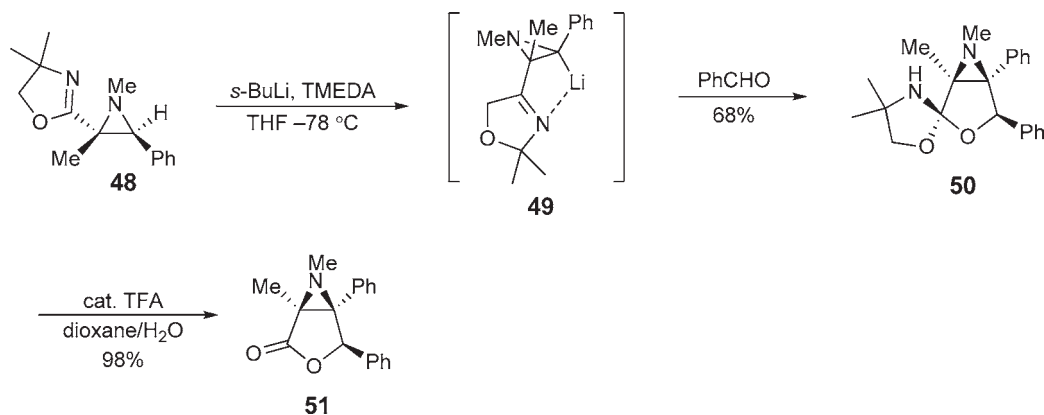


Scheme 7

Cinchona alkaloids have recently been used in an aza-Michael initiated ring closure (MIRC) reaction of α,β -unsaturated ketones under phase transfer catalysis conditions <2000T4311, 2004T8073>. In general, solid-phase conditions gave good yields and enhanced enantioselectivity. Thiophenyl enone **45** together with nosyloxycarbamate, solid calcium oxide and catalytic quaternary *Cinchona* catalyst (ratio = 1:5:6) gave an excellent overall yield and good enantioselectivity of the product thiophenyl aziridine **46** (Equation 17). Two alternate quaternary *Cinchona* catalysts with opposite diastereomeric alcohol and ring hydrogens gave the same major enantiomer as the major product. A chiral version of the nosyloxycarbamate has been used to aziridinate an α,β -unsaturated keto ester with 70% de <2003TL3031>. It is interesting that the same method of aziridination (without the chiral catalyst) with an α,β -unsaturated γ -lactone provides the 2,3-aziridino- γ -lactone in only 30% yield <2003TL4953>.



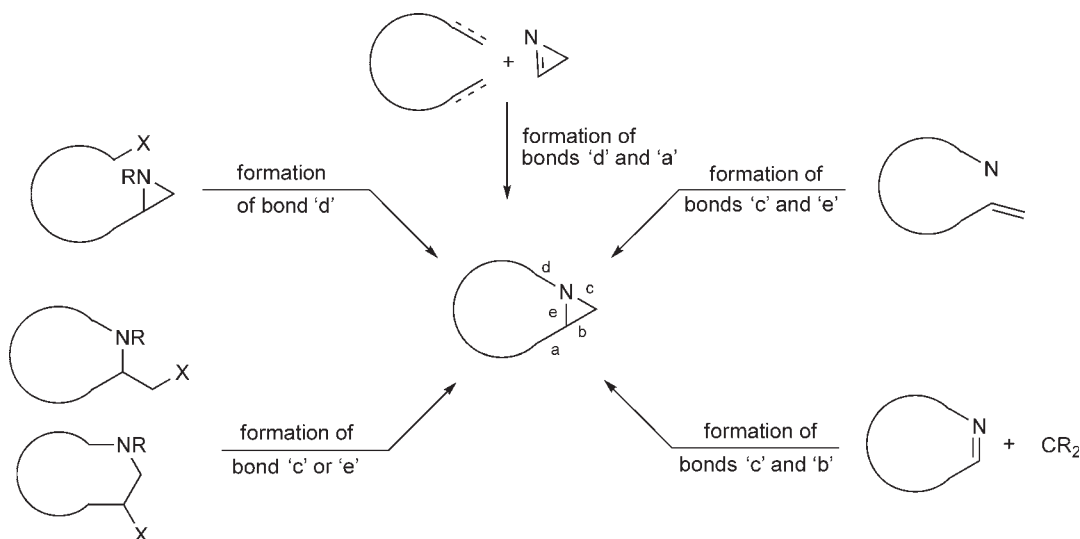
Syntheses of type I aziridines in which the fused ring is formed from a substituted monocyclic aziridine are in general not common. A useful example of this approach is shown in Scheme 8 <2005T3251>. Oxazolinylaziridine **48** was deprotonated with *s*-BuLi/TMEDA (TMEDA=1,2-bis(dimethylamino)ethane) to generate aziridinyllithium intermediate **49**. The addition of benzaldehyde to this organolithium reagent provides type I aziridine **50** with a spiro-fused oxazolidine ring. Hydrolysis of the spirocyclic acetal ring provides the 2,3-aziridino- γ -lactone **51** in excellent yield.



Scheme 8

1.02.3.2 Synthesis of Type II Aziridines

A key issue in the synthesis of type II aziridines is the stability of the product aziridine. Many of the resulting aziridines are not stable as isolated and are quickly used in subsequent reactions. It is not uncommon to see low reported yields in the synthesis of fused-ring aziridines due to the high reactivity of this class of aziridines. The synthesis of type II or endocyclic aziridines typically takes one of five approaches. We have broadly divided these into formation of one bond or the formation of two bonds. Within the group of single bond formation, one can form the aziridine ring from a larger or smaller ring by forming bond 'c'. Alternatively, one can use an intact monocyclic aziridine and through the formation of bond 'd' prepare a type II aziridine (Scheme 9).

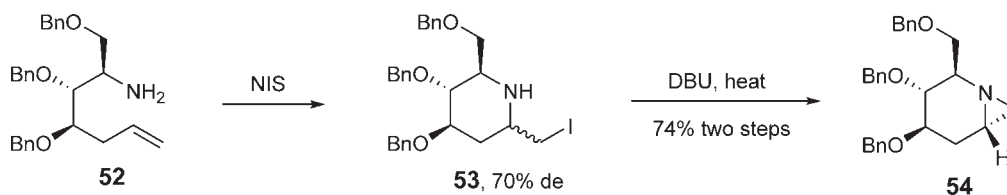


Scheme 9

The formation of type II aziridines can also be carried out via the formation of two bonds simultaneously. One of the most common is the formation of two C–N bonds (bonds ‘c’ and ‘e’) to generate the aziridine ring. This quite often takes the form of a nitrene or nitrene equivalent adding to an alkene. Another highly common route that forms two bonds simultaneously is the reaction of a monocyclic azirine with a difunctional molecule such as a diene or dipole to form bonds ‘d’ and ‘e’. A significantly less common route is the formation of bonds ‘c’ and ‘b’ through the addition of carbene or carbene equivalent to a cyclic imine.

1.02.3.2.1 Formation of aziridines via single bond formation

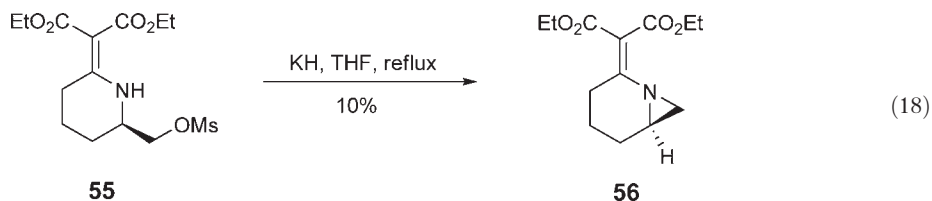
The formation of bond ‘c’ is one of the more common routes to type II aziridines involving a single bond formation. This route typically involves an S_N2 -type nucleophilic attack of a basic nitrogen at an exocyclic sp^3 hybridized carbon [<1995TL799, 2003TL7997>](#). An example is shown in [Scheme 10](#) [<2003TA1969>](#). Compound **52** was prepared in six steps from tri-*O*-benzyl-D-glucal. Treatment of **52** with *N*-iodosuccinimide (NIS) provided the iodomethyl piperidine derivative **53** in 70% de. This compound was apparently not isolated but directly converted to aziridine **54** in 74% overall yield from **53** by heating with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Compound **54** is moderately stable and was purified by flash chromatography.



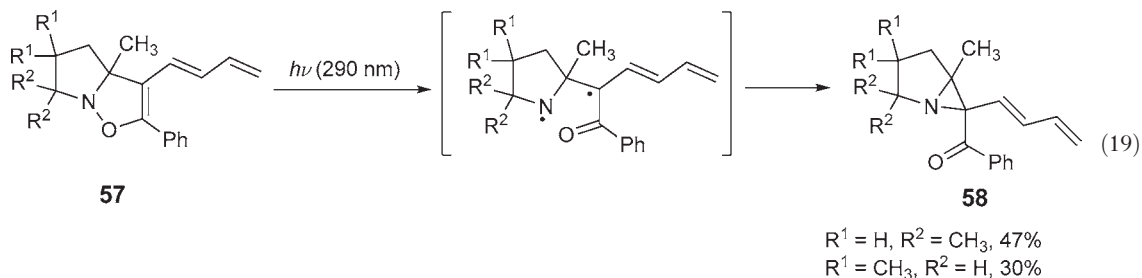
Scheme 10

Fused-ring aziridines such as **56** are common intermediates for the synthesis of azinomycin and related anticancer agents. The presence of the exocyclic olefin/vinylogous amide greatly increases the reactivity of such aziridines.

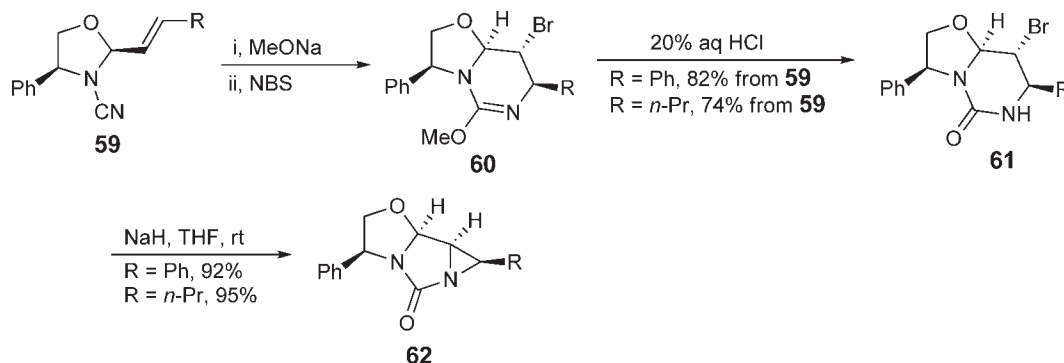
Intramolecular alkylation of the vinylogous amide **55** is initiated by KH <1998T6029>. While the reaction appeared to progress cleanly, the product was difficult to purify. Aziridine **56** was isolated in only 10% yield after chromatography on Florisil (Equation 18).



The methods shown in the previous two examples make use of a nucleophilic nitrogen, which reacts at an electrophilic carbon and displaces a leaving group to generate the aziridine ring. An interesting variation on this general disconnection is the photolytic formation of aziridine **58** <2001T4349>. Photolysis of oxazolidine **57** leads to scission of the N–O bond followed by N–C bond formation to provide aziridine **58** in moderate yield. The relative stereochemistry of **58** was not reported (Equation 19).

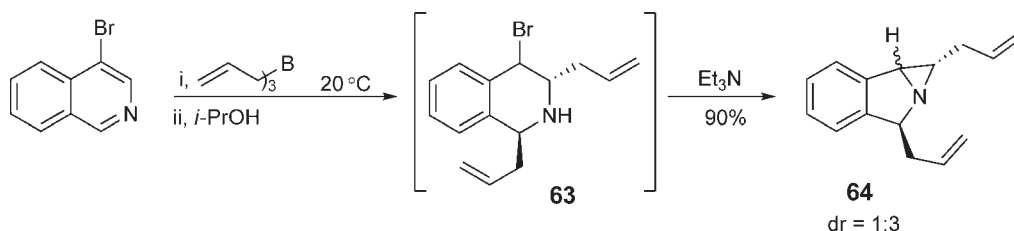


The related formation of bond 'e' via a ring contraction pathway is not often observed in the formation of type II aziridines. An example of an interesting, high-yielding method to prepare a very highly functionalized aziridine is shown in Scheme 11 <1998TL5373>. Treatment of cyanamide **59** with sodium methoxide generates an intermediate imidate. The imidate is then subjected to amidohalogenation conditions to generate bromide **60**. Hydrolysis of the enol ether provides urea **61** in very good yields. The aziridine ring is then formed by treatment of **61** with sodium hydride. This aziridine is reported to be unusually stable, especially given the [3.1.0]-ring system containing both a carbonyl and an aминаl linkage.



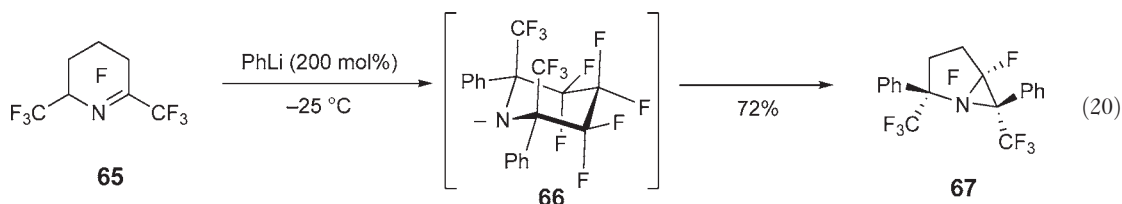
Scheme 11

An operationally simple, yet elegant example of this type of disconnection starting from bromoisquinoline is outlined in [Scheme 12](#) <2002JOM(657)123>. Treatment of bromoisquinoline with excess triallylborane provided diallyl species **63**. The two allyl groups end up *trans* to each other but a mixture of epimers at C-4 is formed. Treatment of **63** with triethylamine generates aziridine **64** in 90% yield as a 3:1 mixture of isomers. The identity of the major isomer was not determined.

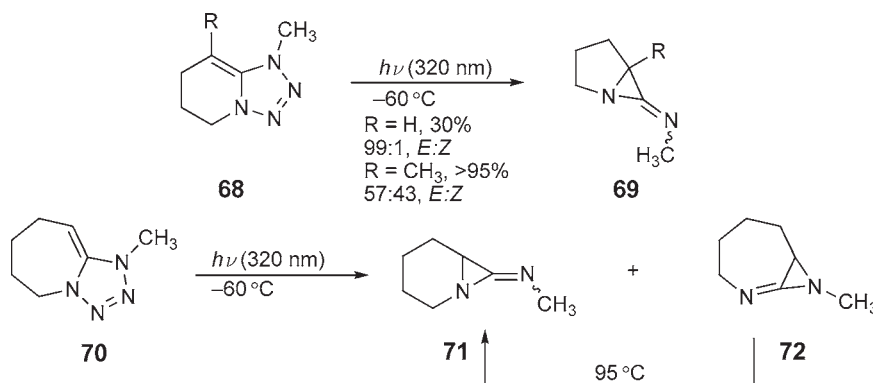


Scheme 12

An interesting use of the bond 'e' disconnection for the synthesis of perfluoro aziridines was reported <1999CC47>. Treatment of perfluoro imine **65** with an excess of PhLi provides the aziridine **67** in good yield ([Equation 20](#)). This reaction is believed to go through intermediate **66** after an initial addition of 2 equiv of PhLi. A subsequent nucleophilic attack of the nitrogen anion to displace a fluorine results in aziridine ring formation. The ease with which this strained system forms is attributed to relief of the 1,3-diaxial interactions found in intermediate **66**. In addition, an X-ray structure of aziridine **67** was obtained.



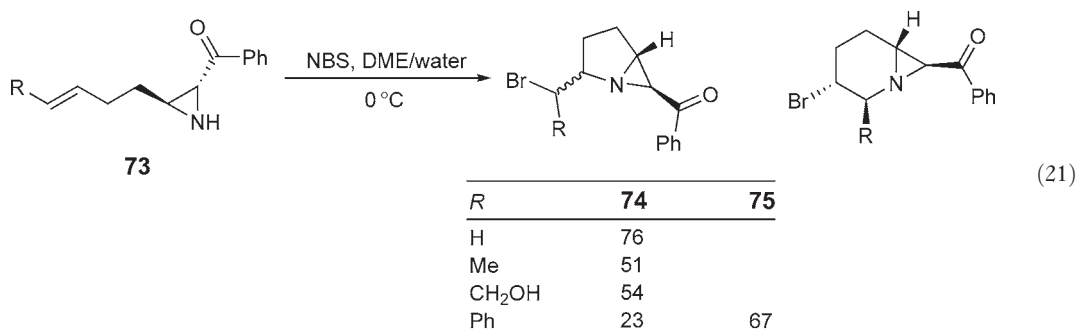
Another example involving a ring contraction leading to fused-ring aziridines is shown in [Scheme 13](#) starting from bicyclic tetrazole **68** <1998EJO317>. Photolysis of annulated dihyrotetrazoles leads to a ring opening and loss of



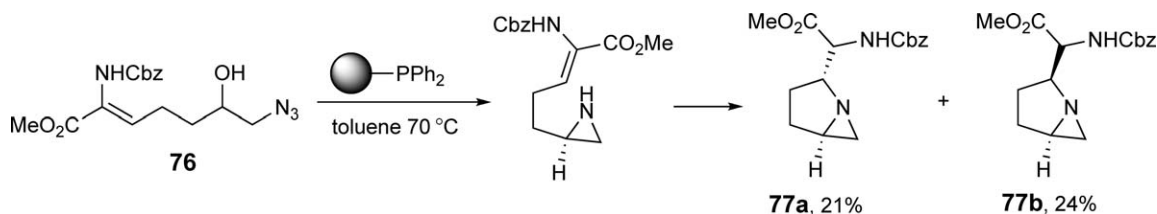
Scheme 13

nitrogen. The resulting diradical recloses to form the imino aziridine **69** in good yield. Photolysis of the larger annulated ring **70** leads to a mixture of two imino aziridines **71** and **72**. Thermolysis of the cyclic imine derivative **72** provides the exocyclic imino aziridine **71** as the sole product.

The other type of single bond formation leading to type II aziridines is the formation of bond 'd'. This is a quite unique type of bond formation in that it uses an intramolecular cyclization between a monocyclic aziridine and an electrophilic carbon. While the N-alkylation or N-acylation of monocyclic aziridines is a fairly common reaction, this type of reaction has not been used in an intramolecular sense to prepare type II aziridines. One such example is based on the intramolecular cycloamination of an olefin <2003JA14242>. The reaction is believed to proceed through an *N*-Br species, which then reacts with the olefin to provide products **74** or **75** in moderate yields. In general, aziridine **74** is the only product formed. However, the phenyl-substituted double bond yields the [4.2.0]heptane system **75**, presumably through stabilization of a benzylic cation. It is interesting to note that a hydroxymethyl group on the double bond is tolerated in this reaction (Equation 21).

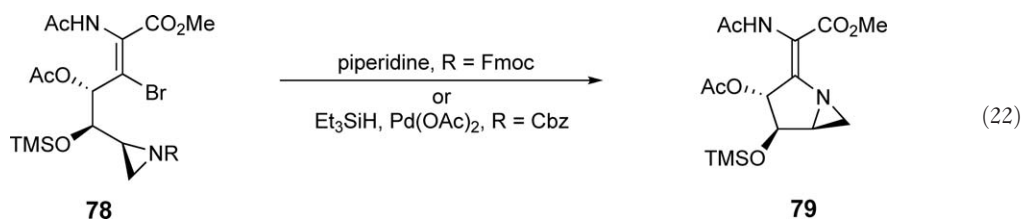


The intramolecular conjugate addition of an aziridine nitrogen to form type II aziridines is a well-studied reaction and an example is found in Scheme 14. Additional approaches to this ring system are also found in Section 1.02.7.1. This type of reaction has been used extensively in the synthesis of the azinomycins and carzinophilins. A synthesis of the skeleton of ficellomycin has recently been reported <2004SL2212>. The azido alcohol **76** (prepared from the corresponding epoxide) was converted to a monocyclic aziridine using a polymer supported phosphine. This aziridine spontaneously cyclized to a 1:1 mixture of diastereomeric fused-ring aziridines **77a** and **77b**. A major complicating factor in this synthesis were difficulties in purifying the fused-ring aziridine **77** from the resulting phosphine oxides. The use of the polymer-supported phosphine allowed for the isolation of aziridines **77a** and **77b** in moderate yields.

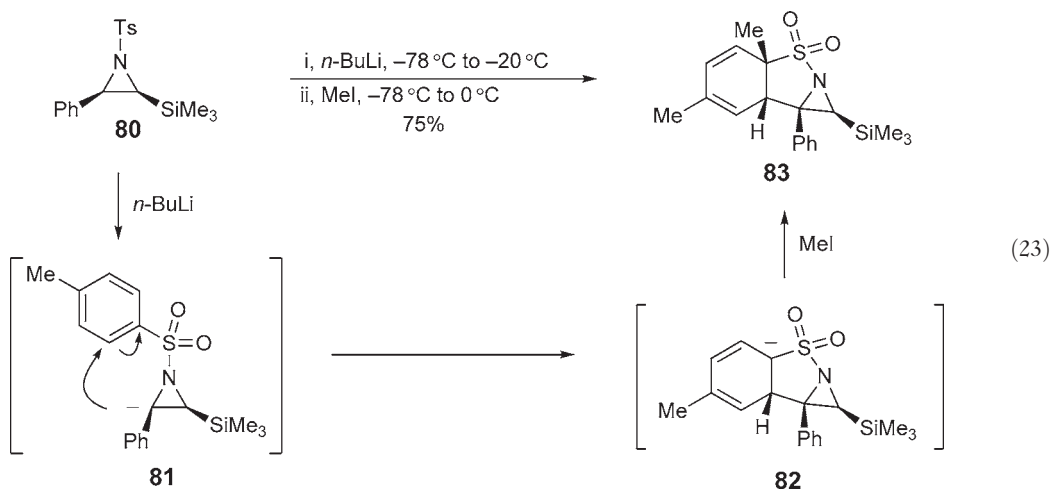


Scheme 14

A conjugate addition–elimination route to prepare the core of azinomycin is another well exemplified approach to this ring system <1998JA3538>. The monocyclic aziridine, protected as either the Fmoc or Cbz derivative, was deprotected to initiate cyclization to form aziridine **79** although no yields were reported due to the extremely unstable nature of **79** (Equation 22).



The formation of bond 'a' between C-2 of an aziridine and an N-linked carbon is a unique route to type II aziridines. An example of this singular reaction is shown in Equation (23) <2002JOC2335>. Aggarwal and co-workers found that the metalation of alkyl-substituted aziridines provided an efficient route to more highly substituted aziridines. In extending this reaction to phenyl-substituted aziridines a quite different product was obtained. Deprotonation of aziridine **80** with *n*-BuLi generates the intermediate aziridino anion **81**. This anion undergoes an intramolecular addition to the activated benzene ring of the *N*-tosyl group to provide stabilized anion **82** which was subsequently alkylated to provide **83** in very good yield. While this is a very interesting approach to type II aziridines, it is not clear how general it will be given the limitations associated with aziridine deprotonation. There are several nitrene-mediated approaches to this structural class of aziridines that do appear to be more general.

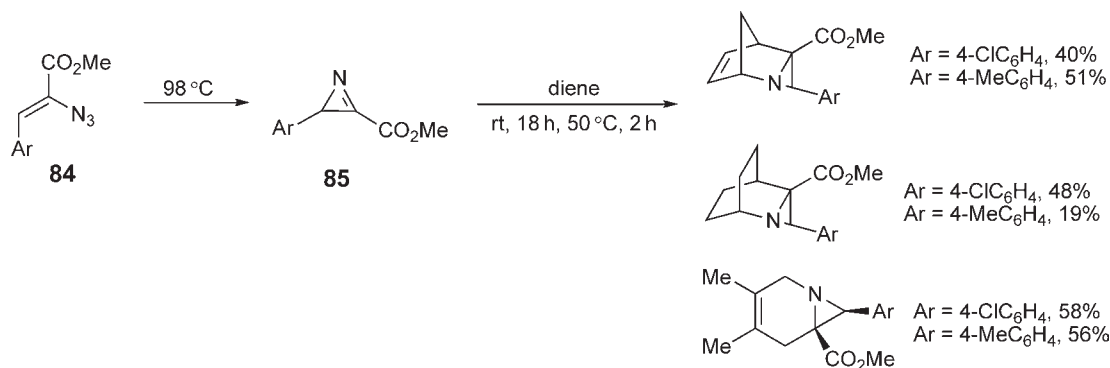


1.02.3.2.2 Synthesis of aziridines via the formation of two bonds

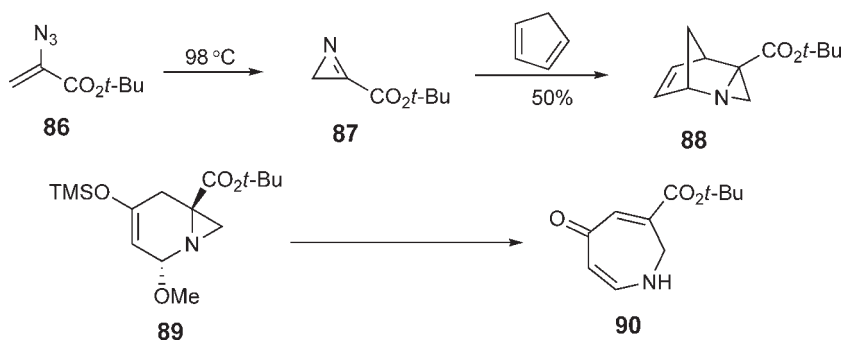
Azirines are generally useful intermediates for the synthesis of substituted aziridines through nucleophilic addition to the C–N double bond <1996CHEC-II(1A)1>. Azirines are also quite useful for the synthesis of type II fused-ring aziridines via Diels–Alder reactions <2001ALD51, 2002OPP219>. Imines are generally poor dienophiles in Diels–Alder reactions. The incorporation of the imine into a three-membered ring as in an azirine makes it a much more reactive dienophile. In general however, even these highly reactive imines only undergo cycloaddition reactions with very reactive dienes. The synthesis and Diels–Alder reactions of carboxylate-substituted 2H-azirines have been extensively investigated <1997S271, 1998J(P1)299, 2005S555>. As shown in Scheme 15, the monocyclic-disubstituted azirines, **85**, are prepared by thermolysis of the olefinic azides **84** in refluxing heptane. The instability of the azirines precludes their isolation and purification prior to cycloaddition. Consequently, the solvent is removed and an excess of the diene added. Three different dienes were examined in this study and the major *endo*-isomers were isolated in moderate yields. Disubstituted azirines such as **85** have also been found to undergo Diels–Alder cycloadditions with azadienes in moderate yields <2003TL5079, 2004T6541>.

Azirines with a single electron-withdrawing substituents at C-3 are considerably less stable than disubstituted azirines. This becomes a considerable challenge in using such azirines in cycloaddition reactions. An approach to

using these monosubstituted azirines is shown in [Scheme 16](#) <1998TL7579>. Operationally, these azirines were not concentrated prior to reaction but the diene was simply added to a solution of the azirine. Thermolysis of azido ester **86** gave the unstable azirine **87** which upon addition of cyclopentadiene provided aziridine **88**. Several other dienes were also used in this study. Of interest is the reaction with 1-methoxy-3-trimethylsilyloxybutadiene initially yielded aziridine **89**. This aziridine readily rearranged to azepinone **90** at room temperature.



Scheme 15

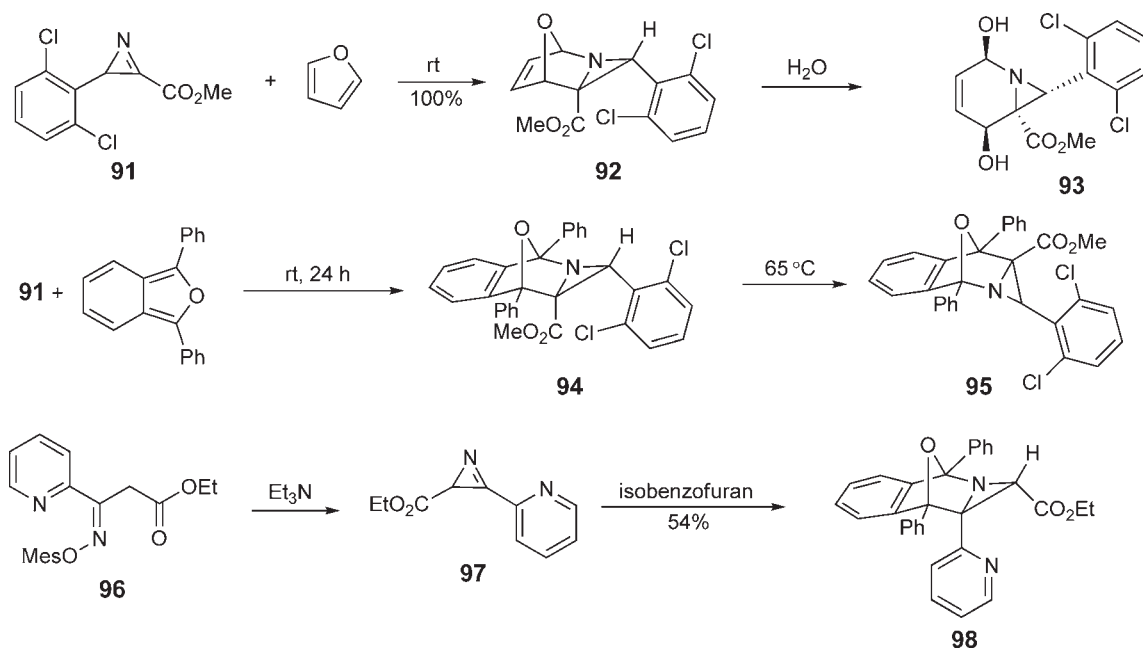


Scheme 16

Furan is an excellent diene in a wide variety of Diels–Alder reactions, providing oxabicyclic compounds with useful synthetic applications. However, Diels–Alder reactions with furans are often reversible and require a highly reactive dienophile in order to provide useful yields of the cycloadduct. As shown in [Scheme 17](#), furans have now been shown to undergo synthetically useful Diels–Alder reactions with azirines. The reaction of furan with azirine **91** provides cycloadduct **92** in 100% yield <1998J(P1)299>. Aziridine **92**, while crystalline, is moisture sensitive, decomposing to aziridine **93**. An X-ray structure of **92** was obtained which confirmed the *exo*-nature of the cycloaddition reaction in contrast to the *endo*-cycloadditions seen in the formation of **88** <2001J(P1)2969>.

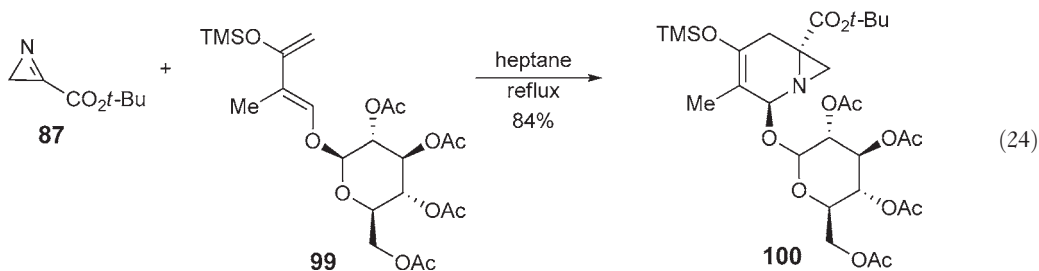
Azirine **91** has also been shown to undergo a Diels–Alder reaction with diphenyl isobenzofuran to provide **94**. The *exo*-isomer was reported to isomerize to the *endo*-isomer **95** upon heating, although no yields for this transformation were reported <2001J(P1)2969>.

The pyridyl azirine **97** was prepared from mesitylsulfonyloxy oxime **96**. This is one of the first examples of heteroaromatic substituted azirines reported. This azirine undergoes a Diels–Alder reaction with isobenzofuran to provide the *exo*-cycloadduct **98** in 54% yield <2005S555>. In addition to isobenzofuran, this azirine undergoes cycloaddition with a number of different dienes, including cyclopentadiene (82%), 1-methoxy-butadiene (58%), and Danishefsky's diene (67%).

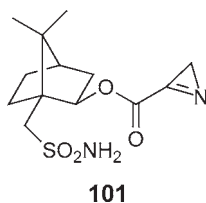


Scheme 17

In an effort to develop enantioselective methods for azirine cycloadditions, azirine **87** was added to chiral diene **99** <1998TL7579, 2003TL6561>. Diene **99** has previously shown facial selectivity in Diels–Alder reactions with a number of dienophiles. Reaction of 2 equiv of azirine **87** with **99** provides aziridine **100** in excellent yield as a single isomer (Equation 24).

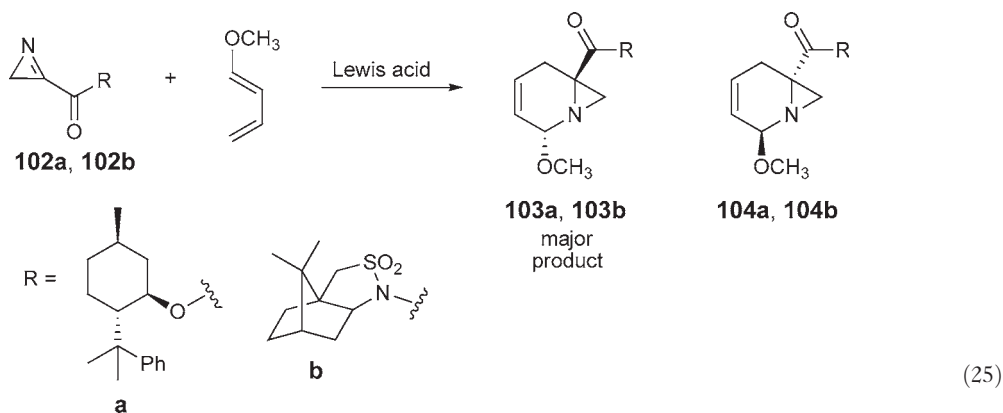


The use of chiral esters has found some success in Diels–Alder reactions. Ester **101** was prepared and the enantioselectivity of this azirine with a series of dienes was examined <1999J(P1)1399, 2002J(P1)1911>. Regardless of the diene used, the cycloadducts with azirine **101** showed low diastereoselectivity (2:1 to 3:1).



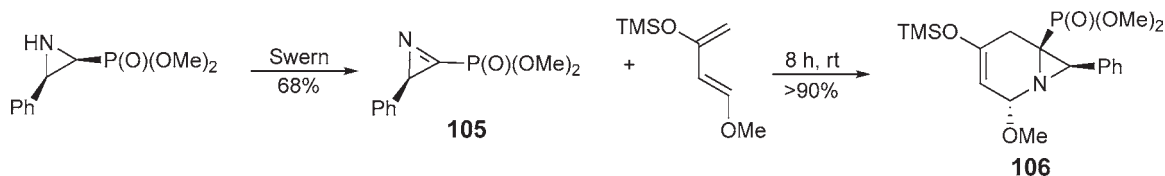
Given the poor diastereoselectivity in Diels–Alder cycloadditions seen with azirine **101**, effort has gone into improving the diastereoselectivity of this reaction. A promising avenue has been the Lewis acid-catalyzed Diels–Alder reaction of azirines with dienes <2001TL9289, 2002T5983, 2003CC1150, 2003JOC9958>. These reaction conditions provide improved yields of the fused-ring aziridines relative to the uncatalyzed reactions. These are surprising reaction conditions for these unstable azirines. The overall yields of the cycloadducts were generally quite good, although not as good as the uncatalyzed reactions. Diastereomer **103a/103b** was the primary product observed

in these cycloadditions. Optimal diastereoselectivity was observed with the phenylmenthol ester and $\text{MgBr}_2 \cdot \text{OEt}_2$ catalysis. Attempts at carrying out catalytic enantioselective Diels–Alder reactions with azirines such as **87** and a chiral Lewis acid were generally not successful, with ee's of only 12–52% (Equation 25).



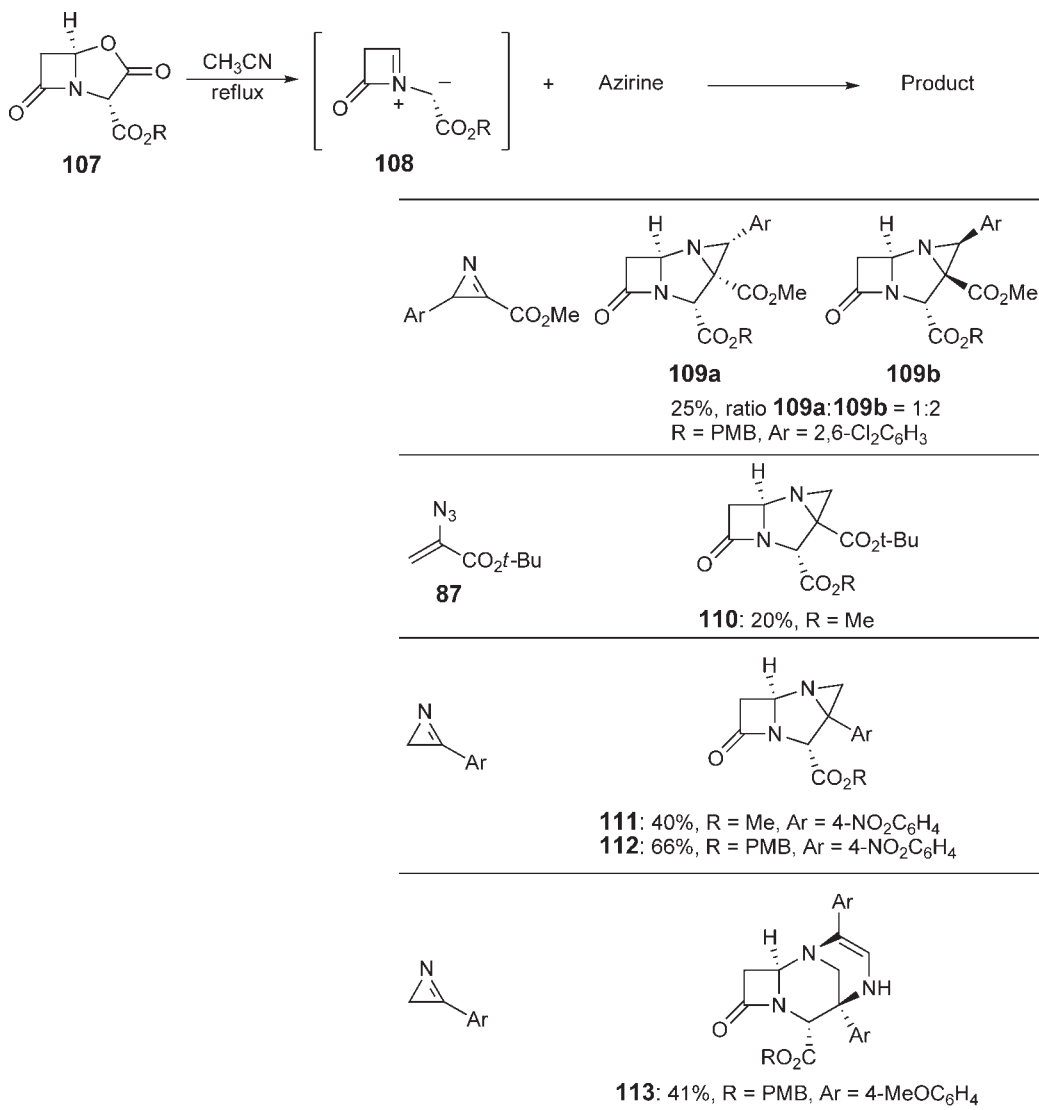
Azirine	Lewis acid	Temp. (°C)	Yield (%)	de (%)
102a		rt	100	0
102b		rt	95	21
102a	$\text{MgBr}_2 \cdot \text{OEt}_2$	–100 to –75	82	87
102b	$\text{MgBr}_2 \cdot \text{OEt}_2$	–78	38	40
102a	$\text{ZnCl}_2 \cdot \text{OEt}_2$	–100	62	80
102b	$\text{ZnCl}_2 \cdot \text{OEt}_2$	–78	69	27
102a	YbCl_3	–78 to –20	43	27
102b	YbCl_3	–78 to –60	100	25

A chiral phosphonate-substituted azirine was prepared and its Diels–Alder reactions studied <2002OL655>. Azirine **105** is prepared by the Swern oxidation of the corresponding aziridine as shown in Scheme 18. The Diels–Alder reaction of azirine **105** with Danishefsky's diene provides aziridine **106** in excellent yield as a single diastereomer. Note that the reaction time for azirines such as used by Gilchrist *et al.* is only 15 min as compared to 8 h with the phosphonate substituted azirines suggesting that the carboxylate-substituted azirines are much more reactive than the phosphonate-substituted azirines <1997S271, 2001J(P1)2969, 2005S555>.

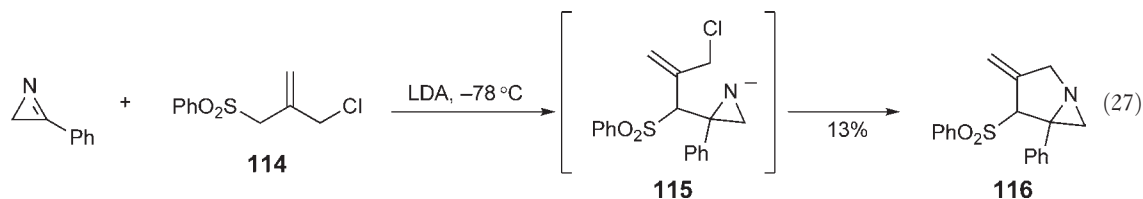


Scheme 18

Azirines are a unique dienophile in that their use in cycloadditions has not been as well investigated as other dienophiles. The use of azirines in dipolar cycloadditions has been investigated to a lesser extent. The reaction of azomethine ylides (e.g., **108**) with a number of dipolarophiles has been found to be a useful route to a beta lactams. Azirines have been recently found to participate in dipolar cycloadditions with azomethine ylides <2002J(P1)2014>. Azomethine ylide **108** was trapped with several different azirines. Surprisingly disubstituted azirines, which participate quite well in Diels–Alder reactions, provide aziridines **109a** and **109b** in only 25% yield. Given the lack of stability of azirines generated from azide **87** (Scheme 16), it is not surprising that this reaction provided only a 20% yield of aziridine **110**. The best azirines in these dipolar cycloadditions were the mono-substituted aryl azirines, which provided aziridines **111** and **112** in moderate yields. The use of *p*-methoxyphenyl azirine did not provide the expected product but rather **113** in which 2 equiv of the azirine added to the dipole (Equation 26).

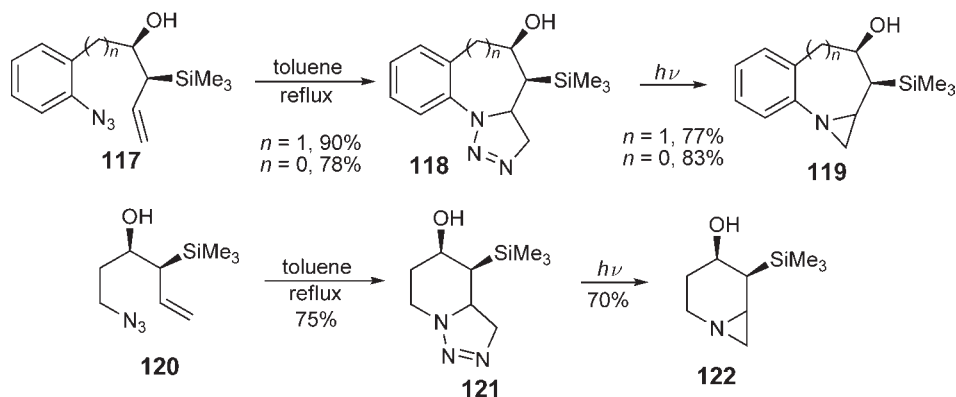


An interesting Darzens-like formal cycloaddition of azirines has also been reported [<2004EJO2421>](#). While this is not a true cycloaddition reaction, two bonds are formed in the same reaction sequence. Reaction of sulfone **114** with lithium diisopropylamide (LDA) generates a carbanion which then adds to the azirine to generate intermediate **115**. Cyclization of this intermediate with the allyl halide provides the product aziridine **116**. This reaction proceeds in only 13% yield but is nonetheless an interesting route to fused-ring aziridines (Equation 27).



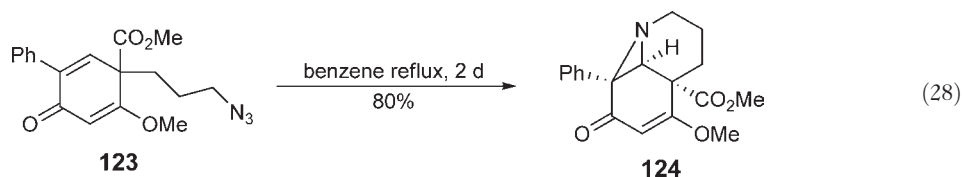
The addition of nitrogen across a double bond to form a fused-ring aziridine of type II generally takes one of two forms. The simplest is the dipolar cycloaddition of an azide across a double bond followed by loss of dinitrogen to provide an aziridine. A second and operationally more complex approach is the generation of a nitrene, which then adds to the olefin to directly provide the aziridine.

The azido olefins **117** and **120** were cyclized to the triazolines **118** and **119** in excellent yields <2001TL9175>. This is an interesting process in that the intermediate triazolines are isolated and then photolytically decomposed to aziridines **119** and **122** in very good yields (Scheme 19). All of these aziridines were reported to be stable compounds especially to acidic conditions. This is significant in that previous examples of silyl-substituted monocyclic aziridines were quite unstable undergoing acid-catalyzed rearrangements.



Scheme 19

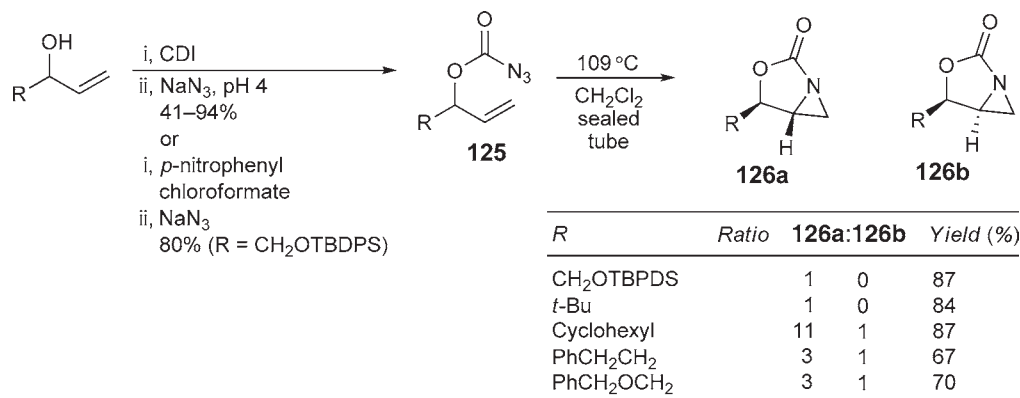
The intramolecular azide cycloaddition has also been used in approaches to the aspidosperma alkaloids <2004TL919, 2005OBC213>. The cycloaddition of **123** proceeds directly to aziridine **124** in 80% yield (Equation 28) <2004TL919>. This is an interesting transformation in that none of the initially formed triazoline is observed and because of the high regioselectivity of the addition. A conceptually related approach to the synthesis of cephalotaxine has also been reported <1997TL4347>.



Intramolecular reactions between nitrenes and alkenes to produce type II aziridines are limited to acyloxy and sulfonyl nitrenes as alkyl and aryl nitrenes undergo rapid rearrangements prior to addition. Of the possible nitrene linking groups, three different variations have been reported to yield carbamate-linked aziridines, sulfonamide-linked aziridines, and sulfamate-linked aziridines. The first that we will discuss are the acyloxy-linked nitrenes (or nitrenoids) leading to carbamate-linked aziridines. Given that one of the primary uses of fused-ring aziridines is a subsequent ring-opening reaction, the incorporation of an activating group on the nitrogen in addition to enhancing the reactivity of type II aziridines, this activating group should also broaden their synthetic utility.

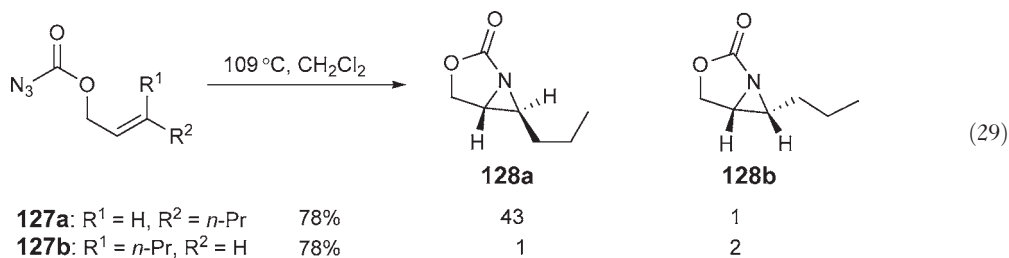
Intermolecular reactions between azidoformate and olefins are well known to produce aziridines <1996CHEC-II(1A)1>. These reactions are limited to strained or otherwise activated olefins. An intramolecular cycloaddition of an azidoformate with an alkene has been reported to give good yields of carbamate-linked type II aziridines <1997JOC4449, 1999JOC2852>. Reaction of an allylic alcohol with CDI/NaN₃ or *p*-nitrophenylchloroformate/NaN₃ provides the azidoformates **125** in good yields. Thermolysis of the azidoformate provides aziridines **126a** and **126b** in good yields. The reactions are optimally carried out in CH₂Cl₂ in a sealed tube. The choice of solvent in the thermolysis reaction is crucial. Previous work showed that the use of higher boiling halogenated hydrocarbon solvents results in the generation of aziridine ring opened products <1995TL4533>. The stereoselectivity of the cycloaddition reaction is moderate and depends upon the steric requirements of the R group (Scheme 20). Straight chain alkyl groups give a 3:1 mixture while cyclohexyl provides an 11:1 mixture. Increasing the size of R to a *t*-Bu or a large silyloxy (TBDPS) group (TBDPS = *t*-butyldiphenylsilyl) provides aziridine **126a** as a single diastereomer in good yield. These aziridines are in general too reactive to purify but can be isolated and spectroscopically characterized. A key question in these reactions is whether or not a nitrene is being generated or if the reaction proceeds via an

initial dipolar cycloaddition followed by loss of N₂ to generate the aziridine. Trapping studies with both dimethyl sulfoxide (DMSO) and toluene showed that the nitrene is indeed generated. Aziridines such as **126** have also been generated photolytically although the yields are considerably lower <1999T9669>.

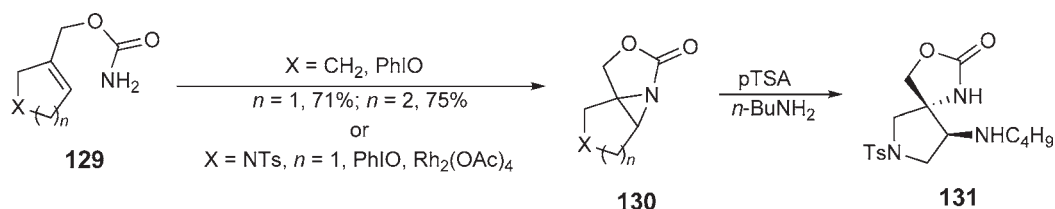


Scheme 20

It was anticipated that the nitrene that formed would add to either a *trans* **127a** or *cis* **127b** olefin stereospecifically, with **127a** producing only aziridine **128a** and **127b** producing only aziridine **128b** (Equation 29). The fact that a mixture of aziridines from both olefin geometries suggests that a reasonable amount of the triplet nitrene is produced in the thermolysis reaction. The triplet nitrene adds to the olefin in a stepwise fashion allowing for a loss of the olefin geometry. It is significant that these aziridines with substitution on the *exo*-carbon of the aziridine are stable to chromatography unlike the unsubstituted aziridines **126**.

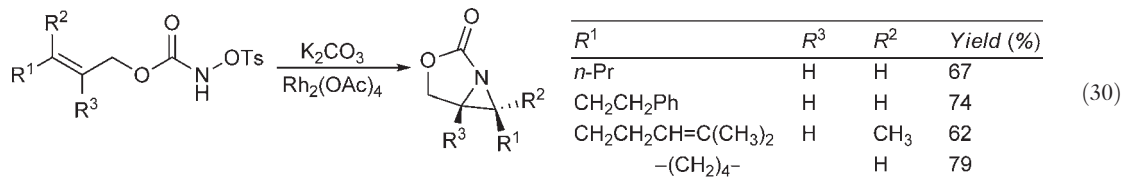


A PhIO-catalyzed route to generate similar aziridines has also been reported <2004JOC6377>. Treatment of carbamate **129** with PhIO yields aziridines **130** in similar yields to those reported from the azidoformates. The reaction was initially examined using Rh₂(OAc)₄ as a catalyst but it was found that the yield of the aziridine product was not dependent upon added rhodium catalyst. However, when X = NTs, the rhodium catalyst was required for aziridine formation. The aziridine resulting from the reaction of carbamate **129** (X = NTs) was unstable but the product of aziridine ring opening with butylamine, **131**, could be isolated in good yield (Scheme 21). A related example of a urea substrate has been converted to the corresponding aziridine <2006OL1073>. A limitation of this methodology is that only aziridines stable enough to be chromatographed can be prepared with this technique.



Scheme 21

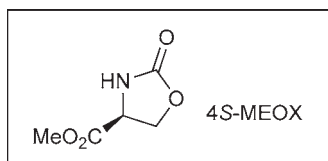
An even more recent approach uses *N*-tosyloxycarbamates as the nitrene precursor species [<2005JA14198>](#). It is interesting to note that this method is very stereospecific with complete retention of the alkene being observed in the product aziridine. The yields are comparable to both the thermal method as well as the PhIO route. Attempts to aziridinate *N*-tosyloxycarbamates derived from homoallylic alcohols gave no aziridine products ([Equation 30](#)).



Both copper and rhodium catalysis have been used to prepare sulfonamide-linked aziridines [<2000OL2327, 2002OL4507, 2004JOC6377>](#). There are some key differences regarding the sulfonamide-linked aziridines relative to the carbamate-linked aziridines previously discussed. A significant difference between the carbamate-linked aziridines and the sulfonamide-linked aziridines appears to be the stability of the aziridine. Sulfonamide aziridines seem to be quite stable to purification and storage unlike similarly substituted carbamate-linked aziridines. The aziridination reactions of sulfonamides have been catalyzed using copper and rhodium catalysts. The rhodium catalysts provide much higher yields of the desired aziridines relative to the copper. An advantage of the copper is of course the cost of the catalyst. The sulfonamide-linked aziridines can be prepared with both five- and six-membered fused ring ([Table 3](#)). This is unlike the carbamate-linked aziridines in which only the five-membered

Table 3 Yields for sulfonamide-linked aziridines

Entry	Substrate	Product	Catalyst	Yield (%)	% ee	Reference
1			PhI(OAc) ₂ , CuOTf	0		2000OL2327
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	80		2004JOC6377
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	82		2002OL4507
			<i>t</i> -BuOCl, PTAB	70		2001TL1037
			PhIO, Rh ₂ (4S-MEOX) ₄	59	76	2003TL5917
2			PhI(OAc) ₂ , CuOTf	60		2000OL2327
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	91		2004JOC6377
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	98		2002OL4507
			<i>t</i> -BuOCl, PTAB	46		2001TL1037
			PhIO, Rh ₂ (4S-MEOX) ₄	50	57	2003TL5917
3			PhI(OAc) ₂ , CuOTf	38		2000OL2327
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	85		2004JOC6377
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	97		2002OL4507
			<i>t</i> -BuOCl, PTAB	70		2001TL1037
4			PhI(OAc) ₂ , CuOTf	61		2000OL2327
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	91		2004JOC6377
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	93		2002OL4507
			<i>t</i> -BuOCl, PTAB	35		2001TL1037
5			PhI(OAc) ₂ , CuOTf	51		2000OL2327
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	70		2004JOC6377
			PhI(OAc) ₂ , Rh ₂ (OAc) ₄	81		2002OL4507
6			<i>t</i> -BuOCl, PTAB	20		2001TL1037

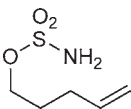
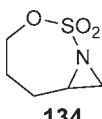


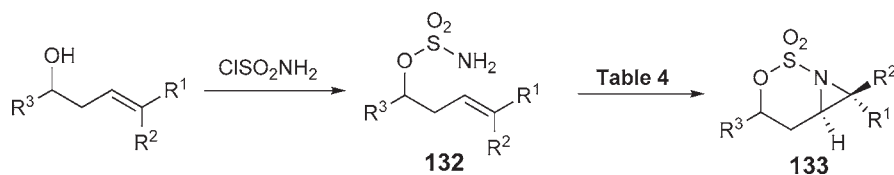
fused ring can be prepared. The copper method is unable to prepare benzofused aziridine (entry 1) while the rhodium-catalyzed method provides this aziridine in excellent yield. Both the copper and rhodium methods can be used to prepare the five-membered ring-fused aziridine (entry 3), although the rhodium method does provide an improved yield (85/97% vs. 38%). Attempts to prepare larger fused-ring aziridines using either copper or rhodium catalysis were unsuccessful with only the C–H insertion product being obtained (entry 5). A chiral catalyst has also been used to carry out some of these aziridinations <2003TL5917>. While the overall yield of the product aziridine is moderate, the % ee of the product is at best 76%.

A bromine-initiated method for the preparation of sulfonate-linked aziridines has been developed <2001TL1037>. Treatment of the sulfonamide with *t*-butylhypochlorite generates the intermediate *N*-chloramine salt. Reaction of the chloramine with phenyltrimethylammonium bromide (PTAB) provides the sulfonamide-linked aziridine. This method does not provide any improvement in yield relative to either the copper- or rhodium-catalyzed reaction systems. It does however work for the preparation of the bicyclo[5.1.0] system as both the copper- and rhodium-catalyzed reactions give C–H insertion products in this attempt to prepare the larger ring system (entry 6).

Intramolecular aziridinations of sulfamates have also been described <2002OL2481, 2003OL4823>. There are of course differences in both preparation and reactivity of the aziridines relative to the carbamate- and sulfonamide-linked aziridines. The sulfamate-linked aziridines, like the sulfonamide-linked aziridines, seem to be stable to storage and purification. Only the six-membered fused-ring sulfamate aziridines and one seven-membered fused-ring aziridine have been prepared. Attempts to prepare smaller fused-ring sizes were unsuccessful. This is attributed to the longer O–S and N–S bond lengths which would make the five-membered fused-ring aziridines too unstable. Two different catalyst systems (Cu and Rh) have been evaluated for the synthesis of these sulfamate-linked aziridines. Unlike the sulfonamide-linked aziridines, both catalytic systems perform equally well in terms of yield. The yields of **133a–d** prepared via Cu catalysis range from 69% to 94%, while the yields of **133e–f** prepared by Rh catalysis range from 84% to 88% (Table 4 and Scheme 22). The two catalytic systems do seem to differ in terms of diastereoselectivity of the cyclization reaction. Compound **133d** prepared by the copper method provides a 1:1 mixture of diastereomers (relative to R³). Compound **133e** prepared by the rhodium method yields a 4:1 mixture of diastereomers. These diastereomeric ratios are comparable to those seen in the carbamate linked aziridines such as **126**.

Table 4 Yields of sulfamate-linked aziridines

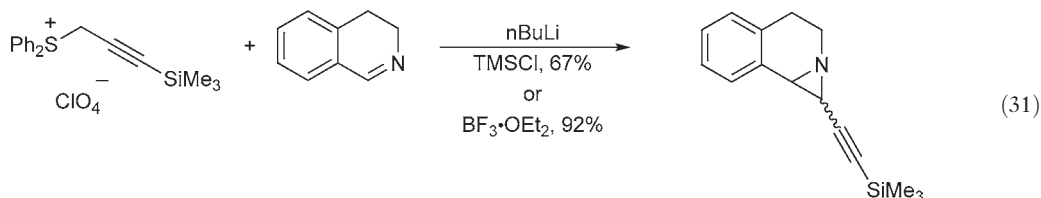
<i>Compd. #</i>	<i>Substitution</i>	<i>Conditions</i>	<i>Yield (%)</i>	<i>Selectivity</i>	<i>Reference</i>
133a	R ¹ = H, R ² = H, R ³ = H	PhIO, 3Å mol sieves	69	NA	2002OL2481
133b	R ¹ = H, R ² = Et, R ³ = H	10 mol% Cu(CH ₃ CN) ₄ PF ₆	80	NA	
133c	R ¹ = Et, R ² = H, R ³ = H		94	NA	
133d	R ¹ = H, R ² = H, R ³ = Me		72	1:1	2003OL4823
133e	R ¹ = H, R ² = H, R ³ = Me	PhI(OAc) ₂ , MgO	84	4:1	
133f	R ¹ = CH ₂ CH ₂ Ph, R ² = H, R ³ = Me	2 mol% Rh ₂ (oct) ₄	88	2.5:1	
133g	R ¹ = H, R ² = C ₈ H ₁₇ , R ³ = Me		84	10:1	
			50		2002OL2481



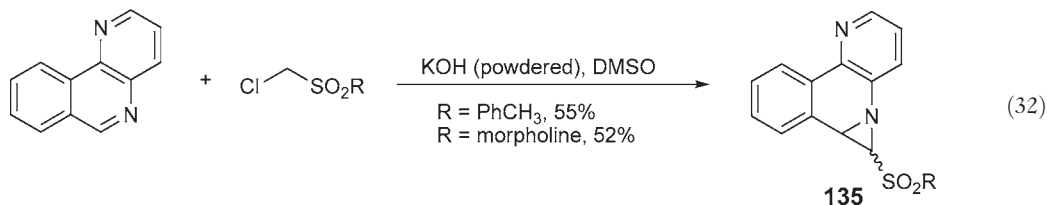
Scheme 22

The formation of bonds 'c' and 'b' can take a couple of forms, either a Darzens-type approach (i.e., addition of a nucleophile bearing a leaving group) or addition of a carbene. Both of these routes have been used in the synthesis of fused-ring aziridines as well as monocyclic aziridines. The addition of a carbene or nucleophile such as an ylide to an imine can provide a nice route to fused-ring aziridines. The necessary cyclic imines are sometimes more readily obtained and used than the acyclic imines. These methods have largely been used on pyridine and quinoline derivatives.

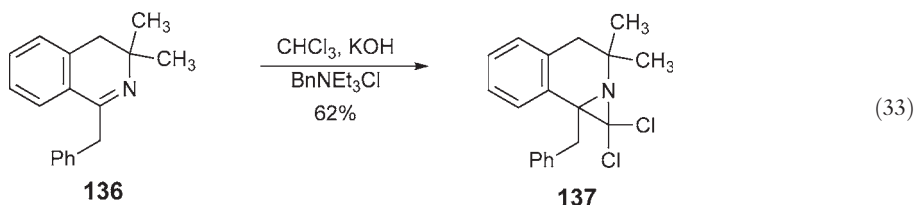
The use of sulfur ylides for the synthesis of aziridines provides a relatively general route to fused-ring aziridines [<1997CC1231>](#). After deprotonation of the propargyl sulfonium salt, it is added to dihydroquinoline which has been pre-activated with either TMS-Cl or $\text{BF}_3 \cdot \text{OEt}_2$. This method gives a roughly 1:1 mixture of aziridine diastereomers regardless of the Lewis acid activating agent used (Equation 31).



A related approach uses a Darzens-type reaction to prepare aziridines [<2001M849, 2002M1071>](#). Chloromethyl sulfones and sulfonamides were deprotonated with powdered KOH in DMSO. Addition of this carbanion to the more electrophilic C=N bond followed by aziridine ring formation provides aziridine **135** (Equation 32). No information was provided on the relative stereochemistry of the aziridine.



Carbenes have also been used for the synthesis of monocyclic aziridines. The use of carbenes to prepare fused-ring aziridines has been much more limited. The reaction of dihydroquinoline **136** with dichlorocarbene provides a reasonable yield of the fused-ring aziridine **137** [<1997S677, 2003OBC4040>](#) (Equation 33).

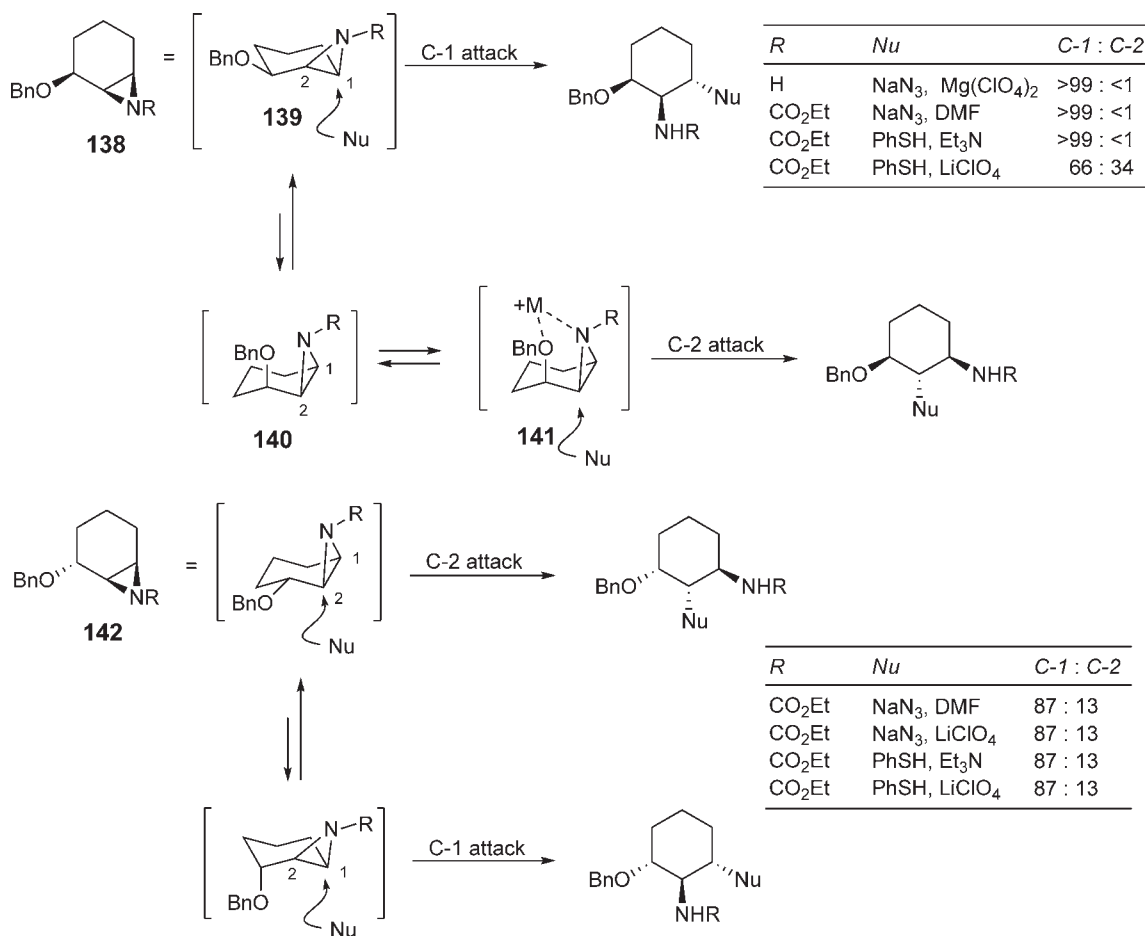


1.02.4 Reactions of Aziridines

1.02.4.1 Reactions of Type I Aziridines

The reactions of fused-ring aziridines are largely limited to ring-opening reactions. An excellent review of nucleophilic ring-opening reactions has appeared [<2004T2701>](#) that contains both fused cyclic systems and acyclic

compounds. There are a number of accounts of nonfused ring-opening reaction that are covered in other sections. A key problem with these ring-opening reactions is the control of both regiochemistry and stereochemistry. The regiocontrol of a variety of nucleophiles adding to a nonsymmetric fused-ring aziridine has been studied [<1997T1417>](#). Some insight into factors that control the regiochemistry of aziridine ring-opening have been provided by the reactions of aziridines **138** and **142** (Scheme 23). The hypothesis was that aziridine **138** should undergo ring opening at C-2 due to the formation of chelated structure **141**, with the exception of PhSH/LiClO₄ which did provide some of the product of C-2 attack. Interestingly, aziridine **142** which could not form a chelate gave a mixture of both C-1 and C-2 products.

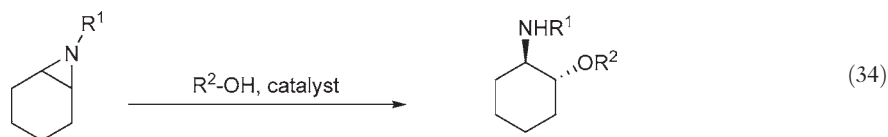
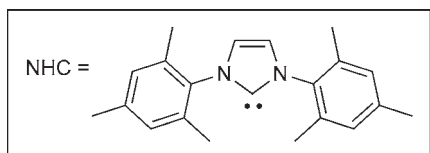


Scheme 23

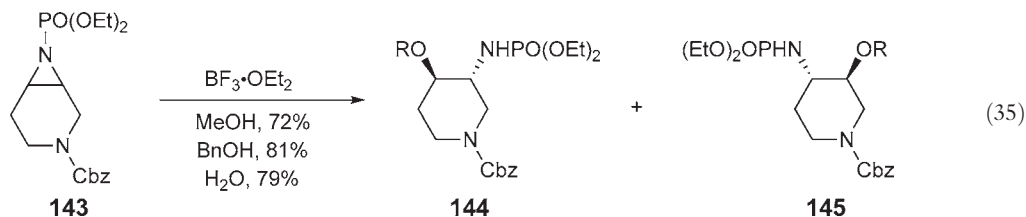
The ring-opening reactions of aziridines with oxygen nucleophiles provide a general route to 1,2-aminoalcohols. A number of different acid catalysts and oxygen nucleophiles including alcohols, water, and carboxylic acids can be used to open these aziridines [<2002T7355, 2000TL4677, 2002TL5105, 2002TL2099, 2003TL4411, 2002JOC5295>](#). A very interesting example is the conversion of cyclohexenimine into the product of acetate opening by reaction with an aldehyde catalyzed by an *N*-heterocyclic carbene (NHC) [<2006OL1521>](#). This unique reaction proceeds by reaction of the aldehyde with the NHC to generate an intermediate alkoxide which then opens the aziridine ring. A further oxidation provides the acetate product (Table 5 and Equation 34).

Table 5 Aziridine ring openings with oxygen nucleophiles

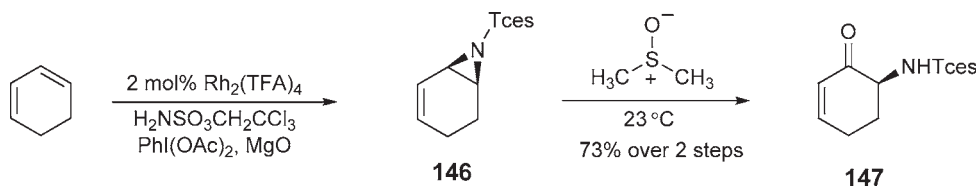
Conditions	R^1	R^2	Yield (%)	Reference
CAN, MeOH	Ts	Me	93	2002T7355
Sn(OTf) ₂ , MeOH	Ts	Me	99	2000TL4677
Sn(OTf) ₂ , MeOH	Ph	Me	76	
BF ₃ ·OEt ₂ , MeOH	Ts	Me	99	
BF ₃ ·OEt ₂ , MeOH	Ph	Me	92	
montmorillonite KSF clay, HCCCH ₂ OH	Ts	CH ₂ CCH	90	2002TL5105
Sn(OTf) ₂ , H ₂ O	Ts	H	89	2000TL4677
Bu ₃ P, AcOH	Ts	CH ₃ CO	85	2003TL4411
In(OTf) ₃ , AcOH	Ts	CH ₃ CO	89	2002TL2099
Bu ₃ P, AcOH	Bz	CH ₃ CO	72	2003TL4411
Bu ₃ P, AcOH	BOC	CH ₃ CO	81	
CH ₃ CHO, NHC, air	Ts	CH ₃ CO	75	2006OL1521



Piperidine aziridine **143** was reacted with a number of simple alcohols to provide a mixture of two possible ring-opened products **144** and **145** (Equation 35) <2002TL5315>. It was found that in all cases, nucleophilic substitution with alcohols gave only ring opening at C-4 giving **144** in a ratio greater than 20:1. Addition at C-3 is blocked by the BF₃ complex of the phosphoramidate.



Du Bois has found that trichloroethoxysulfonyl aziridines were able to undergo facile displacement of the aziridine ring with various nucleophiles <2006T11331>. Aziridination of cyclohexadiene with trichloroethylsulfamate under oxidative conditions provided the relatively unstable vinylaziridine **146**. Stirring the crude vinylaziridine product with DMSO provided the aminoenone **147** (Scheme 24). The nucleophilic nature of the oxygen atom of DMSO provided the driving force to open the aziridine ring generating an intermediate oxosulfonium salt. The salt then underwent elimination of dimethyl sulfide to provide the product ketone **147**. A significant aspect of this reaction is the lack of S_N2' addition. This seems to be a common trait of fused-ring aziridines in that they undergo S_N2 addition in preference to S_N2' addition.

**Scheme 24**

The addition of sulfur nucleophiles can be accomplished with several different catalysts and conditions. The ability to open cyclohexenimine with benzenethiol was investigated as a function of the N-substituent. The first example uses ZnCl_2 in an organic solvent such as CH_2Cl_2 as the catalytic system most useful for opening the aziridine ring <2001J(P1)1314>. Thio-ring-opening of the bicyclic aziridine can be catalyzed with PBU_3 in aqueous solvents <2003JOC726>. The authors screened a number of phosphines, finding that PBU_3 provided the most efficient catalyst for ring opening. In this case both activated ($\text{R}^1 = \text{Ts}$) and unactivated aziridines ($\text{R}^1 = \text{Bn}$) can be used. Ultimately, this catalytic system could provide a truly ‘green reaction’ utilizing the catalytic system in aqueous solvents. Cyclodextrins have also been found to be excellent catalysts for the ring opening of activated aziridines with sulfur nucleophiles (Equation 36 and Table 6) <2005TL6437, 2005SL489>.

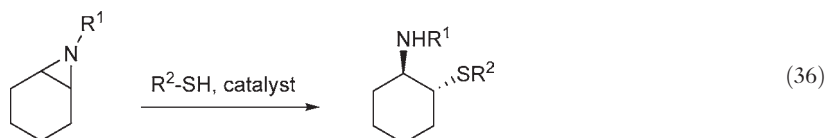
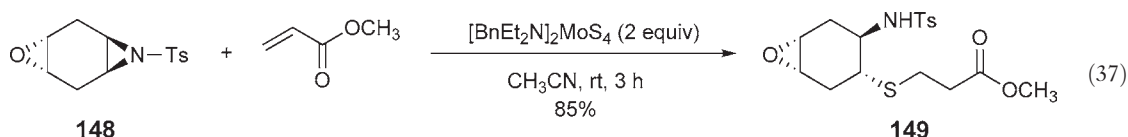


Table 6 Aziridine ring openings with sulfur nucleophiles

$\text{R}^2\text{-SH}$	Catalyst	R^1	Yield (%)	Reference
PhSH	ZnCl_2	Bz	72	2001J(P1)1314
PhSH	ZnCl_2	BOC	81	
PhSH	ZnCl_2	Ts	67	
PhSH	PBU_3	Ts	98	2003JOC726
4-MeC ₆ H ₄ CH ₂ SH	PBU_3	Ts	92	
PhSH	PBU_3	Bn	62	
<i>t</i> -BuSH	PBU_3	Ts	88	2005TL6437 2005SL489
PhSH	β -Cyclodextrin	Ts	90	
KSCN	β -Cyclodextrin	Ts	78	

Benzyltriethylammonium tetrathiomolybdate is an excellent reagent for opening aziridine rings <2005JA12760>. The assumed mechanism involves a disulfide dimer that reacts with a second equivalent of the thiomolybdate anion to leave a pendant thio-anion to further react within the molecule. Additional reactions with other functional groups are possible, either in an intra- or intermolecular sense. Epoxy aziridine **148** and methyl acrylate are reacted with 2 equiv of benzyltriethylammonium tetrathiomolybdate in acetonitrile to prepare the thio-substituted aminoepoxide **149** (Equation 37). The product is formed by a sequence of reactions involving aziridine opening, disulfide formation, disulfide reduction, and finally Michael addition. Other examples provide thioepoxide formation, tetrahydrothiophenes, intramolecular Michael additions, or intramolecular epoxide opening.



Aziridines can be readily opened with halogens. There is little difference in the opening of a fused-ring aziridine with a halogen and the opening of a monocyclic aziridine with a halogen. In some respect, this reaction is the reverse reaction of the aziridine ring formation. A number of different catalysts and halogens have been examined for this ring opening (Equation 38 and Table 7) <2001TL3955, 2001SL1417, 2000JOC1344, 2002TL5315>.

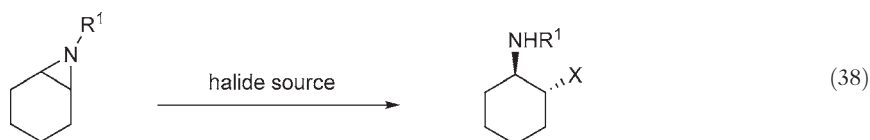
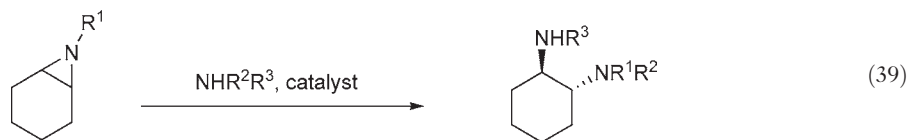


Table 7 Ring-opening reactions of aziridines with halogen

R^1	Conditions	X	Yield (%)	Reference
Ts	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	Cl	92	2001TL3955
Ts	InCl_3	Cl	78	2001SL1417
Ts	TMSCl , $n\text{Bu}_4\text{NF}$	Cl	97	2000JOC1344
Ts	InBr_3	Br	83	2001SL1417
$\text{PO}(\text{OEt})_2$	$\text{BF}_3 \cdot \text{OEt}_2$	F	66	2002TL5315
Ts	NaI , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	I	96	2001TL3955
Ts	InI_3	I	87	2001SL1417

The opening of aziridines with amines provides a facile route to 1,2-diamines. This type of compound is of interest for use as a ligand, or pharmaceuticals. While the nucleophilic nature of an amine might suggest that these would be excellent reagents in opening aziridines, they are quite often not nucleophilic enough. The use of Lewis acid, Lewis base, or protic acid catalysis is typically necessary for efficient ring-opening reactions <2003CL82, 2001CL246, 2002JOC5295, 2002S1061, 2001SC3295, 2003SC547, 2003JOC5160, 2002TL3975, 2002S2211, 1999JOC2537, 2005TL7935>. One of the most difficult types of aziridine to open is the nonactivated aziridine where $R^1 = \text{aryl}$ or alkyl (Equation 39). Two examples (Table 8) provide good methods for the ring-opening of nonactivated aziridines with amines. The reaction of *N*-alkyl aziridines with primary amines can be catalyzed by $\text{B}(\text{C}_6\text{F}_5)_3$ to provide the ring-opened products in excellent yield <2003JOC5160>. The use of silica gel as a catalyst under solvent-free conditions has also been found to be an excellent method for the ring opening of *N*-aryl and *N*-alkyl aziridines with amines <2002TL3975>. In this method the aziridine and the amine are simply mixed with activated silica gel and shaken until the reaction is complete. This method does seem to be limited to anilines as the amine nucleophile. The use of chiral amines to generate chiral diamines has been examined <2005TL7935>. The reaction of cyclohexeneimine with (*R*)- α -methyl benzylamine provided the ring-opening product in excellent yield but as a 1:1 mixture of diastereomers.

**Table 8** Aziridine ring openings with amine nucleophiles

R^1	R^2	R^3	Catalyst	Yield (%)	Reference
Ts	H	Bn	CAN	93	2003CL82
Ts	H	CH_3	CAN	NR	
Ts	H	Ph	β -Cyclodextrin	89	2001CL246
Ts	H	<i>p</i> -MeOC ₆ H ₄	β -Cyclodextrin	92	
Ts	H	Bn	PBu ₃	85	2002JOC5295
BOC	H	Ph	PBu ₃	70	
Ts	H	Ph	InBr_3	90	2002S1061
Bn	H	Ph	LiClO_4	90	2001SC3295
Ts	H	Ph	BiCl_3	96	2003SC547
Ph	H	Ph	BiCl_3	95	
Bn	H	Bn	$\text{B}(\text{C}_6\text{F}_5)_3$	98	2003JOC5160
$(\text{CH}_2)_3\text{OH}$	H	Bn	$\text{B}(\text{C}_6\text{F}_5)_3$	97	
Ph	H	Ph	Silica gel	91	2002TL3975
Bn	H	Bn	LiNTf_2	83	2002S2211
Ts	Et	Et	LiNTf_2	60	
Ph	Me	Ph	$\text{Sn}(\text{OTf})_2$	82	1999JOC2537
Ph	Me	Ph	$\text{Cu}(\text{OTf})_2$	61	
Ts	H	(<i>R</i>)-MeCHC ₆ H ₄	LiClO_4	94	2005TL7935

Azides are excellent nucleophiles for aziridine ring-opening reactions. Azides can later be converted to amines; thus, they can be thought of as a universal amine nucleophile. Typically, some type of acid catalyst is required <2002TL7361, 2000TL10079>. The necessary acid catalyst can be as simple as the use of TMSN_3 or more complex catalysts such as cyclodextrins. A rather unusual catalyst is an NHC which provides the ring-opened product in 99% yield <2006TL4813>. The use of chiral catalysis or a chiral group on the nitrogen of the aziridine to prepare an enantiopure diamine has been examined as well. Cyclohexeneimine with a chiral (*R*)-phenylethylamine on the nitrogen was subjected to ring opening with TMSN_3 to provide the ring-opened product as a 4:1 mixture of the (*R,S,R*)-:(*S,R,R*)-diastereomers <2000TL10079>. A chiral catalyst prepared from chromium(III) chloride and a chiral ligand (L^*) catalyzed the ring opening of cyclohexeneimine where the rather unusual 2,4-dinitrobenzyl group was on the nitrogen of the aziridine <1999OL1611>. These conditions provided the ring-opened product in 95% yield with an ee of 94%. Another asymmetric catalytic method uses yttrium complexed with the chiral ligand ($L2^*$) to provide the ring-opened product in 92% ee <2006JA6312>. Again the rather unique 3,5-dinitrobenzoyl group is required on the aziridine nitrogen in order to provide high levels of enantioselectivity (Equation 40 and Table 9).

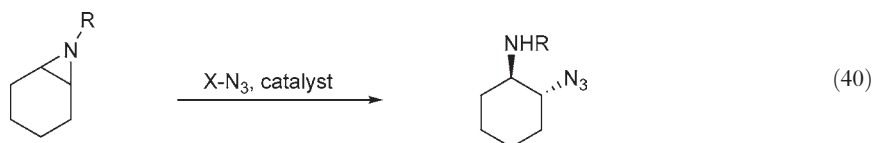
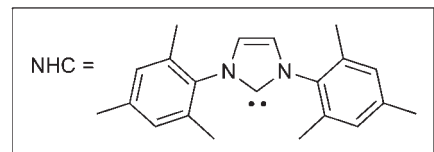
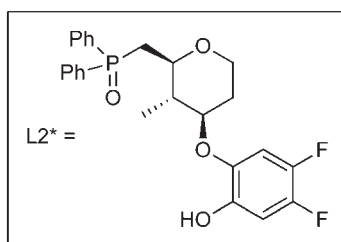
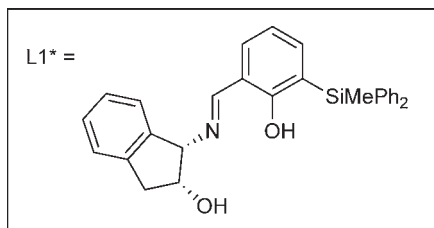
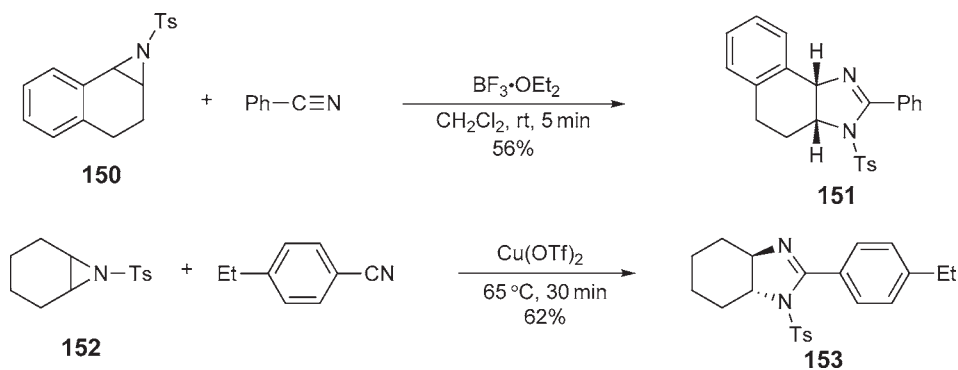


Table 9 Azide openings of aziridines

<i>R</i>	Conditions	Yield (%)	Reference
Ts	NaN_3 , CAN	95	2002TL7361
Bn	TMSN_3	99	2000TL10079
(<i>R</i>)-phenylethylamine	TMSN_3	90 (4:1 dr)	
Ts	TMSN_3 , $n\text{Bu}_4\text{NF}$	99	2000JOC1344
Ts	NaN_3 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	97	2002OL343
Ts	NaN_3 , LiClO_4	85	2002S2383
Ts	NaN_3 , Oxone	98	2002S2254
Ts	TMSN_3 , β -Cyclodextrin		2001CL246
Ts	TMSN_3 , NHC	99	2006TL4813
$\text{CH}_2(2,4-(\text{NO}_2)_2\text{C}_6\text{H}_3)$	TMSN_3 , CrCl_3 , $L1^*$	95 (94% ee)	1999OL1611
$\text{C}(\text{O})\text{-}3,5\text{-(NO}_2)_2\text{C}_6\text{H}_3$	TMSN_3 , $\text{Y}(\text{O}i\text{Pr})_3$, $L2^*$	97 (92% ee)	2006JA6312



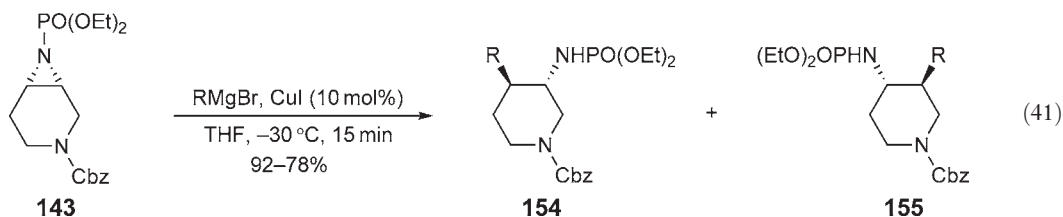
Nitriles can act as nitrogen nucleophiles in aziridine ring-opening reactions. Two examples are shown in Scheme 25 in which a formal [3+2] cycloadduct is the final product. Tosylaziridine **147** was reacted with benzonitrile and $\text{BF}_3 \cdot \text{OEt}_2$ catalysis to produce the *cis*-fused imidazoline **148** <2004TL1137>. The utility of the reaction is limited in the case of cyclic aziridines to benzofused aziridines and either aryl or benzyl nitriles. It was also found that the reaction required stoichiometric BF_3 . Lesser amounts of Lewis acid reduced the chemical yield drastically.



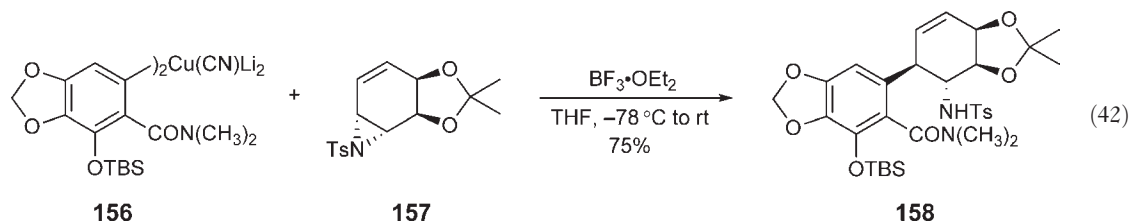
Scheme 25

Copper triflate has been found to promote the [3+2] cycloaddition of *N*-tosylaziridines with nitriles <2006TL5399>. Ghorai has found that aziridine **149** and a substituted benzonitrile were dissolved and added to a suspension of copper triflate, resulting in the formation of good yield of the imidazoline **150**. The mechanism proposed involves the addition of the nitrogen atom of the nitrile to the presumed copper aziridinium ion formed with the triflate catalyst. Subsequently, the *N*-Ts moiety attacks the electrophilic carbon of the nitrilium ion to form the imidazoline.

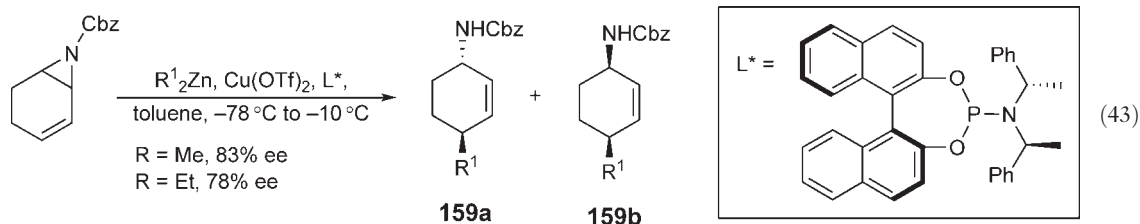
The reaction of fused-ring aziridines with organometallics such as organocuprates or organozinc reagents is a common approach to the synthesis of cyclic amines. Selectivity in unsymmetrical aziridines is still a problematic issue. Piperidine aziridine **143** can also be opened regioselectively with organocuprate reagents <2002TL4289>. In general, it was found that nucleophiles add at C-4, with typical ratios of **154**:**155** = 13:1 (Equation 41). Hindered nucleophiles, olefinic and aryl organocuprates as well as other types of organometallic reagents (Grignard, organozinc) do not react to an appreciable amount with aziridine **143**.



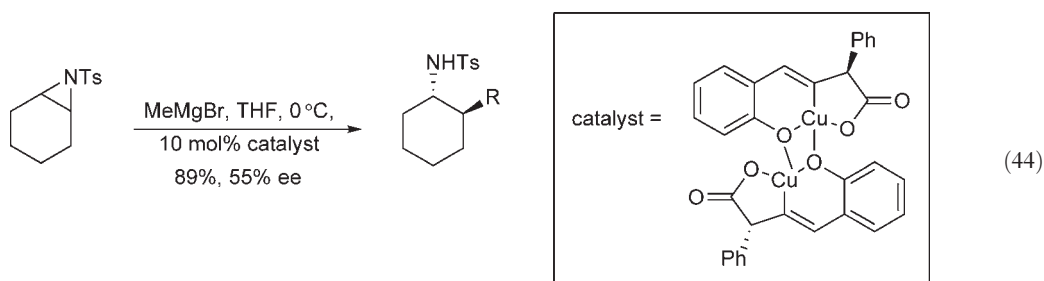
Additions of nucleophiles to vinyl aziridines provide the issue of selectivity of 1,2 (S_N2) or 1,4 (S_N2') additions. During a very short efficient synthesis of pancratistatin, Hudlicky *et al.* chose to open a vinylaziridine **156** with an aromatic cuprate **157** <1996JA10752>. Formation of the *trans*-1,2 adduct **158** was accomplished in 75% chemical yield (Equation 42). They found that the addition of simple lower order cuprates or Grignard reagents (aliphatic or aromatic) reacted to give the *syn*-1,4 addition, whereas higher-order cuprates gave the *trans*-1,2 product.



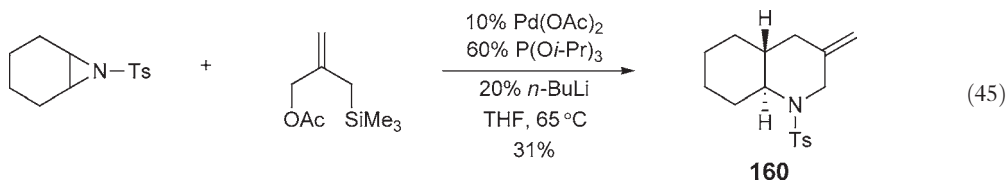
The reaction of simple cyclic vinyl aziridines with organozinc reagents typically provides the 1,4-addition product <2003TL8559>. Several binaphthyl phosphoramidate ligands were examined. In all cases, the *trans*-product **159a** was the major product. When no catalyst was used a roughly 1:1 mixture of the *trans*:*cis* product was obtained. The use of the chiral phosphoramidate catalyst provided **159a** with moderate % ee values (Equation 43).



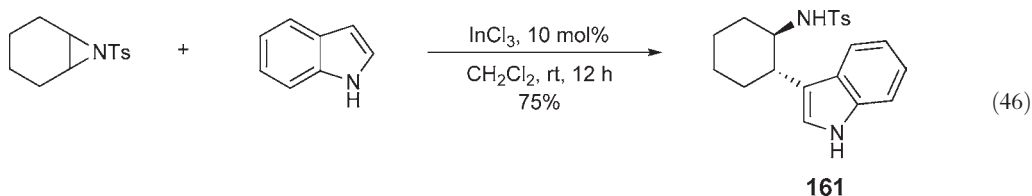
Muller examined the desymmetrization of the meso-*N*-sulfonylaziridines with a number of Grignard reagents <2001HCA662, 1999OL439>. The results shown for MeMgBr are typical with % ee's of 20–89% depending on the quantity of catalyst and the identity of the Grignard reagent. High asymmetric induction required a larger amount of the chiral ligand or more sterically encumbered nucleophiles (Equation 44).



Palladium trimethylenemethanes (TMMs) generated from acetoxy-substituted allyltrimethylsilane have been used in concert with fused aziridines to generate a formal [3+3] cycloadduct with a cyclohexene-derived aziridine <2003JOC4286>. The use of strongly electron-withdrawing groups bound to nitrogen was required for the reaction to proceed at a reasonable rate and provide acceptable chemical yields. The use of the tosyl group provided a reasonable EWG for nitrogen in this case. Alternative catalysts were found to be ineffective. When the starting aziridine was either a cyclopentylaziridine or the cycloheptylaziridine, the reaction provided little to none of the bicyclic product. As is typical of TMM cyclizations, the reaction is believed to proceed through an initial opening of the aziridine ring by the allylsilane followed by a ring closure of the sulfonamide anion on to the π -allylpalladium species. The reaction while providing the product in only 31% yield gave a single diastereomer, **160** (Equation 45).



Ring-opening reactions of aziridines with π -nucleophiles are generally limited to highly active π -nucleophiles such as indoles, pyrroles, or furans. Yadav *et al.* found that indium trichloride catalyzed the reaction of heteroaromatics such as indole with *N*-tosylaziridine to give the aziridine ring-opened product **161** in excellent yield (Equation 46) <2002TL1565>. Regioselectivity in unsymmetrical aziridines appeared to be more problematic.



Despite the fact that the *N*-tosyl group tends to activate the aziridine to ring opening, Yadav found that NaCN would not open the *N*-tosylaziridines without additional activation with LiClO₄ <2002S2383>. Cyanide could also be delivered via TMS-CN catalyzed by tetrabutylammonium fluoride <2000JOC1344>. Aziridines derived from

cyclopentene and cyclohexene provide good yields of product, while larger rings were unreactive. Changing from electron-withdrawing to electron-donating groups on nitrogen also shuts down the reaction providing 0% yield after 24 h. A gadolinium catalyst was used with a chiral ligand (L^*) to desymmetrize a meso-aziridine (Equation 47 and Table 10) <2005JA11252>. The more typical *N*-tosyl aziridine gave the ring-opened product with only a 24% ee. Replacement of the tosyl group with a *p*-nitrobenzoyl group on the nitrogen gave the ring-opening product in 94% yield with an 87% ee. The use of KCN with TMEDA as a catalyst presents a departure from the more typical acid catalysts in these types of ring openings <2005OL3509>.

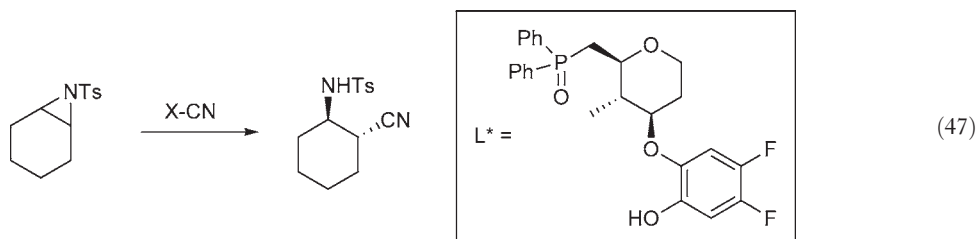
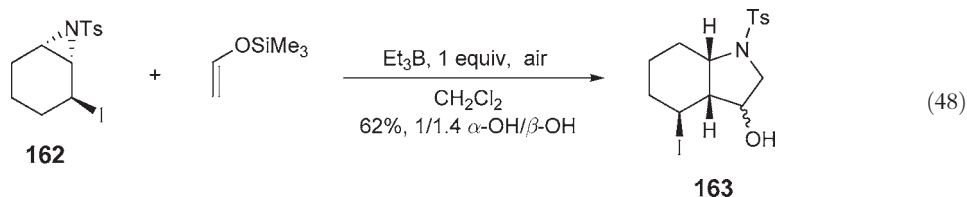


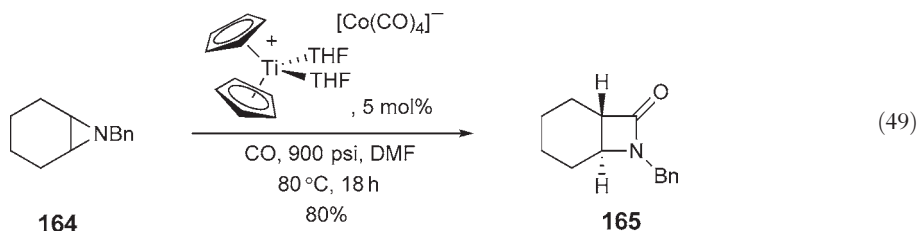
Table 10 Aziridine opening with cyanide

Conditions	Yield (%)	Reference
NaCN, LiClO ₄ , CH ₃ CN, reflux	85	2005S2383
TMSCN, <i>n</i> -Bu ₄ NF, THF, 40 °C	95	2000JOC1344
Gd(O <i>i</i> -Pr) ₄ , TMSCN, L^*	58 (24% ee)	2005JA11252
TMEDA, KCN	57	2005OL3509

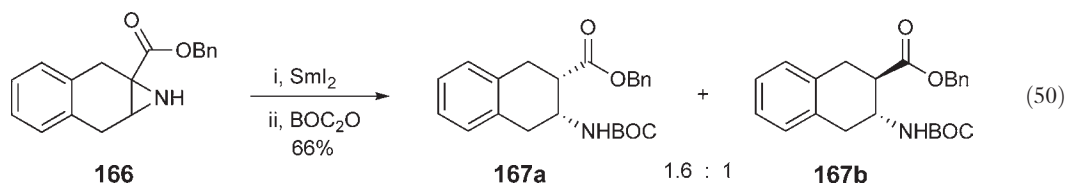
Azabicyclononane **163** is prepared through a novel [3+2] radical cycloaddition process <2003JOC3184>. Iodoaziridine **162** is prepared via the iodoaziridination reaction developed by Taguchi and co-workers <1998JOC4842>. Treatment of iodoaziridine **162** with Et₃B led to homolytic aziridine opening to generate an intermediate radical, which then added to the vinyl ether. Subsequent ring closure provided **163** in very good chemical yield albeit with poor diastereoselectivity (Equation 48).



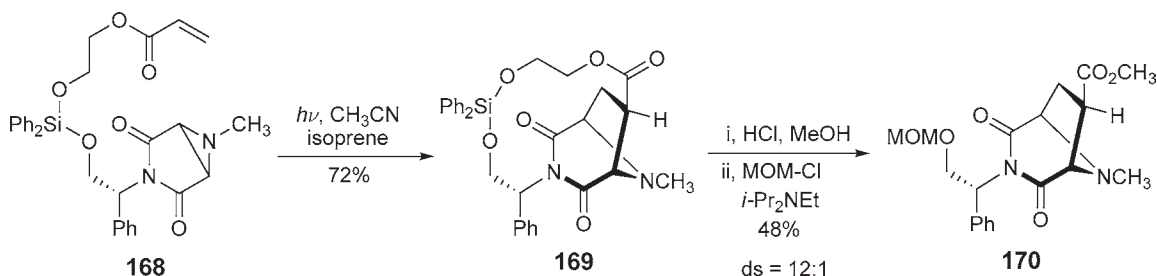
Carbonylation of aziridines is a novel method for preparing azetidine analogs from their aziridine precursor. Coates and co-workers have examined the carbonylation reaction with two alternate catalysts including the titanium catalyst shown and an aluminium salen complex <2002AGE2781>. The two complexes react very differently with cycloalkylaziridines. Aziridine **164** provides an 80% yield of the azetidinone **165** when treated with CO at 80 °C in dimethylformamide (DMF). In contrast, use of an aluminium salen complex provides less than 5% of the azetidinone **165** (Equation 49). Acyclic aziridines with electron-withdrawing N-protecting groups give a much greater yield of the azetidine product using the aluminium salen catalyst. In the case of unsymmetrical aziridine bonds, the CO prefers to insert into the least hindered C–N bond.



Kawahata and Goodman utilized a chiral aziridine **166** as a simple precursor for the synthesis of β -aminoacids <1999TL2271>. The chiral aziridine is prepared in five steps from the corresponding allylic alcohol via a Sharpless asymmetric epoxidation. A one-electron reduction of aziridine **166** with SmI_2 provided the ring-opened aziridine. Protection of the resulting amine as the BOC-derivative provided a 1.6:1 mixture of the BOC-amino ester diastereomers **167a** and **167b** in 66% yield (Equation 50).

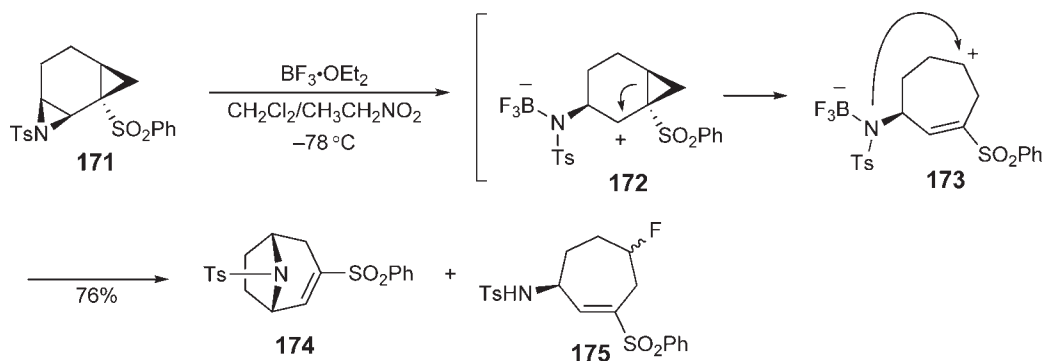


As shown in Scheme 26, Garner *et al.* have prepared a bicyclic aziridine **168** for utilization as an azomethine ylide precursor <1997JOC493>. Using a 'tether-dipole conjugate (TDC)', Garner prepared a silicon-substituted TDC based on the work of Shea and his 'disposable' tether. The requirements of the tether included the formation of the *endo*-formyl group, cycloaddition must proceed via an *endo*-re attack on the prochiral alkene, the tether must be compatible with the photochemical conditions for cycloaddition, and must be easily removable after cycloaddition. Aziridine **168** was irradiated at 300 nm until the reaction was complete by thin-layer chromatography (TLC). The photochemical reaction provided an excellent yield of the 3,8-diazabicyclo[3.2.1]octane core **169** with the tether intact. Cleavage of the silicone tether with acid followed by protection of the resulting alcohol provided the *R,R* core **170**.



Scheme 26

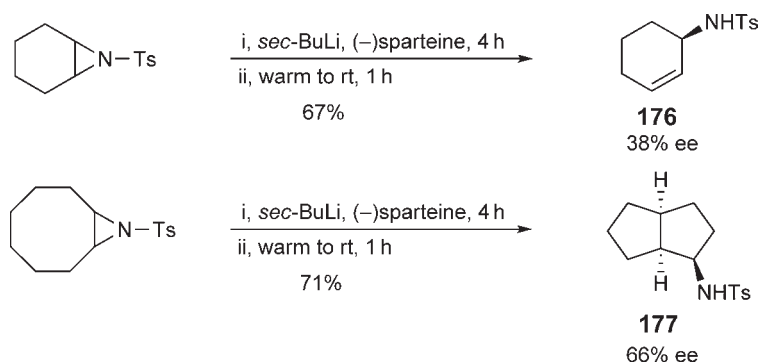
An interesting rearrangement of a type I aziridine that leads to a bicyclo[3.2.1] ring system is outlined in Scheme 27 <2000JOC8454, 1996TL3371>. Aziridine **171** was prepared from the corresponding epoxide via a ring-opening/ring-closing method. Treatment of aziridine **171** with $\text{BF}_3 \cdot \text{OEt}_2$ in a $\text{CH}_2\text{Cl}_2/\text{nitroethane}$ mixture at -78°C provided the tropane alkaloid skeleton **174** in excellent yield. This reaction is believed to go through a cyclopropyl cation **172** intermediate. The lower nucleophilicity of the nitrogen of the tosylamide makes the addition



Scheme 27

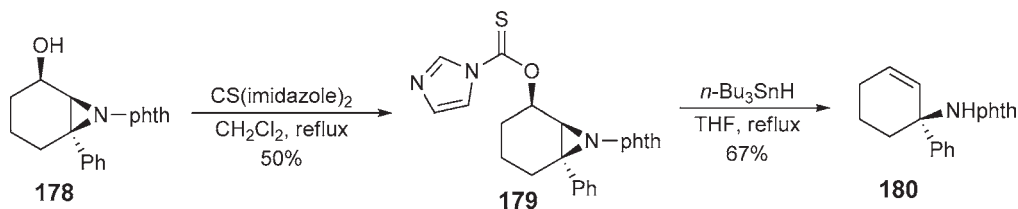
of fluoride from the coordinated BF_3 a viable pathway to produce **175**. The product distribution was found to be highly dependent on the polarity of the solvent. The reaction gave a 40:60 ratio (**174**:**175**) using toluene as a solvent; a 60:40 ratio with dichloromethane; and finally 100:0 when nitromethane was added as a co-solvent to dichloromethane. The attempted cyclization of the anti-diastereomer of **171** did not provide the expected product. Compound **174** was subsequently converted to the natural product ferruginine.

Following the pioneering work of Muller to desymmetrize acyclic *N*-tosylaziridines <2001HCA662>, a number of studies with fused-ring aziridines have been carried out. Caine has looked at similar conditions with azabicyclic-[3.1.0]hexane, azabicyclic[4.1.0]heptane, and azabicyclic[5.1.0]octane systems to determine the sense of asymmetric induction of α -lithioaziridines <2003TL6613>. α -Lithiation of cyclohexenyl *N*-tosylaziridine followed by warming to room temperature gave the allylic amine **176** in good chemical yield but relatively low enantioselectivity. The corresponding cyclooctylaziridine provided the transannular closure to form the amine-substituted bicyclo[3.3.0]octane **177** (Scheme 28). In all cases noted by Caine, the sense of lithiation is the (*S*)-aziridine stereocenter. The presence of the *N*-tosyl group changes the atom discrimination of the lithiosubstrate-(–)-sparteine complex. It is speculated that the change in sense of induction may be due to the complexation of one of the enantiotopic $\text{S}=\text{O}$ groups. This was found to be opposite of the work done by Hodgson with similar epoxide containing substrates <2002AGE4313>.



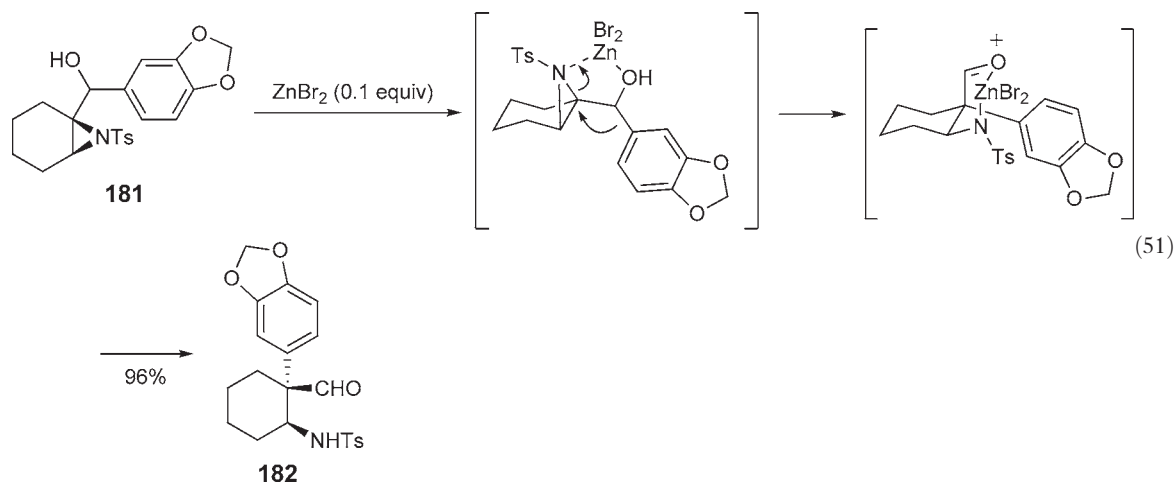
Scheme 28

Aziridinylcarbonyl radicals have been found to undergo cleavage of the aziridine ring <1999TL4873>. In the few examples of β -cleavage of monocyclic aziridinyl radicals, cleavage of the C–C bond is often observed. Calculations carried out on the system shown in Scheme 29 predict that that C–N bond cleavage should be kinetically preferred. Reaction of alcohol **178** with thiocarbonyldiimidazole provided **179**. Treatment of **179** with *n*- Bu_3SnH provided **180**, the product of C–N cleavage.

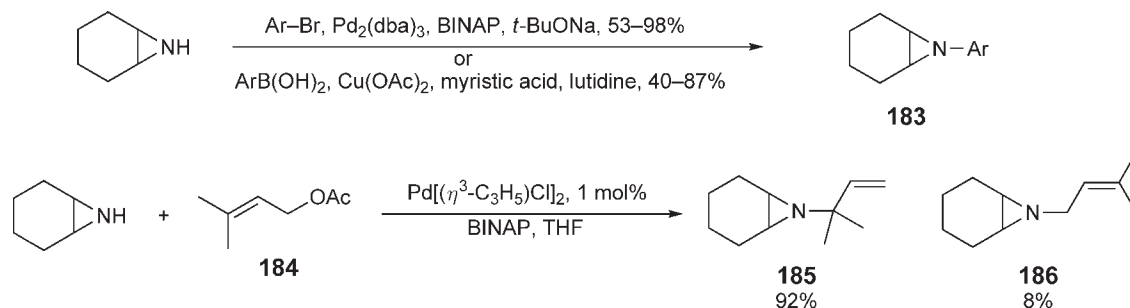


Scheme 29

Reaction of aziridino alcohols with Lewis acids provides β -amino carbonyl compounds in excellent yields <2002OL363, 2003OL2319>. Treatment of aziridine **181** with ZnBr_2 at room temperature initiates a migration of the aromatic ring to provide aldehyde **182** as a single diastereomer in 96% yield (Equation 51).



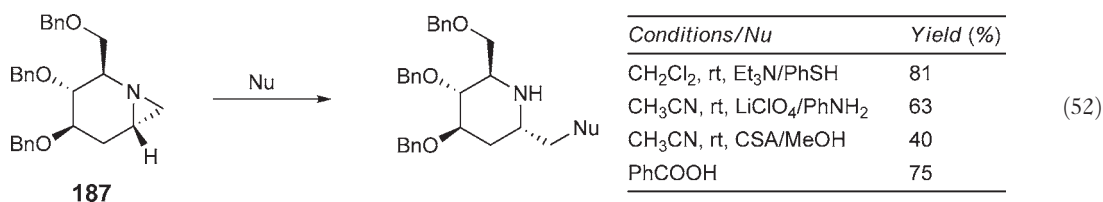
Aziridines that are unsubstituted at nitrogen can of course undergo N-alkylation and N-acylation reactions. Yudin has examined the N-arylation and N-allylation reactions of aziridines as shown in [Scheme 30](#). Under typical N-arylation conditions using with aryl bromides or arylboronic acids, excellent yields of the *N*-aryl aziridines **183** could be isolated [\[2003JOC2045\]](#). The allylation of cyclohexenimine (as well as other aziridines) was also investigated [\[2005JA17516\]](#). A number of different allyl sources as well as ligands and solvents were studied. In general, the ‘branched’ product **185** was the major product. Modifications to the ligand as well as a change of solvent led to a greater percentage of the ‘linear’ product **186**. For example, the use of CH₂Cl₂ rather than tetrahydrofuran (THF) provided a 61:39 mixture of **185**:**186**.



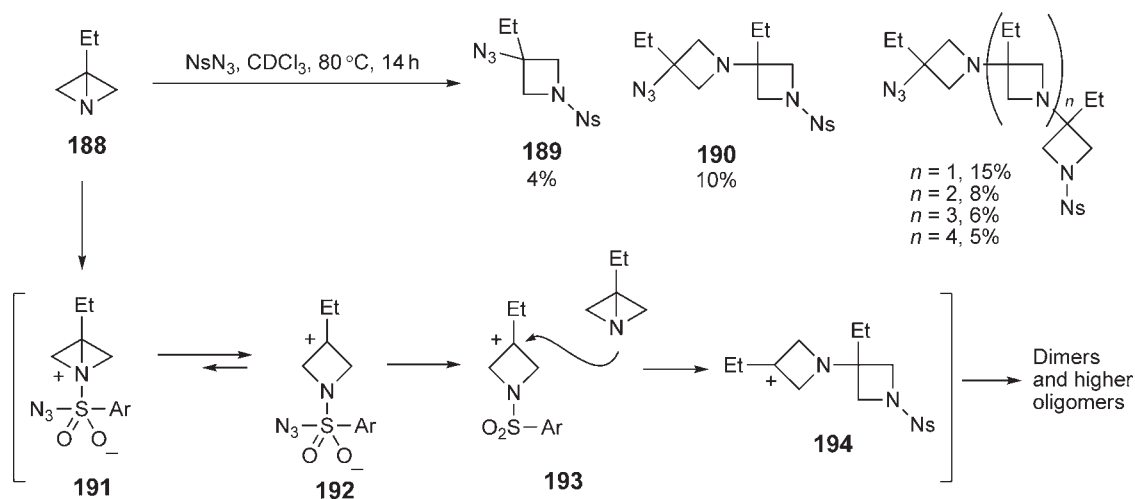
Scheme 30

1.02.4.2 Reactions of Type II Aziridines

One of the primary reactions of type II fused-ring aziridines are ring-opening reactions. The additional strain associated with fused-ring aziridines enhances the reactivity of this class of aziridines. While most ring-opening reactions of monocyclic aziridines require some type of activation (e.g., Lewis acid or electron-withdrawing group) on the nitrogen, many type II aziridines will undergo ring-opening reactions without additional activation or with milder activating agents. A monocyclic *N*-alkyl aziridine generally will not participate in uncatalyzed nucleophilic ring-opening reactions. The sugar-derived aziridine **187** can be opened with a variety of nucleophiles with only mild or no additional activation [\[2003TA1969\]](#). Thiols, amines, methanol, and carboxylic acids will all open the aziridine ring of **187** ([Equation 52](#)). Only products in which nucleophilic attack has taken place at the exocyclic carbon were isolated.



The smallest of the fused-ring aziridines (1-azabicyclo[1.1.0]butane) very readily reacts with nucleophiles. Azide either as HN₃ or an arylsulfonylazide can be used <2005HCA1658, 1998T15127>. As shown in **Scheme 31**, the reaction of **188** with nosylazide (or tosylazide) leads to the formation of monomer, **189**, dimer, **190**, and higher oligomers along with recovered nosylazide <1998T15127>. The mechanism is proposed to go through an initial complexation of the nitrogen with nosylazide to intermediate **191**. This intermediate is in equilibrium with azetidine cation **192**. Reaction of the cation with another equivalent of **188** leads to dimer **194**. Dimer **194** can then go on to product **190** as well as high oligomers.

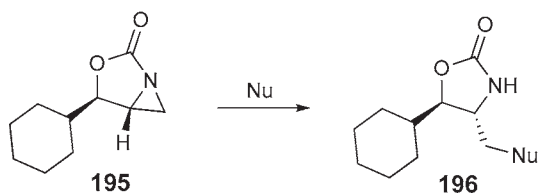


Scheme 31

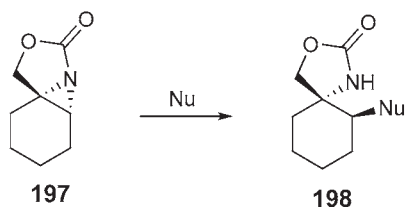
Fused-ring aziridines in which the nitrogen is activated by an electron-withdrawing group are doubly reactive relative to a simple *N*-alkyl monocyclic aziridine. This can be quite useful in subsequent transformations of the aziridine ring-opened products. This double activation can lead to interesting patterns of reactivity. Fused-ring aziridines such as **195** in which the nitrogen is linked via a carbonyloxy group react exclusively at the exocyclic carbon to generate oxazolidinones <1997JOC4449>. In general, these aziridines are not stable to either storage or purification. A lone exception is the trityloxy-substituted aziridine <2002JCO162>. Fused-ring aziridines in which the exocyclic carbon of the aziridine is substituted such as **197** are, however, generally stable to purification (**Scheme 32**) <1997JOC4449, 2004JOC6377>. A related series of fused-ring aziridines also displays the same type of reactivity <1998TL5373>.

Some of the fused-ring aziridines in this structural class are too unstable to be isolated and are simply prepared and used much as aziridinium ions are <1999JOC736, 1999EJO2709>. A particularly interesting example is directed at the synthesis of amino sugars <2001OL381, 2002OL863>. An initial report makes use of a photolytic nitrene formation from an azidoformate to generate aziridine **199** in the presence of a large excess of an alcohol <2001OL381>. The alcohol then immediately opens the aziridine to provide the amino sugar derivative **200** (**Scheme 33**). The yields for this process were only moderate. When more sterically hindered alcohols derived from sugars were used, the yields dropped to 10–15%. The use of the rhodium system gave improved yields of simple alcohols and also gave moderate yields with sterically hindered alcohols <2002OL863>.

As expected sulfonamide-linked aziridines undergo nucleophilic ring-opening reactions. As with type II fused-ring aziridine, the regiochemistry of the ring opening is of interest. As shown in **Scheme 34**, sulfonamide-linked aziridines react with a variety of nucleophiles <2000OL2327, 2004JOC6377>. The benzo derivatives **201a/201b** react at the

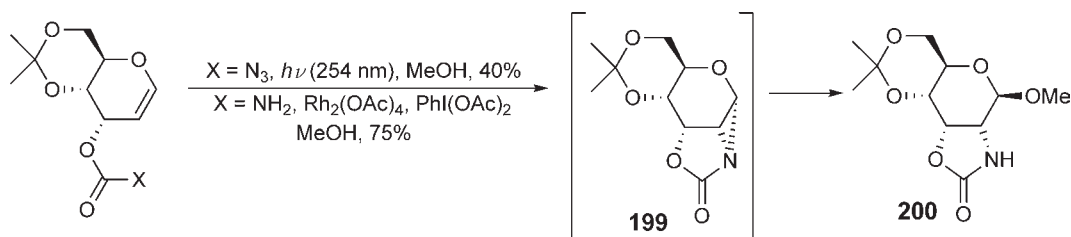


Conditions	Nu	Yield (%)
H ₂ O, cat. TFA	OH	71
MeOH, cat. H ₂ SO ₄	OMe	77
AcOH	OAc	70
AcSH, THF	SAc	81
NaN ₃ , TMSCl, DMF	N ₃	73
<i>n</i> -Bu ₂ CuLi, THF	<i>n</i> -Bu	73

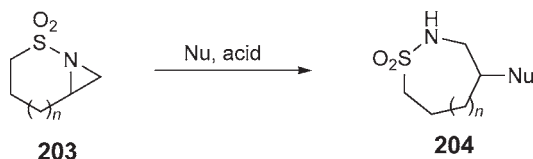
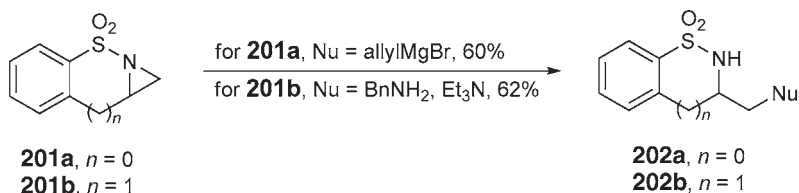


Conditions	Nu	Yield (%)
MeOH, cat. <i>p</i> -TsOH	OMe	83
<i>n</i> -BuNH ₂ , CH ₂ Cl ₂ , cat. <i>p</i> -TsOH	<i>n</i> -BuNH	82
<i>p</i> -MeOC ₆ H ₄ NH ₂ , CH ₃ CN, cat. LiClO ₄	<i>p</i> -OMeC ₆ H ₄ NH	82

Scheme 32



Scheme 33

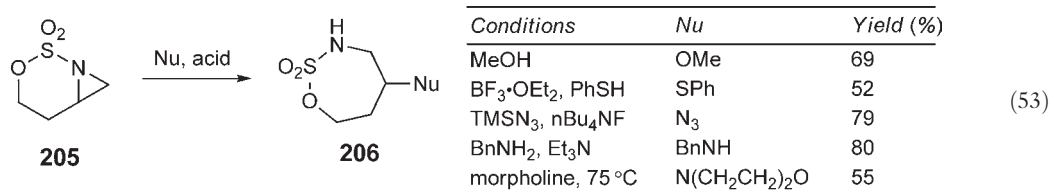


<i>n</i>	Conditions	Nu	Yield (%)
0	BF ₃ ·OEt ₂ , MeOH	OMe	65
0	<i>p</i> -TSA, MeOH	OMe	60
0	BF ₃ ·OEt ₂ , PhSH	SPh	62
1	BF ₃ ·OEt ₂ , MeOH	OMe	92
1	<i>p</i> -TSA, MeOH	OMe	86

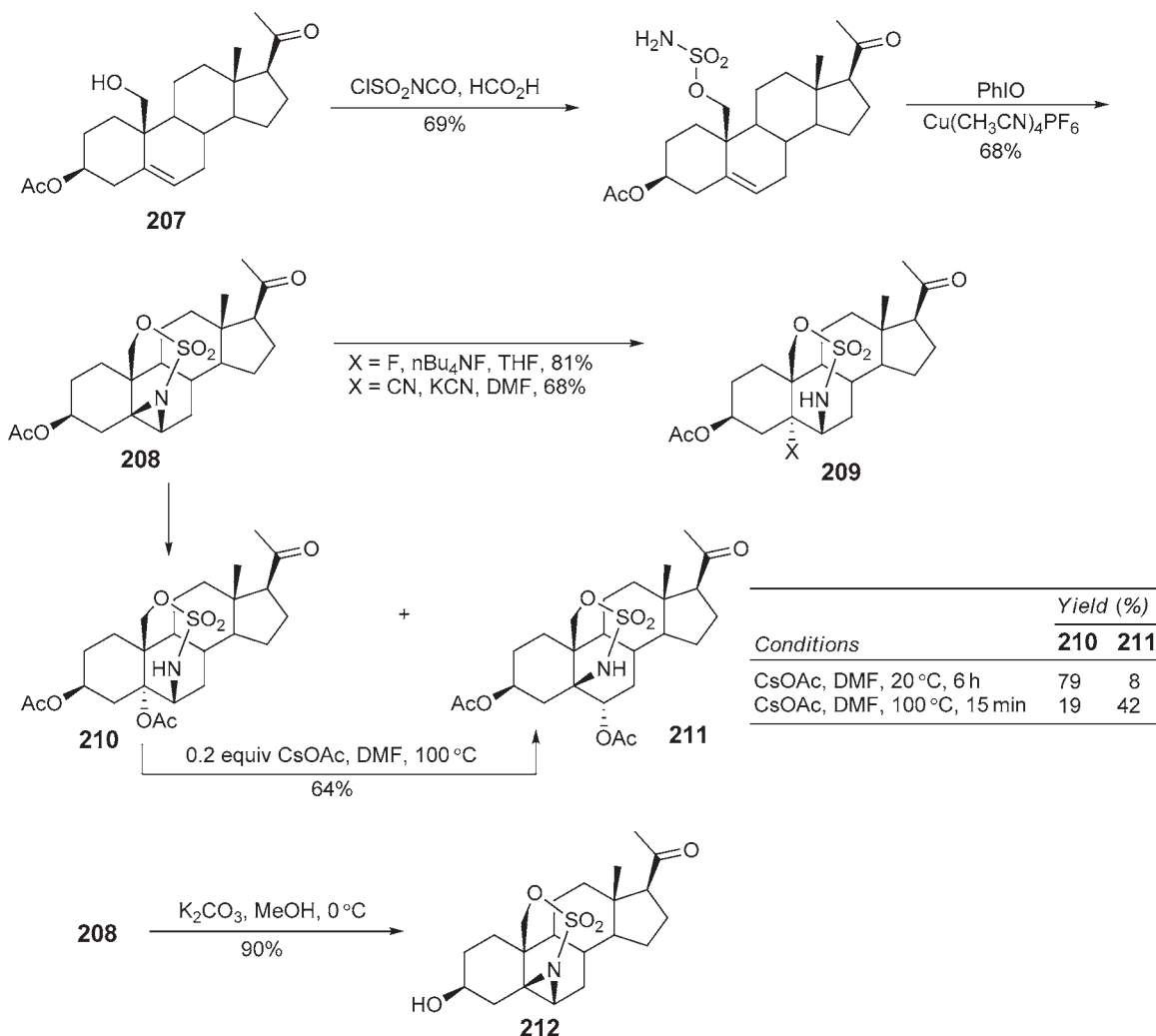
Scheme 34

exocyclic methylene of the aziridine to generate sulfonamides **202**. This pattern of reactivity is similar to that seen in the carbamate-linked aziridines such as **195** and **197**. The aliphatic sulfonamide-linked aziridines exhibit an unusual pattern of reactivity. Nucleophilic ring opening of the aziridine takes place at the bridgehead carbon to provide ring-expanded sulfonamides **204**.

Ring-opening reactions of the sulfamate-linked aziridines such as **205** proceed exclusively at the bridgehead carbon of the bicyclic system to provide **206** (Equation 53) <2002OL2481>. Only heteroatomic nucleophiles have been used in these ring openings. The ring openings of these aziridines are intriguing in that nucleophilic displacement takes place at the sterically more hindered carbon and that no nucleophilic attack takes place at the oxygen-substituted carbon. Other examples of this type of selectivity have been reported as well <2003OL4823, 2005OL4685>.

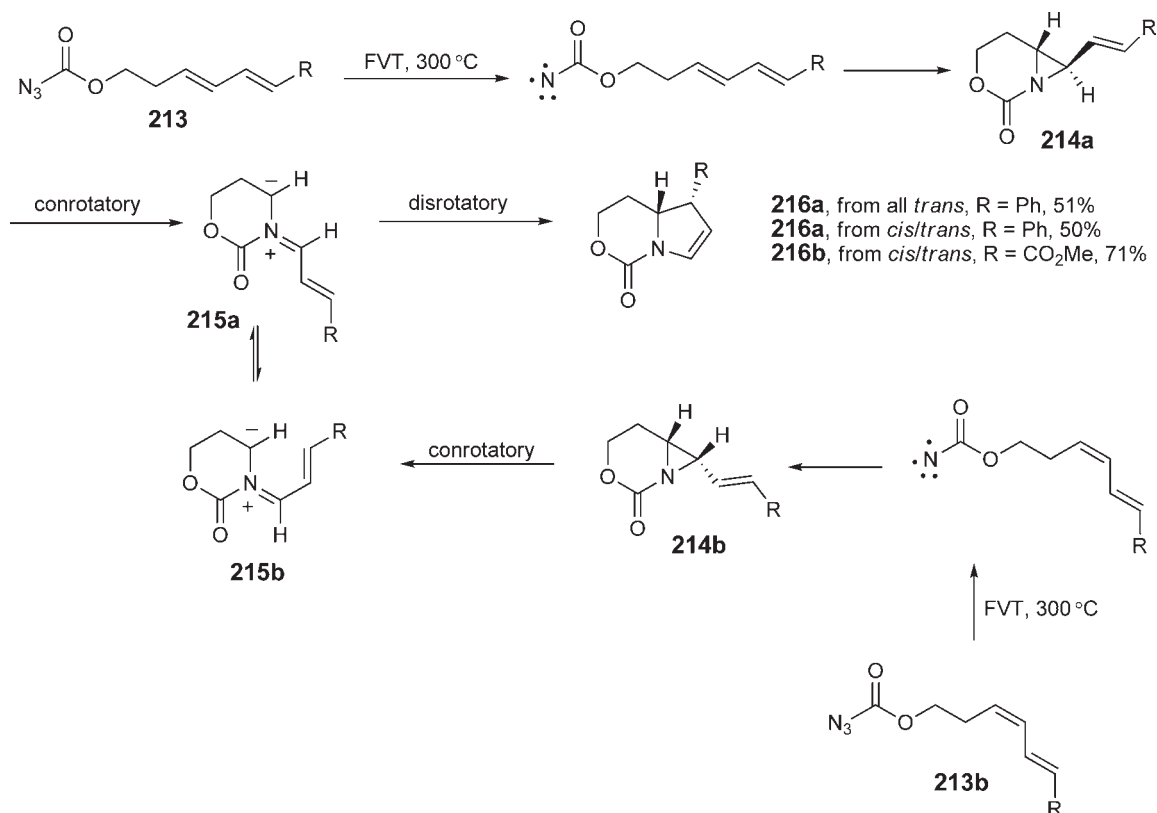


An interesting use of a sulfamate-linked aziridine has been reported for the synthesis of substituted steroids [\[2005JOC8613\]](#). Steroid **207** was converted to the corresponding sulfamate and then cyclized to aziridine **208** in good yield using copper catalysis. This sulfamate-linked aziridine was opened regioselectively to generate **209** in excellent yields. This is the same regiochemistry observed with the simpler sulfamate-linked aziridines discussed previously. The reaction with CsOAc provided a mixture of two ring-opened products **210** and **211**. At room temperature, the expected product, **210**, was obtained in 79% yield but 8% of the regioisomeric acetate **211** was also isolated. Carrying out the ring-opening reaction at high temperature provided a roughly 1:2 mixture of acetate **210**:**211**. It was calculated that acetate **211** was more stable than **210** by approximately 7.8 kcal mol⁻¹. Heating the less stable isomer **210** with catalytic CsOAc leads to complete isomerization to **211**. In addition to the interesting ring-opening reactions, it was found that the 3-acetate derivative **208** could be hydrolyzed in high yield without opening the aziridine ring to provide aziridine **212** (Scheme 35).



Scheme 35

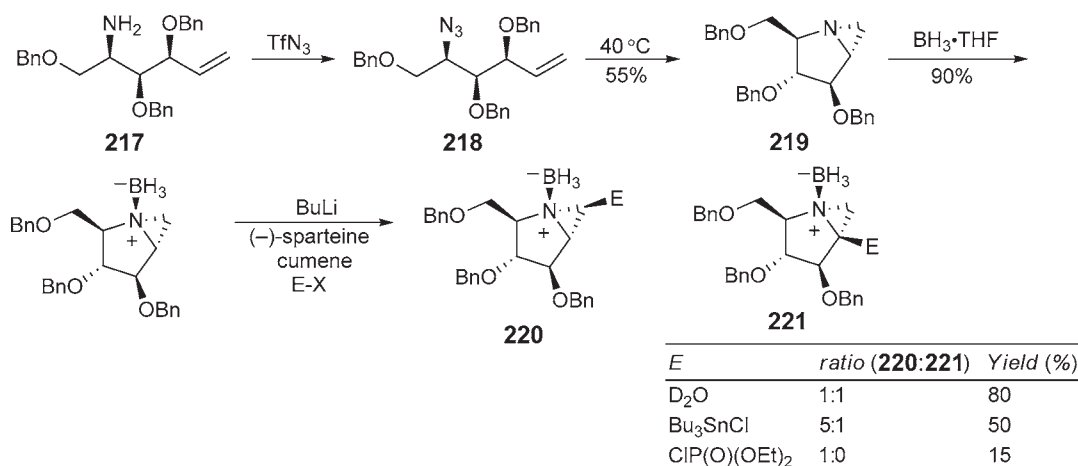
The thermolyses of azidoformates are known to generate nitrenes, which can subsequently add to olefins and produce aziridines. Wu *et al.* have examined the flash vacuum thermolysis of diene-substituted azidoformates <2001JOC6585>. The dienyl azidoformates **213a** and **213b** were prepared by the reaction of corresponding alcohols with triphosgene followed by azide displacement. Upon flash vacuum thermolysis (FVT) of the diene a single product (**216a**, **216b**) was obtained in moderate yields. The authors proposed that an initial nitrene formation was followed by aziridine formation to provide isomeric aziridines **214a** or **214b** (Scheme 36). Both of these aziridines then undergo a four-electron conrotatory process to generate ylide intermediates **215a** or **215b**. These two ylide intermediates readily interconvert and only one **215a** undergoes a six-electron disrotatory cyclization to provide pyrroline **216**.



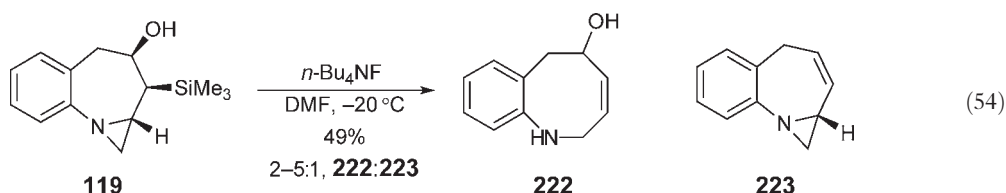
Scheme 36

The lithiation of aziridine·BH₃ complexes and quenching with electrophiles has been reported as a useful strategy for the synthesis of substituted aziridines <1997JA6941>. This strategy has been applied to the synthesis of sugar-derived aziridines as outlined in Scheme 37 <1999OL1181>. The known amine **217** was treated with triflic azide to generate the unstable azide **218**. Upon warming to 40 °C the azide was converted to aziridine **219** in 55% yield from **217**. The borane complex of the aziridine was prepared by treating **219** with BH₃·THF. Deprotonation and quenching was best carried out in cumene with the addition of sparteine as a lithium complexing agent. Deprotonation was generally predominant on the least substituted carbon of the aziridine **220**, although very small electrophiles (D₂O) gave a 1:1 mixture of **220** to **221**.

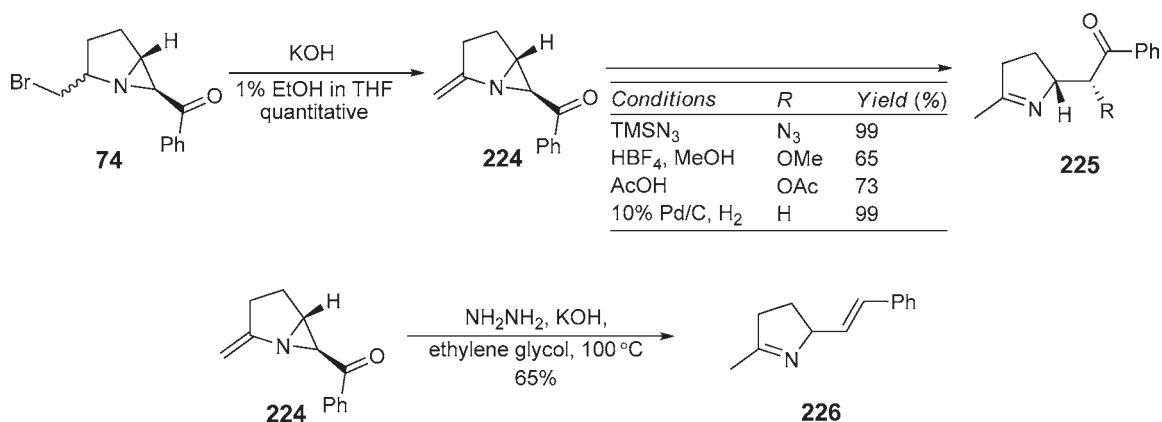
A homo-Brook reaction of silicon-substituted aziridines leading to medium ring heterocycles has been reported <2001TL9175>. The reaction of **119** with a variety of acids including HF and HCl gave no reaction. However, treatment with *n*-Bu₄NF at –20 °C gave a 49% yield of azocenol **222** along with some of the olefinic azepine **223** (Equation 54). Based on mechanistic studies, it appears that the purpose of the *n*-Bu₄NF is to act as a base to deprotonate the alcohol. The resulting alkoxide then attacks the silicon and induces aziridine ring opening.



Scheme 37



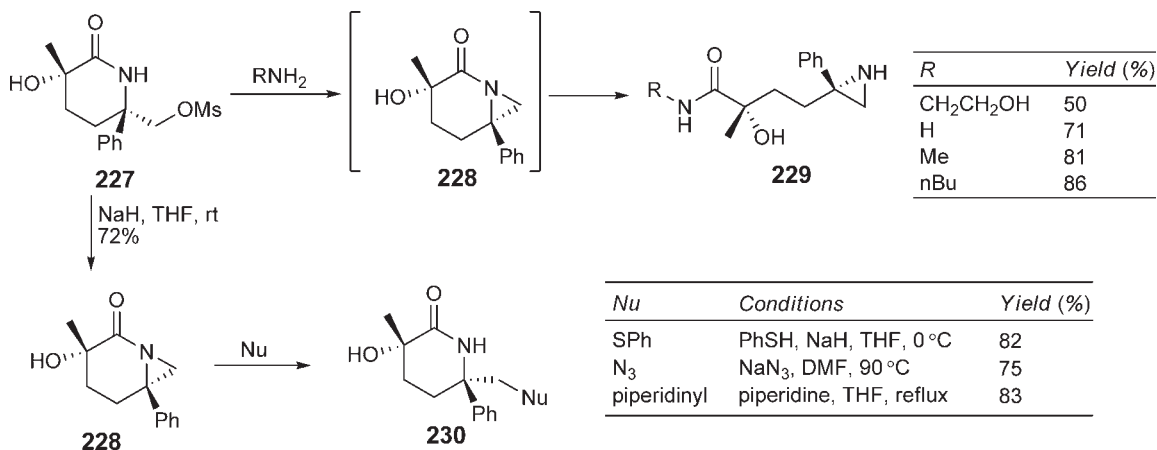
Exomethylene-substituted fused-ring aziridines can be surprisingly stable and undergo a number of useful ring opening reactions [<2003JA14242>](#). The bromomethyl group of **74** can be transformed into an exomethylene group, a grouping of functionality seen in the azinomycin family of antibiotics. This is quite an amazing reaction especially given the high yield of the reaction. The good stability of **224** is attributed to the orthogonal orientation of the nitrogen lone pair relative to the double bond. An X-ray structure of **224** was also obtained. As is seen in many aziridine systems, ring-opening reactions are an important transformation. Ring-opening reactions of this system with a number of nucleophiles provide imine **225**. This is quite useful in that after the aziridine ring is opened another functional group, the imine, is exposed for further reaction. In addition to the typical ring-opening reactions of **224**, a Wolff-Kishner reaction provided the imine **226** in moderate yield ([Scheme 38](#)).



Scheme 38

The amide-linked aziridine **228** has been found to undergo some interesting reactions as shown in [Scheme 39](#) [<2003T1483>](#). Reaction of mesylate **227** with an excess (5–10-fold) of an amine produces the monocyclic aziridine **229**. This aziridine is formed via the intermediacy of fused-ring aziridine **228**. Reaction of **227** with 1 equiv of

ethanolamine provides aziridine **228** in moderate yield. The aziridine **228** can be obtained in good yield by treatment of the mesylate with NaH. This preformed aziridine provides the typical aziridine-opened products upon treatment with a number of nucleophiles including SPh, and N_3 as well as the secondary amine piperidine. The authors explained this divergent reactivity based on the hard or soft character of the nucleophile. Soft nucleophiles such as S and N_3 prefer to react at the soft exomethylene carbon of the aziridine.

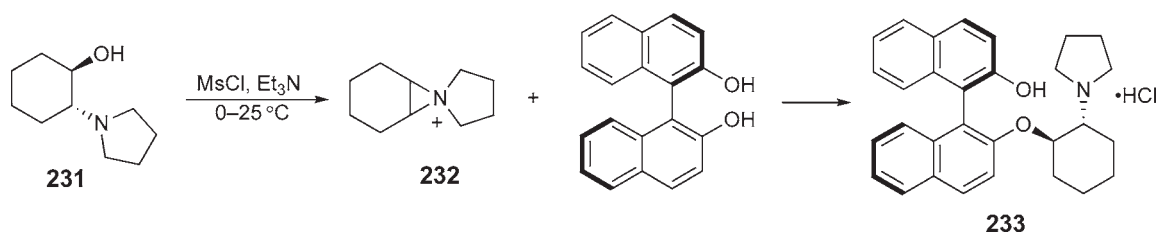


Scheme 39

1.02.5 Aziridinium Ions

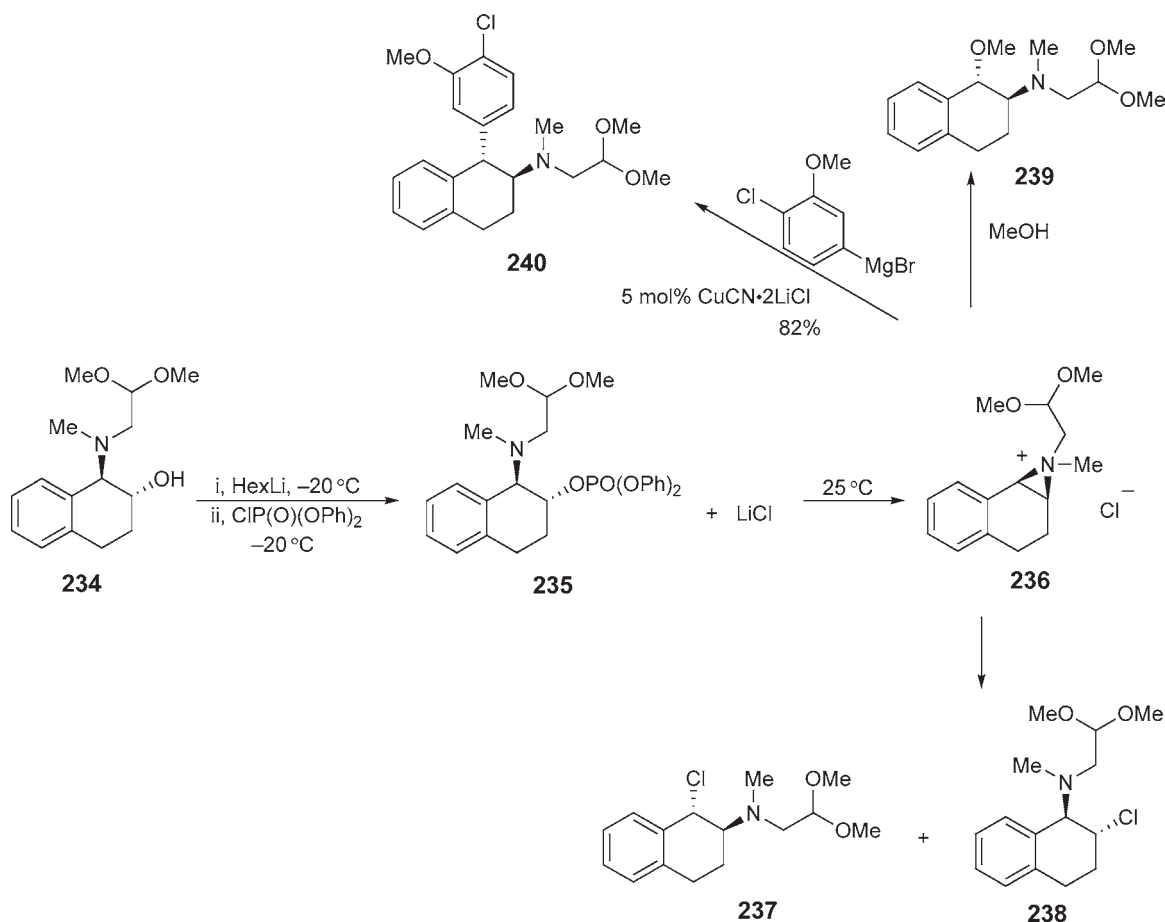
Aziridinium ions or salts are a unique class of three-membered nitrogen-containing rings. Aziridinium salts are of course positively charged and generally much more reactive in the typical ring-opening reactions that aziridines participate in. While most of the fused-ring aziridines are stable, isolable compounds, the corresponding aziridinium ions are generally nonisolable. The aziridinium ions are typically prepared *in situ* and then treated with a nucleophile to provide the ring-opened products. The presence of an aziridinium ion in a reaction is usually inferred from the products obtained. We will consider both the synthesis and reactions of aziridinium salts in a single section as it is difficult to separately consider the synthesis from the reactions. Aziridinium ions of both type I and type II are known and we will discuss type I aziridinium ions first.

Reports on the preparation and use of type I fused-ring aziridinium ions is significantly less than that of the corresponding aziridine. A couple of examples have been reported. A typical method for the synthesis of an aziridinium ion and subsequent reaction with (*R*)-1,1'-binaphthol has been reported [<2004TA3847>](#). The plan here was to carry out an enantioselective reaction between aziridinium **232** and binaphthol. The aziridinium **232** was prepared by treating racemic aminoalcohol **231** with methanesulfonyl chloride and triethylamine. As is usually done, the aziridinium is not isolated but the binaphthol is simply added to the reaction. A 60% yield of (–)-(*R,R,R*)-**233** was isolated along with 30% of a 1:1 mixture of the (*R,R,R*)- and (*R,S,S*)-diastereomers (Scheme 40).



Scheme 40

The use of aziridinium ions in the large-scale process chemistry for the synthesis of ecopipam is outlined in [Scheme 41](#) <2002TL6121>. Aziridinium **236** was most efficiently prepared through conversion of a hydroxyl moiety to a phosphate leaving group. It was noted that **236** could also be prepared by methylation of a preformed aziridine. Extensive studies on the stability of **236** were carried out by NMR. It was shown that the aziridinium ion could not be detected spectroscopically, although clearly it was a common intermediate as evidenced by formation of chloramines **237** and **238**. Aziridinium **236**, as the tetrafluoroborate salt, was however a reasonably stable, isolable compound. A methanolysis reaction, to provide **239**, was carried out which indicated that aziridinium formation proceeded in 90–92% yield. Treatment of **236** with an aryl Grignard reagent provided product **240** in 55–60% yield with the remaining aziridinium ion consumed in unproductive side reactions, primarily generating dimeric products. The addition of a copper catalyst dramatically improved the yield of the reaction providing **240** in excellent yield. The regiochemistry of the ring-opening reaction is consistent with ring-opening reactions of a number of benzylic aziridines and aziridinium ions.

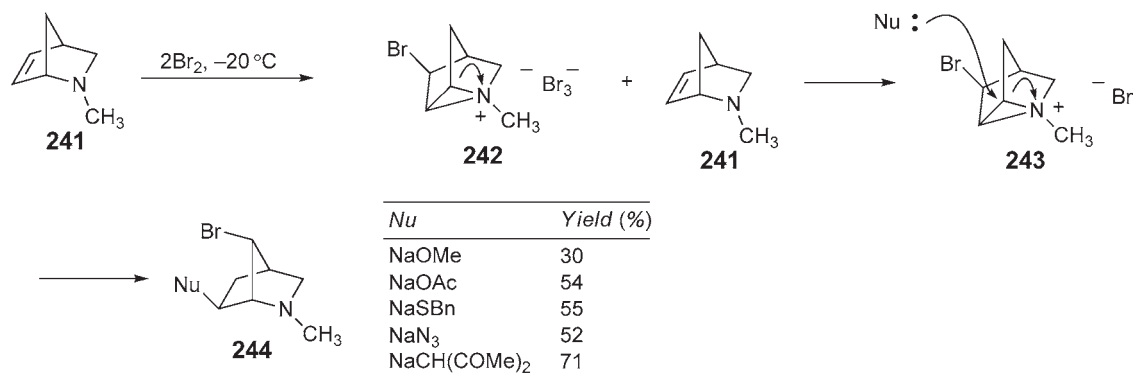


Scheme 41

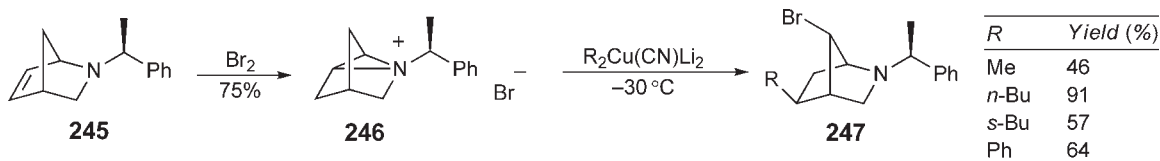
[Scheme 42](#) shows the synthesis of a highly strained tricyclic aziridinium ion <2002RCB1254, 2003RJO415>. Treatment of **241** with 2 equiv of bromine provides the aziridinium tribromide salt **242**. The monobromide salt could then be obtained by treating **242** with an additional equivalent of the starting amine **241**. It is significant that this family of aziridinium salts appear to be stable, isolable solids. An X-ray structure of aziridinium **243** was obtained <2002RCB1254>. This aziridinium was treated with a number of different nucleophiles to generate a 2-azabicyclo-[2.2.1]heptane **244** in moderate yields. It is rather interesting that the products do not undergo additional aziridinium ion formation.

The synthesis and reactions of a related aziridinium ion have been reported <2005ASC1242>. Here the monobromide salt **246** is isolated directly without the intermediacy of the tribromide salt. One key difference may lie in

the method of preparation; this report notes that the olefin **245** is added to a cooled solution of bromine while in the earlier method <2002RCB1254>, bromine is added to a solution of **241**. These researchers examined the reaction of aziridinium **246** with a series of organocuprates to generate **247** (Scheme 43). A related type of aziridinium and subsequent nucleophilic ring opening has been reported with a 2-azabicyclo[2.2.0]hexane system <2003OL2739>.

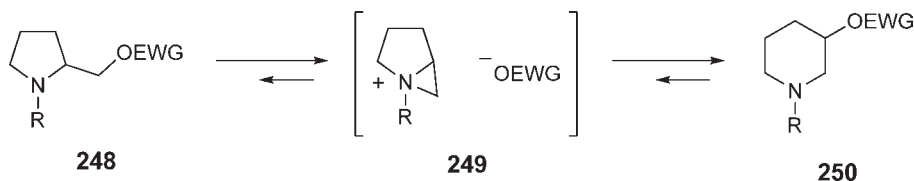


Scheme 42



Scheme 43

Aziridinium salts have been widely used in the synthesis of hydroxylated pyrrolidines and piperidines <1996TL1613, 1996TL1609, 1998JOC4755, 1999EJO1693, 2003JOC9598, 2004SL901>. Azasugars and polyhydroxylated alkaloids have been widely explored as synthetic targets. The combination of functionality makes them an attractive target for aziridinium-based synthetic methods. The general reaction process is outlined in Scheme 44. A pyrrolidine bearing a 2-methyl group, itself bearing a leaving group (OEWG) is expected to undergo an intramolecular alkylation to generate aziridinium **249**. Nucleophilic ring opening of **249** is expected to then provide piperidine derivative **250**. The piperidine product generally predominates in these reaction systems. The ring-opening reactions are stereoselective with inversion of configuration seen.

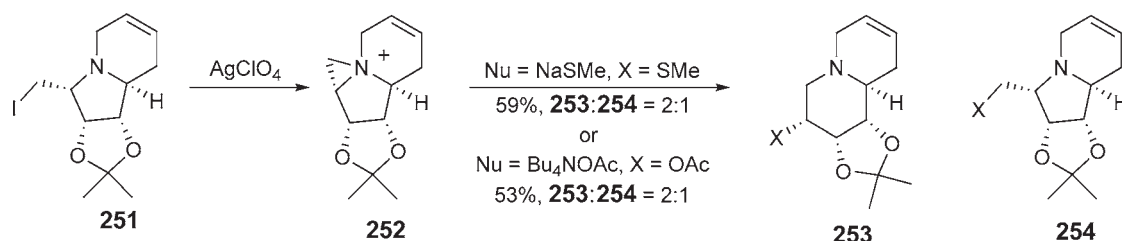


Scheme 44

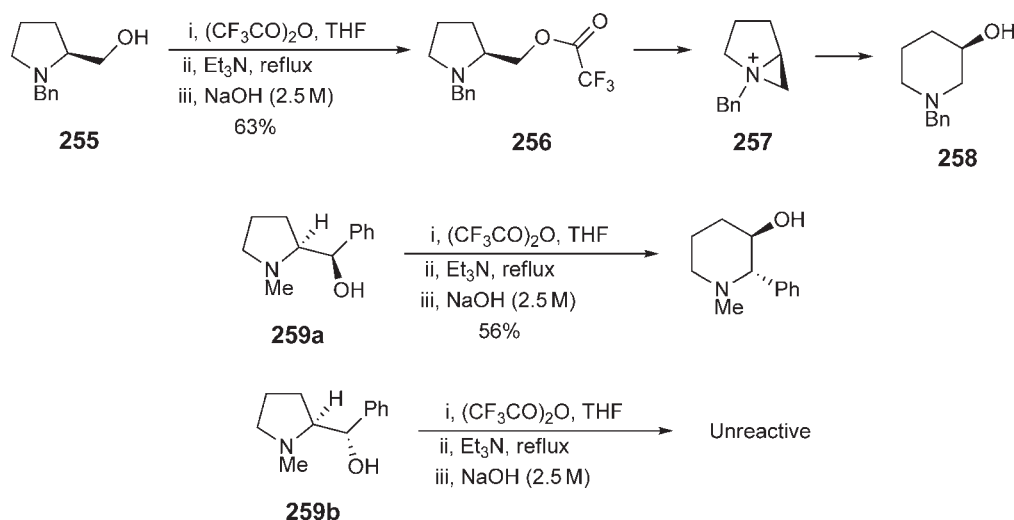
The example shown in Scheme 45 is typical of these types of aziridinium-opening reactions <2003JOC9598>. Indolizidine **251** was prepared via a ring-closing metathesis. The aziridinium was prepared by treatment with AgClO₄ followed by a nucleophile being added to the reaction. Reaction of the aziridinium **252** with either methylthiolate or acetate provides a mixture of quinolizidine **253** and indolizidine **254** in moderate yield. Both nucleophiles gave comparable ratios of **253** to **254** of 2:1.

Most of the methods to prepare aziridinium ions such as **252** require the use of a preformed leaving group such as mesylate or halogen. A very nice method has been reported which uses a hydroxyl group and an *in situ* conversion to a

leaving group <1999EJO1693>. Treatment of hydroxymethyl pyrrolidine **255** with trifluoroacetic anhydride is expected to generate the trifluoroacetate **256**. The addition is followed by addition of Et₃N and heating to generate aziridinium **257** which is then opened by subsequent addition of hydroxide to provide **258** in good yields as a single enantiomer. A number of substituted pyrrolidines were used as well as the simple system shown in **Scheme 46**. An alkyl group on the nitrogen is required, as the N–H compound did not provide any of the desired products. Secondary alcohols, **259a**, can also be used; however, the diastereomer of **259a** (**259b**) did not undergo the expected reaction. This was attributed to gauche interactions between the phenyl and the C-2 and C-3 bond in the aziridinium ion.



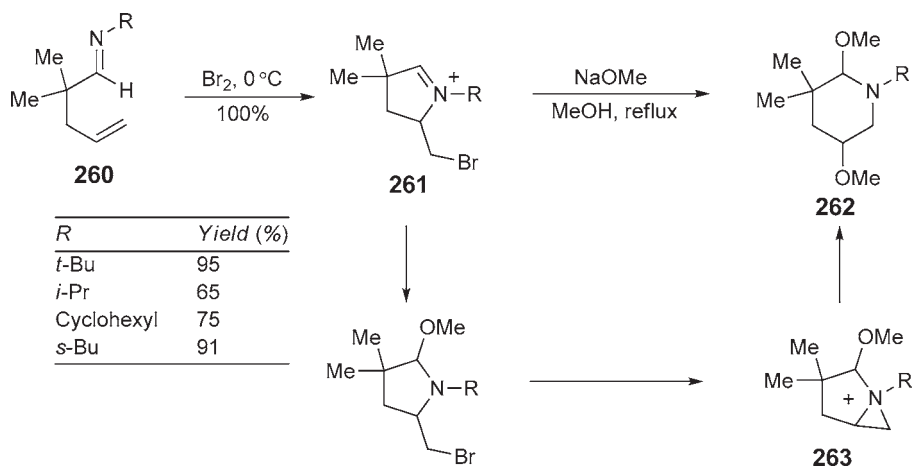
Scheme 45



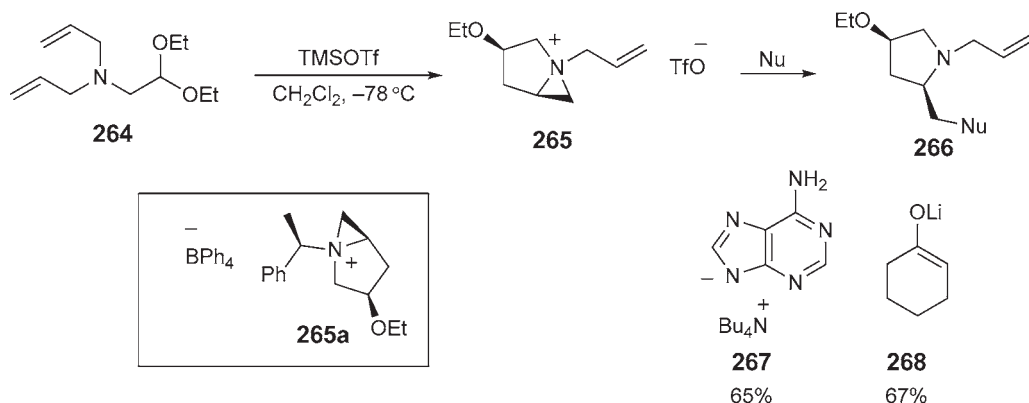
Scheme 46

A unique method for the synthesis of aziridinium ions starting from an imine has been reported <1996TL3171, 1996TL3303, 2000TL2507>. 5-(Bromomethyl)-1-pyrrolinium bromides, **261**, are easily prepared by treatment of **260** with bromine <1996TL3171>. The pyrrolinium bromides are readily converted to the dialkoxypiperidines by treatment with alkoxide in refluxing methanol. This reaction proceeds by an initial addition of methoxide followed by aziridinium ion, **263**, formation (**Scheme 47**). The aziridinium ion reacts with the nucleophile at the internal carbon of the fused-ring aziridine to provide piperidine **262**. Compound **262** is reported to be obtained as a single, *trans*-diastereomer. A related reaction starting with α,δ -dichloroaldehydes that proceeds via an **263**-like intermediate has been reported. In this report the nucleophile adds to the less sterically hindered external carbon to generate pyrrolidines <1996TL3303>.

An interesting and stereoselective aziridinium ion formation is shown in **Scheme 48** <2001CC966>. Reaction of diallylamine **264** with TMSOTf provides aziridinium salt **265**. The compounds were prepared as the triflate salts but could be converted to the tetraphenyl borate salts by treatment of the triflate salt with NaBPh₄ followed by precipitation with ether. The tetraphenyl borate salts were stable solids which could be stored and used later. An X-ray structure of the tetraphenyl borate salt **265a** was determined. A number of nucleophiles were used in opening these aziridinium salts to give pyrrolidine **266**. A couple of interesting nucleophiles used were **267** and **268**. The use of an enolate is significant in that addition of enolates to aziridines or aziridinium salts is a rarely reported reaction. The use of MeOH, NaOMe, or NaOAc as the nucleophile gave significant amounts of the piperidine products as well as the expected pyrrolidines **266**.



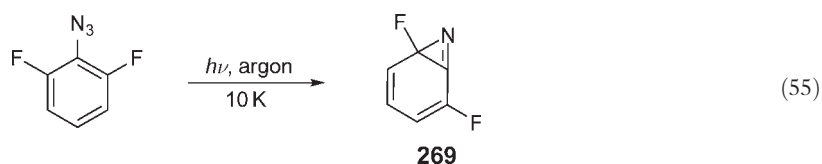
Scheme 47



Scheme 48

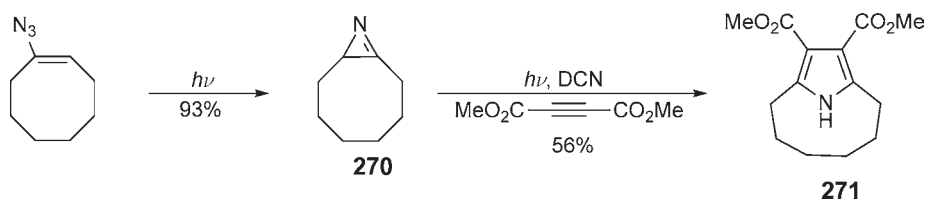
1.02.6 Azirines

As noted in Section 1.02.1, the focus of this chapter is fused-ring derivatives of aziridines and azirines. Unlike aziridines, the presence of an azirine in a fused-ring system is relatively rare due to the unstable nature of this highly strained ring system. For example, the photolysis of difluoroazido benzene at 10 K produces azirine **269** <1996JOC4351>. This compound readily rearranges to the corresponding azepine at higher temperatures. Additional studies on the preparation and physical properties of azirines such as **269** have been reported (Equation 55) <2004JA237, 2004PCA1169>.



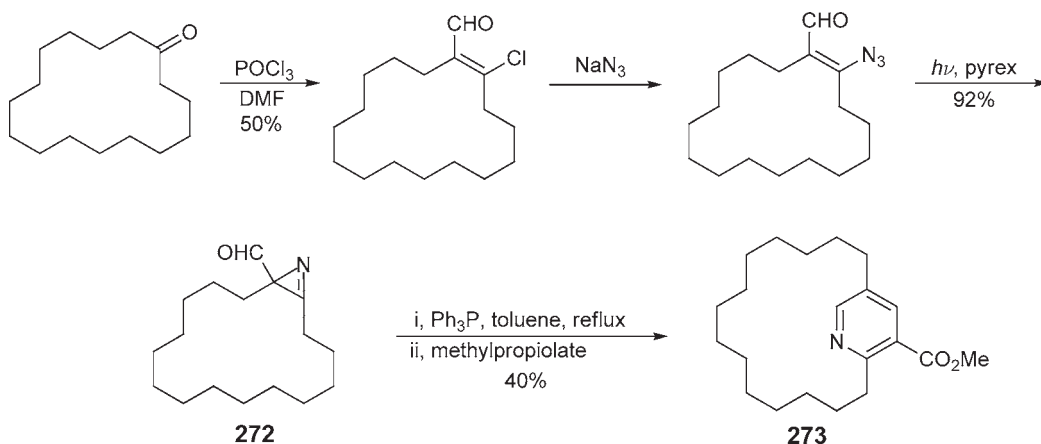
The first synthesis of an isolable fused-ring azirine was reported in 1968 <1968JA2869>. Much of the strain associated with the incorporation of an azirine ring into a fused ring system is lost when larger rings are used. Compound **270** is relatively stable and is prepared in 93% isolated yield. A unique type of reaction that this class of

azirines undergoes a photoinduced cyclization. Photolysis of **270** in the presence of a sensitizer such as 1,4-naphthalene dicyanide (DCN) and dimethyl acetylenedicarboxylate provides the macrocyclic pyrole **271** in reasonable yield (Scheme 49) <1992AGE209>. These cycloaddition reactions are believed to proceed through the intermediacy of the azaallyl radical cation. Several other dipolarophiles such as imines and nitriles will also participate in this reaction.



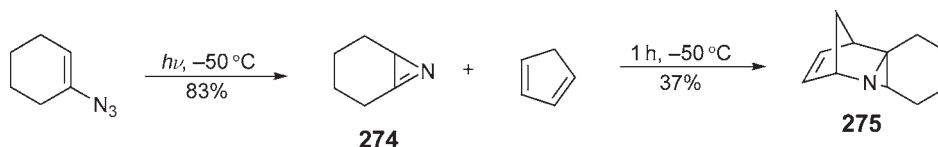
Scheme 49

A more recent example of this general type of reaction uses the formyl azirine **272** to generate a [14](2,5)pyridophane **273** in 40% yield <2006T4128>. The reaction proceeds via the formation of a (vinylimino)phosphorane by opening the azirine ring with triphenylphosphine. The (vinylimino)phosphorane reacts with the methyl propiolate to provide **273** (Scheme 50). Yields for the conversions of the formyl azirines to the pyridophanes are quite sensitive to ring size. The [6]pyridophane cannot be prepared and the [9]pyridophane is obtained in only 7% yield.



Scheme 50

Recently the synthesis and subsequent reactions of smaller ring fused azirines has been reported <2006AGE4015>. Until this report azirines such as **274** could only be generated *in situ* and their presence detected by trapping reactions. Azirine **274** was prepared via photolysis and characterized spectroscopically (^1H , ^{13}C NMR, DEPT135, nuclear Overhauser effect (NOE), and correlation spectroscopy (COSY)). As might be expected these compounds are exceedingly reactive and even traces of water lead to dimerization of the azirine. These azirines undergo a number of cycloaddition reactions quite rapidly even at -50°C . For example, the reaction of **274** with cyclopentadiene provides **275** in 37% isolated yield (Scheme 51).

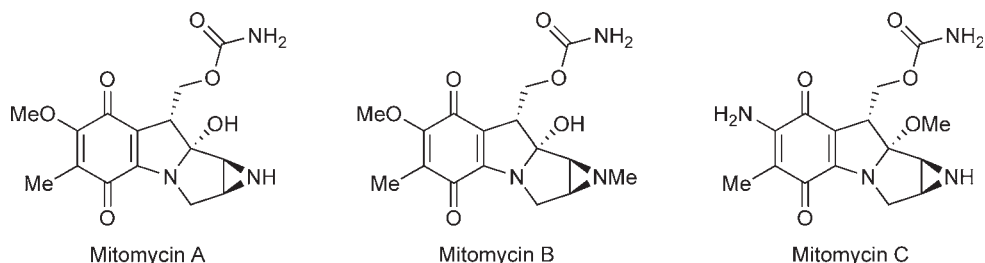


Scheme 51

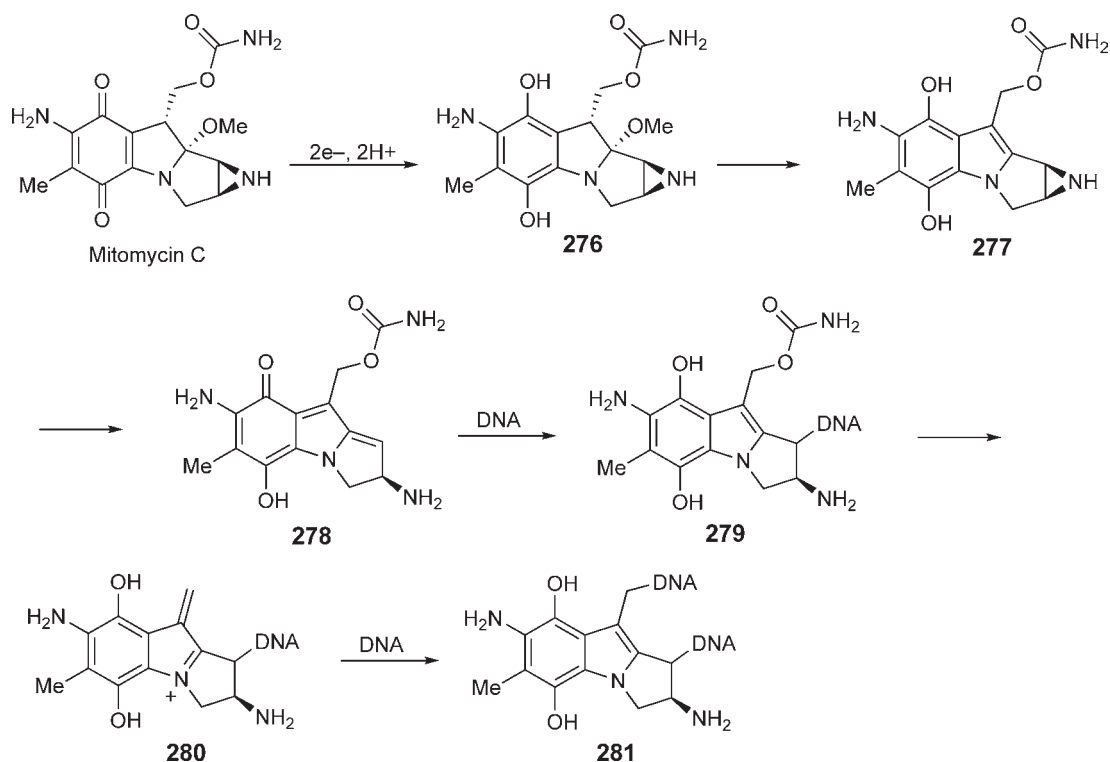
1.02.7 Important Compounds and Applications

1.02.7.1 Natural Occurrence and Important Compounds

There are a number of naturally occurring compounds as well as medicinally interesting compounds that contain a fused-ring aziridine. In the natural product area there are few natural products that contain an aziridine ring. Of these few aziridine containing natural products, the majority are fused-ring derivatives. Three of these aziridine-containing natural products have been found to be potent DNA-alkylating agents <2002CRV2477, 1998CRV2723>.

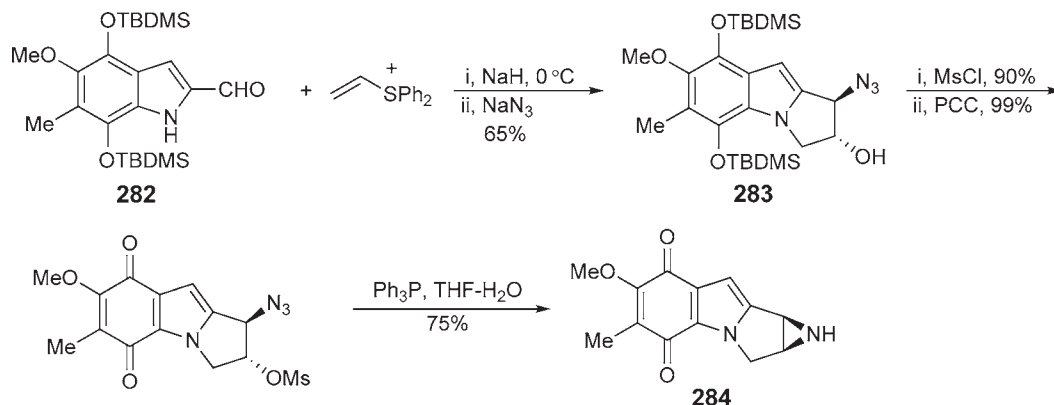


The mitomycins are the oldest of the aziridine-containing natural products and were originally isolated in the late 1950s from *Streptomyces caespitosus* <1956JAN141, 1958ACM228>. Mitomycin C is clinically used against a number of tumors today. The mitomycins, like many of the other aziridine-containing natural products, are DNA cross-linking agents <2002CRV2477, 1998CRV2723>. As might be expected, the aziridine ring plays a crucial role in the DNA cross-linking. Mitomycin is unreactive toward DNA at physiological pH, but upon enzymatic reduction it becomes a highly reactive alkylating agent as shown in **Scheme 52**. Upon loss of the 9a-oxygen a leucoaziridinomitosenone **277** is generated. These types of intermediates are too reactive to be isolated but they have been observed in solution. After opening of the aziridine to form intermediate **278**, DNA will alkylate to form initial DNA adduct **279**. The carbamate is then lost to generate another active alkylating agent which leads to the dialkylated adduct **281** <1963PNA355, 1964SCI55>.



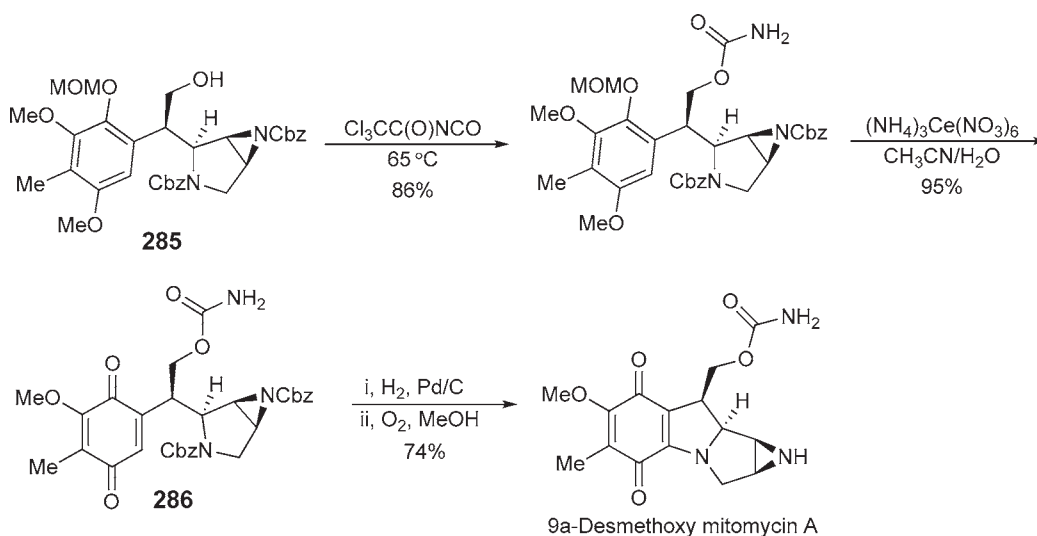
Scheme 52

Numerous syntheses of the mitomycins as well as analogs have reported in the years since these compounds were isolated [<2001MI435>](#). Research on these unique natural products continues to this day. A key issue with any approach to the synthesis of the mitomycins is how and when to introduce the aziridine ring. There have been four general approaches to the mitomycin skeleton since 1995. From the aziridine perspective, one of the most straightforward is the formation of the aziridine ring on a more or less intact tricyclic pyrroloquinone [<1996JOC816, 2001TL7513, 2004T7367>](#). An example of this approach is outlined in [Scheme 53](#) [<1996JOC816>](#). Reaction of indole **282** with a vinyl sulfonium salt followed by addition of NaN_3 provides azido alcohol **283**. The alcohol was mesylated and the azide reduced (Ph_3P) to provide the simplified mitomycin analog **284**.



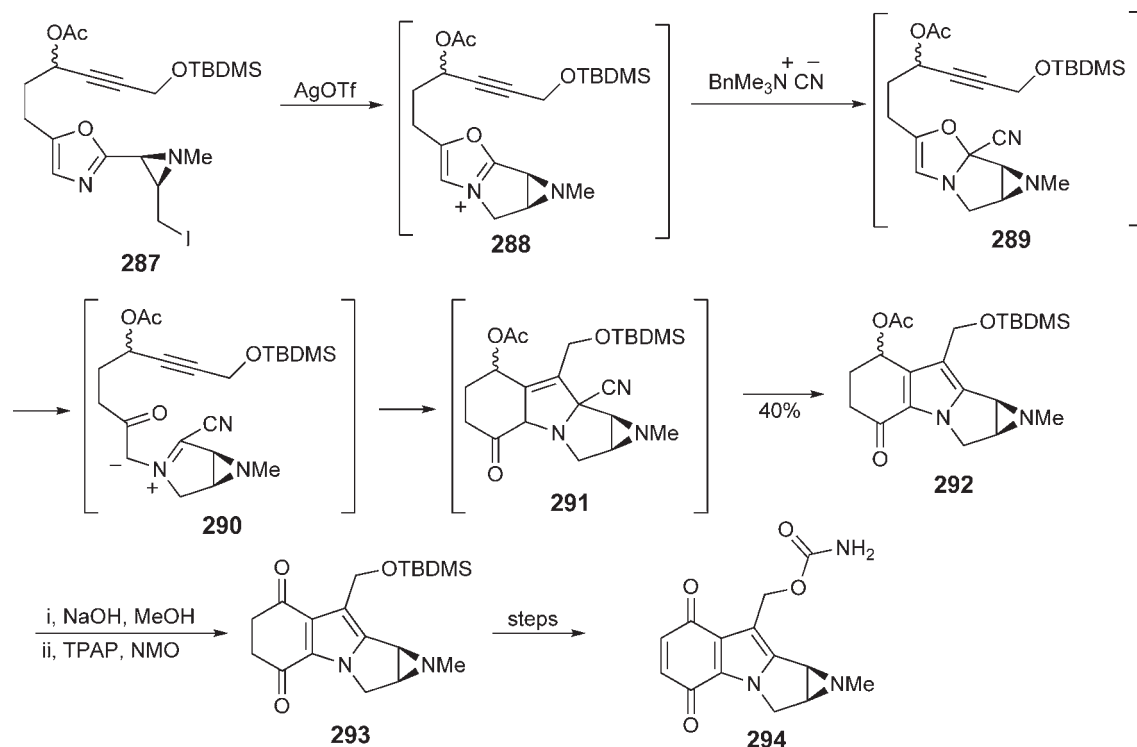
Scheme 53

An approach that prepares the aziridine ring in much the same manner but introduces it early on is shown in [Scheme 54](#) [<2004JOC7309>](#). The aziridine ring of pyrrolidine derivative **285** was prepared through a standard epoxide opening/aziridine formation process. After conversion of the free hydroxyl group to a carbamate, the aromatic ring was oxidized to quinone **286**. Both nitrogen-protecting groups were removed by hydrogenolysis to generate the free amines. The pyrrolidine nitrogen underwent a spontaneous conjugate addition to the quinone. Subsequent oxidation provided 9a-desmethoxy mitomycin A in good yield. This is an interesting synthesis in that the *N*-Cbz aziridine withstood the oxidation reaction and was subsequently readily deprotected.



Scheme 54

Another very useful approach to the mitomycins is a cycloaddition method shown in **Scheme 55**. A monocyclic aziridine is linked to a mono- or bicyclic-ring system in order to form the tetracyclic ring system of the alkaloid <2000JA5401, 2000JOC5498, 2003JA15796>. Monocyclic aziridine **287** was prepared via a stepwise approach from the oxazole ring. Reaction of **287** with AgOTf initiated alkylation of the oxazole ring to generate intermediate oxazolium salt **288**. Treatment with soluble cyanide source, benzytrimethylammonium cyanide, led to cyanide addition product **289**. The oxazolidine ring then spontaneously opened to form ylide **290** which underwent a dipolar cycloaddition to form the tetracyclic compound **291**. A final loss of cyanide provide the mitosene **292** in 40% yield. A further series of functional group modifications then converted **292** to the 9a-desmethoxy mitosene **294**.

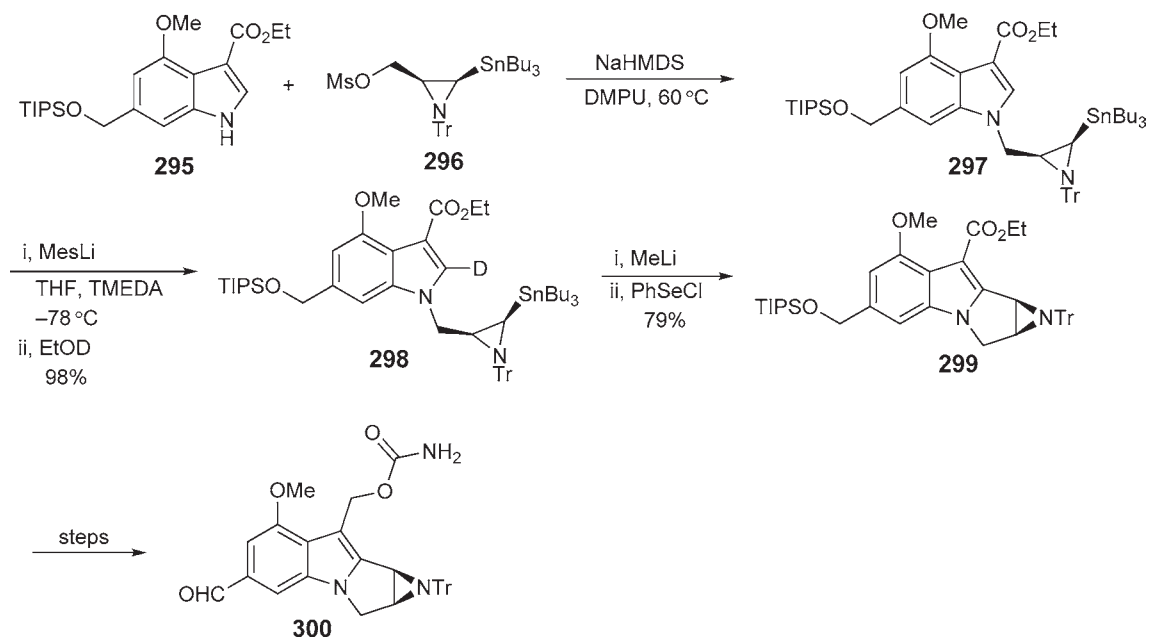


Scheme 55

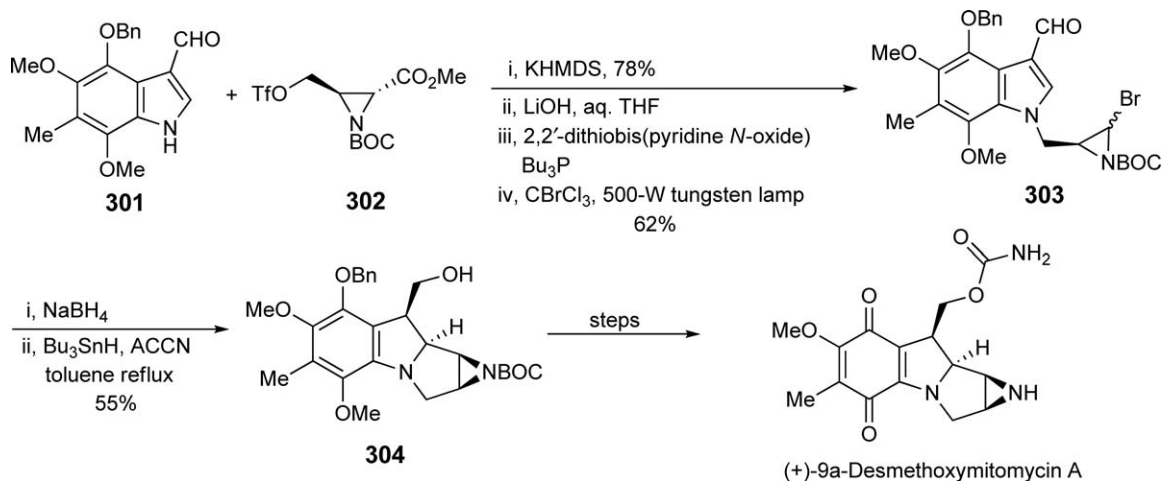
Two final approaches form a bond between C-2 of a monocyclic aziridine and a bicyclic nucleus in order to form the tetracyclic molecule <2004JOC7262, 1998TL2455>. The first of these is shown in **Scheme 56** <2004JOC7262>. Indole **295** was alkylated with aziridine **296** to provide substituted indole **297**. A threefold excess of the aziridine was required in order to provide a 95% yield of **297** based on recovered indole. The next process was to lithiate the aziridine ring so that it would undergo a conjugate addition. In order to do this the indole was first deprotonated and then deuterated to provide **298** in excellent yield. The presence of the deuterium provided a favorable kinetic isotope effect such that the tin–lithium exchange was the major reaction pathway. Treatment of **298** with MeLi followed by PhSeCl provided the tetracycle **299** in excellent yield. This molecule was later converted to the more advanced intermediate **300**, but the trityl group could not be effectively removed.

A second approach to this type of ring formation is shown in **Scheme 57** and uses a radical cyclization to form the tetracyclic nucleus <1998TL2455>. Indole **301** was alkylated with the aziridiny triflate **302** and then the carboxylate was hydrolyzed, activated, and irradiated to prepare bromoaziridine **303** in 62% yield. This is remarkable series of transformations, especially for an activated aziridine. The aldehyde is then reduced and *n*-Bu₃SnH is used to initiate a stereoselective radical cyclization to form the tetracycle **304**. A series of functional group transformations then converts **304** into (+)-9a-desmethoxymitomycin A.

FR900482 and FR66979 were isolated from *Streptomyces sandaensis* 6897 in 1987 <1987JA4108, 1987JAN594>. In addition to these naturally occurring compounds, several semisynthetic analogs of FR900482 and FR66979 are



Scheme 56

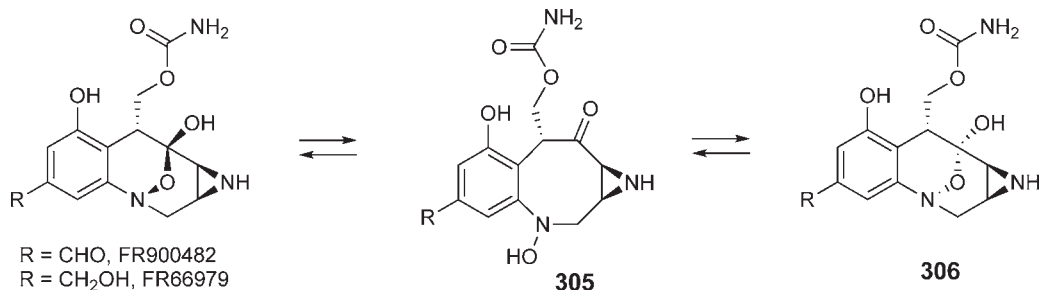


Scheme 57

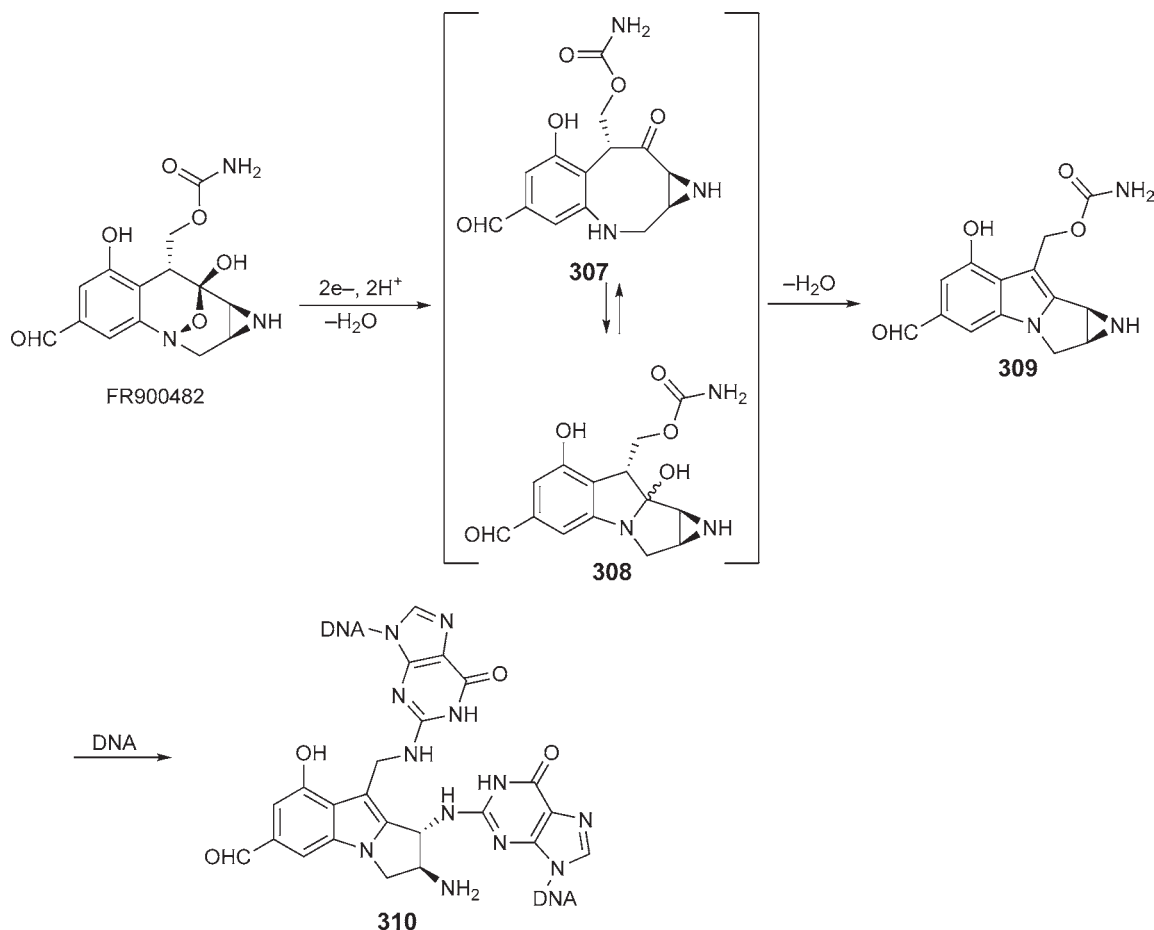
known. These compounds all contain a type I aziridine fused to a unique tricyclic skeleton that contains a cyclic hemiaminal. The formation of the hemiaminal containing ring system is one of the primary challenges in the synthesis of this family of compounds. Compounds FR900482 and FR66979 both exist in equilibrium with azocinone **305** which can then re-close to diastereomer **306** (Scheme 58).

These compounds exert their biological activity as DNA cross-linking agents. The anticancer activity of this series of compounds is almost identical (albeit more potent and less toxic) to the mitomycins in that the natural product itself must be activated in order to cross-link DNA. A two-electron reduction of FR900482 converts it to a mixture of **307** and **308**. Loss of water provides a leucoaziridinomitosenone **309**. It is this metabolite that undergoes DNA cross-linking to form the DNA adduct **310** (Scheme 59).

As with the mitomycins, general routes to the synthesis of FR900482 and analogs have evolved. A very straightforward approach is the formation of the aziridine ring late in the synthesis using an intramolecular *N*-alkylation. A second is the incorporation of an intact monocyclic aziridine as part of the formation of the tricyclic ring system.



Scheme 58

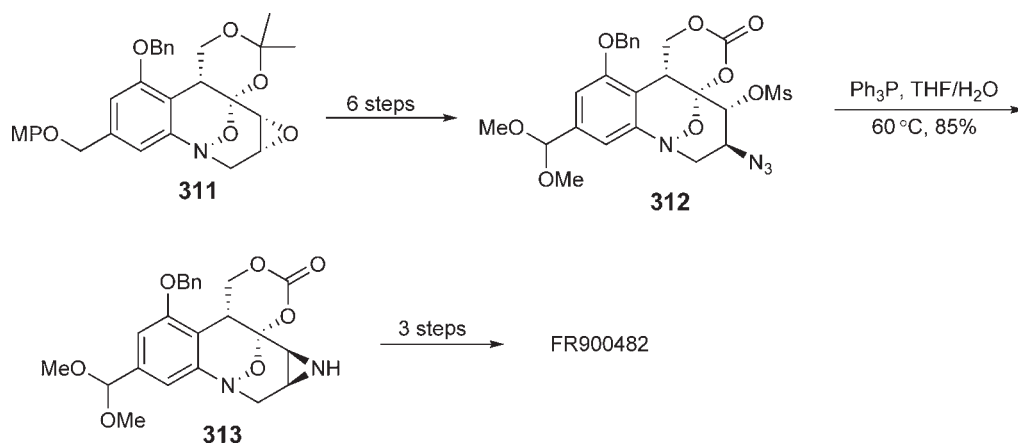


Scheme 59

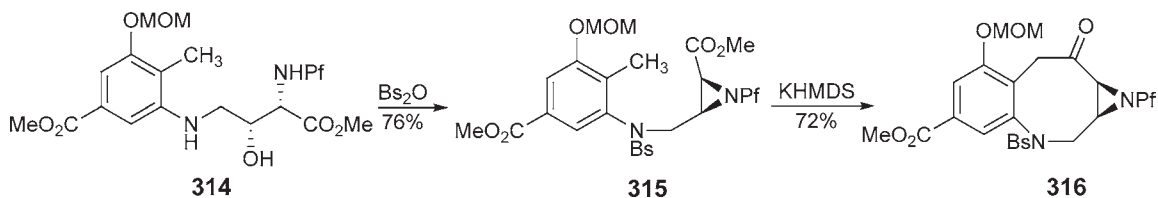
The synthesis shown in [Scheme 60](#) exemplifies the first approach [\[2001OL2575, 2004JOC2831\]](#). A rather lengthy series of transformations provides epoxide **311**. The epoxide is opened with azide and the resulting alcohol converted to the mesylate. A few additional functional group modifications are then necessary for the synthesis of **312**. A standard azide reduction followed by an intramolecular alkylation provides the aziridine **313**. This aziridine is then carried on to FR900482 in three additional steps.

Two approaches to bring in a monocyclic aziridine have been reported; they differ largely in which bond is formed first. As shown in [Scheme 61](#), Rapoport and co-workers create the C(11)–N bond first to form **314** [\[2003JOC130\]](#). Treatment of **314** with benzenesulfonyl anhydride (Bs₂O) leads formation of the aziridine **315** through an initial di-phenylsulfonylation of the N–H and hydroxide followed by an intramolecular alkylation of the *N*-(9-phenylfluoren-9-yl)

(NPf) protected amine. The final ring formation was carried out by deprotonation of the benzylic methyl with potassium hexamethyldisilazide (KHMDs) which then added to the methyl ester to provide ketone **316**. This compound was then carried on through a series of transformations to provide a common intermediate for every member of the FR900482 family.

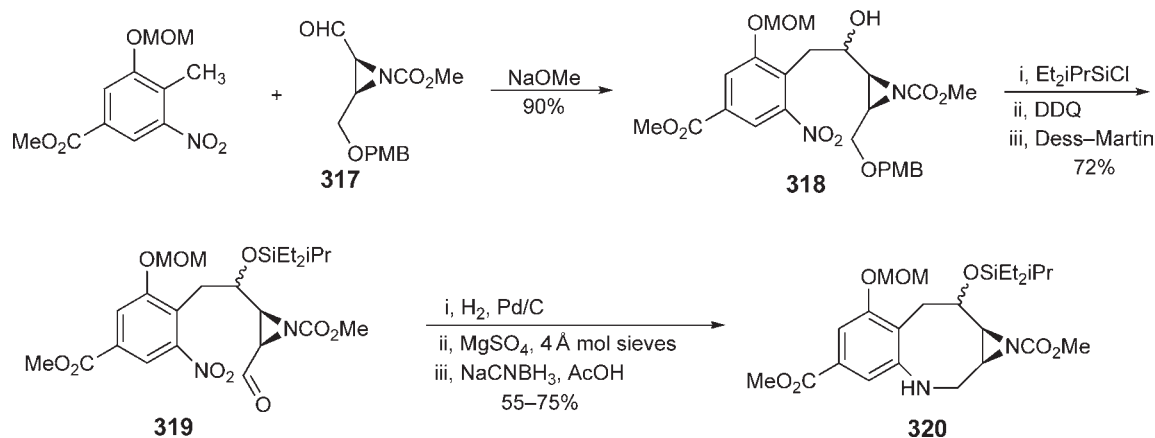


Scheme 60



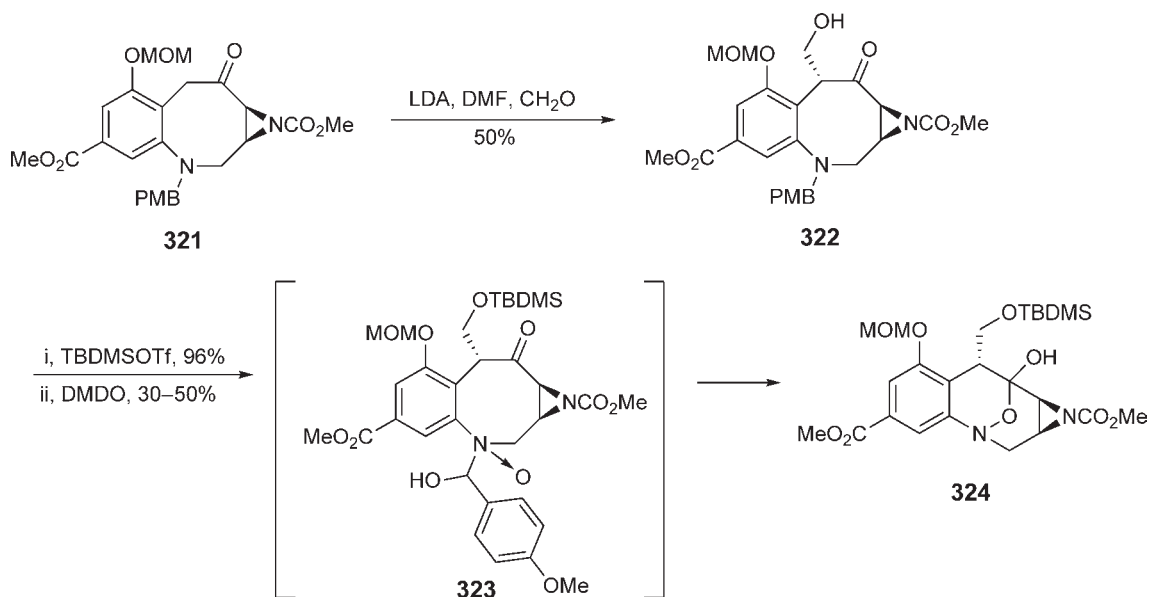
Scheme 61

Williams and co-workers form the C(7)–C(8) bond first through the addition of benzyl anion to an aziridino aldehyde **317** [\[2002OL3711, 2004JOC2825\]](#). The resulting hydroxyl group is protected and the *p*-methoxybenzyl (PMB) group is removed and the hydroxyl-oxidized to aldehyde **319** (Scheme 62). An intramolecular reductive amination was used to form the final bond of the tricycle.



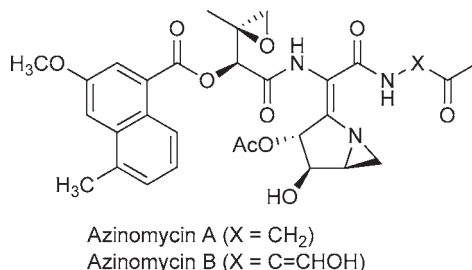
Scheme 62

While many of the remaining steps to convert **320** to FR900482 are simple functional group transformations, it is worthwhile to look at some of these steps as examples of reactions that can be undertaken in the presence of an aziridine. Compound **320** is converted to **321** through a series of deprotection, oxidation, and N-protection. The enolate of **321** is treated with formaldehyde to generate **322** as a separable 1:1 mixture of diastereomers. The unwanted diastereomer could be converted to a 70:30 mixture of diastereomers by treatment with DBU in toluene. The hydroxyl of **322** was protected and then the compound was oxidized with dimethyldioxirane (DMDO) to provide intermediate *N*-oxide **323**. Loss of anisaldehyde followed by intramolecular cyclization provided the tetracyclic **324** (Scheme 63). This compound was then converted to FR900482.



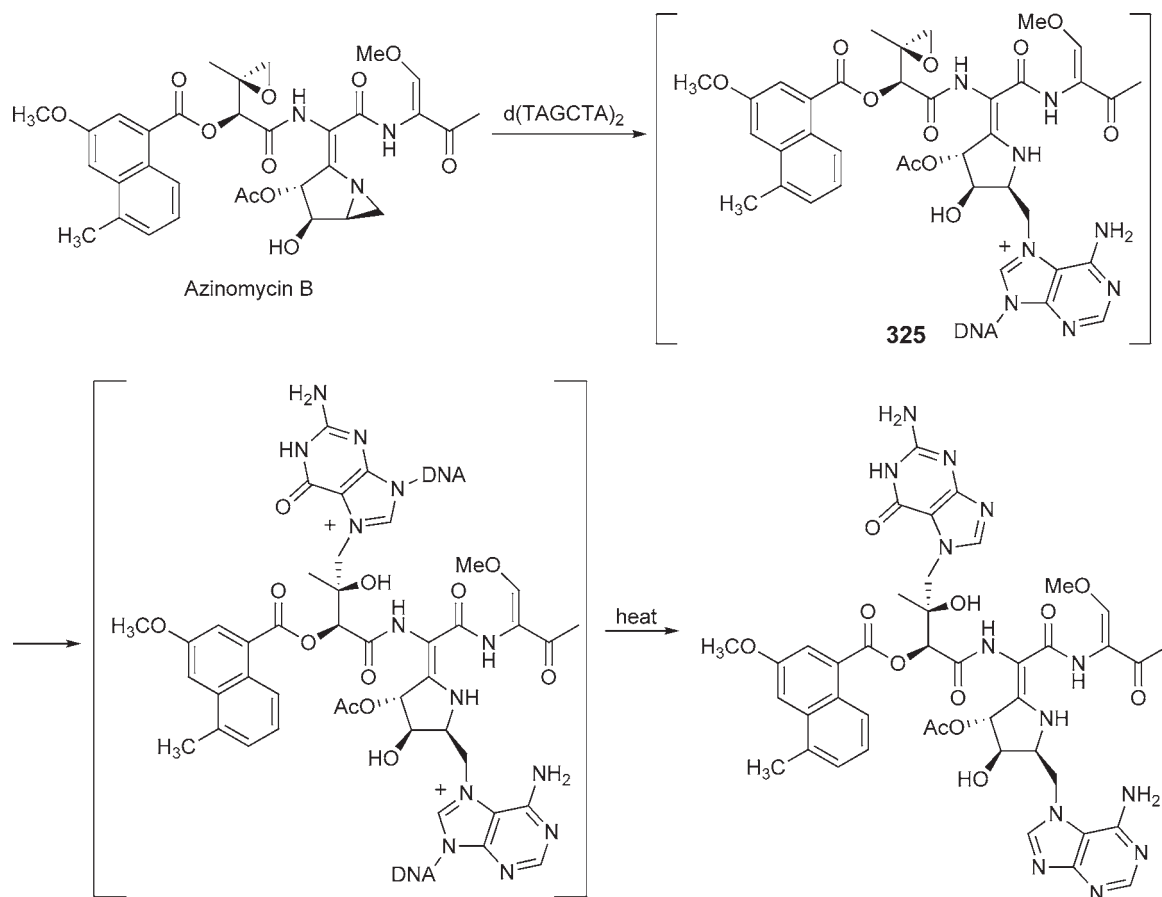
Scheme 63

Azinomycins A and B are antibiotics with significant *in vivo* and *in vitro* antiproliferative activity. These compounds act by creating interstrand cross-links in DNA. Two reviews on the synthesis and biological activity of these natural products have been published [\[2001T4467, 2004MI51\]](#). The azinomycin story is complicated by the discovery of carzinophilin approximately 30 years previous to azinomycin. The structure of carzinophilin has only recently been found to be identical to that of azinomycin B [\[1991TL3807\]](#). Work on the biosynthesis of this family of natural products has begun to elucidate how these unique compounds are formed [\[2004CC990, 2004CC2600, 2006OL1065\]](#).



The method by which azinomycins undergo DNA cross-linking is outlined in Scheme 64. A DNA nucleophile adds to the aziridine ring to generate adduct **325** [\[1999TL315\]](#). The DNA nucleophile then adds to the epoxide.

Unlike the mitomycins and FR900482, the azinomycins do not need to be activated prior to cross-linking. This has no doubt contributed to the difficulties in synthesizing these molecules.

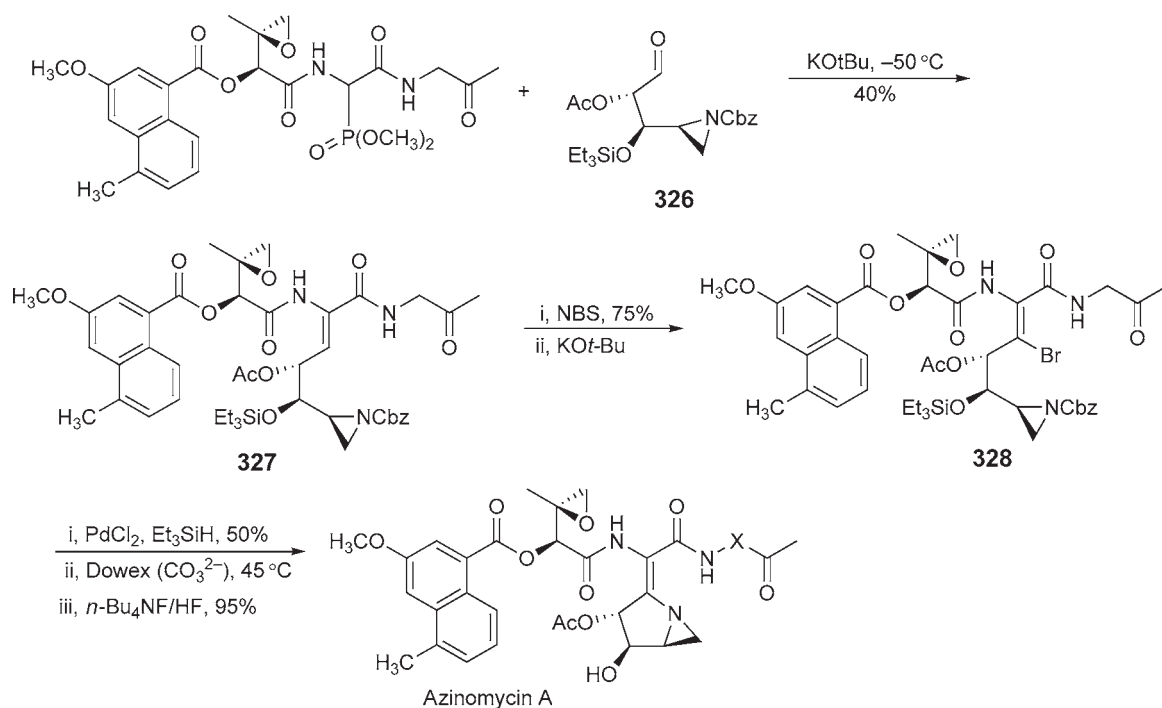


Scheme 64

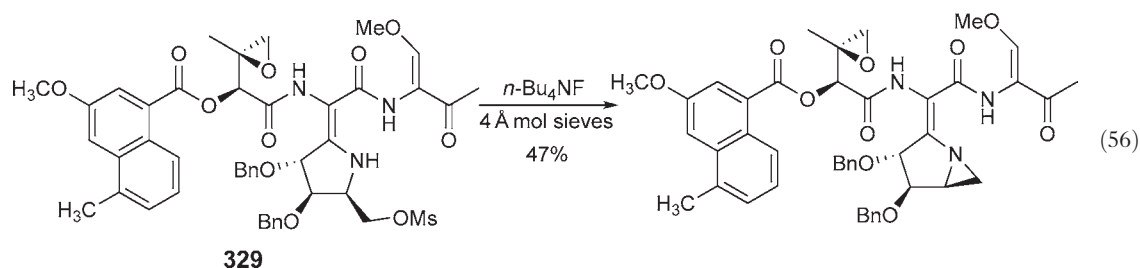
There are two general routes toward the synthesis of azinomycin. Both approaches generally prepare the top half of the molecule and then generate the reactive aziridine ring late in the synthesis. The two general approaches to aziridine formation are the formation of the exocyclic C–N bond through a nucleophilic displacement or an intramolecular conjugate addition/elimination of an intact monocyclic aziridine.

Only one complete total synthesis of an azinomycin has been reported [\[2001AGE1736\]](#). The final steps of this synthesis and the incorporation of the aziridine are outlined in [Scheme 65](#). Due to the highly unstable nature of the final product, this lone successful synthesis relied upon a convergent strategy that created the type II aziridine in the penultimate step. A Wadsworth–Horner–Emmons olefination with aldehyde [326](#) provided monocyclic aziridine [327](#) in moderate yield. The olefin was brominated and isomerized to generate [328](#) as a mixture of *E/Z* isomers. The Cbz group was removed in good yield and then cyclization was effected by treatment of the N–H aziridine with basic Dowex resin to provide the protected azinomycin in 64% yield via an addition/elimination pathway. The final step was the removal of the final triethylsilyl-protecting group. A variety of model studies and syntheses of portions of the molecule via this approach have been reported as well [\[1999JA9088, 1998JA3538\]](#).

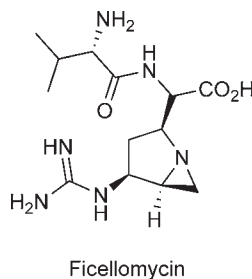
The other primary route to the azinomycin family of alkaloids is through the formation of the exocyclic C–N bond. As with most successful routes to the aziridine ring system, the aziridine ring is incorporated late in the synthesis. An example is shown in [Equation \(56\)](#), where treatment of amide [329](#) with $n\text{-Bu}_4\text{NF}$ leads to formation of the aziridine ring [\[2003T3063\]](#). This system was ultimately not converted to the natural product due to problems in hydrogenolysis of the benzyl-protected diol. All attempts at removing the benzyl group resulted in cleavage of the recently formed C–N bond.



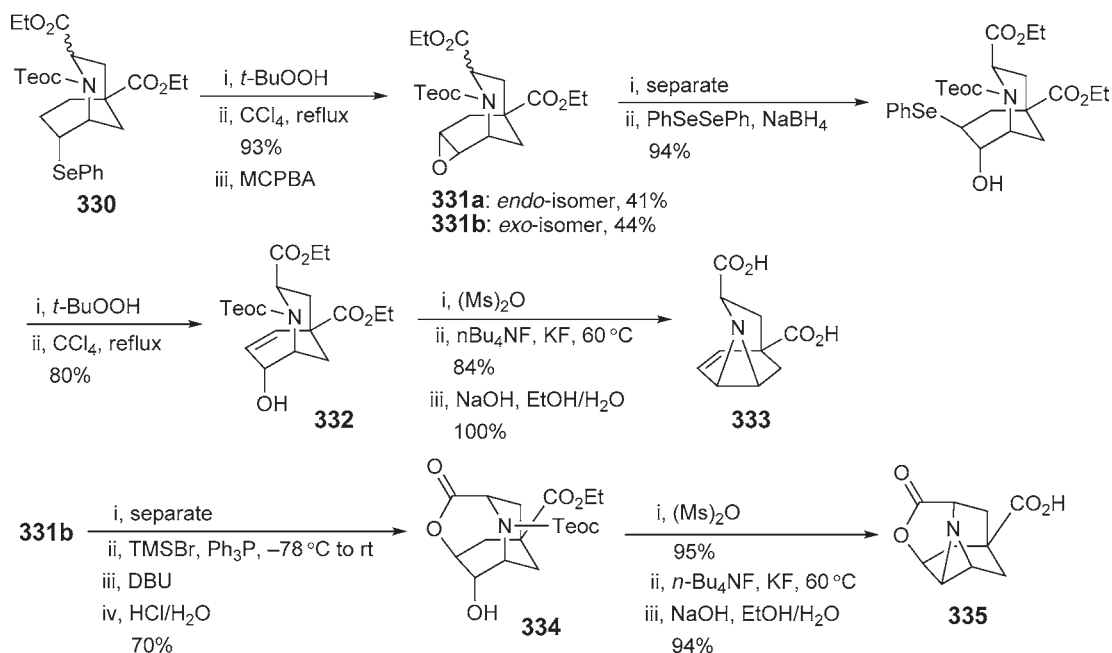
Scheme 65



Ficellomycin is a structurally unique natural product that contains a type II fused-ring aziridine. Structurally, one can look at this compound as a reduced and structurally less complex version of the azinomycin family of natural products. Ficellomycin was initially isolated in 1976 [\[1976JAN1001\]](#). The structure was later determined [\[1989JAN357\]](#) and then slightly revised as shown. Ficellomycin is an antibiotic that inhibits the growth of Gram-positive bacteria *in vitro*. This antibiotic acts by impairing the semiconservative DNA replication but not DNA repair in bacteria [\[1977B3406\]](#). Only one synthesis of the core azabicyclo[3.1.0]-hexane system has been reported [\[2004SL2212\]](#).

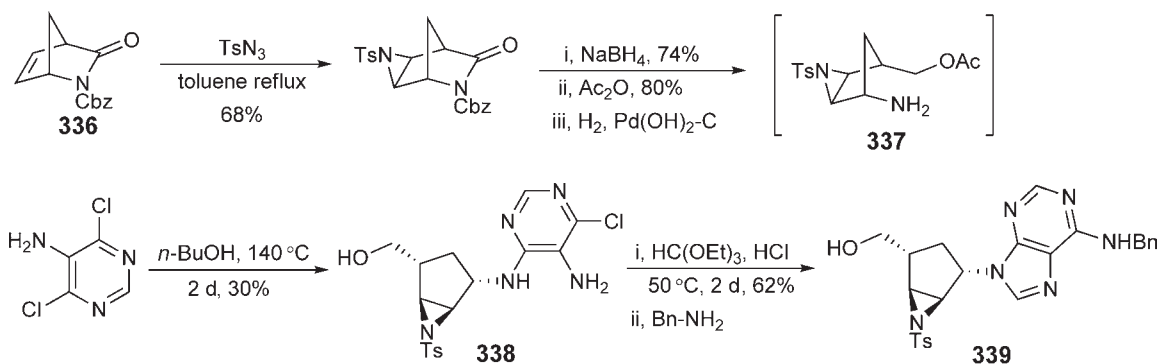


In addition to the naturally occurring fused-ring aziridine, a few examples of biologically interesting fused-ring aziridine containing molecules are known. Chorismate mutase is an enzyme that catalyzes a formal Claisen rearrangement of shikimic acid. An aziridine analog of a chorismate mutase inhibitor was prepared and evaluated [\[2004BMC4995\]](#). Two interesting fused-ring aziridines were prepared as part of this study. Starting from bicyclic amine **330**, the selenium was oxidized, eliminated, and epoxidized to form to diastereomeric epoxides **331a** and **331b**. After separation, the epoxide was opened with phenylselenide anion and eliminated to form allylic alcohol **332**. The alcohol was converted to the mesylate and the nitrogen-protecting group removed which initiated cyclization to form the fused-ring aziridine **333**. The other diastereomeric epoxide **331b** was converted to lactone **334**. Aziridine **335** was prepared from **334** in much the same manner as **333** (Scheme 66). Neither of these aziridines showed appreciable inhibitory activity toward chorismate mutase.



Scheme 66

Carbocyclic nucleosides have been found to be potent antiviral compounds. In an attempt at preparing conformationally rigid analogs, an aziridino-carbocyclic nucleoside was prepared [\[2003OBC452\]](#). The synthesis of epimino-carbocyclic nucleosides was available through a TsN₃ aziridination of **336**, followed by opening, not of the aziridine ring, but reductive cleavage of the Cbz-protected amide to form the unstable aziridinoamine **337**. The aziridinoamine **337**, without purification, was reacted with an aminopyrimidine to prepare the pyrimidine **338** in fair chemical yield. Ethyl orthoformate provides the final carbon needed to prepare purine ring. Finally, reaction with benzylamine forms the target epimino-carbocyclic nucleoside **339** (Scheme 67).

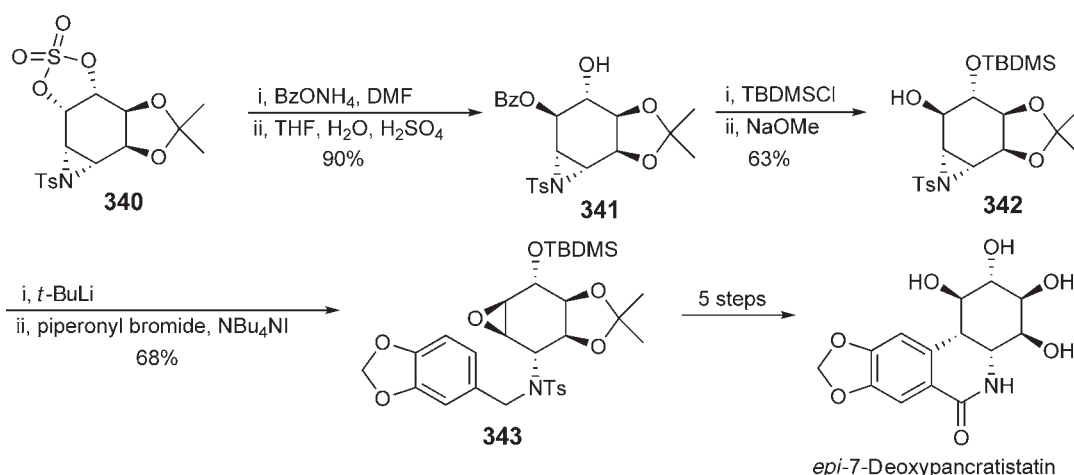


Scheme 67

1.02.7.2 Application of Fused-Ring Aziridines to the Synthesis of Natural Products

Fused-ring aziridines have found broad application to the synthesis of complex natural products. The ability of these fused-ring aziridines to be converted to other nitrogen-containing molecules under mild conditions with wide functional group compatibility makes these heterocycles quite useful.

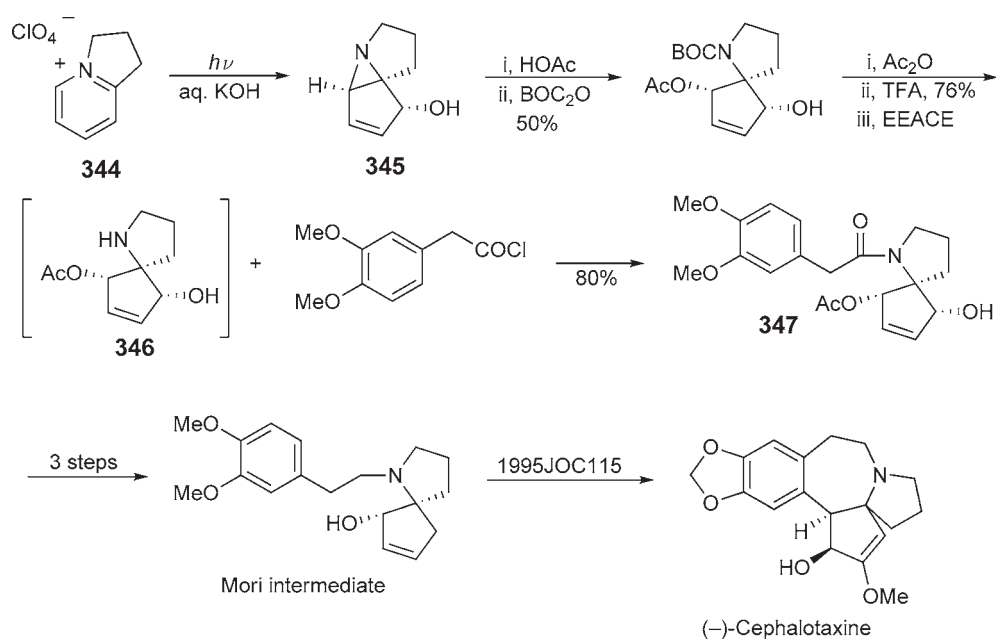
The *amaryllidaceae* alkaloids are interesting synthetic targets due to their potent anticancer activity as well as their limited natural supply. As shown in **Scheme 68**, an intramolecular aza-Payne rearrangement of a type I fused-ring aziridine is a key step in the synthesis of *epi*-7-deoxypancratistatin [<2002OL115>](#). Previous attempts to add a nucleophile to an epoxide in the presence of a fused-ring aziridine proved futile with ring opening always occurring at the aziridine [<2001CJC1659>](#). The differential reactivity of the cyclic sulfate relative to the aziridine proved important. Reaction of **340** with ammonium benzoate provided the hoped for selective sulfate opening, and after mild acid hydrolysis gave benzoate **341**. Modification of protecting groups provided the aza-Payne precursor, alcohol **342**. Treatment of **342** with *t*-BuLi generated the alkoxide which underwent the aza-Payne rearrangement followed by N-alkylation to give **343**. This intermediate was converted to *epi*-7-deoxypancratistatin in five additional steps. A noteworthy aspect of this synthesis is the number of transformations of the system that were carried out in the presence of the fused-ring aziridine.



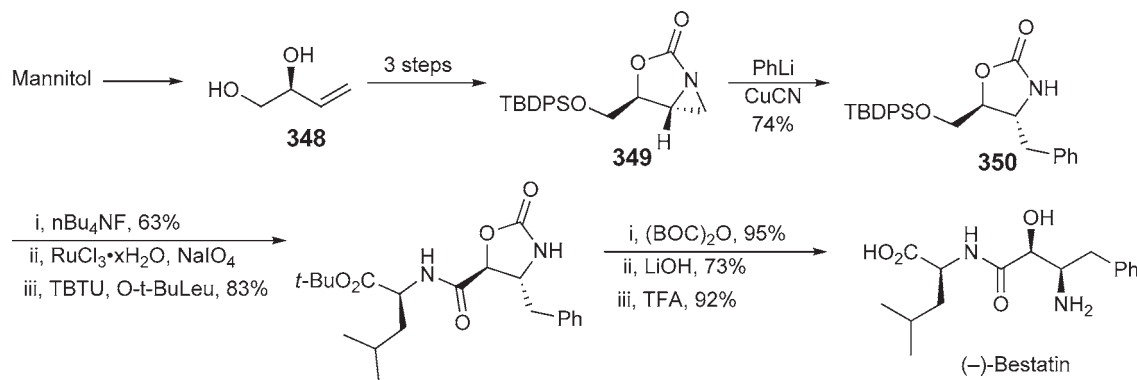
Scheme 68

Cephalotaxine is a member of the harringtonine alkaloid family. This group of alkaloids is of interest due to its potent anticancer activity and the unusual azaspiro system fused to an azepine ring. The photocyclization of pyridinium salts is an elegant route to type I aziridines. This method has been applied to the formal total synthesis of cephalotaxine [<2006T7266>](#). Bicyclic pyridinium perchlorate **344** was subjected to photocyclization conditions to yield the highly reactive aziridine **345**. Treatment with AcOH opened the aziridine then the nitrogen was protected as the BOC derivative in 50% overall yield. The monoacetate was converted to a meso-diacetate and then resolved with electric eel acetylcholinesterase (EEACE) to generate the enantioenriched (80–90% ee) monoacetate **346**. This unstable intermediate was immediately acylated to provide amide **347** (**Scheme 69**). Reduction, deoxygenation, and hydrolysis gave the Mori intermediate [<1995JOC115>](#) to complete a formal total synthesis of (–)-cephalotaxine. This synthesis shows the utility of the photocyclization reaction to generate complex spirocyclic molecules.

A number of small biologically active peptides containing a nonproteinogenic α -hydroxy- β -amino acid at the N-terminus are known. One of these peptides that has attracted some synthetic attention is (–)-bestatin. A fused-ring aziridine **349** has been used in a synthesis of this peptide as well as several analogs [<1999JOC2852>](#). Mannitol was used as the chiral building block for this synthesis and converted to diol **348**. The primary alcohol was selectively protected and the free secondary alcohol was converted to an azidoformate and cyclized to aziridine **349**. Aziridine **349** was opened with an organocuprate reagent to form oxazolidinone **350** in good yield (**Scheme 70**). The oxazolidinone was converted into the natural product (–)-bestatin in six additional steps. Significantly, this method was amenable for the synthesis of a number of analogs of bestatin by adding different organocuprate reagents. This method has also been used for the synthesis of oxazolidinone libraries [<2002JCO162, 2006BML3600>](#).



Scheme 69

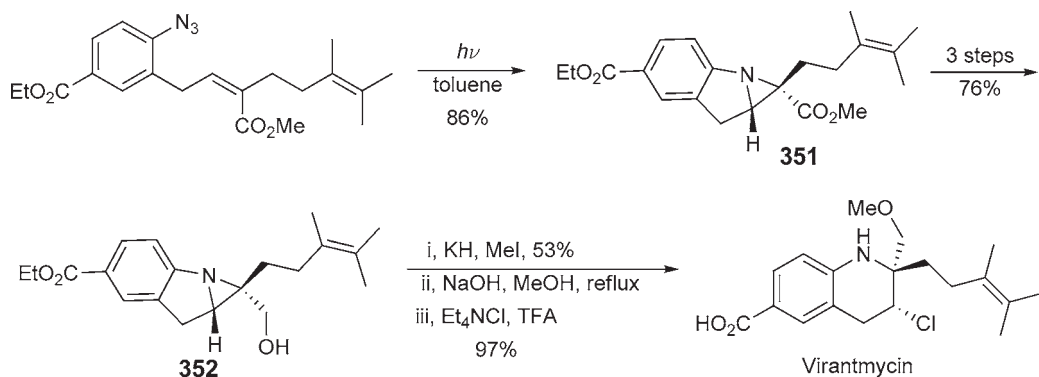


Scheme 70

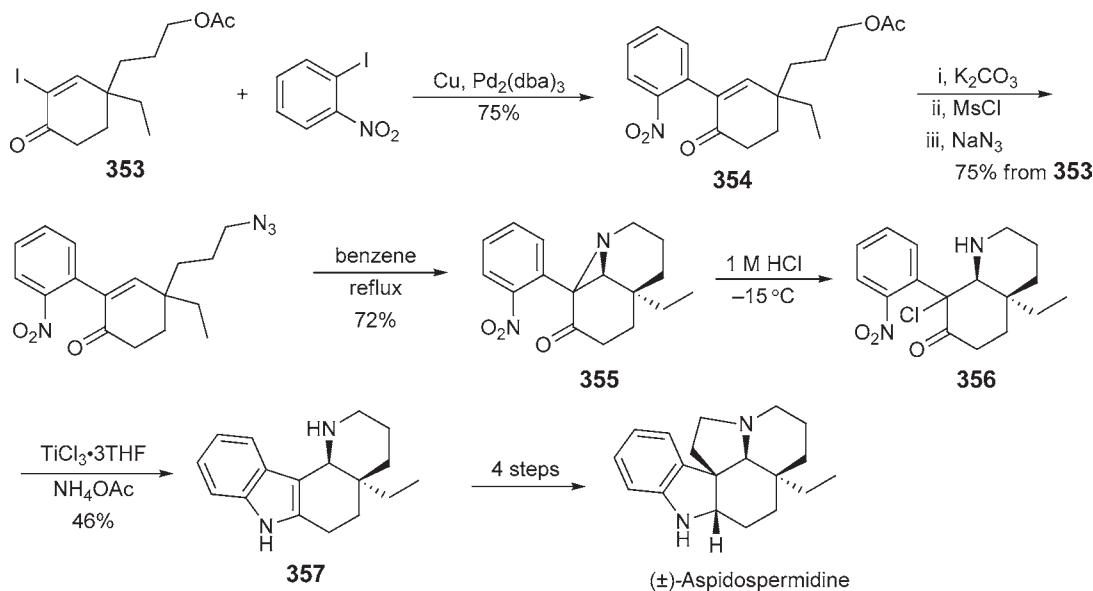
Virantmycin is a tetrahydroquinoline alkaloid that has inhibitory activity against DNA and RNA viruses. A total synthesis of virantmycin making use of a key type II aziridine has elucidated the absolute stereochemistry at C-2 and C-3 [<1996T10609>](#). An intramolecular photocyclization of an azide onto a Z-alkene produces type II aziridine **351** in excellent yield. A three-step reduction/selective reoxidation proceeds yields key aziridine alcohol **352** in 76% overall yield ([Scheme 71](#)). The alcohol is methylated and the ester hydrolyzed without harm to the aziridine. A TFA-induced ring opening of the aziridine by chloride provides the natural product virantmycin in good yield. This entire process was also carried out with the *E*-alkene to produce *epi*-virantmycin, thus proving the stereochemistry at C-2 and C-3.

The dipolar cycloaddition of an alkyl azide with an alkene to form an aziridine has been exploited in the total synthesis of the alkaloid ($\pm$)-aspidospermidine [<2005OBC213>](#). Enone **353** was prepared in 11 steps from 3-ethoxycyclohexenone and coupled to 2-iodo nitrobenzene under Ullman cross-coupling conditions. The acetate group of **354** was hydrolyzed and the resulting alcohol converted to an azide using standard conditions in 75% overall yield. The cycloaddition of the azide with the enone was conducted in refluxing benzene for 3 days. The fused-ring aziridine **355** was the only product isolated. None of the initial dipolar cycloadduct triazoline was observed. The

aziridine was opened using anhydrous HCl to provide the unstable chloride **356**. This compound was immediately reduced with $\text{TiCl}_3 \cdot 3\text{THF}$ to provide indole **357** in 46% yield. This compound was converted to aspidospermidine in four additional step (Scheme 72).



Scheme 71

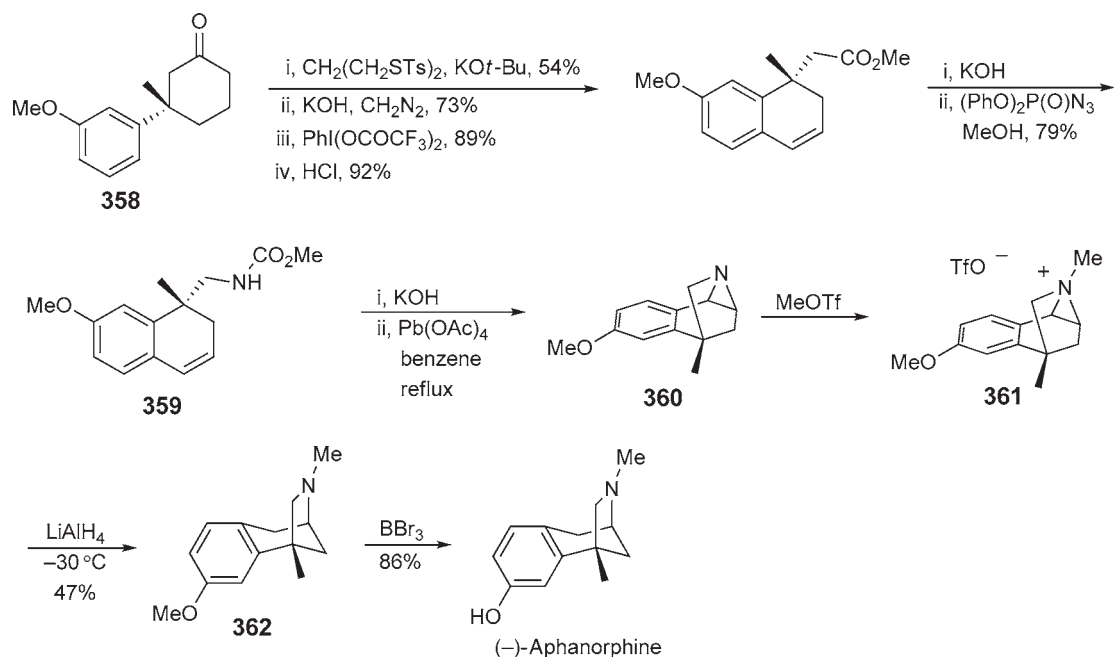


Scheme 72

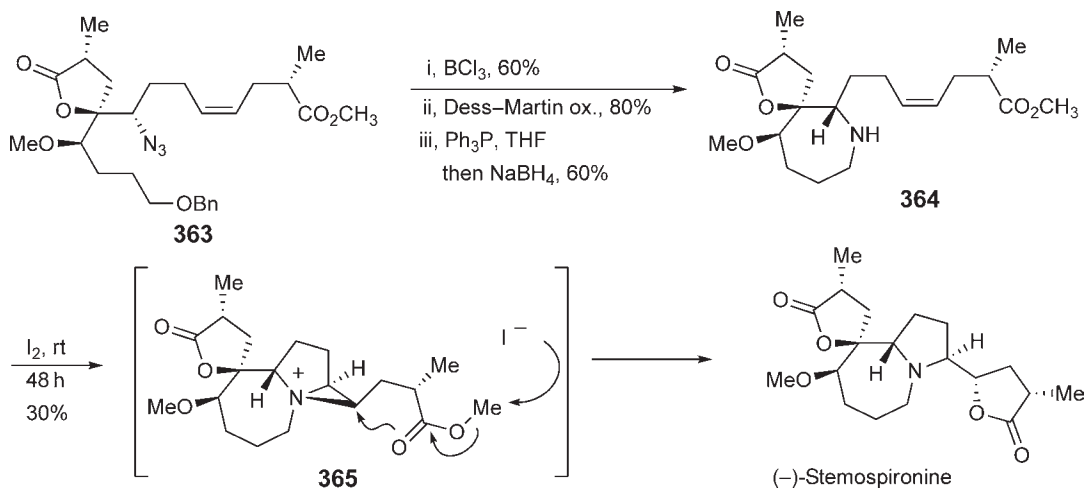
Aphanorphine is a naturally occurring alkaloid with structural similarity to the benzomorphan family of analgesics. This alkaloid has been prepared through the intermediacy of a fused-ring aziridinium salt [<1997H\(46\)21>](#). Enantiomerically pure ketone **358** was transformed into the α -diketone monothioacetal in 54% yield. Alkaline cleavage gave the dithiane in 73% yield after esterification. The dithiane was then converted to the acetal which cyclized to the dihydronaphthalene in good yield upon treatment with HCl. Hydrolysis of the ester followed by Curtius rearrangement provided carbamate **359**. The carbamate was hydrolyzed and treated with $\text{Pb}(\text{OAc})_4$ to provide an unstable aziridine **360** (Scheme 73). This aziridine was treated with methyltriflate to generate aziridinium salt **361**. Reductive cleavage of the benzylic aziridinium C–N bond provided the tricyclic precursor to aphanorphine **362**.

The synthesis of (–)-stemospirine provides another example of the use of aziridinium ions in natural product synthesis [<2001OL2721>](#). The *Stemona* alkaloids are characterized by the 1-azabicyclo[5.3.0]decane nucleus. Azide **363** was the key intermediate for the aziridinium-mediated synthesis. Debenzoylation at low temperature

(-78°C to -10°C) followed by a Dess–Martin oxidation provided the necessary azidoaldehyde. An intramolecular Staudinger cyclization followed by reduction of the resultant amine provided azepine **364**. Treatment of **364** with iodine induced an interesting double cyclization. Initial iodination of the double bond is followed by aziridinium ion formation **365**. An intramolecular and stereospecific ring opening by the carboxylate provides the target (–)-stemospirone.



Scheme 73



Scheme 74

1.02.8 Conclusion

We have presented in this chapter a selection of the chemistry of fused-ring aziridines and fused-ring azirines. As expected this chemistry, to some extent, parallels that of monocyclic aziridines and azirines. Many of the syntheses of aziridines work equally well for both monocyclic and type I fused-ring aziridines. There are however a number of significant differences. For example, methods for the synthesis of type II aziridines are often not viable routes to

monocyclic aziridines. The photolytic conversion of pyridinium salts to type I aziridines and the relative lack of examples of fused-ring azirines are additional differences. The reactions of fused-ring aziridines again offer a number of parallels to that of monocyclic aziridines especially in the general area of nucleophilic ring-opening reactions. There are of course a number of highly useful differences in reactivity relative to monocyclic aziridines. These differences include rearrangements to form other ring systems and the ability to control the regiochemistry of nucleophilic ring-opening reactions in ways that are not available to monocyclic aziridines. Fused-ring aziridines are found in a number of biologically significant aziridine-containing natural products such as the mitomycins, the azinomycins, and the FR900482 family of natural products. Natural products containing fused-ring aziridines comprise the majority of natural products containing any sort of aziridine ring. Fused-ring aziridines and azirines encompass a wealth of useful and interesting heterocyclic chemistry, which complements and extends the chemistry of monocyclic aziridines.

1.02.9 Further Developments

Progress in the area of fused-ring aziridines has continued since this chapter was completed. We note here some significant and interesting new chemistry. A review on the synthesis and reactions of C-heteroatom aziridines has been published <2007CR2080>. This review provides some intriguing examples of fused-ring aziridines. Two notable methods for the synthesis of type II aziridines have been reported. One method uses a copper catalyzed intramolecular cyclization of N-tosyloxy carbamates to form type II aziridines with the general structure of **126** or **128** <2007JOC5587>. An extension of work previously reported <2002OL2481> now provides an enantioselective method to prepare sulfamate linked aziridines such as **133** <2007SI251>.

In addition to the synthesis of aziridines, a number of improved methods for the ring opening reactions of fused-ring aziridines have been reported. These include the use of ionic liquids <2007CJC366> and polyethylene glycol <2007S666> as superior solvents for aziridine ring opening reactions. In addition advances in the desymmetrization of *meso*-aziridines have been reported using a multidentate niobium catalyst <2007JA8103> and a cinchona-derived catalyst <2007TA443>.

Two interesting ring opening reactions have been reported for the synthesis of pharmacologically interesting molecules. One uses a ring opening reaction of a fused-ring aziridine with 3-butanol to generate a key intermediate enroute to a synthesis of tamiflu <2007OL259>. Another method uses a sugar derived N-nosyl aziridine as an effective method for the synthesis of disaccharides <2007T2482>. In addition a new review on the synthesis of FR900482 has recently been published <2007MI470>.

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Biographical Sketch



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1.03

Oxiranes and Oxirenes: Monocyclic

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1.03.1 Introduction to Oxiranes and Oxirenes

“If carbonyl compounds have been said to be virtually the backbone of organic synthesis, the epoxides correspond to one of the main muscles.” – Dieter Seebach <B-1983MI5>.

One of the simplest heterocycles, the oxirane ring, is also a fundamental functional group in organic chemistry. Its formation can be accomplished using one of a set of simple strategies. Even so, a large number of reagent systems have been developed for their production. The importance of these compounds has stimulated a number of protocols for their enantioselective preparation. In addition, the inherent ring strain of the heterocycle ($27.2 \text{ kcal mol}^{-1}$) coupled with the polarization of the carbon–oxygen bonds generates a substantial reactivity profile. It is, quite frankly, impossible to comprehensively cover all the scholarly investigations dealing with oxiranes and oxirenes since 1995 within the scope of this chapter. As such, representative examples of oxirane synthesis and reactivity are highlighted. For specific details, readers are encouraged to consult one of the many reviews that have been published since the review in CHEC-II(1996) <1996CHEC-II(1)97> in 1995. These are cited in specific sections in the chapter.

The three-membered oxygen heterocycle, or oxirane (Figure 1), is also described in the current literature as an (1,2-)epoxide, an oxacyclopropane, or, using additive nomenclature, an ethylene oxide.

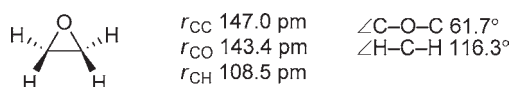


Figure 1

1.03.2 Oxiranes: Experimental Structural Methods and Relevant Theoretical Investigations

A number of structural properties of oxiranes, including spectroscopic features (nuclear magnetic resonance (NMR), mass spectrometry (MS), ultraviolet (UV), and infrared (IR)), were discussed in detail in CHEC(1984) and CHEC-II(1996) <1996CHEC-II(1)97, 1984CHEC(7)95>. Oxygen-17 NMR chemical shifts were analyzed using magnetically corrected basis sets <2002PCA4176>. The facility of double coordination of an oxirane oxygen atom to metal salts was investigated <2001IC6086>.

Improvements in computing technology and processing rates have made high-level theoretical calculations easier and more informative. Understandably, the chemistry of epoxide functional group has been an important subject for theoretical studies in the last decade. A discussion of some quantum chemical calculations with regard to the industrially relevant peroxometal epoxidation catalysts has recently appeared in the literature <2004ACR645>. As epoxidation of alkenes using peracids and dioxiranes is one of the fundamental processes generating oxirane rings, a number of calculations probing the reaction surface and transition state structure have been performed. In most cases, a spiro ‘butterfly’ transition state structure is found. Calculations have been performed at varying levels of theory. In the realm of peracid epoxidation of alkenes, MP2/3-21G, MP2/6-31G*, and MP2/6-311G** (to optimize geometries) and CASSCF(4,4)/3-21G was used to determine the transition state <1996JOC616>; Becke3-LYP/6-31G* (B3LYP)10 was used in an experimental and theoretical study <1997JA3385>; B3LYP/6-311+G**//B3LYP/6-31G theory was used to examine the geometry, diradical character and transition state flexibility of oxaziridine and dioxirane epoxidations <1997JA10147>. The rate acceleration of epoxidation using *meta*-chloroperbenzoic acid (MCPBA) in the presence of strongly acidic additives was analyzed at the B3LYP/6-311G(d,p) level <1997JOC5191>. Alkene substituents decreased the barrier to oxidation at the QCISD/6-31G* level <1998JA9902>. The directing group effect of hydroxyl groups at the allylic position of an alkene was analyzed at the MP2/6-31G(d) level of theory. These effects were probed further using the B3LYP method using three basis sets (i.e., 6-31G*, 6-311G**, and 6-311+G**) <1999JOC3853>. A spiro transition state was found at B3LYP/6-311+G**//B3LYP/6-31G* theory levels <2000JOC2030>. Hydroxy-group directing effects were examined using B3LYP

density functional method with 6-31G(d) and 6-31G(d,p) basis sets. The four lowest-energy transition structures and their respective pre-reaction clusters were fully re-optimized by employing 6-311+G(d,p) and correlation-consistent polarized valence triple- cc-pZTV basis sets <2000JOC6715>. The uncommon 'planar' transition state was uncovered in an examination of the reaction of bridged alkenes with peracids <2002JOC8519>. A calculation finding planar transition states suggested that density functional theory (DFT) may not be adequate to examine these reactions <2002TL4215>, but this result was not supported upon reexamination using complete active space self-consistent field (CASSCF) (12,12)/6-31+G(d,p) <2003PCA4300>. The optimized spiro CASSCF (12,12)/6-31+G(d,p) transition structure is a first-order saddle point that is 4.0 kcal mol⁻¹ lower in energy than the corresponding planar TS after correction for dynamic correlation [CASSCF(MP2)]. Transition structures from the epoxidation of allylic alcohol with performate ion at the B3LYP/6-31+G(d,p) level in a conductor-like polarizable continuum model (CPCM) for water <2002OL2661>. Their findings indicate a preferential hydrogen bonding of performate with the substrate hydroxyl group rather than with water, leading to a directed epoxidation. The gas-phase reactivities of oxiranes and peracids were compared using experiment and theory [QCISD(T)//QCISD/6-31+G(d,p)] and QCISD(T)/6-31G(d)//B3LYP/6-311+G(3df,2p)] <2003JA924>. The effect of *s-trans* and *s-cis* peroxy acid conformers in the epoxidation of acyclic allylic alcohols was studied using RB3LYP calculations <2005JOC9573>.

Epoxidations using dioxiranes have been evaluated using the B3LYP/6-31G* level, generally supporting the conventional *spiro* 'butterfly'-shaped transition state <1997JA12982>. The presence of hydrogen bond donors significantly decreased activation barriers for the reaction <1998JA1872>. Radical intermediates were not found along the reaction surface in reactions between 1,1-disubstituted alkenes and dioxiranes (Becke3LYP/6-31G*) <1998JOC8565>. Fluorinated dioxiranes and oxaziridines were also examined using this level of theory <2000JA6297, 2000JA2948>. CASSCF calculations suggest that a symmetrical spiro-oriented transition state is lower in energy compared to a nonsymmetrical one <2004PCA6886>.

Increases in processor speed for computations have spurred the examination of metal-catalyzed epoxidation reactions at high levels of theory. Different density functionals were examined using epoxidation catalyzed by transition metals as a test case <2003PCA5466>. The mechanism of oxygen transfer using inorganic peroxides is the topic of a short review <2004ACR645>. The diastereoselective epoxidation of chiral allylic alcohols using titanium peroxy complexes has been examined <1995JOC673, 2002JOC1427>. Hybrid density functional theory has been used to examine catalysis using methyltrioxorhenium and related complexes <1998JOC1752, 2001JA2365, 2001IC3755>.

Its synthetic importance combined with its mechanistic uncertainty has made the Jacobsen–Katsuki epoxidation of alkenes and related reactions subject to intense examination over the past decade <2006OM177, 2004OL59, 2004IC2175, 2003JOC6202, 2001JOC5796, 2001IC4040, 2000AG(E)589>. Metallooxetanes were suggested as intermediates early on <1995JA11035>. Models of these systems using DFT (Becke3LYP) suggest that this intermediate exists in either a high-spin quintet or triplet state <1999OL419>. The known predilection of these catalysts to form *cis*-epoxides has been rationalized by invoking a spin transition from a triplet to a quintet state along the reaction pathway <1999JA5083>. Hybrid density functional calculations <2001AGE2073> support the idea that *N*-oxides, frequently used as additives to enhance reactivity and selectivity, operate by coordinating in the axial position and inducing a conformational change to a highly reactive nonplanar species. The *N,N'*-bis(salicylaldehyde)ethylenediamine(salen) ligand itself is involved in the transition state of the epoxidation <2003JOC6202, 2004OL59>.

Molybdenum and tungsten catalysts have been examined <2000JA10101, 2000IC2314, 2000JOC2996, 2001PCA4765, 2001PCA9231>. Iron complexes, including those relevant to the study of cytochrome P450, have also been the subject of recent investigations <2002JA2806, 2002JA4135, 2002JA11809>.

Titanosilicate catalysis has been examined by DFT studies <2001PCB3493>. The reaction of vinylcarbenoids and aromatic aldehydes has also been studied <2001JOC5395>. A DFT study of a model system for epoxide formation using a sulfur ylide has been published by Aggarwal *et al.* <2002JA5747>.

Oxirane reactivity has also been studied by theoretical methods. Chief among these are enzyme-catalyzed reactions such as the cyclization of oxidosqualene cyclization <1998JA4045>, glycosidase <1998JOC8157>, or hydrolase activity <2005JA11226, 2005JA14339, 2002JA14558>. Other oxirane reactions investigated include alkylation reactions using lithium organocuprates <2000JA7294>, reactions with phosphine nucleophiles <2005TL4087>, oxygen transfer to carbenes <2002PCA9563>, abstraction reactions <2002JA12335>, and bidentate acid activation <2000JOC2464>.

1.03.3 Oxiranes: Reactivity

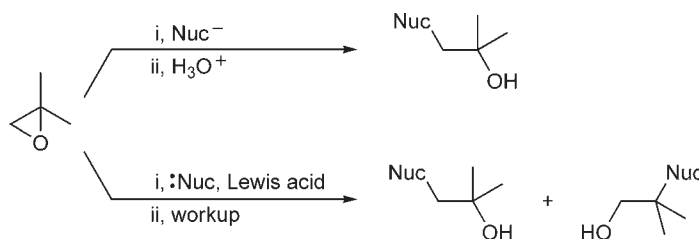
1.03.3.1 Thermal and Photochemical Reactions

Epoxides engage in 1,3-dipolar cycloadditions in the guise of carbonyl ylides under thermal conditions, a behavior that can be facilitated through the use of microwave radiation <2003SC1861>. Photoinitiated polymerization of

epoxides has been investigated <2005MM3584>. The photolytic reaction of butadiene monoepoxide and organomercurials has been examined <1999TL7699>. The transfer of oxygen atoms from oxiranes to singlet carbenes has been examined by laser flash photolysis <1998JA8681>.

1.03.3.2 Oxiranes as Electrophiles (Nucleophilic Attack at Ring Carbon)

The ring opening of oxiranes by nucleophiles is, arguably, the most important reaction of this ring system. Factors that enable this reactive paradigm are the (1) relief of ring strain, (2) the polarization of the C–O bond, and (3) the basicity of the oxirane oxygen. As expected, the stereoselectivity of oxirane ring opening is typically anti. The regioselectivity of oxirane ring opening depends on oxirane structure and reaction conditions (**Scheme 1**). The S_N2 reaction between strong nucleophiles and oxiranes takes place typically at the least-substituted carbon atom for steric reasons. In the presence of Brønsted or Lewis acids, the activation of the electrophile can lead to so-called ‘borderline S_N2' ’ (i.e., bimolecular substitution having considerable S_N1 character in the transition state) or S_N1 processes. In these instances, reactions can occur at the more substituted carbon atom.



Scheme 1

The regioselective opening of 1,2-disubstituted oxiranes is even less predictable. Unsurprisingly, the nature of the nucleophile, the specific reaction conditions, and the structure of the oxirane electrophile can have a dramatic effect (**Figure 2**). Typically, substituents are required on the oxirane electrophile that (1) activate one terminus via either a directing effect (i.e., an *in situ* coordination event) or stabilization of the S_N2 transition state (resonance effect) or (2) deactivate one terminus via destabilization of the S_N2 transition state (inductive effect). In highly functionalized oxirane-containing substrates, the prediction of regioselectivity is not always trivial. Operationally well-defined approaches for controlled regioselective additions of a variety of nucleophile types to highly functionalized oxiranes remains a major challenge.

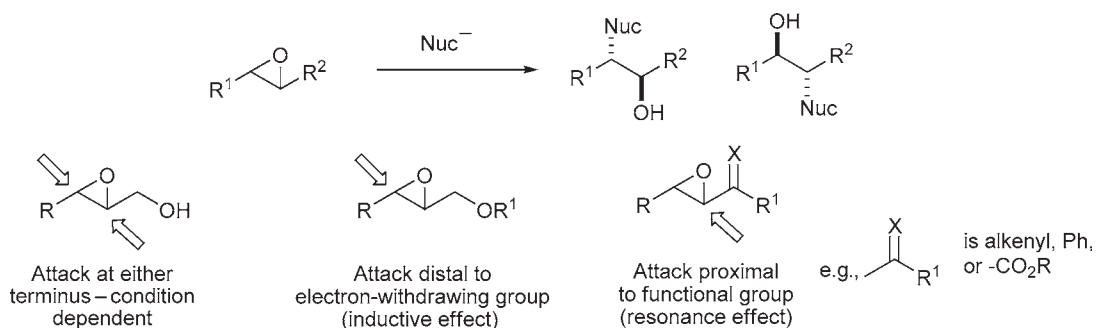


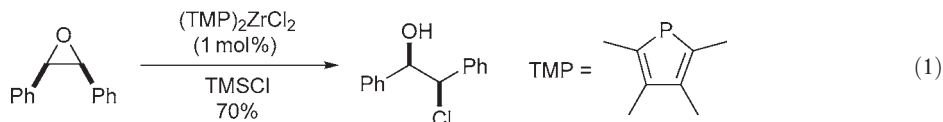
Figure 2

1.03.3.2.1 Halides as nucleophiles

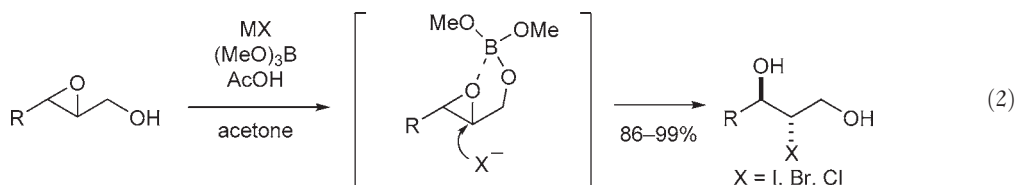
The ring opening of oxiranes using halide ions as nucleophiles is well established. The use of epoxides as key intermediates for the synthesis of oxygen, nitrogen, and halogen-substituted tertiary stereogenic centers has been reviewed <2004COR149>. These reactions can be induced using silica-gel supported lithium halides <1996TL1845>, or lithium bromide and Amberlyst resin <2005JOC1605>.

Metal catalysis can enable efficient ring-opening reactions. Recent examples include the use of 1 mol% of a phosphaziracene catalyst with trimethylsilyl chloride (TMSCl) <2003OL2543> (**Equation 1**), nickel or metal

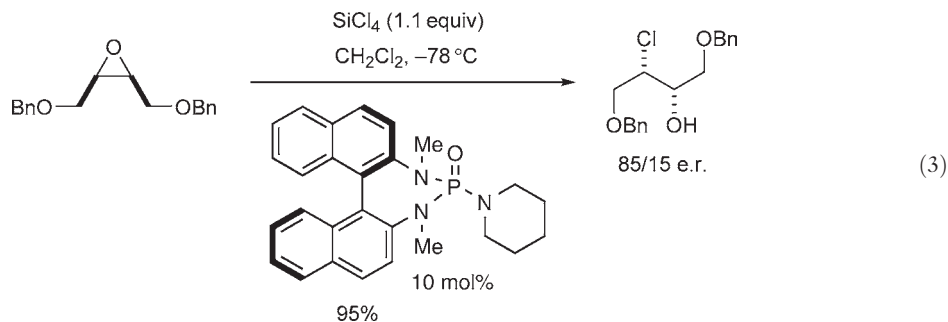
salt-promoted reactions between halogens and fluorinated epoxides <1996JA8140, 2004JOC2394, 2005TL5439>, with bis(chlorodibutyl)tin oxide in 2-chloroethanol <2001SL65>, bismuth salts <2005TL8229>, magnesium bromide <2004TL5969>, crown ethers <1998JOC1455>, or ionic liquids <2005JOC4517, 2004TL2435>. A recent article presents the case that thiourea does not promote the conversion of epoxides to halohydrins, in contrast to previous work <2005T4233>. The ring-opening reactions of α,β -epoxyamides with a variety of nucleophiles, including halide ions, thiolides, selenides, etc., has been examined <2004TL9069>.



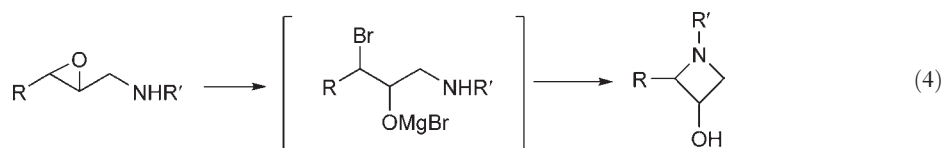
2,3-Epoxy-1-hydroxylated substrates react at C-2 using metal halides <1995JOC4803>. This reactivity pattern is also promoted by the presence of trimethylborate additives (Equation 2) <2003TL8975>. For 1,2-disubstituted epoxides, the regiochemical outcome of nucleophilic attack becomes less predictable. However, in the case of epoxy ethers, chelation control can be used to deliver the nucleophile preferentially to the epoxide carbon 'away from' the ether moiety. As an example, the additive [Cr(*N*-*t*-Bu)Cl₃ 1,2-dimethoxyethane (dme)] leads to clean reaction via initial formation of a chelated species and subsequent nucleophilic attack <2000SL677>. Unsaturated halohydrins can be generated in a stereocontrolled manner from unsaturated epoxides <2001JOC7231>.



Exciting results dealing with the enantioselective ring opening of epoxides have been obtained. Chiral Lewis base-induced ring-cleavage using silicon tetrachloride has been performed <1998JOC2428> (Equation 3). A zirconium-based chiral catalyst with a tripodal hydroxylamine ligand scaffold has been used for the desymmetrization of *meso*-epoxides, although most of the examples used in this instance are cyclic epoxides <1998JA7139>.



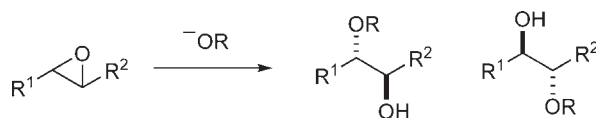
Occasionally, these ring-opening reactions can be used in tandem with other chemical processes, such as oxidation <1995T2467>, intramolecular nucleophilic attack leading to azetidines (Equation 4) <1997TL6059>, or 1,3-allylic transposition leading to 2° and 3° allylic alcohols <1997TL4675>.



1.03.3.2.2 Oxygen-based nucleophiles

1.03.3.2.2(i) Intermolecular addition reactions

Hydrolysis or alcoholysis is certainly one of the typical ring-opening reactions of an oxirane ring (Scheme 2). Transition state effects in acid-catalyzed ring openings have been examined <2004JOC5204>. A number of catalysts



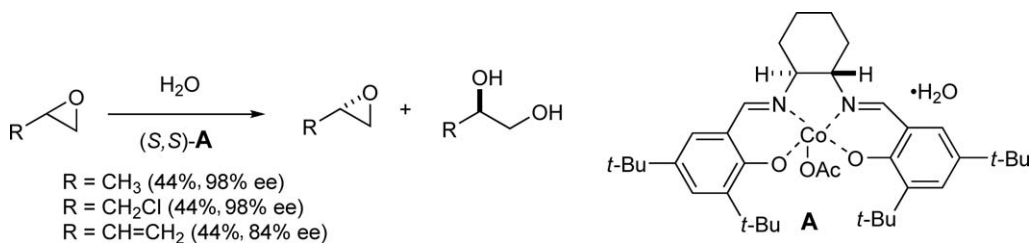
Scheme 2

have been developed to facilitate this process. Titanium salts such as $\text{TiCl}_3(\text{OTf})$ or $\text{TiO}(\text{TFA})_2$ have been reported to function as efficient catalysts for the stereospecific acid-catalyzed alcoholysis of asymmetric monosubstituted epoxides <1999SC1017>. A related process using a carboxylic acid as a nucleophile was recently described <2005T7481>. A particularly mild and selective method has been reported using catalytic amounts (1 mol%) of ferric perchlorate <2000SC2967>. Ammonium molybdate and hydrogen peroxide promotes the smooth formation of α -hydroxy ketones (presumably through the intermediacy of 1,2-diols <2000CL844>). Copper(II) tetrafluoroborate can be used to activate oxiranes for alcoholysis <2002OL2817>. Similar outcomes have been observed with the assistance of aminopropyl silica gel (APSG)-supported iodine in catalytic quantities <2002SL1251>. Chromium(III) ethanoate activates reactions between carboxylic acids and oxiranes <2002OPD234>. Tin(II) chloride converts epoxides to 1,3-dioxolanes <2003JOC9144>. Ketones can be used as nucleophiles for opening oxirane rings under Bronsted acid catalysis <2005OL247>. This reaction type has been used in a number of practical synthetic applications, as exemplified by the synthesis of the herbicide (*S*)-indanofan <2002JOC3131>. Monoalkylphosphonic acids have been demonstrated to add to trialkyl-substituted epoxides <2001JOC3767>.

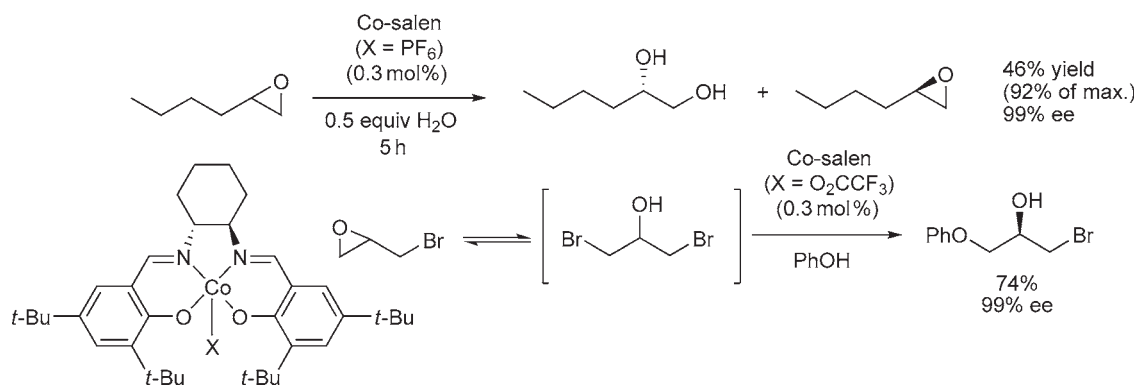
An interesting alcoholysis is promoted by the π -acid tetracyanoethylene (TCNE) in alcoholic media. The affinity of these alkenes for the oxirane oxygen is highly selective, allowing for selective epoxide alcoholysis in the presence of tetrahydropyran (THP) ethers and ethylene acetals <1996BCSJ195>. Anhydrides can be used to activate epoxides toward nucleophilic attack <2005T3659, 2005TL1601, 2002TL1759>. The oxirane function in γ,δ -epoxy- α,β -unsaturated esters can be opened in a regioselective manner using alcohols under Lewis acid catalysis <2000TL3829>. This process was used in a synthesis of muricatacin <2000TL3833>. Gallium heterobimetallic complexes activate epoxides for attack by substituted phenols in an enantioselective manner <1998AGE2223, 2000JA2252>.

The ring-opening reaction is not limited to conventional nucleophiles. Ceric ammonium nitrate in the presence of excess nitrate ion converts oxiranes to β -nitrate alcohols <1995T909>. The reaction is believed to proceed via a one-electron transfer to form an oxiranium radical cation that is subsequently captured by a nitrate ion. Nitric oxide adds to 2,3-epoxy phenyl ketones <2004TL1565>.

The hydrolytic kinetic resolution of racemic terminal epoxides using metal salen catalysts has become one of the premier methods for the formation of enantioenriched oxiranes or 1,2-diols (Scheme 3) <2002JA1307, 1997SCI936, 1998JOC6776, 2000AGE3604>. This topic has been reviewed <B-1999CAC1309, 2000ACR421>. As further examples, a cobalt(III)salen complex catalyzed the enantioselective hydrolysis of racemic hexene oxide in the presence of 0.5 equiv of water to provide the (*R*)-enantiomer in 99% ee (Scheme 4). In this instance, the inorganic hexafluorophosphate ligand was found to be important for catalyst activity and selectivity, as the conventional acetate ligand gave inferior results <2003TL5005>. In an interesting example, a cobalt salen catalyst generated a chiral bromohydrin in excellent ee (>99%) and good yield (74%) from the racemic bromo-epoxide (Scheme 4). The yield is attributed to a bromide-induced dynamic equilibrium with the dibromo alcohol, allowing for conversion of unused substrate into the active enantiomer <1999JA6086>. Polymer-supported Co(salen) complexes have been developed, and these in certain instances provide superior results compared to the solution-phase systems <1999JA4147, 2002JP1870, 2002HCA913, 2003TL7081>. Other types of nucleophiles such as carboxylic acids <1997TL773> or phenols <1999JA6086> can be used. Mechanistic investigations have led to technical improvements through catalyst



Scheme 3

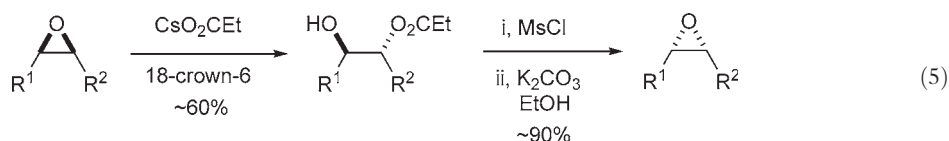


Scheme 4

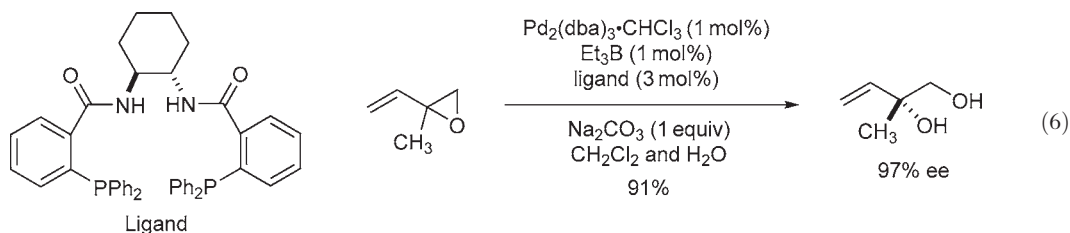
modification <1996JA10924, 2001JA2687, 2004JA1360, 2004TL7429>. Interestingly, the discrimination between enantiomers through epoxide ligation to chiral vanadium salen compounds has been directly observed using ENDOR <2004JA15660>. A number of applications of this technology have been reported <2005TL5239, 2005T6243, 2003TA3589, 2001TL4907, 2001AGE3877>.

The kinetic resolution of epoxides can also be carried out using water as a nucleophile under the influence of epoxide hydrolases. This area has been recently reviewed <1997T15617>. Furstoss has examined these enzymatic hydrolysis processes from a mechanistic viewpoint <1996JOC7402, 1998JOC3532, 1999JOC5029, 2001JOC538>. The use of 'directed evolution' to improve the catalyst system has achieved real successes <2005JA13338, 2004OL177>. These biological catalysts have been used to resolve 1,2-dialkyl epoxides <1999T11589> and *meso*-epoxides <2004JA11156>. Further examples of hydrolases in reactions are located in the followed references: <2004TA2801, 2004CEJ3467, 2004T601, 2002TA2399, 2001T2775, 2001T695, 2000TA4451, 2000JP13779, 2000TA3041, 1999TA3327, 1999TA3167, 1999T11589, 2003JCI1934>.

Opening epoxides with oxygen nucleophiles under basic conditions is also a common reaction. For example, epoxide inversion occurs upon treatment of an acyclic oxirane with cesium carboxylate salts followed by treatment of that product with methanesulfonyl chloride and potassium carbonate in methanol (Equation 5) <2002TL4111>. Phenoxides open oxiranes in the presence of cyclodextrins in water <2003JOC4994> or using cadmium salts <2002JA7075>. Tributylphosphine promotes ring opening of epoxides in water <2003JOC726>.



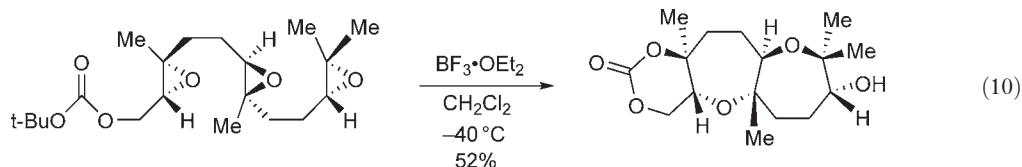
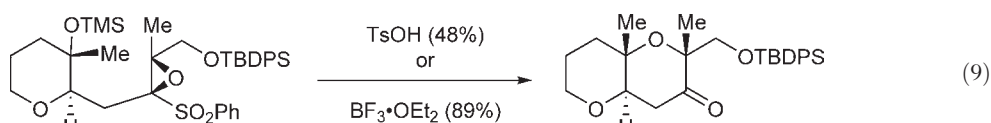
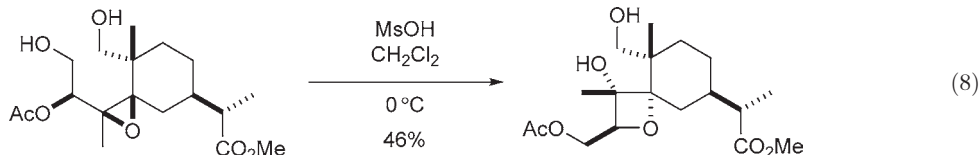
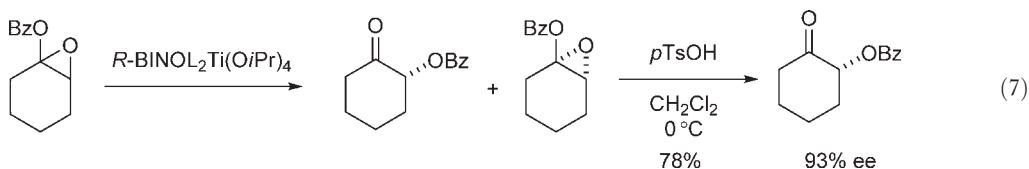
Oxygen nucleophiles can attack oxiranes under the influence of metal catalysts. In the following examples, the metal complexes do not behave as a Lewis acid activator, but rather affect oxirane reactivity in a more profound way. Allylic epoxides, due to their ready conversion to metal-stabilized allylic cation equivalents, are frequent precursors for metal-catalyzed processes. Rhodium salts open vinyl epoxides using alcohols as nucleophiles <2000OL2319>. A combination of allylic epoxide, palladium catalysis, and boron-derived additives enables a regioselective diol synthesis through a π -allyl intermediate <2004CL764>. These reactions can be rendered enantioselective through the judicious selection of chiral ligand and other additives (Equation 6) <1998JA12702, 1999JA8649>.



1.03.3.2.2(ii) Intramolecular addition reactions

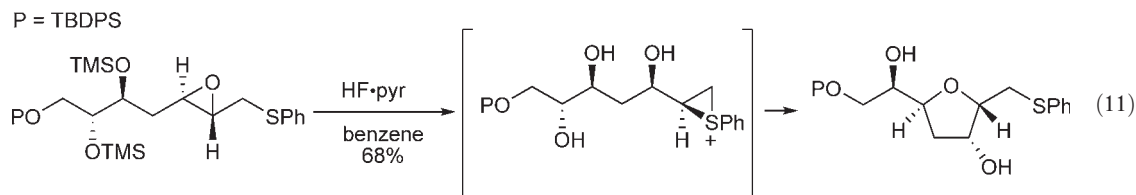
The addition of oxygen nucleophiles to epoxides in a ring-forming process is a useful protocol for synthesis [<2000T8747, 2003TL3175>](#) and has been reviewed [<2004RJO1227>](#). Interestingly, in some instances, the selectivity of the process can be modified by the selection of reaction solvent [<2003TL5547>](#).

A consecutive treatment of a racemic enol ester epoxide with a chiral titanium–BINOL Lewis acid complex followed by *p*-toluenesulfonic acid generates a single enantiomer of an α -acyloxy ketone (BINOL = 1,1'-bi-2-naphthal; Equation 7) [<1999JA4080, 1999JA11002, 2001JOC1818, 2002JOC2831>](#). Acid-induced cyclization reactions have been exploited in total synthesis ventures (Equation 8) [<2004OL1477, 2003JOC4422>](#). The ladder polyether antibiotics provide an excellent framework to explore acid-promoted intramolecular ether formation processes (Equation 9) [<1998TL393, 1999TL8019, 2000TL3805, 2000TL7701, 2000OL2917, 2002JOC2515>](#), as exemplified by a biomimetic tandem oxacyclization of the triepoxide in the presence of boron trifluoride etherate, generating a bis-oxepane (Equation 10). The construction of ladder polyethers has been reviewed [<1996AGE589, 2004BCSJ2129>](#).

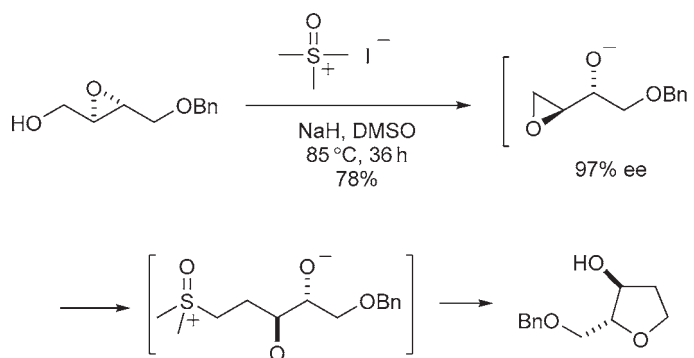


The enantioselective ring opening of epoxides by Co(salen) complexes provided the context for a creative ring-closing reaction [<1999AGE2012>](#). Scandium–bipyridine complexes have also been used to activate *meso*-epoxides toward ring opening in a highly enantiocontrolled manner [<2004AGE5691>](#).

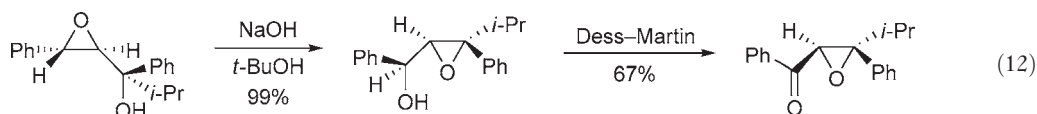
Cyclizations of hydroxyl functions onto intermediate episulfonium ions forms the basis for useful transformations forming highly functionalized tetrahydrofurans (THFs; Equation 11) [<2003TL5547>](#).



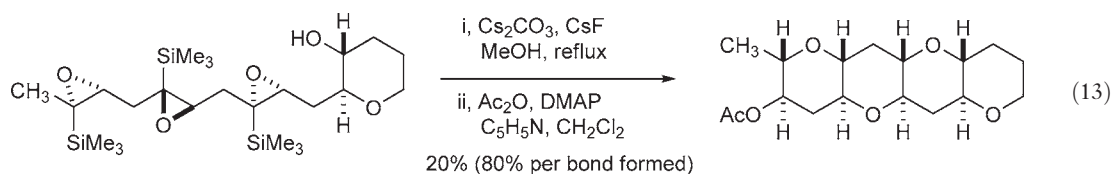
Nucleophilic ring opening of epoxides is exemplified by the Payne rearrangement reaction. The Payne rearrangement has been recently reviewed [<2002OR1>](#). Borhan and co-workers have introduced a tandem Payne rearrangement–cyclization cascade process induced by the nucleophilic ring opening of a terminal epoxide (formed by a Payne rearrangement) using a sulfur ylide [<2004JA13600>](#). This process has proved to be a useful approach for the synthesis of substituted tetrahydrofurans (Scheme 5). Following Payne rearrangement, Dess–Martin oxidation of the subsequently formed hydroxy-epoxide provided an epoxyketone. This compound is formally derived from β -disubstituted enones, which are difficult to access directly in an enantioselective fashion (Equation 12)

**Scheme 5**

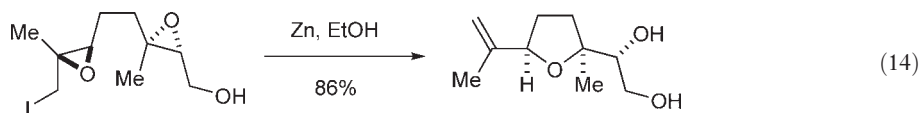
<2001JP11109>. As expected, these processes can be used to form other cyclic ethers in a straightforward manner <2005TA3570, 2005TL5239, 2004T4037, 2000T5289, 1999T9205>.



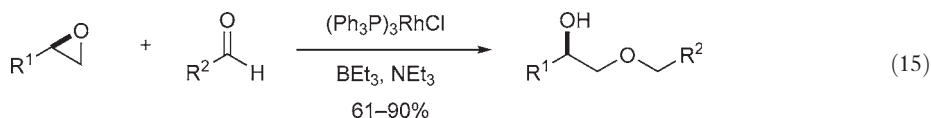
Jamison, following the precedent of Hudrlik, has used a trimethylsilyl substituent on a polyeпоxide that enables both a highly stereoselective epoxidation process, but also directs intramolecular attack (Equation 13). Conveniently, the silyl substituents are cleaved under the reaction conditions <2003OL2339, 2006JA1056>.



Tandem Vasella-type elimination can be followed by intramolecular attack on a nearby epoxide to form 2,5-disubstituted tetrahydrofurans (Equation 14) <2003OL1931>. Substituent effects on epoxide cyclizations have been examined <1996JOC2075>.



Wilkinson's catalyst in the presence of an amine base and triethylborane enables a reaction between aldehydes and epoxides that is equivalent to nucleophilic opening of an epoxide by an oxyanion (Equation 15). Interestingly, the catalyst interacts with the epoxide prior to the carbonyl function <2005AGE129>.

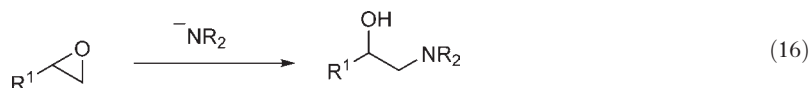


1.03.3.2.3 Nitrogen-based nucleophiles

1.03.3.2.3(i) Intermolecular addition reactions

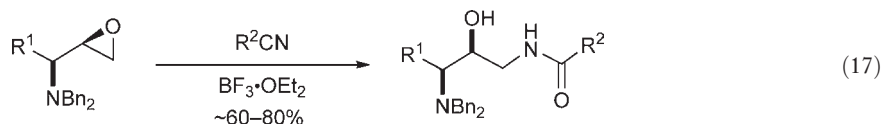
The donor properties of nitrogen-containing systems make these nucleophiles excellent participants in substitution reactions of oxiranes (Equation 16). The major issue for additions to unsymmetrical epoxides is one of regioselectivity. Both steric and electronic effects within the electrophile and the nucleophile can play a significant role in these

processes. In the past decade, a large number of additives that facilitate the addition of nitrogen nucleophiles to acyclic oxiranes have been examined.

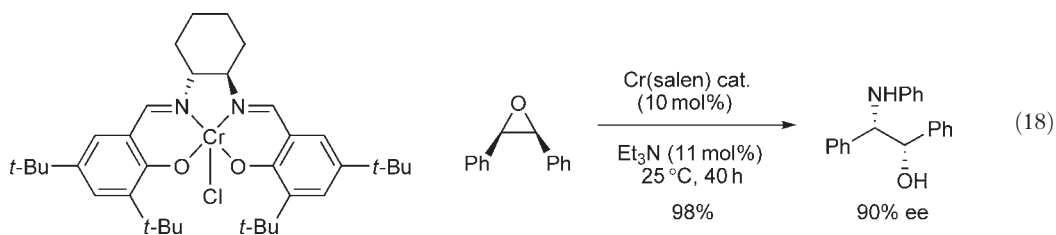


A number of salts that promote the addition reaction of aliphatic or aromatic amines to oxiranes have been examined. These include lithium bis-trifluoromethanesulfonimide <1997TL2027, 2002TL7083>, lithium trifluoromethanesulfonate <1996TL7715>, lithium bromide <2004EJO3597>, montmorillonite K10 clay <2004T9085>, stannic trifluoromethanesulfonate <1999JOC287>, cupric trifluoromethanesulfonate <1999JOC287>, zirconium(IV) chloride <2003TL8315>, zinc salts <2003TL6025>, ytterbium trifluoromethanesulfonate (solvent-free) <2003SC2989>, bismuth trichloride <2002TL7891> or trifluoromethanesulfonate <2004CL304, 2004TL49>, aluminium trifluoromethanesulfonate (solvent-free) <2004JOC7745>, calcium trifluoromethanesulfonate <2003T2435>, nickel(II) acetate <2004SL846>, stannic chloride in the presence of a ruthenium catalyst <2003TL2975>, and indium bromide <2004TL7495>. In certain instances, no additives are required <1998SL510, 2004SC2393, 2004T11709>, although solvent effects can be observed <1999TA2655, 2003TL9383>. The reactions readily take place in water <2000TL1019, 2005OL3649> or fluorinated alcohols <2000JOC6749>. In this latter instance, interestingly, aliphatic amines are deactivated toward ring opening.

Functionality adjacent to the epoxide can modify its reactivity. For example, 2,3-epoxy sulfides can be converted to a thiiranium species upon treatment with TMS triflate. This intermediate reacts with *O*-silyl amides regioselectively to form 1-substituted-3-hydroxy-2-thioethers. Simple primary amines undergo polyalkylation, but imines can be used as an indirect amine equivalent <1996T3609>. Nitriles react with functionalized oxiranes in a regioselective manner in a tandem epoxide opening–Ritter reaction (Equation 17) <2005JOC7447>.

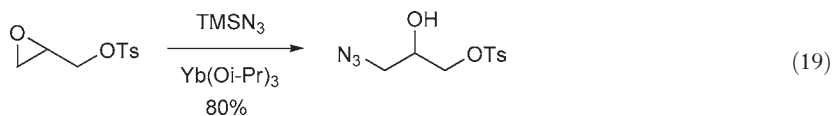


Chromium(salen) catalysts are excellent reagents for the desymmetrization of *meso*-epoxides. Thus, *cis*-stilbene oxide is converted to the (*S,S*)-aminoalcohol in the presence of catalytic quantities of chromium–salen complex in methylene chloride solution open to the atmosphere. The addition of small quantities of triethylamine was found to dramatically increase enantioselectivities (by almost 25%). This catalytic system also promotes an efficient aminolytic kinetic resolution (AKR) of racemic epoxides with *C*₂-type symmetry (Equation 18) <2004OL2173, 1999TL7303>. *Meso*-Epoxides can be opened with aromatic amines in water in the presence of 1 mol% of an Sc(III) catalyst ligated to 1.2 mol% of a chiral bipyridine ligand <2005OL4593>.



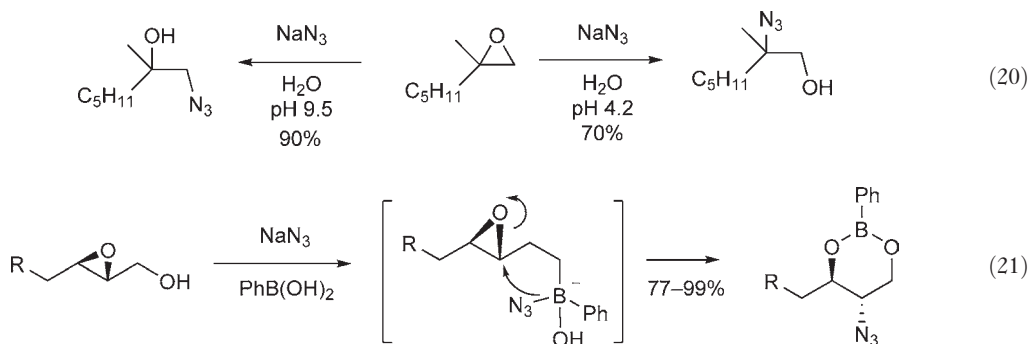
A chiral, nonracemic oxirane, (*S*)-2-[(*R*)-fluoro(phenyl)methyl]oxirane, can react with (chiral) amines under the influence of lithium perchlorate using either heat or microwave irradiation. This reaction sequence provides a material from which the ee of chiral α -branched amines can be determined <2005OL3829>. Guanidines serve as a useful nitrogen nucleophile for the direct conversion of epoxides to aziridines <2004JOC8504>.

Azides are excellent nucleophiles for the ring-opening reactions of oxiranes. Ytterbium triisopropoxide, prepared *in situ* from Yb(OTf)₃ and LiOiPr in THF, can be used in a very mild, highly efficient, and widely applicable procedure for the azidolysis of epoxides (Equation 19) <1995CC1021>.

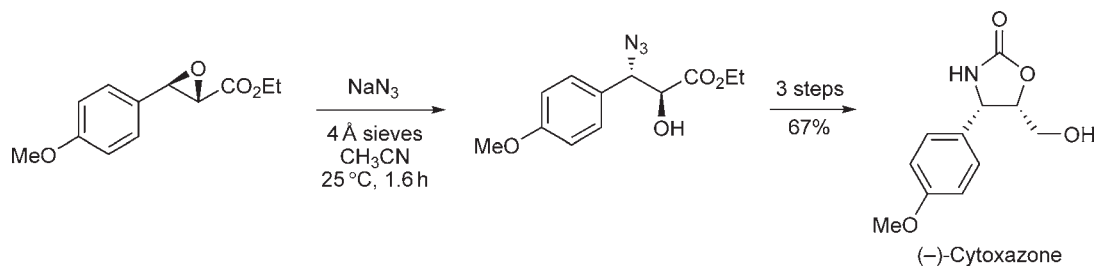


Epichlorohydrin reacts smoothly with sodium azide under the influence of lithium tetrafluoroborate <2003SC999>, samarium chloride hexahydrate <2003SC1603>, or cerium(III) chloride <2002OL343>. In each of these examples, attack occurs at the less-substituted carbon. Diethylaluminum azide promotes ring opening at the more substituted position, often occurring with predominant inversion of configuration <1998TL7971, 2003JOC75>. A similar situation occurs using ceric ammonium nitrate as a promoter, although the regioselectivity in this instance will depend on the electrophile structure <1999SC561>. In an interesting example of functional group compatibility, epoxides functionalized with a nitroxyl radical can be reacted with azide ion <2002TL553>.

Epoxides substituted with aryl groups can be opened in a highly regioselective and enantioselective manner using biocatalysis <2001OL41>. A useful illustration of the effect of reaction conditions on the regioselectivity of epoxide openings is found in Equation (20). Modification of the pH of the reaction media, water in this instance, results in a regioselective switch in reactions between azide ion and nonsymmetrical oxiranes <1999JOC6094>. Diphenylphosphorazidate opens oxiranes in a regio- and stereoselective fashion at the less-substituted carbon atom under the influence of 4-dimethylaminopyridine (DMAP) and lithium perchlorate <1999TL7105>. The addition of azide ions to oxiranes can be directed through an azidoboronate tether generated *in situ* (Equation 21). Yields range from good to excellent <1999TL4589>.

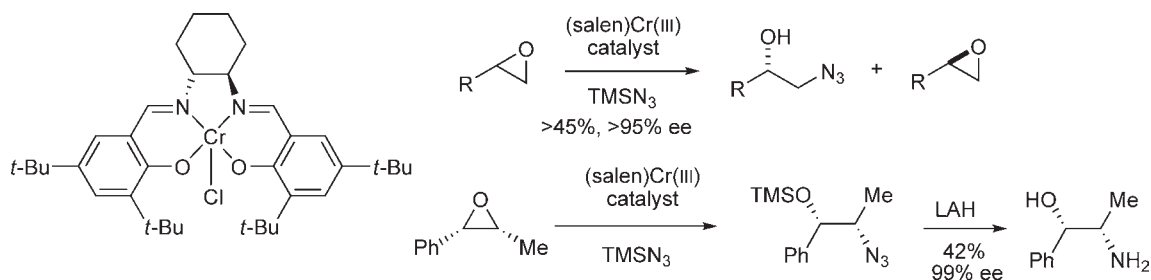


The synthesis of (–)-cytoxazone, a cytokine-modulating natural product, utilized a regioselective oxirane ring-opening reaction (Scheme 6) <2004TL7355>. A one-pot, enantioselective epoxidation–ring-opening process using α,β -unsaturated amides has been described <2005JA2147>.



Scheme 6

The kinetic resolution of terminal epoxides using trimethylsilylazide in the presence of a Cr(III) catalyst provides an efficient, catalytic route to 1,2-amino alcohols <1996JA7420>. When an optically pure nonsymmetrical 1,2-disubstituted epoxide is treated with a chiral (salen)chromium(III) azide complex, only one approach results in a chiral ‘match’; thus azide is delivered selectively to one position (Scheme 7). Using this protocol, (1*S*,2*S*)-norpseudoephedrine was synthesized in three steps with 42% overall yield and >99% ee <2001SL1013>. Mechanistic studies established that the catalyst serves to activate the electrophilic oxirane and the azide nucleophile (Figure 3). As the azide ion can be viewed as a nucleophile with potential practical concerns, a protocol using sulfonamides can be adopted, allowing for a simple route to enantioenriched terminal aziridines <2004AGE3952>. Scandium–bipyridine complexes have also been used to activate *meso*-epoxides toward highly enantiocontrolled ring-opening reactions <2004AGE5691>.



Scheme 7

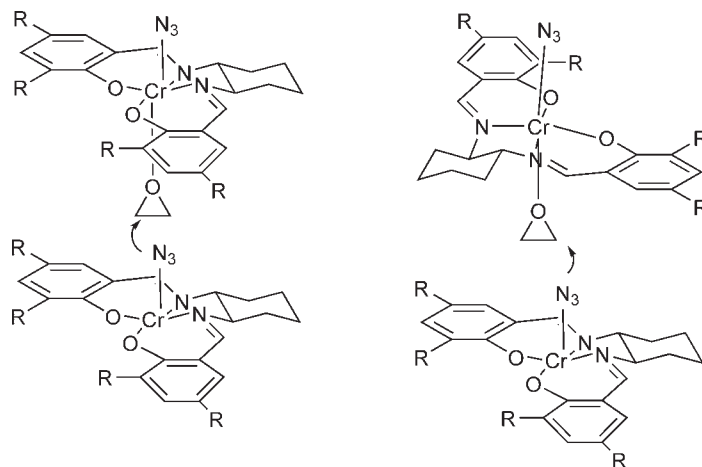
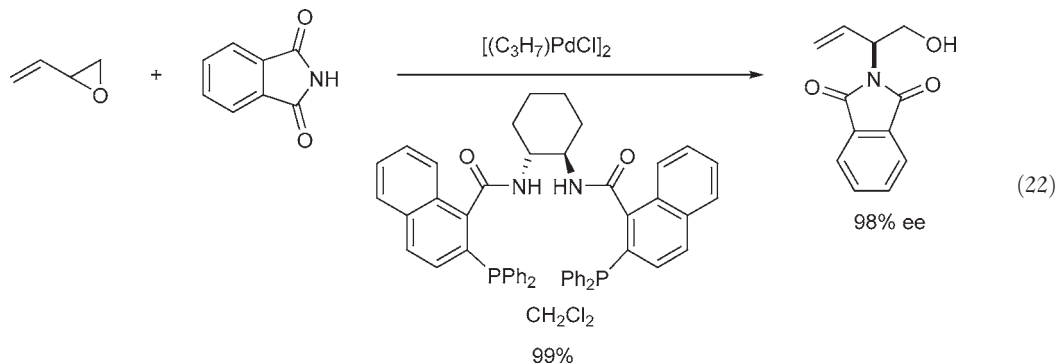


Figure 3

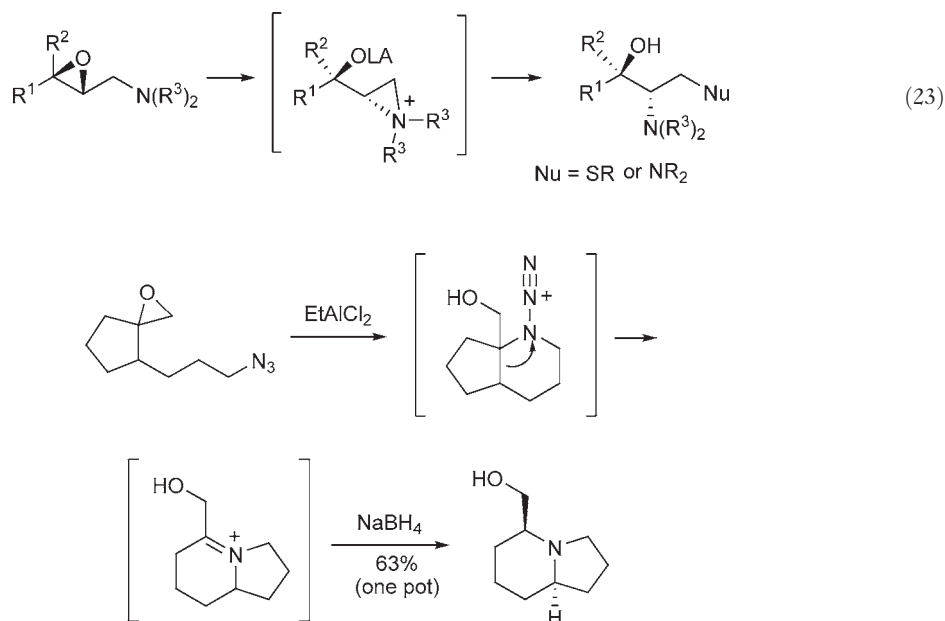
Nitriles add to glycidic esters and acids under BF_3 catalysis to form 2-oxazolines [\[2000TL5357\]](#).

The addition of phthalimide to butadiene monoepoxide can be rendered enantioselective using catalysis by palladium(0) ligated to chiral phosphines (Equation 22) [\[2000JA5968\]](#). The use of palladium catalysis to desymmetrize vinyl epoxides with a variety of nucleophiles has been reviewed [\[2004JOC5813, 2004CRV3453\]](#). This and similar processes were used to generate enantioenriched intermediates for the synthesis of broussonetine G [\[2003AGE5987\]](#), norsecurinine [\[2005OL5107\]](#), and branched amino sugars [\[2005S3335\]](#). Trimethylsilylazide reacts with styrene oxide in the presence of group VI transition metal catalysts [\[1995TL107\]](#). The regioselectivity of the reaction corresponds to the formation of the more stable carbocation. Samarium diiodide catalyzes the ring opening of styrene oxides by trimethylsilylazide [\[1995TL1649\]](#). Palladium catalysis has been used to enable the addition of azide ion (from trimethylsilyl azide) to α,β -unsaturated- γ,δ -epoxy esters with double inversion of configuration [\[2005AGE5094\]](#). The rhodium-catalyzed mode of addition is complementary to that typically observed with analogous palladium-promoted ring openings [\[2000OL2319\]](#).



1.03.3.2.3(ii) Intramolecular addition reactions

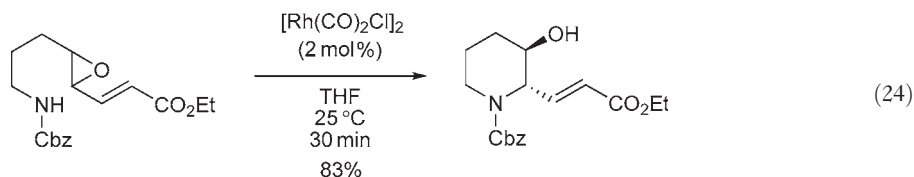
Treatment of 2,3-epoxy-1-amines with Lewis acid induces a rearrangement to aziridinium ions that react efficiently with a nucleophiles to give functionalized hydroxy sulfides or hydroxy amines (Equation 23) <1997SL11>. Under the influence of ethylaluminium chloride, an epoxide tethered to an azide undergoes Lewis acid-assisted cyclization followed by an intramolecular Schmidt reaction and subsequent *in situ* reduction of the intermediate iminium species upon addition of sodium borohydride (Scheme 8). This protocol was used as a key step in a novel synthesis of indolizidine alkaloids of pharmaceutical interest <2003OL583, 2004JOC3093>.



Scheme 8

Guanidines are useful nucleophiles in the intramolecular ring opening of epoxides <2003TL3075>. The intramolecular addition of an amide anion to an oxirane in a 6-*exo*-fashion formed 2-ketopiperazine derivatives <2004OL4069>. This reaction type was also used in a recent quinine synthesis <2004TL3783>.

Monomeric zirconium imido complexes have been used to open oxirane rings <2003JA14276>. In analogy to the chemistry of palladium(0), rhodium(I) catalysis activates vinyl epoxides through the formation of a metal-stabilized allyl cation. These intermediates undergo intramolecular reaction with nucleophilic functional groups. As an example, intramolecular nucleophilic attack by carbamate functionality enables the formation of a functionalized piperidine ring (Equation 24) <2004TL4193>.



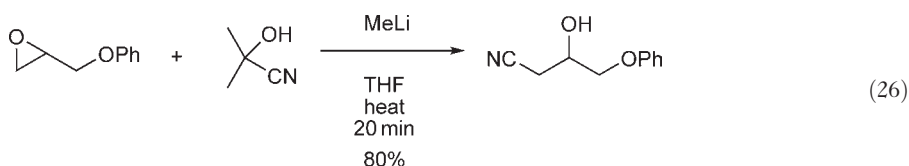
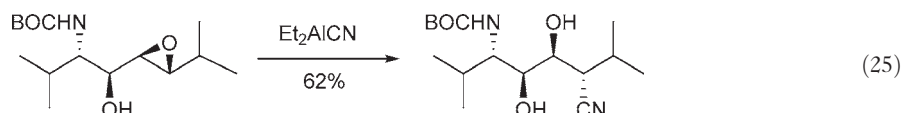
1.03.3.2.4 Carbon-based nucleophiles

1.03.3.2.4.(i) Intermolecular addition reactions

The addition of carbon nucleophiles to alkynyl-substituted oxiranes has been reviewed <2002CUOC539>. The reaction between indoles and oxiranes occurs readily under catalysis using indium(III) bromide <2002JOC5386>. A related process involves solid-state activation using silica gel to promote the reaction <2005JOC3490>, or

alternatively, high pressure [<1996JOC984>](#). This process can be made enantioselective in the presence of chromium–salen complexes [<2004AGE84>](#).

Lanthanide ions coordinated to pybox ligands activate *meso*-epoxides for reaction with trimethylsilyl cyanide [<2000OL1001>](#). The Nagata reagent (diethylaluminum cyanide) reacts with epoxides in a highly regioselective and stereoselective manner (Equation 25) [<1999TL1041>](#). The regioselectivity is directed by coordination of the Lewis-acidic reagent to the proximal alcohol function. Cyanide can be conveniently prepared *in situ* from methyl-lithium and acetone cyanohydrin (Equation 26). Reaction occurs at the less-substituted position of an unsymmetrical epoxide [<2004TL7201>](#). Terminal epoxides undergo ring-opening reactions with metal cyanide salts in the presence of cerium(IV) triflate [<1999SC2249>](#) or immobilized metal salen complexes on mesoporous material [<1999SC1121>](#). Titanium complexes catalyze enantioselective addition to epoxides [<1996AGE1668>](#). Clean attack at C-2 of 2,3-epoxy-1-alcohols using sodium cyanide is possible using a trialkylborate-based Lewis acid promoter [<2003OL1789>](#).



Isocyanides react with epoxides in the presence of gallium(III) chloride to form α,β -unsaturated α -amino imino-lactones [<2003OL4991>](#). Oxazolidinones are formed on solid phase by the reaction between epoxides and isocyanates [<2003JCO789>](#).

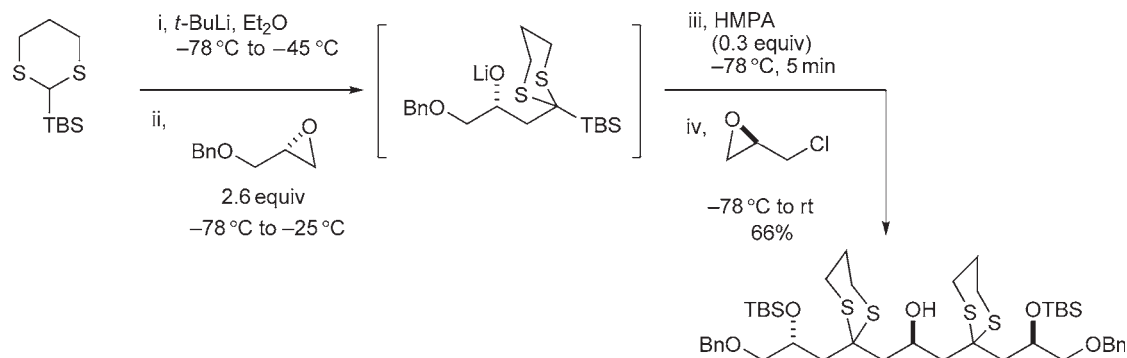
Terminal epoxides undergo ring-opening reactions with the dianion of carboxylic acids – lithium chloride is usually used as a Lewis acid additive [<2004EJO2160>](#). A ‘masked form’ of the carboxylate dianion, a silyl ketene acetal, will react with a terminal epoxide at its less-hindered position in the presence of titanium(IV) chloride [<2004T8957>](#). 1,3-Bis(trimethylsilyloxy)-1,3-butanadienes add cleanly to terminal epoxides in the presence of Lewis acid promoter. The initially formed adducts cyclize to form functionalized oxygen heterocycles [<2000AGE4343>](#).

Allylmagnesium halides under the influence of $\text{ClTi}(\text{OiPr})_3$ add at the more-substituted position of unsymmetrical epoxides, generating quaternary carbon centers [<2005T6726>](#).

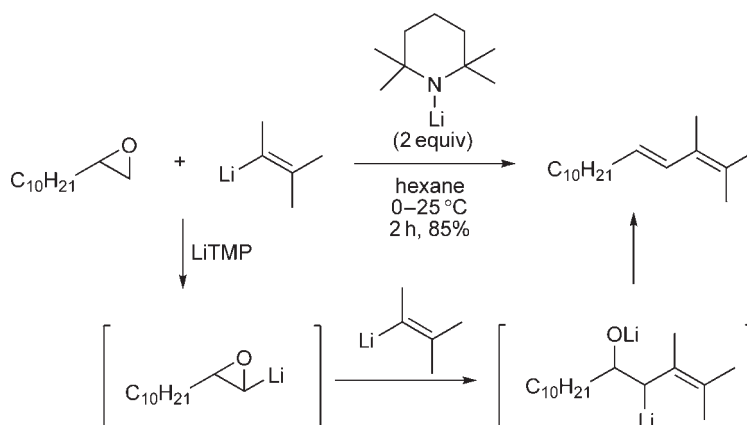
Lithiated dithianes will react with either terminal epoxides or vinyl epoxides. In concert with silicon-based rearrangements, this method is a rapid means to construct fragments suitable for the synthesis of complex molecules (Scheme 9) [<2002JA14516, 2003JA14435, 2005OL5183>](#). The effect of hexamethylphosphoramide (HMPA) on the substitution reactions of organometallic species such as lithiated dithianes with oxiranes and other electrophiles was examined. As the epoxide electrophile is believed to be activated by lithium ion during substitution reactions, the addition of HMPA suppressed this mode of activation, resulting in somewhat slower reactions [<2002JA13386>](#).

Alkylolithium reagents attack the unsubstituted carbon of terminal epoxides. In the presence of excess amide base, the intermediate alkoxides eliminate to form alkenes (Scheme 10) [<2004JA12250>](#).

Vinylolithium reagents, generated using Schlosser’s reagent, attack monosubstituted oxiranes to produce homo-allylic alcohols (Equation 27) [<1996T1433>](#). The addition reaction of lithiated alkynes to epoxides was observed to

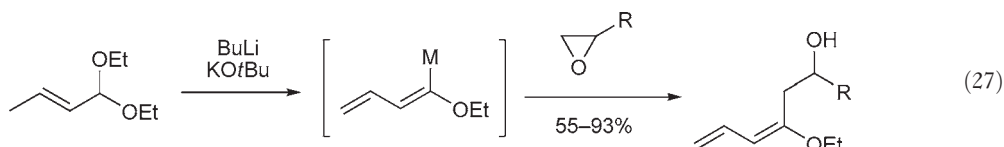


Scheme 9



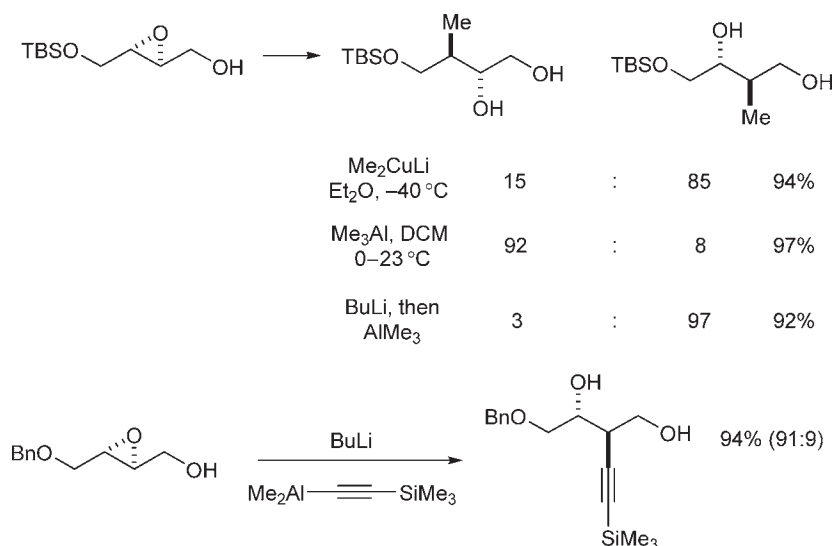
Scheme 10

proceed in much higher yield when promoted by BF₃·THF rather than the more common BF₃·Et₂O <2001TL6947>. The reactions between lithium acetylides and para-functionalized styrene epoxides were examined to address electronic effects on the regioselectivity (C1 vs. C2) of epoxide ring opening <2004TL9265>.



Trialkylalanes add to epoxides. The selectivity of these reactions is often dictated by additional functionality. For example, 1-phenylthio-2,3-epoxyalkanes react with trimethylaluminum to give exclusively C-2 alkylated products with retention of configuration. Neighboring group participation forming an episulfonium ion intermediate is believed to be the cause of this effect <1996BCJ2095>. Similar reactivity is observed in the ring opening of 2,3-epoxy amines with organoaluminum reagents <1996TL6177>. Similarly, episelenium ions are intermediates in addition reactions of 2,3-epoxy-1-selenides <2004TL1911>. In the presence of water, trimethylaluminum adds to epoxides smoothly, although the regioselectivity is often poor <1999TL5369>. Alkynyl (diethyl) aluminium species efficiently serve as alkynylating reagents with functionalized epoxides <2005TL797>.

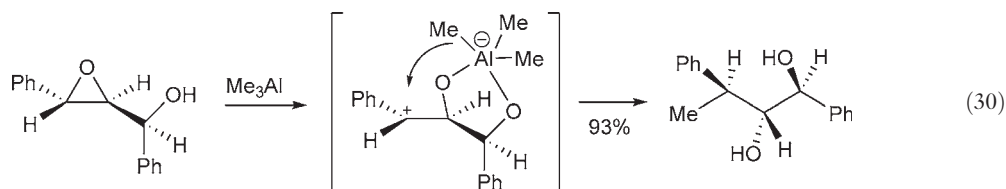
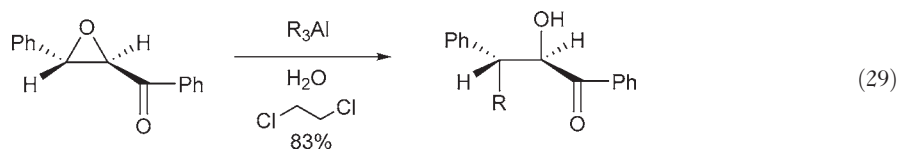
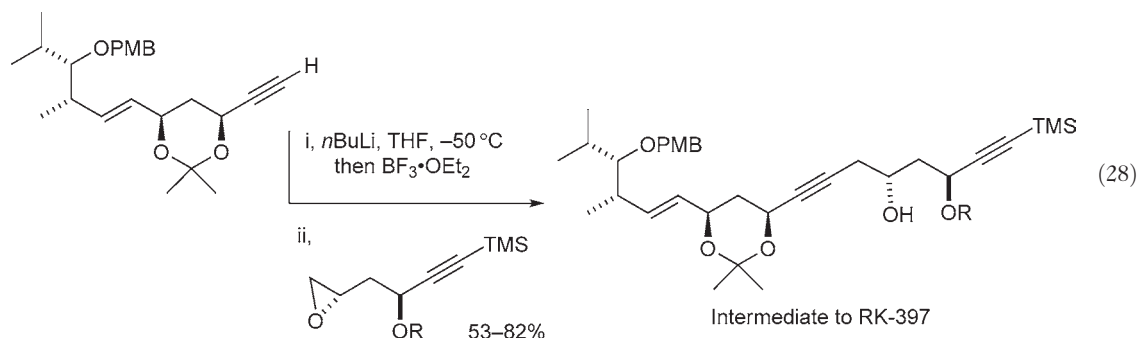
An interesting study of regioselective ring-opening of 2,3-epoxy-1-hydroxylated substrates is presented in Scheme 11. Complementary reactivity was found in reactions of cuprates and trialkylalane reagents. Interestingly,



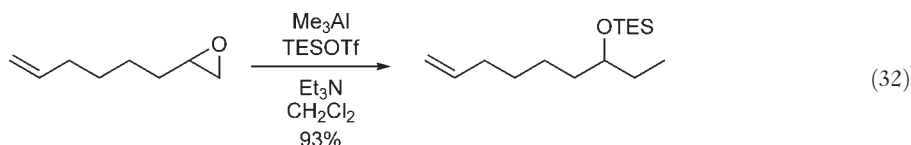
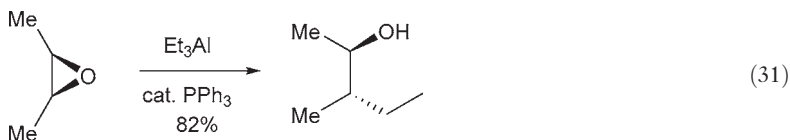
Scheme 11

however, the use of 'ate' complexes led to high regioselectivity favoring reaction at C-2. The 'ate' complexes appear to be much more reactive toward epoxide substrates as compared to copper-based chemistry. A further practical consequence is exemplified by the use of an aluminium acetylide 'ate' complex as a nucleophilic partner, as copper acetylides would be unreactive <2001OL1765>.

Trimethylaluminium also catalyzes the addition process of alkynyllithiums to terminal epoxides to generate secondary alcohols <1999JA3328>, although 1-lithioalkynes still react readily with terminal epoxides (Equation 28) <2005TL5393, 2000JP153, 1998TL5261, 2004JA2495>. Pentacoordinate aluminium complexes are postulated to be important intermediates <1997JA5754>. The regioselectivity of diethylalkynyl aluminium addition to 2-methyl-3,4-epoxy-alcohols has been examined <2005TL1867>. Epoxyketones react with trialkylaluminium reagents proximal to aryl functionality with inversion of configuration (Equation 29). Tertiary alcohols can be used to direct the nucleophilic addition of organoaluminium reagents with 'retention' of configuration (Equation 30) <2000JP12455>.

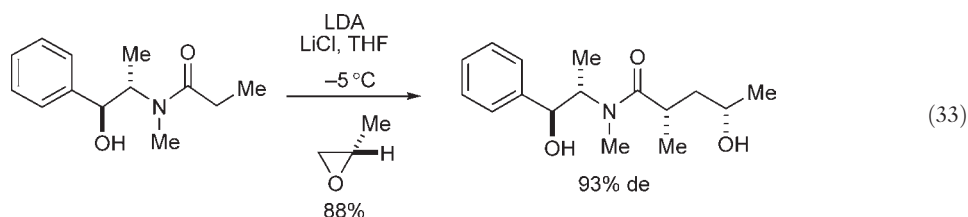


Triphenylphosphine (5 mol%) can also be used to activate an organoaluminium reagent for addition of nonfunctionalized oxiranes (Equation 31) <2000TL3043>. Imidazolinium salts catalyze the ring-opening alkylation of *meso*-epoxides <2001OL2229>. A novel trimethylaluminium/trialkylsilyl triflate reagent combination has been reported for the one-pot alkylation and silylation of epoxides, as exemplified in Equation (32). The methyl group is delivered via backside attack on the less-substituted terminus of the epoxide <2003OL3265>. Allyllithiums react readily with epoxides <2004TL9189>.

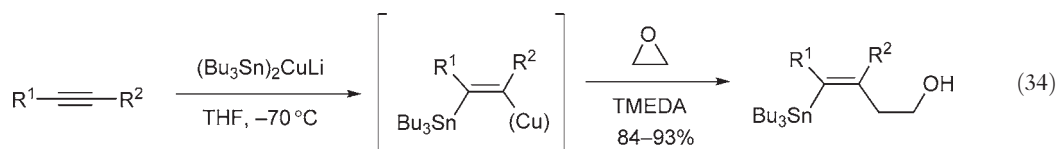


Lithium enolates of ketones react with cyclic epoxides in the presence of boron trifluoride etherate <2003JOC3049>. The reactions between carbonyl enolate ions and epoxides have been reviewed <2000T1149>. The pseudoephedrine

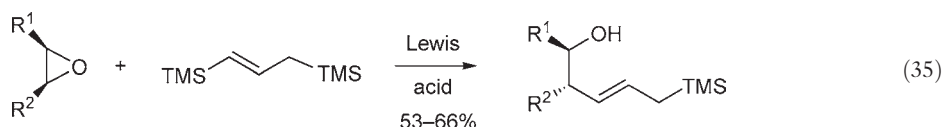
auxiliary system of Myers can be used in substitution reactions of epoxides. Importantly, the mnemonic for diastereoselectivity for these reactions reverses as compared to the reactions of alkyl halides (Equation 33) <1996JOC2428>. These reactions can also be performed using metal salts as catalysts <1996JOC9548>. The lithium anion of an alkylphosphonic ester was reacted smoothly with a terminal epoxide for the preparations of sphingolipid analogs <2004JOC7694>. The dianions derived from dithionamides efficiently add to epoxides <2005JOC8148>.



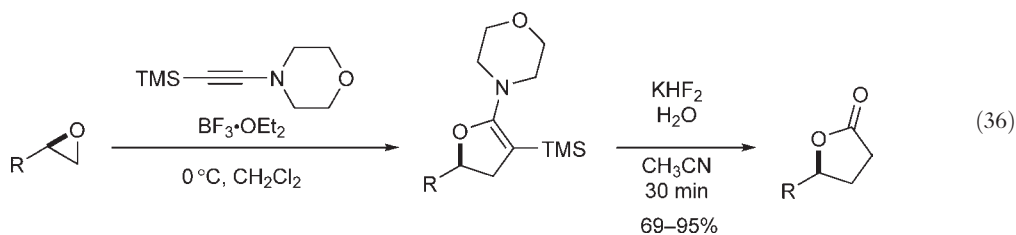
Stannylcupration of acetylenes can be followed with reaction of epoxides (ethylene oxide) (Equation 34) <1998JOC7531>. This process serves as the starting point for a synthesis of cyclobutene derivatives. The S_N2' reaction between cuprates and vinyl or alkynyl epoxy sulfoxides can be controlled by a pendant sulfoxide group <2004T8171>. The addition of Grignard reagents to propargylic epoxides to form functionalized 2,3-allenols is catalyzed smoothly by iron(III) complexes <2003AGE5355>. The asymmetric addition of carbon nucleophiles to vinyl epoxides can be carried out using palladium complexes in the presence of chiral ligands <2001JA12907>.



Epoxides can react smoothly with allylsilane reagents. For example, 1,3-bis-trimethylsilyl-1-propene can react with one of a variety of epoxides under Lewis acid catalysis to generate a highly functionalized alkenol (Equation 35). Yields are modest, with best results being obtained using monosubstituted epoxides <1998TL529>. Trimethyl silyl ethers can serve as nucleophiles under similar conditions <2000TL763>.



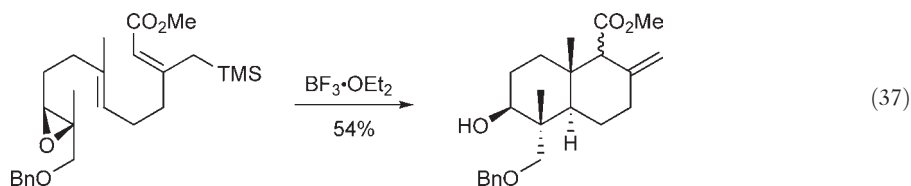
The Jacobsen group continues to fashion new uses for enantioenriched terminal epoxides. In this example, *N*-alkynylmorpholines serve as useful nucleophiles for the conversion of terminal epoxides into γ -butenolides (Equation 36) <2002JA2456>. Silyl ketene acetals react with epoxides to form γ -butenolides <2004T8957>. Oxazolidinones can be generated from the reaction of terminal epoxides with carbenes <2005OL1983>. Dimethylsulfonium methylide converts *cis*-epoxides to homologated allylic alcohols <2001OL4051>. In a related conversion, the same reagent can be used for the synthesis of 1,3-butadien-2-ylmethanols <2005OL1399>.



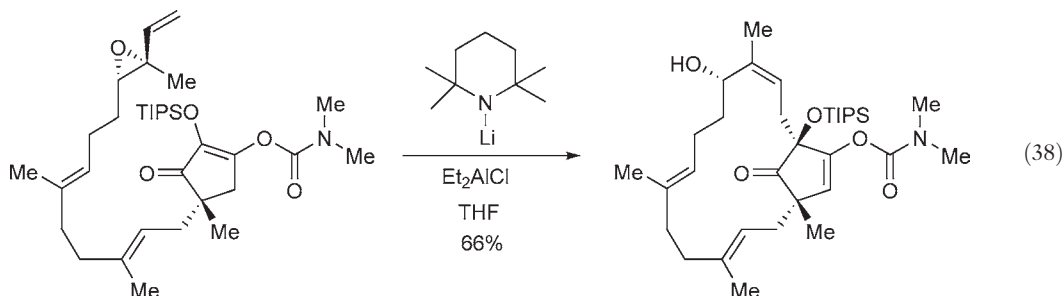
1.03.3.2.4(ii) Intramolecular addition reactions

Lewis acid templation between an epoxide and an adjacent hydroxyl function sets the stage for an intramolecular addition process using an alkyne as a nucleophile <1995TL7145>. Cyclization reactions wherein the regioselectivity of the addition reaction is dictated by a proximal hydroxyl function is the subject of a review <2000T8779>.

Nucleophiles for these reactions can be allylsilanes (Equation 37) <1999CC325>, or arenes in a Friedel–Crafts-type process catalyzed by acids on solid support <1999EJO837>. Lewis acids such as stannic chloride <2002JOC6954>, bismuth trifluoromethanesulfonate <2005TL8507>, or cationic gold species <2004JA5964> have been used. Acid-promoted cyclizations relevant to steroid biosynthesis proceed in a concerted path <1998JA3526>. Oxirane cleavage coincides with A-ring formation <1997JA1277>. Somewhat related is the observation that immobilized cells of baker's yeast efficiently catalyze the cyclization of squalene epoxide to lanosterol <2002T7291>.



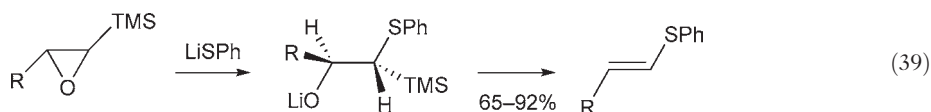
Macrocyclic ring opening of a vinyl epoxide occurred in an S_N2' sense, as exemplified in the example below. The reaction of the ketone enolate and the Lewis acid activated oxirane enabled the formation of the desired macrocycle (Equation 38) <2002T6397>. The (Z)-geometry of the newly formed alkenes suggests that this macrocyclization could proceed by a diethylaluminium chloride-mediated ring opening of the oxirane to form a (Z)-allyl halide that undergoes nucleophilic attack by the ketone enolate. The enolates of amides as nucleophilic partners in ring-forming reactions has also been used <2003TL9383>. Cyclopropanes could be synthesized via the reaction between an enolate (generated by a Michael addition process) and a nearby epoxide <2006TL205>. Epoxides can be used as electrophiles for sulfone anions in Ramberg–Bäcklund-like reactions <1997TL3055>.



1.03.3.2.5 Sulfur, phosphorus, and other nucleophilic species

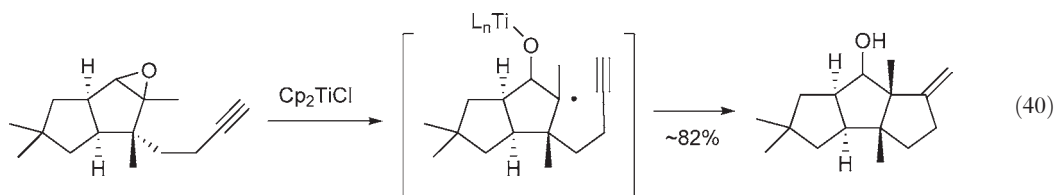
Sulfur nucleophiles are, not surprisingly, quite useful species for the ring opening of oxirane rings <2001TL3167>. These processes can be carried out in an enantioselective manner using bimetallic gallium–lithium binaphoxide complexes <1997JA4783>, or salen complexes <1998JOC5252>. Similar processes have been developed for Se-based nucleophiles <2005OL1927>. The ring opening of oxiranes with S-based nucleophiles can also be carried out using zinc(II) cation catalysis <2003JOC8248>, or molybdate-based systems <2002JOC9417>, or ionic liquids <2003JOC2525>. Conversions of oxiranes to 1,3-oxathiolane-2-thiones <1995JOC473> or other sulfur heterocycles <2004JOC8780, 2004TL6523, 2004TL1535, 1996S821> can also be carried out.

Clever functional group transformation methodology has been developed using a tandem process which involves initial nucleophilic ring opening of an epoxide. For example, trimethyl- and dimethylphenylsilyl epoxides react with lithium phenylsulfide to give regio- and stereodefined vinyl sulfides resulting from α -ring opening and Peterson elimination (Equation 39) <2000TL1111>. Unfunctionalized epoxides can be transformed into allylic alcohols through an initial epoxide ring opening with a thiol in hexafluoroisopropanol (HFIP) and *in situ* oxidation to a sulfoxide, followed by pyrolysis in the presence of potassium carbonate <2000TL2895>. Cesium hydroxide promotes the addition of phosphines with epoxides <2003TL7579>.

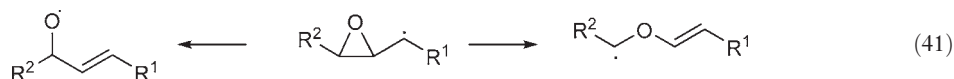


1.03.3.3 Free Radical Reactions

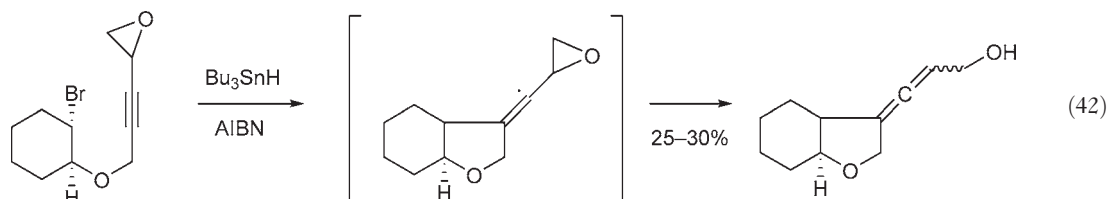
The chemistry of oxiranes involving free radical intermediates has been reviewed <2001T1>. Cleavage of the carbon–oxygen bond of an oxirane ring using an appropriate metal source provides a useful, and synthetically important, route to organic radicals. For example, a bis(cyclopentadienyl)titanium(III) chloride-initiated radical cascade sequence was used to construct a linear triquinane intermediate (Equation 40) <1995TL15>. In contrast, ‘standard’ radical conditions generated only an undesired bridged product. Cyclizations initiated in this manner have been used in a number of synthetic applications <1998JOC2829, 1999OL607, 2002JOC3242, 2002AGE3206, 2005JOC8252>. A catalytic variant of this process has been established <1998AGE101, 1998JA12849>. Chiral ligands for titanium have enabled a substrate-controlled stereoselectivity <1999AGE2909, 2003CEJ531>. A novel development involves THF formation occurring via homolytic cleavage of a Ti–O bond <2003AGE3687>.



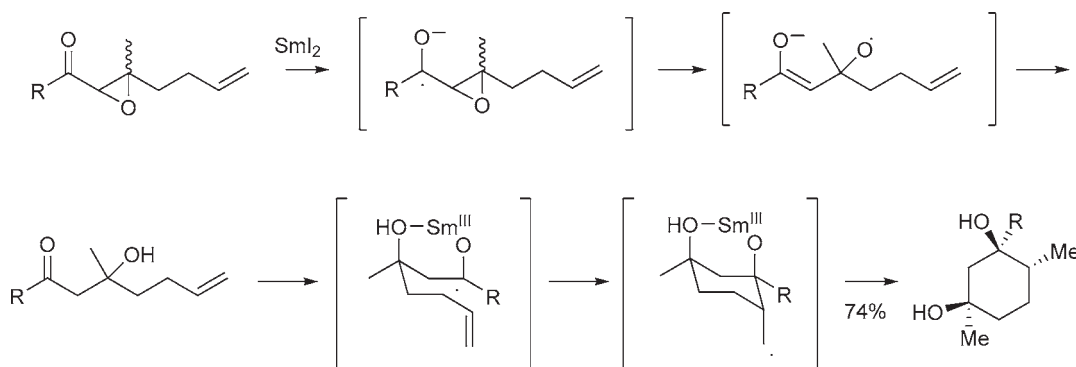
Oxiranylcarbonyl radicals can undergo eliminative ring opening through either C–O or C–C bond cleavage to give oxygen-based or carbon-based radicals, respectively (Equation 41). Marples *et al.* <1997TL3599> have shown that the C–C bond cleavage is reversible, and that it can occur even when no products of C–C scission are observed. An example of this reactivity in synthesis is described in Equation (41).



Allenyldiene-THFs can be prepared by the tributyltin hydride-mediated radical cyclization of bromoalkynyl-oxiranes, where the epoxide ring serves as an efficient radical terminator (Equation 42). The reaction proceeds through the normal 5-*exo*-mode <1995CC897>.

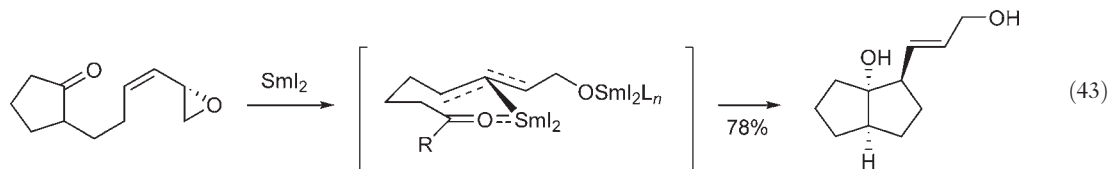


The radical ring opening of epoxides can be used to advantage in a sequential reductive coupling process promoted by samarium(II) iodide <2000TL9337, 1999T11395>. For example, treatment of a ketoepoxide with SmI₂ in methanol leads to a cascade epoxide ring opening and ketyl radical olefin cyclization to give a *cis*-1,3-cyclohexanediol (Scheme 12) <1996JOC5885, 1997JOC2935, 1998T5819>.



Scheme 12

Molander and Shakya <1996JOC5885> have developed a reductive annulation method for vinyl epoxides bearing a distal ketone functionality. Radical ring opening of the oxirane moiety using SmI_2 induces an intramolecular ketyl olefin coupling reaction, leading to a hydroxylated [3.3.0]bicyclooctane in very high diastereoselectivity. This cyclization is generally limited to the formation of a five-membered ring (Equation 43).



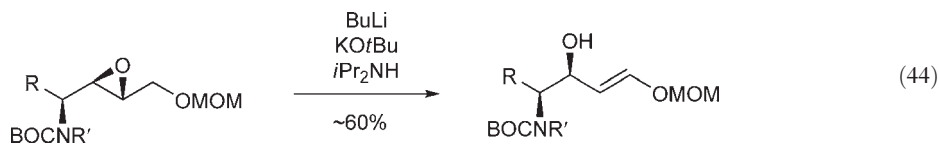
2,3-Epoxy-1-haloalkenes undergo novel reductive cleavage reactions with samarium diiodide to give cyclopropanols or allylic alcohols depending upon the substrates and reaction conditions. Formation of the cyclopropanol is believed to proceed through a diradical intermediate <1998SL1073>.

Samarium diiodide promotes the reaction between epoxides and imines to form oxazolidinones <2000TL3389>.

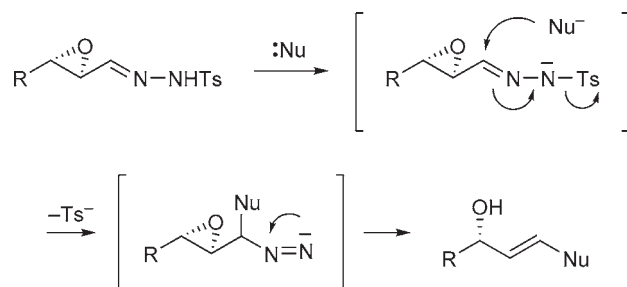
1.03.3.4 Isomerizations

1.03.3.4.1 Base promoted

The base-promoted isomerization of epoxides to alkene-containing products has been reviewed <2002EJO393, 2002CSR223, 1998JP11439, 1996T14361>. Oxirane rings undergo cleavage through eliminative mechanisms. For example, treatment of the ether in Equation (44) with butyllithium/diisopropylamine/potassium *tert*-butoxide easily provides an allyl alcohol <1996TL5209>. A number of studies examining the cumulative effect of base, solvent, and chiral additives on the enantioselectivity of these processes have been carried out <1996JOC6108, 1999JA11114, 2000JOC1461>. Interestingly, a profound dependence of the mechanism on the reaction solvent has been uncovered <2003JA15893>.



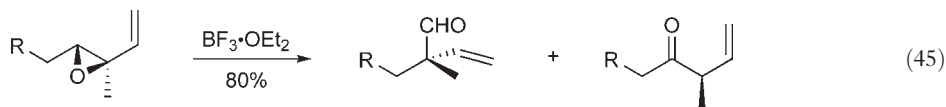
Catalysts have been developed for the rearrangement of *meso*-epoxides to chiral allylic alcohols, in some cases achieving near-perfect induction <1998JA10760, 2000JA6610, 2002JOC1567, 2002AGE2376>. This technique has been extended to enable kinetic resolutions of racemic epoxides <2002OL3777>. The effect of the trimethylsilyl substituent on the regioselectivity of base-induced oxirane ring opening has been examined <1997JA11689>. A mechanistically related oxirane ring-opening process involves the addition of a nucleophilic species to an α,β -epoxy-tosylhydrazone such as that in Scheme 13. These processes produce *trans*-allylic alcohols. The stereochemistry of the carbinol-bearing carbon is strictly retained <1995TL307>. A base-promoted isomerization set the stage for a tandem Brook–2,3-sigmatropic rearrangement in which the stereochemistry of the carbanion was relayed from the initial epoxide <2005OL5913>.



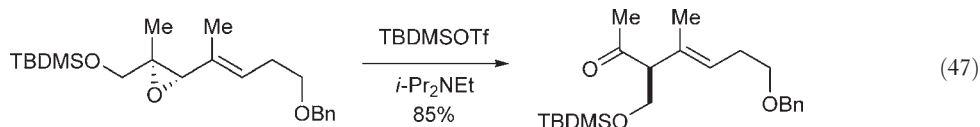
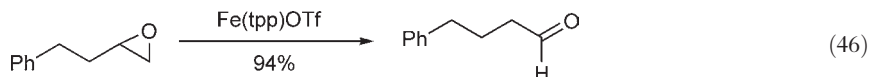
Scheme 13

1.03.3.4.2 Bronsted/Lewis acid promoted

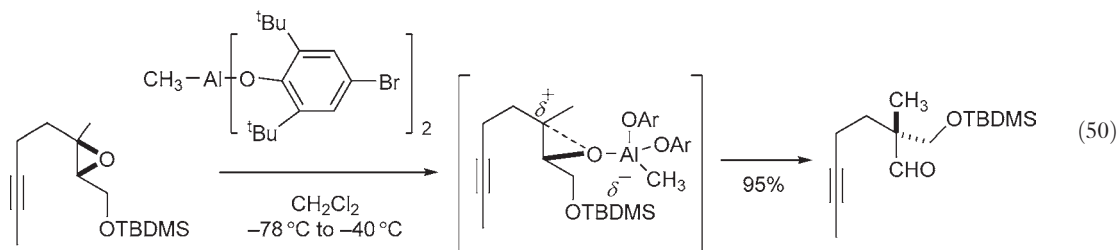
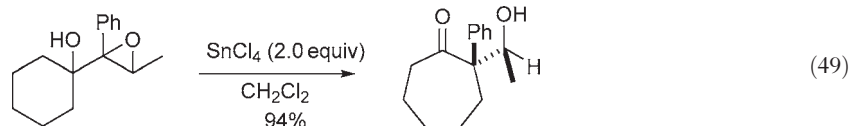
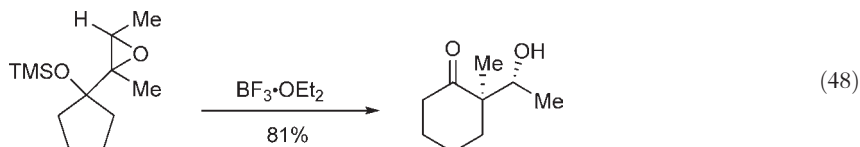
The propensity for epoxides to undergo various rearrangements under Lewis-acidic conditions is also well known. Typically, Lewis acid ‘catalysts’ such as $\text{BF}_3 \cdot \text{OEt}_2$ must be used in quantities approaching stoichiometric amounts due to their instability under the reaction conditions. As a specific example, chiral tertiary allylic epoxides undergo a stereospecific rearrangement in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give optically active quaternary aldehydes (Equation 45). The stereospecificity of the process is rationalized on the basis of hindered rotation of the intermediate carbocation. Furthermore, eclipsing interactions hinder the alignment necessary for hydride shift. Only in cases of low migratory aptitude (i.e., cyclohexylmethyl, phenethyl) does hydride migration become significant <1995JA7379, 1997JA12150, 2001JP1789>.



The course of the rearrangement reaction is strongly dependent on the substrate structure. As illustrative examples, a simple monoalkyl-substituted epoxide undergoes regioselective rearrangement in the presence of iron(III)tetraphenyl-porphyrin to give the corresponding aldehyde via a 1,2-hydride shift (Equation 46) <1999TL7243>. On the other hand, rearrangement of the allyl epoxide proceeds via a 1,2-alkyl shift to give the corresponding multifunctional ketone (Equation 47) <1999TL3129>.



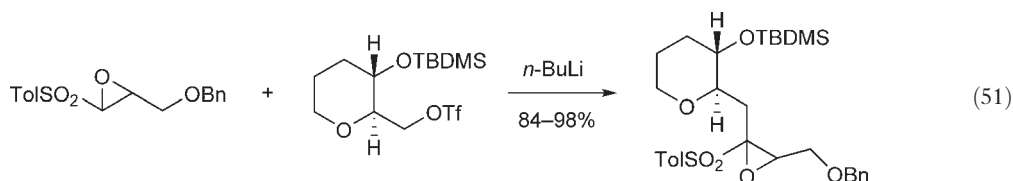
A number of Lewis acids and other reagents have been used to promote rearrangements of this general type: $\text{B}(\text{C}_6\text{F}_5)_3$ <1995SL721>, bismuth(III) oxide perchlorate <2000TL1527>, bismuth triflate <2001TL8129, 2003TL6501>, ytterbium triflate <2001JP11253>, high-valent chromium metalloporphyrin complexes <2004JA9554>, indium(III) chloride <1998JOC8212>, lithium iodide <2000SL749>, lithium perchlorate in diethyl ether <1996JOC1877>, and indium metal in the presence of an allyl bromide. Migration with retention of configuration was observed using bis(iodozincio)methane as the activating reagent <2002AGE2837>. These reactions can also take place with concomitant ring enlargement (Equations 48 and 49) <1999JOC629, 2000OL1193, 2002TL6637>. Lewis acid-promoted rearrangement reactions have been used as key step in synthetic ventures <2003JA5415, 2005JOC6541>. A Lewis-acid rearrangement process was utilized in a synthetic approach to sesterterpene natural products (Equation 50) <2006JOC4237>. The Kita group has developed and utilized a Lewis acid promoted rearrangement of ‘epoxy-acylates’ in a number of total synthesis contexts <2001T815>.



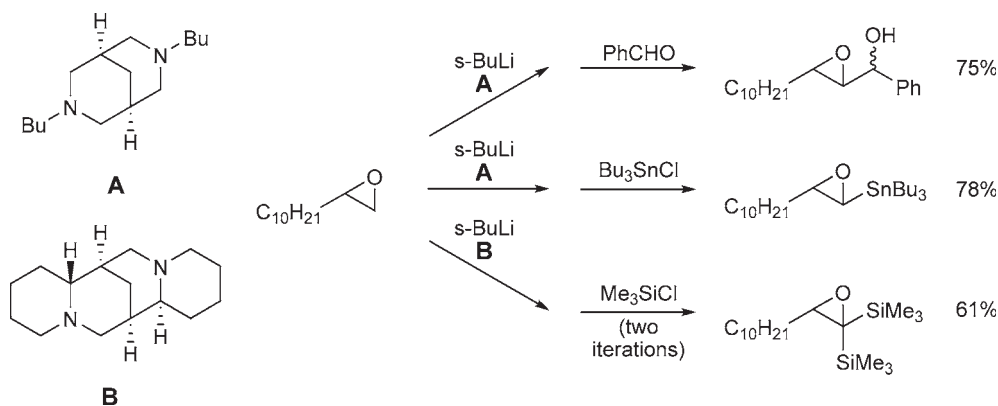
Alkenes have been transformed into aldehydes using a sequential alkene oxidation–epoxide rearrangement sequence <2004AGE4950>, and these aldehydes have undergone addition reactions *in situ* <1997BCJ707, 2004AGE1702, 2001AGE3877, 2003TL2911>.

1.03.3.5 Oxiranes as Precursors to Carbenes/Nucleophiles

Although the reactivity of an oxirane is typically as an electrophile, the inductive effect of the oxygen atom enables deprotonation reactions. If the oxiranyl anion is sufficiently stabilized (by an electron-withdrawing group, for example), the anion can be alkylated by electrophiles without ring opening. A number of reviews covering this area of work are available <1996CRV3303, 1997RHA183, 1998SL337, 2002S1625, 2005SL1359>, and a symposia-in-print on this area has been published (*Tetrahedron* 2003, 59(49)). As a specific example, the sulfonyl-substituted oxirane can be deprotonated and alkylated using a complex triflate (Equation 51) <1996TL2605>. This method has been used in a number of synthetic approaches to complex molecules such as hemibrevetoxin B <1996JA8158, 1997JA4557, 1998JOC6200, 2001JOC3049, 2003JOC9050, 2003OL2723>. These anions undergo substitution with vinylzirconium species, leading to zirconium enolates <2003T9857>. Amides, alkynes, or silyl substituents can also be used to stabilize oxiranyl anions <2003H137, 2003T9793, 2003T9759>. Certain functional groups can also direct lithiation at a ‘remote’ position on the epoxide <2003T9825>.



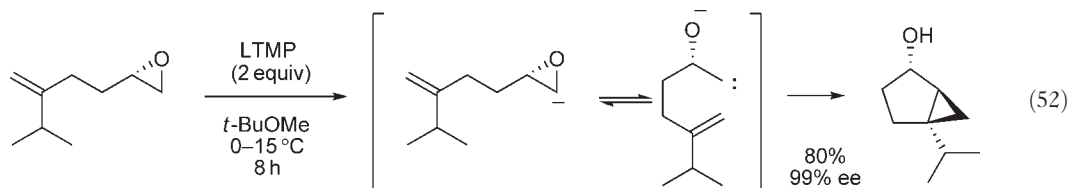
Conditions have been developed that enable the trapping of lithiated nonstabilized epoxides with electrophiles <2001OL461, 2002TL7895, 2004OL4187>. The lithiation of terminal epoxides is carried out with *sec*-butyllithium assisted by diamine ligands, such as dibutylbispidine or (–)-sparteine. The oxiranyl anions thus formed engage in smooth nucleophilic addition onto aldehydes to form epoxyalcohols; the same conditions can be used for the stannylation of epoxides. Similarly, epoxydisilanes can be accessed through two sequences of deprotonation followed by treatment with chlorotrimethylsilane (Scheme 14) <2004SL1610>. These anions can be reacted for bis(pinacolato)diboron to form vinylboronates, as in the synthesis of panomifene <2004AGE879>. α -Stannylepoxides can be induced to stereoselectively cross-couple with various reactive electrophiles in the presence of Cu_2S <1997SL481>. When a leaving group is situated vicinal to the nascent oxiranyl anion, elimination ensues to provide an allene oxide that can undergo a number of interesting transformations <1997TL897>.



Scheme 14

Another key reaction of lithiated epoxides is α -elimination to form carbene intermediates. This reactivity has been developed to be a highly effective method for the functionalization of organic molecules.

The fascinating carbenoid character of the epoxide anion is also manifested in an intramolecular cyclopropanation reaction, in which the anion adds across a tethered olefin to provide bicyclo[3.1.0]hexanols (Equation 52). The reaction is remarkably chemo- and diastereoselective. No C–H insertion is observed, and yields are generally very good. The stereochemical outcome is rationalized on the basis of a *trans*-lithiation, as well as the geometric constraints imposed by the [3.1.0] bicyclic system <2004JA8664>.



In the absence of well-positioned double bonds, the oxiranyl anions can undergo another well-known reaction of carbenes, namely a 1,2-hydride or 1,2-alkyl shift <1998JOC3808, 2004OL3509>.

The reaction of terminal epoxides with hindered lithium amide bases followed by organometallic reagents generates alkenes <2004JA12250>. Related reactions are the formation of enamines <2004JA6870> from terminal epoxides, 2-ene-1,4-diols from terminal epoxides <2005OL2305>, and allylamines from amino epoxides <2006OL349>.

1.03.3.6 Reductions

Reductive ring opening of epoxides is a standard method for the formation of chiral secondary alcohols, as in the recent synthesis of chiral α - and β -hydroxy amides <2004AGE317>. A number of reagents can be used to accomplish this transformation: nucleophilic hydride reagents <1998JHC865>, hydride reagents in the presence of borane <1997JOC9223>, transfer hydrogenolysis using ammonium formate and palladium catalysis <1995SC2267, 1995JOC4922>, microencapsulated Pd(0) nanoparticles <2003OL4665>, ruthenium complexes <2003OM4190>, metal borohydrides in the presence of zirconium chloride and L-proline <1997SC1731>, bis(cyclopentadienyl)titanium chloride and cyclohexa-1,4-diene <1997JP11257, 1998JOC356>, or lithium di-*t*-butylbiphenyl (DTBB) in THF <2005T3865>.

1.03.3.7 Deoxygenations

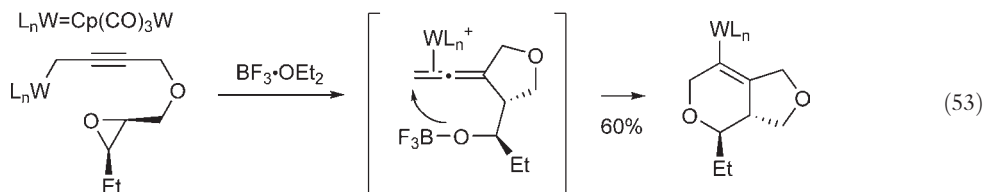
Epoxides can be deoxygenated to the corresponding alkenes using a number of reagents, including molybdenum hexacarbonyl <2003TL2355>, the low-valent titanium catalyst Cp₂TiCl (readily available by the *in situ* reduction of Cp₂TiCl₂ with activated zinc) <2003TL435>, [tris(3,5-dimethylpyrazolyl)hydridoborato]rhenium oxides <2000OM944>, indium metal <2005JOC4118>, lithium iodide with Amberlyst (to enones) <2000T7133>, phosphonium anhydrides <1996SL661>, thiourea dioxide <1997TL745> and phosphines <2004JOC689, 2002TL7037>, zirconium chloride and sodium iodide <2005TL4107>, and metal salen complexes <1999TL8747>. The deoxygenation of epoxides using dichlorocarbene was examined using kinetic isotope effect experiments and theoretical methods <2005TL2033>.

1.03.3.8 Oxidations

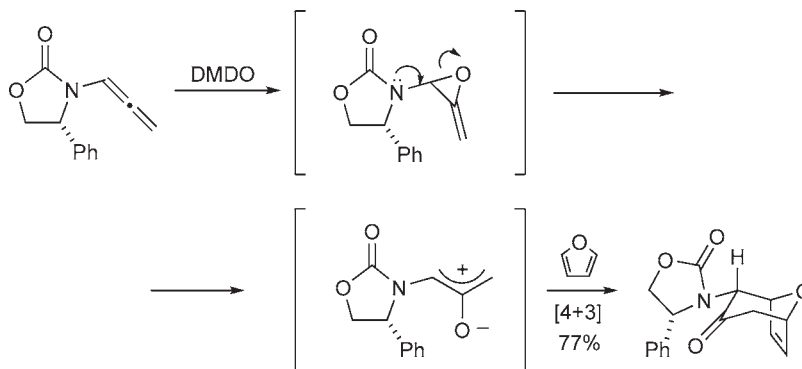
This reaction set has been reviewed <2003S2753>. Epoxides can be cleaved oxidatively using cyclodextrins and 2-iodoxybenzoic acid (IBX) in water <2003JOC9119>.

1.03.3.8.1 Cycloadditions

A variety of interesting cycloaddition reactions involving epoxides have been reported. For instance, an epoxypropargyltungsten species, prepared from NaCpW(CO)₃, undergoes Lewis acid-catalyzed [3+3] cycloaddition (Equation 53). The proposed mechanism for this reaction involves a tungsten- η^2 -allene cation produced by *exo*-attack of the epoxide, followed by secondary ring closure onto the terminal allene carbon. These cyclizations proceed with high diastereo- and enantioselectivity <2001JA7427, 2001JOC8106, 2003JOC1872>.



An allene precursor forms the basis of a [4+3] cycloaddition protocol yielding bicyclic ketones (Scheme 15). An allenamide functionalized with an oxazolidinone chiral auxiliary is oxidized using dimethyldioxirane (DMDO) to generate a intermediary vinylidene epoxide. Ring opening of this species produces a stabilized oxallyl cation that can be trapped with furan to give an *endo*-cycloadduct. The best diastereoselectivity in these reactions is observed when 2 equiv of ZnCl_2 was added <2001JA7174>.

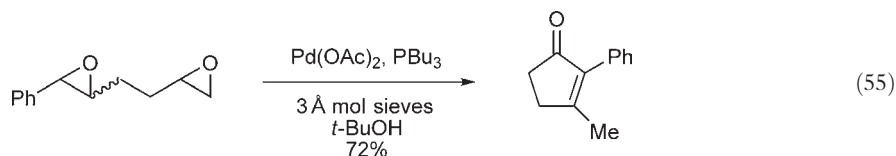
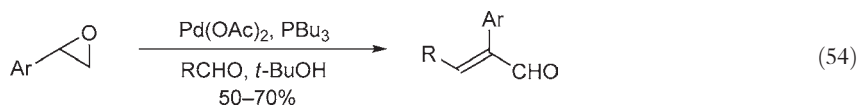


Scheme 15

Alkynes will react with epoxides in the presence of gallium trichloride through tandem ring opening and cyclization to give naphthalene derivatives <2002SL1553>. Vinyl oxiranes will undergo cycloadditions with activated alkenes to form functionalized THFs under palladium catalysis <1998JOC3067>.

1.03.3.9 Metal-Catalyzed Reactions

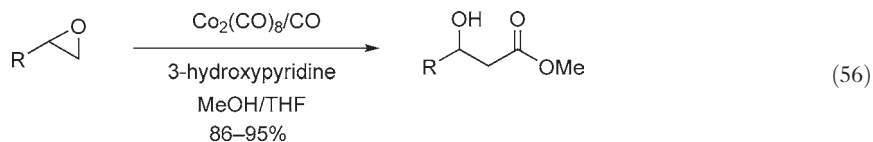
Epoxides can isomerize under the influence of transition metal catalysts. This formal 1,2-hydride shift is a method to prepare unsaturated carbonyl compounds from epoxides (Equation 54) <1998T1361>. This method has been extended as a double epoxide isomerization–intramolecular aldol condensation (Equation 55) <1996JOC7656, 1998TL3107>. *cis*-Epoxides are isomerized to *trans*-epoxides under ruthenium catalysis <2003TL3143>.



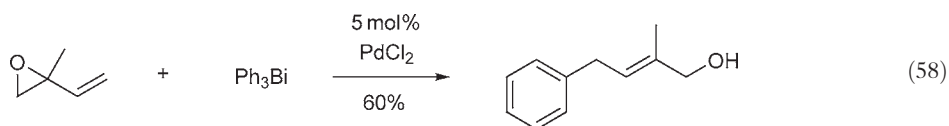
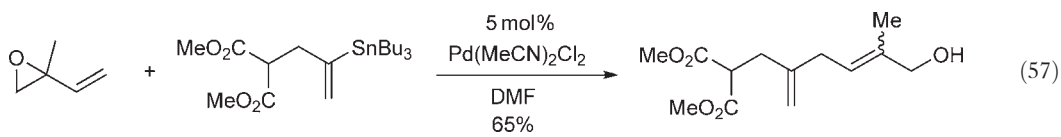
1,3-Dioxolanes can be produced from epoxides and acetone using ruthenium trichloride <1998SC3189>. Thiiranes can be made using titanium(III) reagents <1998SC3913>. Europium(III) reagents catalyze the trapping of epoxides with acyl halides to form 2-haloalkyl esters <1998TL4559>. Cyclic carbonates are fashioned through the reaction of oxiranes with carbon dioxide in the presence of rhenium or chromium complexes <2001JA11498,

2005JOC381, 2004JA3732>. Vinyl epoxides can be cross-coupled using palladium pincer complexes as catalysts and organoboronic acids as the organometallic component <2005CEJ5260>. Propargyl oxiranes and arylboronic acids can be coupled in aqueous media <2005TL6705>.

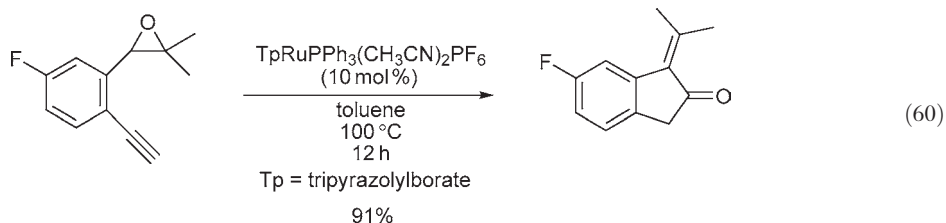
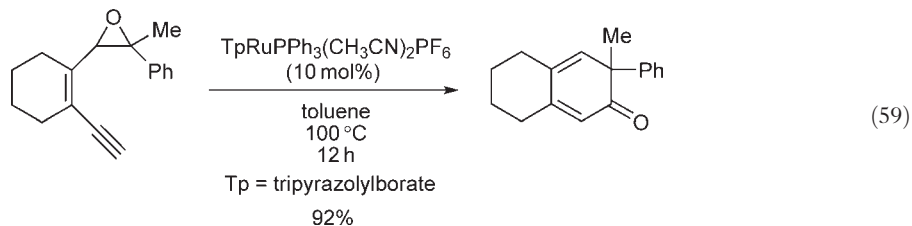
Terminal epoxides can be carbomethoxylated under mild conditions using CO/H₂ in the presence of salen complexes <1999JOC2164>. Alkynyl epoxides can be carbonylated to produce dienolate esters <1997JOC8484>. The carbonylation of epoxides to esters and lactones has been an area of extensive study (Equation 56) <2001JOC5424, 2002JA1174, 2002AGE2781, 2004OL373, 2005JA11426, 2005OM2533> in the past decade. This area has been recently reviewed <2004PAC557>. The conversion of epoxides to β -hydroxy morpholine amides using mild conditions has been disclosed <2002AGE4703>.



Vinyl epoxides can be cross-coupled with vinylstannanes <2001JOC589>. This reaction proceeds through an (η^3 -allyl)palladium complex (Equation 57) <2001JOC589>. Similar reactivity can be observed using bismuth reagents (Equation 58) <2001SC2365>. Vinyl oxiranes react with substituted allenes to form functionalized allyl alcohols <2004JOC4686>.



Unusual cyclizations onto epoxides can take place through presumed ruthenium ketene intermediates. Two examples are shown here (Equations 59 and 60) <2004JOC7700, 2004JA6895, 2005OL1745>.



Epoxides can be used as nucleophiles in intramolecular Nicholas reactions <2004OL565>. A nickel-catalyzed C–C bond-forming reaction between alkynes and epoxides has been developed <2003JA8076, 2005T6243>. Both inter- and intramolecular reactions are possible. 2-Diazo-1-oxiranyl-ethanone has been synthesized in an enantioselective manner and used in a number of reactions characteristic of rhodium-catalyzed processes of diazo compounds <2000OL2393>. Oxiranes can be converted to cyclic carbonates using carbon dioxide <2006CEJ1004>. The kinetics and mechanism of rhenium-catalyzed oxygen transfer from epoxides have been examined <2003JA11018>.

1.03.3.10 Polymerization

The importance of epoxides in the generation of polyesters is undisputed. To this end, a number of researchers have been examining the copolymerization reactions between oxiranes and carbon dioxide under the influence of a variety of catalysts. This area has been reviewed <2004AGE6618, 2004ACR836>. Initiators that have been developed to induce polymerization include titanium reagents <2004JA15932>, zinc complexes <1995MM7577, 1998JA11018, 2000AGE4096, 2005JA3031>, fluorenylphosphonium salts <1999MM1293, 2001MM1518>, chromium complexes <2002JA6335, 2004IC7278, 2004IC1831, 2005CEJ6298>, cobalt complexes <2003AGE5484, 2001IC6543, 2002JA5646, 2004JA1831, 2006JA1664>, among others <2004AGE3574, 2003AGE64, 2002AGE2599, 2001MM3205, 2003MM5902, 2003MM967, 2004MM1671>. Mechanistic aspects have been studied <2005CEJ5327>.

1.03.4 Oxiranes: Synthesis

1.03.4.1 General Survey of Synthesis

The synthesis of the oxirane functional group generally follows one of three possible approaches (Figure 4). The intramolecular displacement of a nucleofuge by an oxide, such as within a halohydrin, is of some importance. The most common technique involves oxygen atom transfer to a double bond. In addition, the transfer of a methylene equivalent to a carbonyl group is also often used. The development of these methods to provide chiral epoxides in significant ee's has been an important development since 1995. The industrial production of optically active epoxides has been summarized in a recent review <2004AGE788>.

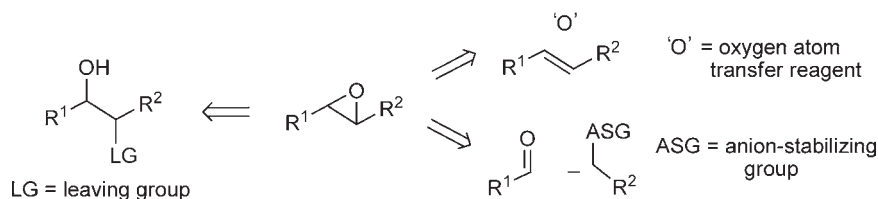


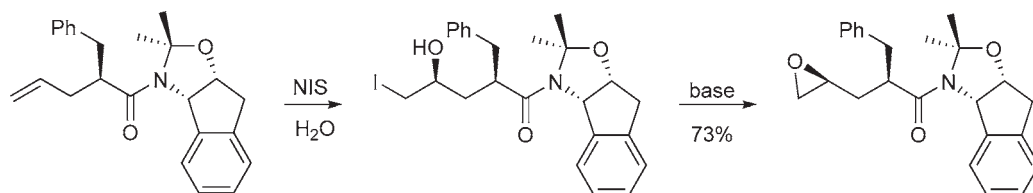
Figure 4

1.03.4.2 Nonenantioselective Methods

1.03.4.2.1 Oxiranes by intramolecular substitution

The formation of oxiranes by intramolecular substitution is a straightforward approach <2005TA2449, 2005TL5393, 2003TL9383, 2001T1935, 2005TL5811, 2005TL1867>. Tri- and tetrasubstituted oxiranes containing $-\text{CF}_3$ groups were made in a highly stereoselective manner using a rearrangement of a β -oxido carbenoid <2001JA6947, 2003T9811>. These rearrangements forming epoxides have been reviewed <2001CRV697>.

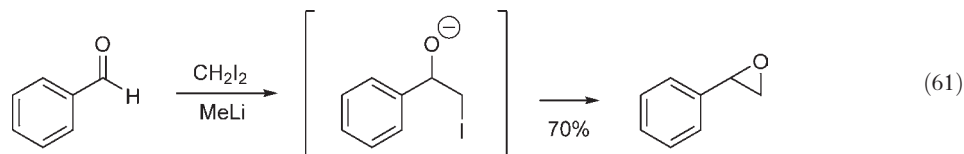
Either the *threo*- or the *erythro*-diastereomer of α -amino epoxides can be accessed from α -amino acids <1995JOC6696, 2001JOC5790, 2005TL5811>. Aryl aldehydes can be converted directly to *trans*-oxiranes using a proazaphosphatane as a promoter <2000JOC4560>. Chemists at Merck have illustrated an excellent example of diastereocontrol for the formation of a terminal epoxide. Diastereoselective iodohydration was followed by ring closure to provide a critical oxirane intermediate for an HIV protease inhibitor (Scheme 16) <1995TL2195, 2003TA3557>.



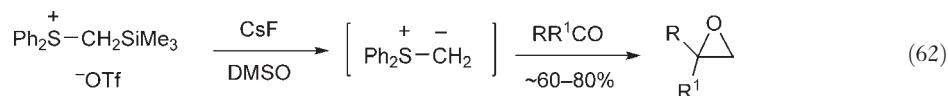
Scheme 16

1.03.4.2.2 Oxiranes from carbonyl compounds with CH₂ fragments (ylides)

A broad category of epoxide synthesis is based not on olefins, but on carbonyl compounds, in which the oxygen atom of the carbonyl function becomes the oxygen atom of the oxirane. One of the most straightforward manifestations of this approach is the conversion of benzaldehyde to styrene oxide by treatment with diiodomethane and methyl-lithium at 0 °C <2001T8983>. Lithium–halogen exchange followed by carbonyl addition generates an intermediate iodoalkoxide that rapidly undergoes ring closure, providing the desired oxirane (Equation 61).



The use of a sulfur ylide as in the Corey–Chaykovsky synthesis <1962JA867> is a standard method, but a number of interesting advances have been made recently. Sulfur ylides can be produced by the desilylation of (trimethylsilyl)methylsulfonium salts using CsF in DMSO (Equation 62) <1995S649>. This protocol avoids strongly basic conditions. Sulfur ylides can alternatively be generated *in situ* by decarboxylation of a carboxymethylsulfonium betaine <2003OL2283>. A convenient ‘instant methylide’ reagent produced from a dry mixture of trimethylsulfonium iodide and sodium hydride has been produced <2003SC2135>. These reactions have been carried out in an ionic liquid medium, such as (bmim)PF₆ <2003TL3629>. Simmons–Smith reagents have been used for the generation of sulfur ylides from sulfides <1997JOC8628>. By increasing the stability of the ylide intermediate, epoxides could be generated from diazoacetates using rhodium(II) catalysis <2001OL933>. The extent of trapping of carbonyl ylide intermediates in epoxidation and dipolar cycloaddition reactions was examined <2004JOC5269>.

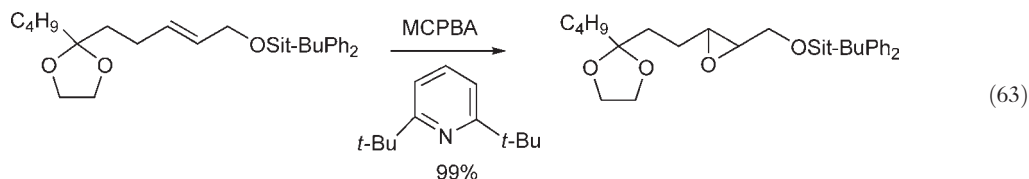


The synthesis of vinyl oxiranes using this methodology is complicated due to a problematic [2,3]-sigmatropic rearrangement of the ylide. Two solutions for this side reaction have been recently presented. The first solution utilizes tetrahydrothiophene as a catalyst <2003CC2074>. The rearrangement is prevented in this instance by geometric means. An alternative is the use of telluronium salts <2003TL4137>. Sulfur ylides can be generated *in situ* by the decomposition of diazo compounds. This process has been used to make ferrocene-substituted epoxides <2002TL3475>.

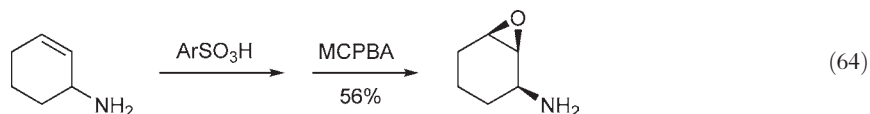
1.03.4.2.3 Oxirane synthesis from [2+1] fragments

1.03.4.2.3(i) Peroxy acid epoxidation

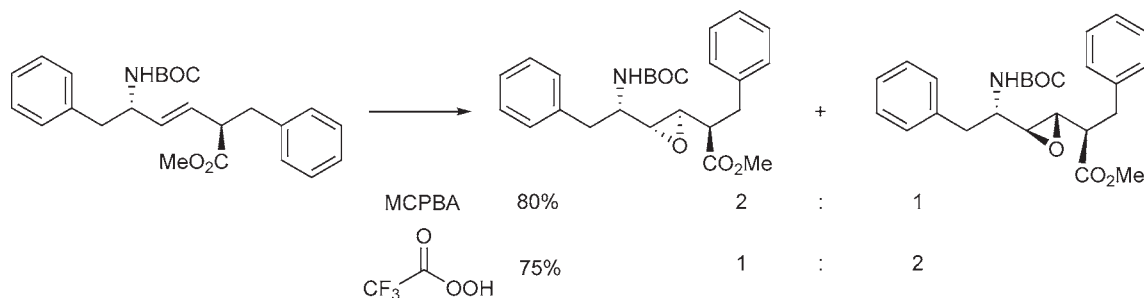
The epoxidation of an alkene using a peracid is arguably the most common technique for oxirane formation. The rate constants for peroxy acid reaction with a variety of alkenes correlate well with ionization potential, suggesting that frontier molecular orbital interactions are important, with minimal electron transfer from the alkene to the peracid <1998JA9513>. The primary and secondary kinetic isotope effects for MCPBA oxidation has been examined, giving results consistent with a spiro transition state <1997JOC6083, 1999JOC196>. The consequences of allylic strain and hydrogen bonding on the stereoselectivity of hydroxyl-directed epoxidations of chiral allylic alcohols have been summarized <1998JA680, 1999ACR703>. In this study, the examination of the ratio of diastereomeric products provides useful information regarding the reaction mechanism and transition state geometry of these oxidation reactions. Alkene oxidations using MCPBA have been carried out using fluoruous solvents in a ‘phase-vanishing’ technique <2003OL3787>. Buffered two-phase MCPBA systems are useful in situations where either the starting materials or products would be sensitive to acids <1996SC2235, 1996SC2875>. As an illustration in Equation (63), the addition of 2,6-di-*t*-butylpyridine to buffer MCPBA during this epoxidation gave superior results.



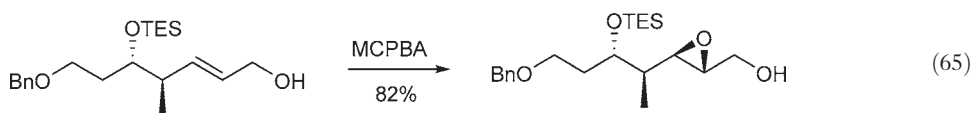
The ability of Lewis-basic functional groups to 'direct' the epoxidation event makes peracid oxidation a powerful synthetic technique. Although simple amino-alkenes typically cannot be epoxidized due to competitive N-oxidation, protonation of the amino group with a sulfonic acid to form an ammonium salt enables chemoselective oxidation. Interestingly, the ammonium functional group can additionally act as a useful directing group (Equation 64) <1995JOC3692>.



Allylic carbamates have been shown to be competent coordinators for directed epoxidations using MCPBA, and in a study comparing the relative effects of substituents, the following order of 'directing group ability' was established: carbamate > methyl ester > homoallylic alcohol = acetate <1995JOC1026>. 2-Cyclohexen-1-ylamine derivatives can be converted using MCPBA to either the *trans*- or *cis*-oxirane derivatives, depending on the substituents on the nitrogen atom <2003OL4955>. The facial selectivities for these oxidation reactions are still not completely understood, as exemplified in Scheme 17. Although MCPBA in dichloromethane produced mainly the *threo*-epoxide, epoxidation using trifluoroperacetic acid generated mostly the *erythro*-isomer. Subtle effects in the coordination of the allylic functional groups in the transition state are obviously at play <1998TL3213>. In the example in Equation (65), the triethylsilyloxy functional group overrides the effects of the adjacent methyl substituent <1998TL4517>.



Scheme 17



Alkenes with *gem*-deactivating groups, although unreactive with MCPBA itself, react smoothly with MCPBA and KOH to generate oxiranes in high yields (see Section 1.03.4.2.5) <2005JOC4300>.

The preparation of acid-sensitive oxiranes has inspired the use of sulfonic peracids that can (1) be generated *in situ* and (2) typically react with a greater stereoselectivity than typical organic peracids <1996T2957>. For industrial applications, Johnstone and co-workers have developed 5-hydroperoxycarbonylphthalimide as a new reagent <1998CC429> (Figure 5). This reagent is easily prepared and shock stable. Yields using this reagent are excellent with a variety of alkenes. Sodium chlorite can also produce epoxides from alkenes without the aid of a catalyst <2005JOC9610>.

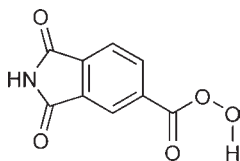
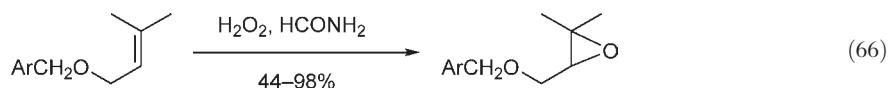


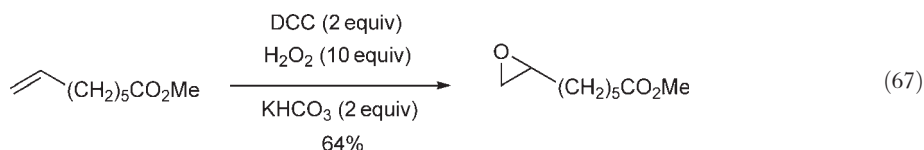
Figure 5

1.03.4.2.3(ii) Epoxidations with hydrogen peroxide

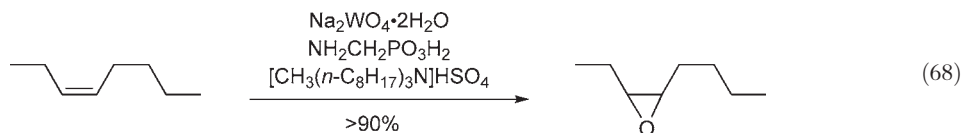
Hydrogen peroxide is an attractive oxidant for epoxidation reactions. As water is its primary reaction by-product, a number of studies for the use of hydrogen peroxide as a terminal oxidant in epoxidation reactions have been reported. Fluorinated alcohols as solvents enable the oxidation of alkenes using hydrogen peroxide <2003JOC2903>. It is suggested by theoretical calculations that the solvent provides a complementary charge template that stabilizes the transition state. A similar effect has been observed using phenol as a solvent for epoxidation using hydrogen peroxide <2003OL1777>. Reactions also proceed in supercritical carbon dioxide without any added metal catalysts or peroxyacids <2002IEC316>. The combination of formamide and hydrogen peroxide effectively oxidizes tri- and *cis*-disubstituted alkenes (Equation 66) <1995TL4015>. No reactions are observed with *trans*-disubstituted or terminal alkenes. In addition, water-soluble alkenes can be epoxidized directly using bicarbonate-activated hydrogen peroxide in a mixed solvent system <2000JA3220>.



Commercially available 30% hydrogen peroxide solution can oxidize alkenes readily in the presence of a carbodiimide promoter <1996SL649, 1998JOC2564, 1998JOC1730> (Equation 67). A method to epoxidize propene using aqueous hydrogen peroxide and a reaction controlled phase-transfer catalysts was developed <2004OPD131>.



Noyori and co-workers have developed an industrially relevant sodium tungstate-mediated epoxidation reaction using 30% hydrogen peroxide in the absence of solvents <1996JOC8310, 1997BCJ905>. Key elements of this technique are the use of an (α -aminoalkyl)-phosphonic acid and a lipophilic ammonium hydrogensulfate (vs. the corresponding chloride) as a phase-transfer catalyst. The scope appears to be fairly broad, and yields are typically quite high (Equation 68). A 'triphase' catalyst based on phosphotungstic acid, an *N*-(isopropylacrylamide)polymer, converted allyl alcohols to epoxides using hydrogen peroxide in water at very low loadings (27 ppm) <2001OL1837>. The catalyst exhibits a very high turnover rate (35 000), is easily recoverable by filtration, and is reusable. In fact, twice-recovered catalyst provided a 97% yield of epoxide in subsequent reactions. Titanium-silsesquioxane catalysts have been prepared by the complexation of titanium to incompletely condensed silsesquioxanes. The activity of the catalyst was found to be highly dependent upon the nature of the monosilane precursor <2001AGE740>. The oxidation of lipophilic alkenes in ionic liquids with epoxidation components provided by the aqueous phase, and the products extracted into a pentane layer, have been presented <2003OL3423>. The kinetics of the reaction of styrene to styrene oxide with hydrogen peroxide using 'Ishii-Venturello' conditions (heteropoly-acids and phase-transfer catalysis in biphasic media) was examined <2000OPD88>.

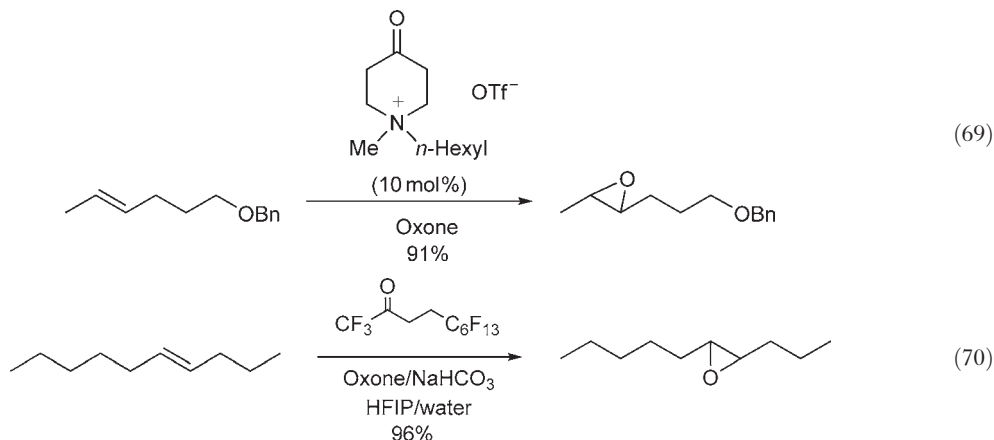


1.03.4.2.3(iii) Epoxidations with dioxiranes

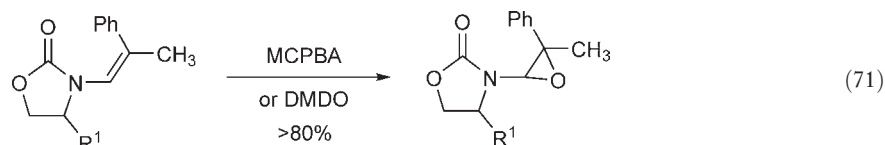
The conversion of alkenes to oxiranes using ketone catalysts in the presence of a terminal oxidant such as Oxone has proved to be an important advance in the past decade, especially for the formation of chiral oxiranes (see Section 1.03.4.3.3(ii)). The conversion of alkenes to oxiranes has been comprehensively reviewed <2002OR219>. The formation of the dioxirane species usually proceeds *in situ*, whether it be the formation of methyl(trifluoromethyl)-dioxirane in an academic setting <1995JOC3887>, or under conditions amenable to large-scale conversion of aromatic alkenes to oxiranes (oxone, acetone, ethyl acetate, no phase-transfer catalysis) <2002OPD405>.

A number of ketone catalysts have been developed. Crucial considerations are solubility and stability. As an example, catalytic amounts of ammonium salts such as 1-hexyl-1-methyl-4-oxopiperidinium triflate with Oxone in a buffered water-dichloromethane mixture are effective oxidation agents (Equation 69) <1995JOC1391>. Other

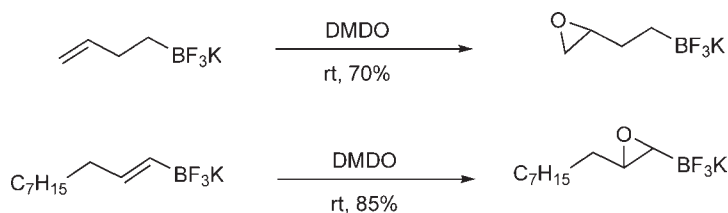
systems have been developed <1998JOC2810, 1998JOC6425>. An example of a system modified for use in a fluororous solvent is shown in Equation (70). The fluoroketone acts as a capable oxidant of aliphatic alkenes in a buffered water/HFIP medium <2001TL4463>. These ketone catalysts have been immobilized on polyethylene glycol (PEG) solid supports, enabling the efficient oxidation of even relatively sensitive substrates <2004TL6357>.



Hydrogen-bonding effects have been demonstrated to be quite important in dioxirane oxidations, lowering the activation barrier for reaction <1998JA1875>. The site-selective epoxidation reaction of geraniol using DMDO is affected by the reaction solvent <1996JOC3506>. In nonpolar solvents, hydrogen-bonding interactions between the hydroxyl group in the substrate direct the oxidation reaction to the proximal alkene. Kinetic studies of the reaction between alkenyl ammonium salts with either DMDO or MCPBA give results consistent with the existence of hydrogen-bond interactions between the protic substrates and the oxidant <1999JOC4705>. Complementary diastereoselection was observed in the epoxidation of an α,β -unsaturated amide attached to a camphor-based auxiliary using either methyl(trifluoromethyl)dioxirane or urea hydrogen peroxide <2003JOC9816>. Hydrogen-bonding interactions proved important in the dioxirane-promoted oxidation of chiral oxazolidine-substituted alkenes <2001JA7228, 2001OL79>. ‘Capping’ the free N–H functionality by methylation of the substrate resulted in a substantial decrease in the diastereoselectivity of the process. The diastereoselectivity of epoxidation reactions of enecarbamates derived from ‘Evans-type’ oxazolidinones using either dioxiranes or MCPBA was examined (Equation 71) <2004JOC1704, 2003OL819>. The diastereoselectivity of oxirane formation in reactions between chiral allylic alcohols and hexafluoroacetone perhydrate with hydrogen peroxide suggests hydroxy-group direction by hydrogen-bonding interactions <1999JOC1274>. Chiral 2,2-dimethyloxazolidine derivatives of tiglic amides undergo epoxidations with complementary diastereoselectivity using either DMDO or MCPBA <2000OL1019>. The selectivity of the dioxirane epoxidation is believed to be primarily driven by steric factors, while hydrogen-bonding effects dominate when MCPBA is used. Dioxiranes have also been used in epoxidations of alkenes in the presence of camphorsultam and related auxiliaries <2004T6657>.



Finally, in a dramatic example of chemoselectivity, potassium 1-alkenyltrifluoroborates can be epoxidized readily using DMDO to yield highly functionalized trifluoroborate salts (Scheme 18) <2003JA11148>.



Scheme 18

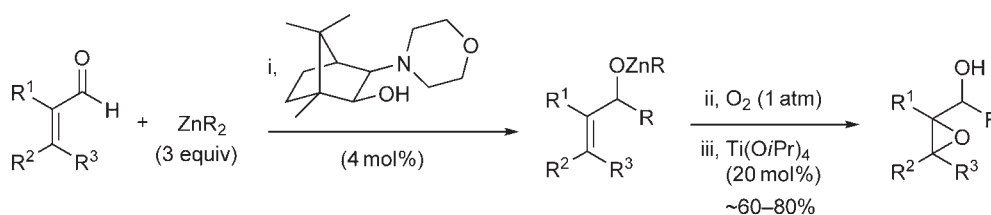
1.03.4.2.3(iv) Epoxidations with molecular oxygen

One of the most attractive oxidants for the conversion of alkenes to oxiranes is molecular oxygen (dioxygen). Convenient methods that do not incorporate a metal salt are available. Terminal alkenes could be oxidized to epoxides using 2-ethylhexanal and oxygen without any added catalyst or solvent <1999OPD101>. This procedure is suggested to be of some use as the by-product derived from the aldehyde, 2-ethylhexanoic acid, is suggested to be a commercially important material. A practical, large-scale procedure for the isolation of the oxirane product is still under investigation. A metal-free epoxidation protocol was reported that proceeds by the *in situ* generation of hydrogen peroxide from O₂ through a complex series of steps involving *N*-hydroxyphthalimide (NHPI). Once formed, the H₂O₂ is activated by addition onto the solvent, trifluoroacetone, to give 2-hydroperoxy-hexafluoropropan-2-ol as the oxygen-transfer reagent. Although the reaction appears to be general and yields are very good, a strong preference for the formation of *trans*-epoxides was observed regardless of the starting configuration of the alkene <1999CC727>. Nitrogen oxides have been shown to catalyze the oxidation of alkenes to oxiranes through the intermediacy of alkene cation radicals generated by electron transfer <1996JA1319>. A clever experiment demonstrated that the epoxidation of alkenes using oxygen in the presence of an aldehyde *in situ* proceeds by formation of an acyl peroxy radical, not a peroxy acid <2000OL357>.

In terms of metal-promoted reactions in the presence of oxygen and aldehydes, a detailed mechanistic study of the conversion of alkenes to oxiranes suggested that the primary oxidant in these reactions is also an acyl peroxy radical derived from the aldehyde <1996IC1045>. A second investigation of the Mukaiyama epoxidation (oxygen, Ni(acac)₂, and an aldehyde) suggested that reactions proceed via peroxyacyl radicals and a peracid <2004JOC3453>.

Other metal-centered catalysts that have been studied include (bis)strapped chiral porphyrins derived from L-proline, which can induce modest (<30%) enantioselectivity <2002EJI1666>. Supported amide-bridged platinum blue complexes, which have not yet been applied to chiral epoxidation, but which show promise of utilizing molecular oxygen as the terminal oxidant, have also been used. Thus, cyclohexene was epoxidized in 99% yield in the presence of isobutyraldehyde, atmospheric oxygen, and a carbon-supported platinum complex prepared from [Pt₄(NH₃)₈((CH₃)₃CCONH)₄](NO₃)₅ <2002SC17>. Some interesting solid-phase catalysts were developed by the introduction of Co(III) or Mn(III) ions into the precursor gels of molecular sieves before calcining (heating to high temperature). These novel complexes appear to catalyze the aerobic epoxidation of alkenes, although the methodology requires forcing conditions and the use of a sacrificial aldehyde, such as benzaldehyde <1999CC829>.

A nucleophilic addition of organozinc reagents to enones under the influence of a chiral promoter will generate an allyl alcoholate that, when subjected to oxygen gas with a titanium-based Lewis acid, produces epoxy alcohols in a one-pot process (Scheme 19) <2003JA9544, 2004JA13608>. Interestingly, the diastereoselectivity of these epoxidation reactions in this one-pot process is often superior to standard epoxidation reactions performed on the allylic alcohols. This work has been extended to allow for allylation–epoxidation sequences of cyclic enones <2004JA12580>, and vinylation–epoxidation reactions to produce acyclic epoxy alcohols <2005JOC1262>.



Scheme 19

1.03.4.2.3(v) Oxaziridine epoxidations

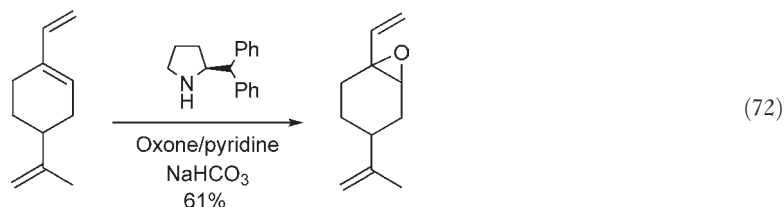
In situ formation of an oxaziridine is possible using a reagent combination of chloramine-M, benzaldehyde, and benzyltrietethylammonium chloride <2000JA4039>. While the oxidation of *trans*-alkenes generates *trans*-oxiranes, the corresponding reaction of *cis*-alkenes produces *trans*-oxiranes as major products.

Oxaziridinium salts were designed with the intent to act as 'hydrophobic' epoxidation reagents <2005JA10812, 2005TL2207>. This reagent shows a high degree of selectivity for reaction with cinnamate salts compared to crotonate salts in aqueous solution, suggesting that site-selectivity problems may be solvable with this reagent combination.

Fluorinated derivatives of oxaziridines have been developed for oxirane formation <1996JOC8805>.

1.03.4.2.3(vi) Epoxidations with amines

Simple amines in the presence of Oxone oxidize alkenes to oxiranes. For example, Oxone, pyridine, and a 2-pyrrolidine derivative in a medium of aqueous acetonitrile selectively converts the triene in Equation (72) to a single epoxide. This process also proceeds using noncyclic alkenes. The mechanism is believed to proceed via a single-electron transfer (SET) process involving radical cation intermediates <2000JA8317>.

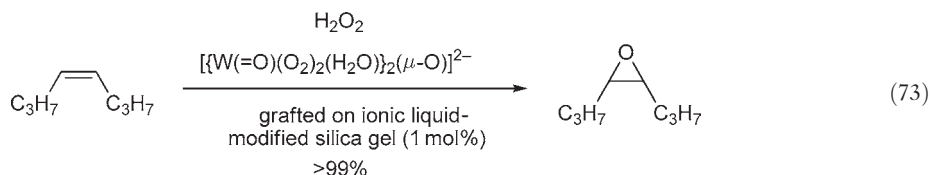


1.03.4.2.4 Metal-mediated epoxidations

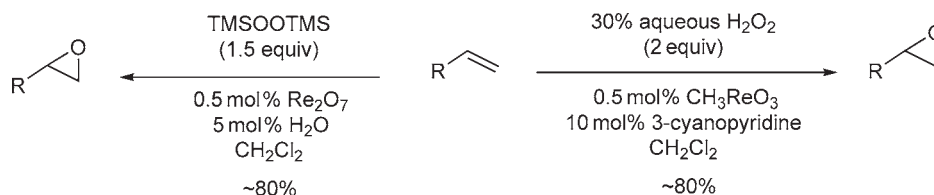
Metal-catalyzed oxygen-transfer reactions from hydrogen peroxide to the organic substrates catalyzed have been reviewed <2003CRV2457>. A review of copper(I) systems containing polypyrazolylborate ligands as catalysts for the conversion of alkenes into small-ring compounds has been published <2001JOM110>. The examination of epoxidation catalysts based on titanium-silica using a synchrotron has been reviewed <2001ACR571>.

Conditions developed by Sharpless ($\text{VO}(\text{acac})_2$ -*t*-butylhydroperoxide (TBHP)) define the standard for the diastereoselective epoxidation of allylic alcohols. New observations using this technology continue to be made <1995TL5979, 1996TL1205, 1997TL1369>.

A number of polyoxometallates were discovered to catalyze the reaction between allyl alcohols and hydrogen peroxide to form epoxides <2003JOC1721>. Hydrotalcites and amides also promoted epoxide formation from alkenes and hydrogen peroxide <1999JOC2966>. A heterogeneous catalyst system based on peroxotungstate immobilized on 'ionic liquid-modified' silica enables the epoxidation of alkenes with hydrogen peroxide (Equation 73) <2005JA530>. The crucial feedstock propylene oxide can be produced using molecular oxygen and a catalytic system of palladium(II) acetate and a peroxo-heteropoly compound in methanol <2004CC582>. A conveniently prepared amorphous silica-supported titanium catalyst exhibits activity similar to that of Ti-substituted zeolites in the epoxidation of terminal linear and bulky alkenes <2000CC855>.



Peroxide complexes derived from methylrhenium trioxide was demonstrated to convert styrenes to styrene oxides using hydrogen peroxide <1995JA9243>. The use of this reagent to oxidize alkyl-substituted alkenes, monoterpenes, and allyl alcohols was also examined <1996JOC3969, 1998TL8521, 1999IC881>. The addition of pyridine additives enhances the selectivity and the rate of oxirane formation using methylrhenium trioxide in aqueous systems (Scheme 19) <1997JA6189, 1997CC1565, 1997JOM319, 1998JA11335, 2000JOC8651>. These catalyst systems have been placed on solid support <2002JOC1323>. The regio- and diastereoselectivity of this catalyst system compared to peracids and dioxiranes have been studied <1999JOC3699>. The use of bis(trimethylsilyl) peroxide as co-oxidant enables the use of inorganic rhenium oxides as catalysts rather than organometallic derivatives (Scheme 20) <1997JA11536, 2001JOC4713>. Sodium percarbonate can also serve as the terminal oxidant for



Scheme 20

these epoxidations <2000JOC4210>. The urea–hydrogen peroxide adduct can also serve a terminal oxidant <1996TL2717>. Fluorinated solvents can be used readily, as high yields of either terminal or internal epoxides result <1999CC821>.

An unusual example of copper-catalyzed epoxidation using substoichiometric amounts of soluble Cu(II) compounds in methylene chloride uses MCPBA as a terminal oxidant. As a mixture of *cis*- and *trans*-epoxides can be obtained from a single stereoisomeric alkene, a stepwise radical mechanism is suggested <2000TL1013>.

Acylperoxoiron(III) porphyrin complexes can act as a potent catalyst for the oxidations in dichloromethane <1995JA6691>. A water-soluble iron porphyrin system has been developed for hydrogen peroxide or *tert*-butyl peroxide promoted reactions in aqueous solvents <1998IC606>. An evaluation of the oxidation reaction using iron porphyrin systems and hydrogen peroxide in protic solvents has been carried out <2003JOC7903>. An iron(IV) system ligated to an electron-deficient porphyrin ligand generated epoxides in a stereospecific manner <2003JA14674>. A ‘self-assembled’ catalyst system based on iron(III) efficiently oxidizes terminal alkenes using aqueous hydrogen peroxide <2001JA7194>. An iron(III) dimer, [(phen)₂(H₂O)Fe(III)₂(μ-O)](ClO₄)₄ efficiently catalyzed the peracetic acid promoted epoxidation reaction of terminal alkenes <2003OL2469>. DFT analysis has been used to examine reaction paths in P450 catalysis to examine the detailed mechanism, including the formation of reaction by-products <2005CEJ2825>.

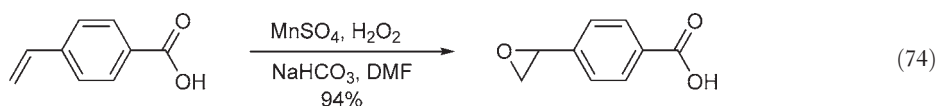
Studies in a cryogenic matrix provide evidence for epoxide complexes of chromium(IV) complexes <1999IC2106>. The mechanism of chromyl chloride epoxidation has been evaluated <2003JA11188>.

The kinetics of the epoxidation of alkenes using [Ru(IV)(bpy)₂(py)(O)]²⁺ in acetonitrile was evaluated <1995JA2520>. The catalytic mechanism using *trans*-dioxoruthenium(IV) porphyrins as catalysts was evaluated <1999JOC7365>. Ruthenium(II) porphyrins have been placed on Merrifield support <2000JA5337>. This process yielded a catalyst system having unusual selectivity properties. These catalyst systems have also been attached to PEG supports, generating soluble catalyst systems <2002OL1911>. The diastereoselectivity of substrate-controlled processes using ruthenium porphyrins has been examined <2004OL1597>. A ruthenium-terpyridine complex is an effective precatalyst for the epoxidation of alkenes using aqueous hydrogen peroxide <2005OL987>.

Vanadyl salen complexes epoxidized cyclohexene presumably through intermediate hydroperoxides formed by radical chain autoxidation <1997IC5927, 1998TL5923>. Reactions using vanadium complexes have been carried out in liquid carbon dioxide <1999OM4916>.

A novel Mn(II)-based polyoxometallate species was developed for oxygen transfer reactions <1998JA7252>. This system epoxidizes limonene using only a small molar excess of hydrogen peroxide. The catalytic lifetime of an Mn(III) porphyrin system has been extended by the addition of anthracene or structurally similar compounds <2005IC5523>. The regio- and diastereoselectivity of reactions catalyzed by Mn(salen) and Fe(porphyrin) complexes on chiral substrates has been examined <1999JA1879>. An Mn–porphyrin system was used for a diastereoselective epoxidation process of allyl alcohols, amines, and esters <2005JOC4226>. Experiments using an Mn(III) triazacorrole-based catalyst system suggest the participation of a ‘third oxidant’ in oxidations of this type <2004JA18>. A buffered Mn–trimethyltriazacyclononane catalyst system is also highly efficient in the epoxidation of terminal or electron-deficient olefins with H₂O₂ <1998TL3221>.

Simple Mn(II) salts (e.g., MnSO₄) provide an inexpensive, scalable, environmentally friendly solution to the problem of large-scale epoxidation reactions with commercially available hydrogen peroxide solutions <2001JA2933>. Thus, when the styrene derivative was treated with 1 mol% of MnSO₄ and 10 equiv of H₂O₂ in a DMF/bicarbonate buffer medium, the corresponding epoxide was produced in 94% yield (DMF = dimethylformamide; **Scheme 16**). These conditions selectively epoxidize an internal double bond in the presence of a terminal olefin, in contrast to the corresponding rhodium-catalyzed reactions. A cationic manganese(II) complex catalyzes the peracid epoxidation of electron-deficient alkenes <2003JA5250>. Nineteen ligand–manganese combinations were screened in the peracid oxidation of terminal alkenes <2004OL3119>. The effect of pH on this reaction was also investigated. A substantial screening effort was used to identify an Mn(II)-based epoxidation system in bicarbonate solutions using hydrogen peroxide as the terminal oxidant (Equation (74)) <2002JA1194>. Substantial practical advantages derive from this method. A similar reaction can be carried out in ionic liquids <2003OL3423>. A non-heme manganese(IV) was observed to catalyze reactions through the intermediacy of a metallo-peracid complex rather than a metallo-oxo species <2005JA17170>. Another selective catalytic oxidant based on Mn was developed <2005JA7990>.

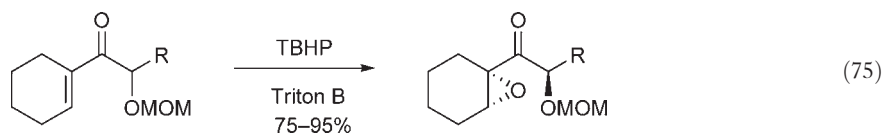


New dioxo Mo(VI)-based catalysts with monoanionic tridentate ligands have been developed <2001JA862>. The coordination environment of these catalysts remain well defined during the reaction, and simultaneous coordination of the substrate and oxidant is not observed. New Mo(VI)-based complexes containing modified cyclopentadienyl ligands can be used for alkene epoxidation <2003OM2112>.

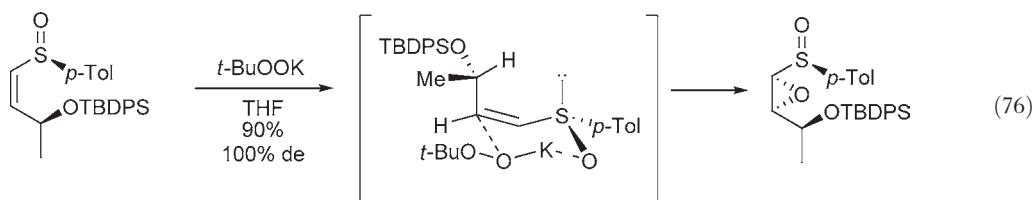
Cobalt(III) diketonate complexes generate alkyl peroxo adducts that can oxidize alkenes to oxiranes <1999IC1603>. *O*-Phenylenebis(oxamate)-ligated square-planar cobalt(III) complexes catalyze high-yield epoxidations of unfunctionalized tri- and disubstituted alkenes <1997TL2377>. Low yields are obtained with terminal alkenes. Terminal alkenes can be converted smoothly to aldehydes using an epoxidation–isomerization with ruthenium(II) porphyrin catalysts <2004AGE4950>.

1.03.4.2.5 Nucleophilic epoxidations

The epoxidation of non-nucleophilic alkenes such as those with electron-withdrawing substituents requires a tactical adjustment. These oxidations are best carried out using nucleophilic oxidants <1997TL3009, 2004JOC2580>. This subject has been the topic of a short review <2000CC1215>. Interesting diastereoselectivities can be observed in the nucleophilic epoxidation process (Equation 75). In this instance, Felkin–Anh-type transition structures are invoked to explain the sterically controlled approach of the nucleophilic peroxide to a specific conformer of the substrate <1995TL6611>. Similar models are invoked in additions to vinyl sulfone substrates <1995JP1141>.



Vinyl sulfoxides have been converted to sulfinyl oxiranes <1996JOC3586>. Protected hydroxyl substituents can have an effect on the diastereoselectivity <2002JOC8166, 2003JOC4797, 2006JOC1569> (Equation 76).

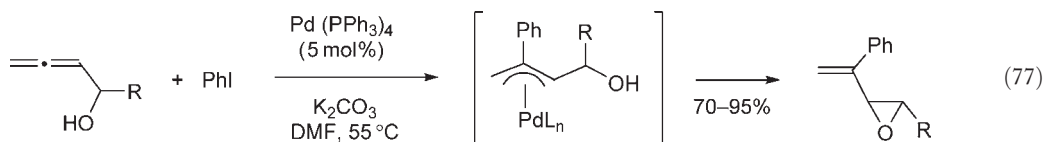


In a similar fashion, γ -hydroxy- α,β -unsaturated esters were shown to undergo diastereoselective epoxidation in the presence of lithium *t*-butylperoxide, in which the delivery of the epoxide oxygen is guided by the solvent system <2004TL5359>. Enones can be epoxidized using hydrogen peroxide in the presence of a heterogenous basic hydro-talcite catalyst <2000JOC6897>. A tartrate salt-mediated nucleophilic epoxidation was key to the synthesis of (–)-cycloepoxydon <2001JA11308>. The epoxidation of phosphinoyl alkenes with basic hydrogen peroxide was examined <2006TL421>. Nucleophilic epoxidations have also been carried out using iodine-based reagents <2000OL2923>.

1.03.4.2.6 Miscellaneous methods

Proteins can be modified to acquire peroxxygenase activity <1999OL1025, 1997JA6666>.

2,3-Allenols undergo a palladium(0)-catalyzed cyclization process to yield highly functionalized vinyl oxiranes in a diastereoselective manner (Equation 77) <1999JA7943>. Initial carbon palladation forms a palladium allyl intermediate that suffers subsequent attack by the internal oxygen nucleophile to generate the oxirane fragment.



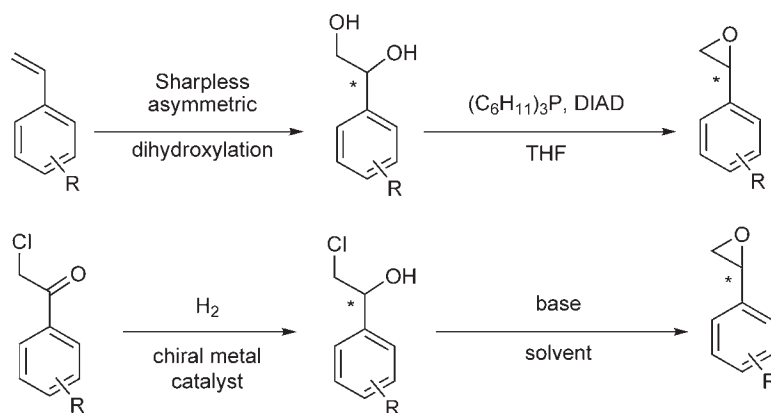
An easily prepared acetonitrile complex of hypofluorous acid (HOF·CH₃CN) serves an excellent reagent for the oxidation of alkenes with pendant alcohol or carboxylic acid functionalities <1996TL531>.

A Diels–Alder reaction between an 2-azadiene and an aldehyde forms an adduct that can be converted in a straightforward manner to a *cis*-epoxy-carboxylic acid <2004T8347>.

1.03.4.3 Enantioselective Methods

1.03.4.3.1 Oxiranes by intramolecular substitution

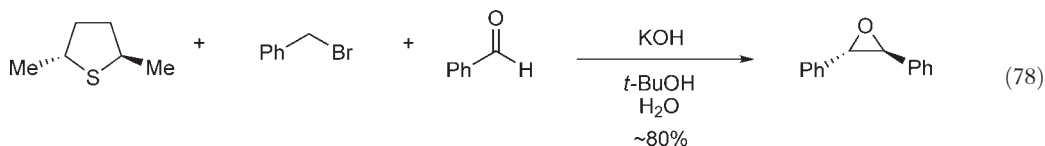
An asymmetric carbonyl addition reaction catalyzed by a Cr(salen) complex generates functionalized chlorohydrin products that can be trivially converted to vinyl epoxides <2001OL1153>. Chlorohydrins can undergo chemoenzymatic dynamic kinetic resolution, providing a route to chiral epoxides in enantioenriched form <2002JOC9006>. The synthesis of cryptophycin 52 demanded a diol (derived from a Sharpless asymmetric dihydroxylation) to epoxide transformation <2000JOC3143>. In a similar vein, simple alkenes were converted to nonracemic epoxides via a two-step sequence of asymmetric dihydroxylation (AD) and Mitsunobu cyclodehydration of the intermediate diol (Scheme 21) <2001OL2513>. The reactions performed best using electron-poor alkenes. Related reactions have been used in synthesis <2002T6685, 2000JP1153>. The enantioselective reduction of a α -halocarbonyl compound generates a chiral alcohol from which a chiral epoxide can be produced (Scheme 21) <2006TL349, 2004T7411>.



Scheme 21

1.03.4.3.2 Oxiranes from carbonyl compounds with CH₂ fragments (ylides)

A number of research groups have been responsible for the development of catalytic, enantioselective preparation of oxiranes using sulfur ylides as intermediates in the past decade. A number of reviews of this topic by Aggarwal and co-workers have been published <1997CRV2341, 1998SL329, 2003CC2644, 2004ACR611>. This procedure has the advantage of directly converting aldehydes to the desired products (Equation 78) <1996JA7004>.



One method involves the use of chiral sulfimides rather than the corresponding sulfides <1997JOC6512>. Much work has gone into the design of sulfides to enable high enantioselectivities and diastereoselectivities (Figure 6) <1989JOC4222, 1995JOC3494, 1996JOC489, 1998JOC4532, 1999JP1731, 2005JOC4166, 1998JA8328, 2000TL7309, 1999SL1328, 2001JOC5620, 2001TL57, 2002JOC9083, 2001T4629, 2002H(8)1399, 2002TL5427, 2004CC1076, 2001AGE1430>. This process has been used for the synthesis of functionalized, trisubstituted epoxides <2003AGE3274>. The sulfur ylides can be generated in a classical fashion <2001JOC5620>, or can be generated by the interception of diazo compounds (Scheme 22) <1998TL8517, 1998JP12037, 1998JA8328, 2001TL6803, 2003JA10926, 2003AGE3274>.

This route can be used to generate vinyl oxiranes, useful intermediates for organic synthesis <2000TL7309, 2002JOC9083, 2003JOC2060>. Aryl epoxides have been made and have been used as intermediates in the context of total synthesis venture <2004T9725>.

In a related report, a Darzens-type reaction performed in the presence of BINOL-derived phase-transfer catalyst allowed for epoxide formation with high enantioselectivity and moderate diastereoselectivity <1996TL1845>.

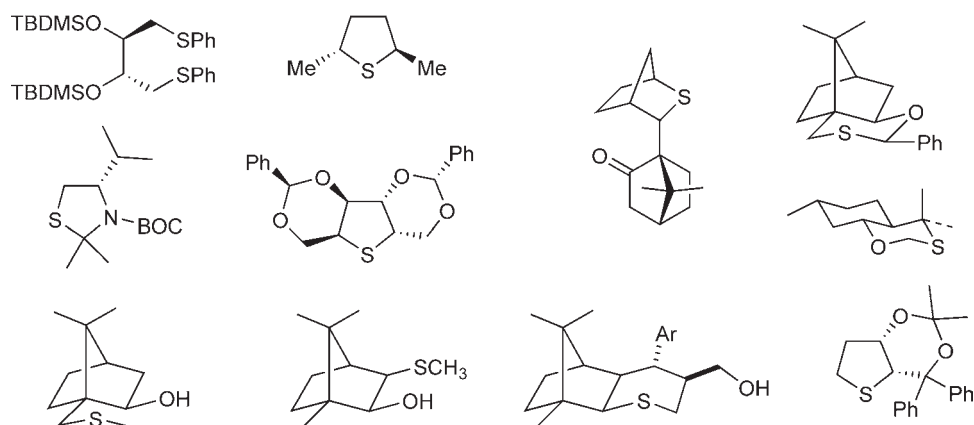
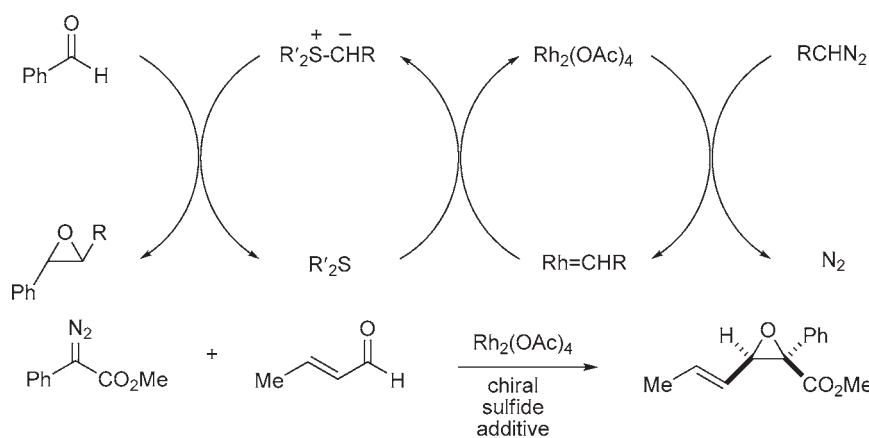


Figure 6

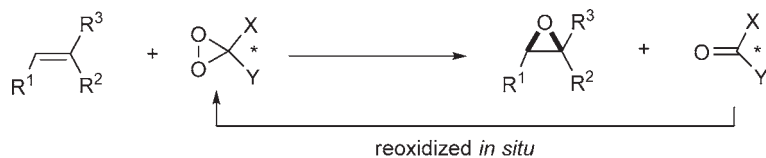


Scheme 22

1.03.4.3.3 Oxirane synthesis from [2+1] fragments

1.03.4.3.3(i) Epoxidations with dioxiranes

One of the most important advances in the past decade has been the development of asymmetric epoxidation methods for unfunctionalized alkenes using dioxiranes generated from chiral ketone precursors (Scheme 23) <1995TL5831, 1997JOC8964>.



Scheme 23

A number of review articles summarizing this work have appeared <1999SL847, 2000S1979, 2004ACR488, 2004ACR497>. Since the initial reports <1996JA491, 1996JA9806, 1996JA11311, 1997JOC2328, 1997JOC8288, 1997JOC8622, 1997JA11224, 1998JA5943, 1998JA7659>, the structures of the ketone precatalysts and the reaction conditions have been systematically modified and improved <1998TL4425, 1998TL7819, 1998JOC2948,

1998JOC8475, 1998JOC8952, 1998JOC6425, 2001JOC521, 2000JOC8807, 2001H615, 2005T6409>. Specific problems such as the nature of the co-oxidant, the decomposition of the ketone precatalyst through Baeyer–Villiger reaction, and the substrate specificity required solutions. Although the original reports focused on oxirane formation from (*E*)-alkenes, predictable epoxide synthesis is now available using hydroxyalkenes <1998JOC3099>, conjugated enynes <1999JOC7646>, vinylsilanes <1999JOC7675>, (*Z*)- and terminal alkenes (e.g., **Scheme 23**) <2000JA11551, 2001OL1929, 2002JOC2435> and enoates <2002JA8792>. A number of modified ketone catalysts have been developed to improve (1) their stability to the oxidizing reaction conditions and (2) the overall reactivity and selectivity to a variety of classes of alkenes (**Figure 7**) <2000OL3531, 2001OL715, 2003JOC4963, 2003OL293, 2005JOC7279>. A number of approaches to this problem have been developed, including 6-oxo-1,1,4,4-tetramethyl-1,4-diazepinium salts <1998JOC2810>, ketones related to tropinone <1998CC621, 2002JOC8610, 2003JOC3232>, keto bile acids <2002JOC5802>, and fluorinated derivatives <2002JOC3479>. As an example, the epoxidation reaction between (*Z*)-1-phenyl-1-propene using a fructose-derived catalyst provides the epoxide product in 87% ee in a very high conversion (**Scheme 24**). This process has been used in a number of approaches to chiral, nonracemic epoxides <2002OL1813, 2004JOC4216>.

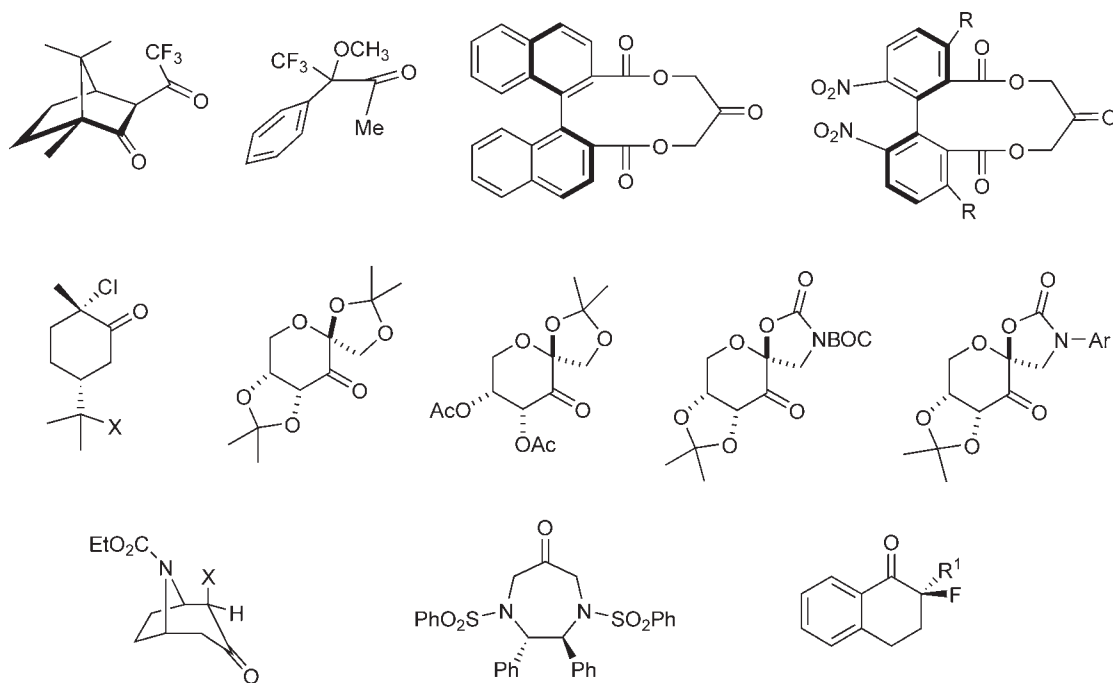
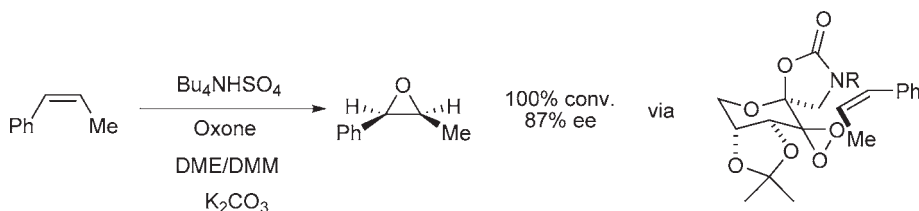


Figure 7



Scheme 24

1.03.4.3.3(ii) Epoxidations with molecular oxygen

A one-pot method oxygen involving molecular oxygen in the presence of diethylzinc and (*R,R*)-*N*-methylpseudoephedrine enables an asymmetric epoxidation of enones in high yields and ee's [<1996AGE1725>](#).

1.03.4.3.3(iii) Oxaziridine epoxidations

A number of chiral oxaziridines generated *in situ* from iminium salts and Oxone have proved to be useful for alkene epoxidation. A number of iminium salts that have proved useful as precursors to oxaziridine catalysts are shown in **Figure 8** <1996CC191, 2001JOC6926, 2001OL2587, 2004OL1543> (first high selectivities), <2004JOC3595> (nonaqueous conditions), <2005OL375> (*cis*-alkenes) <2005TA3488>.

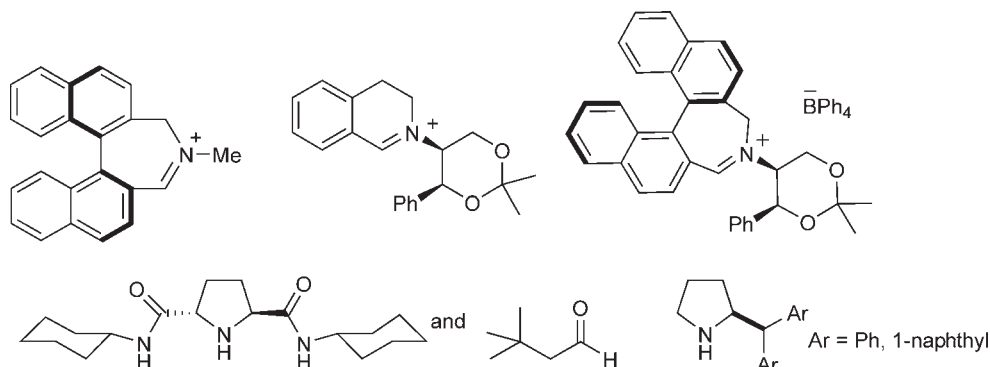


Figure 8

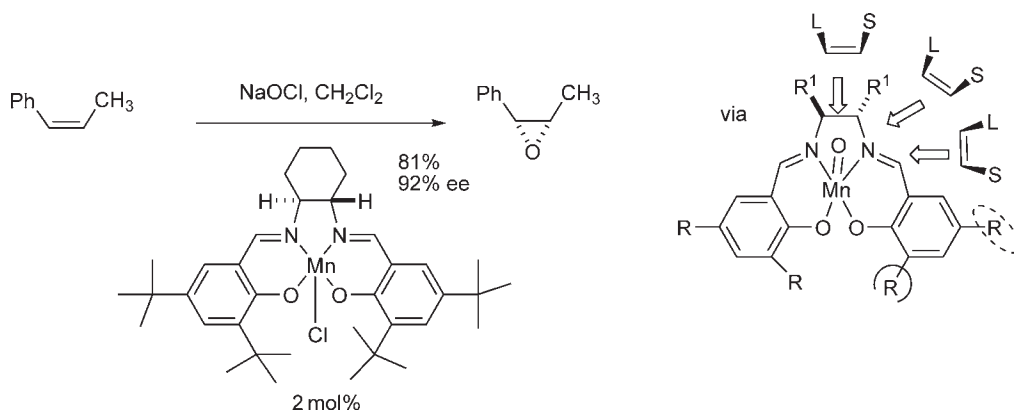
Chiral secondary amines can be used to produce iminium ions with carbonyl compounds that are converted to reactive oxaziridines *in situ* <2001OL2587>. In other instances, a chiral salt formed between the amine salt and Oxone is believed to be oxidizing reagent <2004AGE1460>. This interaction could form a radical cation or also in some instances form a useful phase-transfer catalyst <2000JA8317, 2002JA11223, 2003JA7596>. In some cases, the amine can be reisolated after the oxidation process <2003JOC6576>. Fluorinated versions of these amines have been developed <2005JOC898>.

1.03.4.3.4 Metal-mediated epoxidations

In terms of enantioselective alkene oxidations to oxirane systems, the standard to which all comparisons are made remains the Sharpless epoxidation process <B-2000MI2, B-2000MI3>. The requirement for an allylic hydroxyl functional group to act as a directing group remains its main drawback (incorporates potentially unneeded functionality), yet it provides the method's best attributes (predictability, coupled with selectivity). Many applications of this technique within total synthesis exercises are available <2003JOC3026, 1996JP11729>. Polytartrate ester ligands to generate a solid-supported Sharpless-type catalyst have been pursued <1997CC123, 2005JOC1728>, and tartrate ligand libraries have been developed <2004JOC2042>. Vinylsilanols successfully undergo Sharpless epoxidation <1997T10197>. Peroxides have been used as the co-oxidant for these reactions <2002TL5629>. A related zirconium-tartrate ligand system with cumene hydroperoxide was used for the enantioselective epoxidation of homoallyl alcohols <2003OL85>.

The enantioselective epoxidation of unfunctionalized alkenes using Mn complexes coordinated to salen ligands as developed by Jacobsen and Katsuki represents a standard to which other oxidation reactions are compared. Reviews on this topic are available <2003SL281, 2001OL663, B-2000MI4>. These metal complexes in the presence of an external oxidant such as NaOCl or PhIO are capable of converting conjugated alkenes to their corresponding epoxides in high yields and high ee's (**Scheme 25**). These complexes can be produced in 75% yield from commercially available starting materials <2001SC2913>.

A number of studies have been carried out to improve the reaction selectivity and efficiency in specific contexts (**Figure 9**) <1995TL319, 1995TL5123, 1995TL5457, 1995SL827, 1995JOC4378, 1995SL827, 1995SL197, 1996TL4533, 1998TL4325, 1999TL1001, 2001JOC5796> and to determine the details of the reaction mechanism <1991JA6703, 1995JA11035, 1997AGE1723, 1997JOC2222, 1997T9541, 1998JA948, 1999OL419, 1999JA5083, 2000JA9685, 2000EJO3519, 2000AGE589, 2000TL7053, 2001JOC5796, 2002JA5068, 2003JOC6202, 2002CEJ4299, 2002CEJ2568, 2004JA15560, 2004IC2672, 2005JA13672>. A number of efforts to improve the efficiency of this catalyst system by using solid-phase supports or alternate fluorous phases have been made <1996TL3375, 2000CC615, 2000JA6929, 2000CC2171, 2000CC837, 2002TL2665, 2004OL59, 2005TA3562>. At times, better results are obtained using achiral metal salen complexes with chiral *N*-oxide-based ligand systems <1999SL783>. The ligand sets for the Mn catalyst system have been perturbed to explore the reactivity of catalyst system <1999SL1157>. Efficient systems for the epoxidation of terminal alkenes have been uncovered <1999JA460>.



Scheme 25

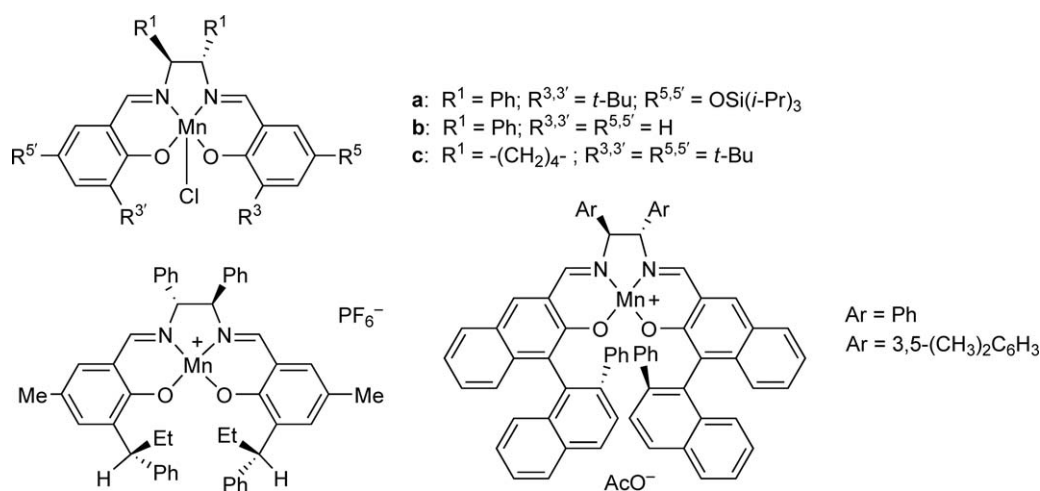
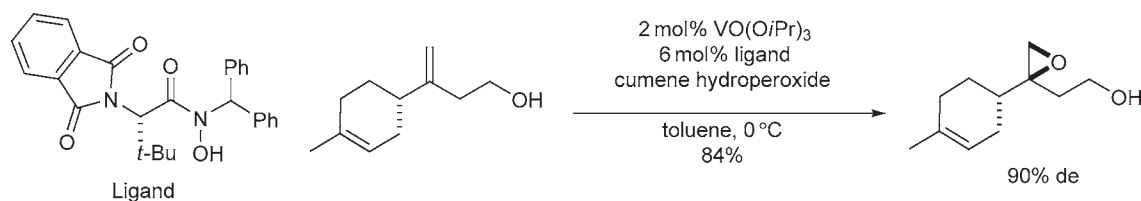


Figure 9

Although the reaction of (*E*)-alkenes tends to produce oxiranes in low enantioselectivities, the corresponding Cr(salen) complexes oxidize alkenes with better selectivities [<1995TL7739, 1999TL3613, 1999CC1789, 2001OL663, 2001OL3435, 2003IC7258>](#). The use of chromium(III) salen catalysts for alkene epoxidations have been reviewed [<2002CC919>](#). Organorhenium(VII) catalysts and organomolybdenum(VI) compounds as catalysts for asymmetric alkene epoxidation reactions have been reviewed [<2005TA3469>](#).

Vanadium-catalyzed reactions of allyl alcohols with peroxides have been explored using paracyclophane-derived or TADDOL-based ligands (TADDOL = (–)-*trans*-4,5-bis(diphenyl-hydroxymethyl)-2,2-dimethyl-1,3-dioxolane) [<1999OL2077, 2000SL899, 2003OL725>](#). A microencapsulated version of VO(acac)₂ has been developed [<2002OL1519>](#). An impressive epoxidation of a homoallylic alcohol was achieved using a vanadium-based system in the presence of a hydroxamic acid-derived ligand set (Scheme 26) [<1999JOC338, 2000JA10452, 2003AGE941>](#). This oxidation was exemplified in a route to (–)-α-bisabolol.

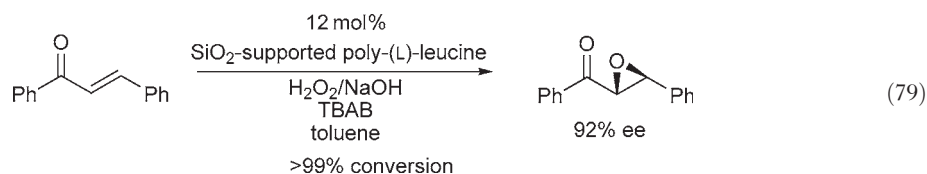


Scheme 26

Iron- and ruthenium-based chiral porphyrin catalysts can perform fair to good conversions of terminal or *trans*-disubstituted alkenes to chiral oxiranes <1997JOC5514, 1999JA460, 1999IC1446, 1999CC409, 1999OL2077, 2000OM4117>. Other ligand sets for Ru have been developed <1999OM5691, 2005OL3393, 2005TA3536>. Cytochrome P450-inspired oxidations have also been performed <2003JA3406, 2005JA6540>. A bioengineered cytochrome P₄₅₀ enzyme served as an intriguing epoxidation catalyst <2006CEJ1216>. An optically active Fe(III)(porph^{*}) catalyst has been examined as a catalyst for epoxidation reactions <2001TA2677>.

1.03.4.3.5 Nucleophilic epoxidations

A variety of methods for the enantioselective conversion of electron-deficient alkenes to epoxides have been developed. The so-called Juliá-Colonna oxidation reaction, the nucleophilic epoxidation of enones and related compounds using poly-(L)-leucines as 'enzyme surrogates', can be an effective method <2003OPD509>. Much effort has been expended to effectively immobilize these synthetic peptides on solid supports (Equation 79). These catalysts are most effective at promoting the epoxidation reactions of chalcones and related compounds <1997CC739, 1998CC1159, 1999JCS(P1)103, 1999JP11397, 2000BCJ2115, 2000JA5654, 2000CL366, 2001TL3471, 2001OL683, 2001OL3839, 2002SL707, 2004TL5069, 2004TL507>. The mechanism for this process has been investigated <2005OL4847>.



A polymeric binaphthyl zinc complex has been used for related epoxidation reactions <1999JOC8149>. A bimetallic samarium-based Lewis acid complex catalyzes the nucleophilic epoxidation of unsaturated carbonyl compounds very efficiently <2002JA14544>. The use of amino acids as organocatalysts for asymmetric epoxidations of enones and enals has been investigated <2005OL2579, 2005JA6964>.

A number of chiral phase-transfer salts capable of catalyzing the epoxidation of electron-deficient alkenes have been developed. The molecular framework provided by the *Cinchona* alkaloids have appeared to be a useful starting

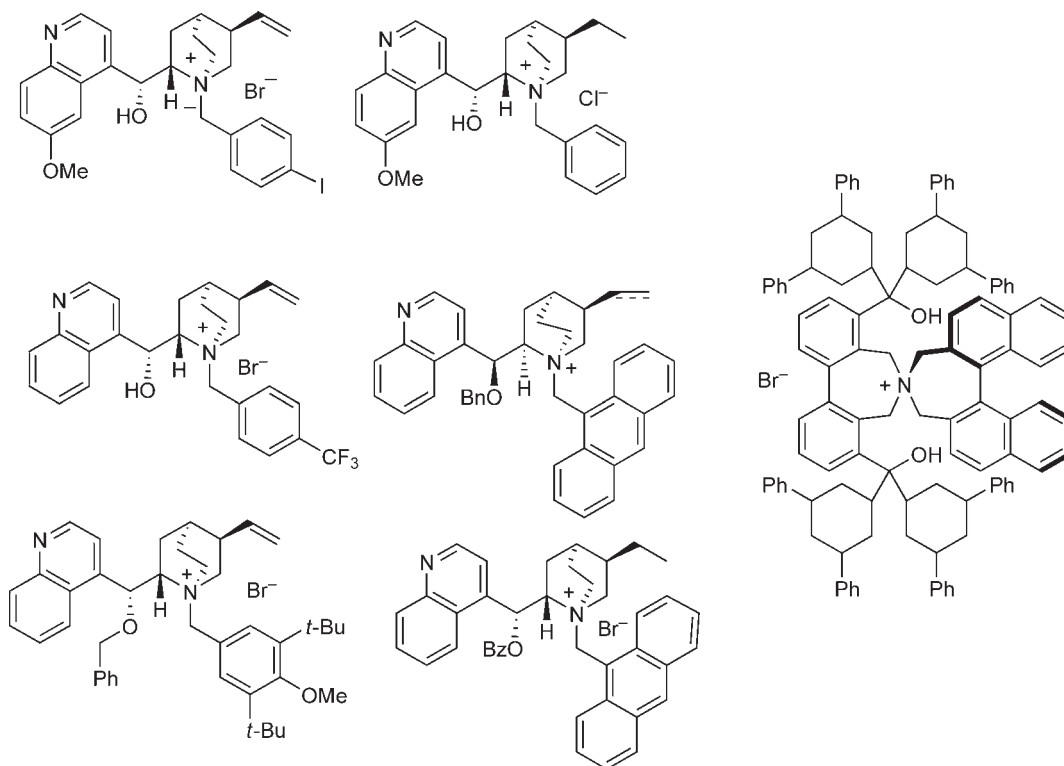
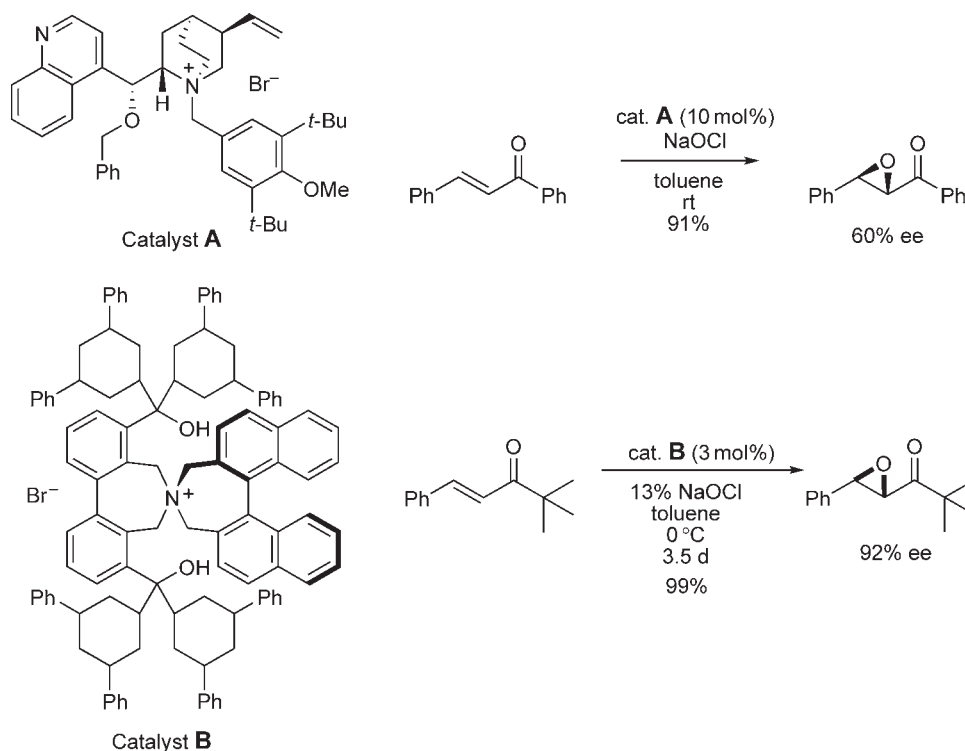


Figure 10

point for catalyst development (Figure 10). These systems are effective at promoting the epoxidation of acyclic enones and related systems <1998TL1599, 1999T6289, 1999OL1287, 2001TL1343, 2002T1623, 2003SC435, 2003T4549>.

As examples, the use of sodium hypochlorite in a biphasic system in the presence of phase-transfer catalysts, a high-yielding epoxidation of a variety of electron-deficient trisubstituted and *trans*-disubstituted olefins with excellent enantioselectivity, can take place (Scheme 27) <2004JA6844>.



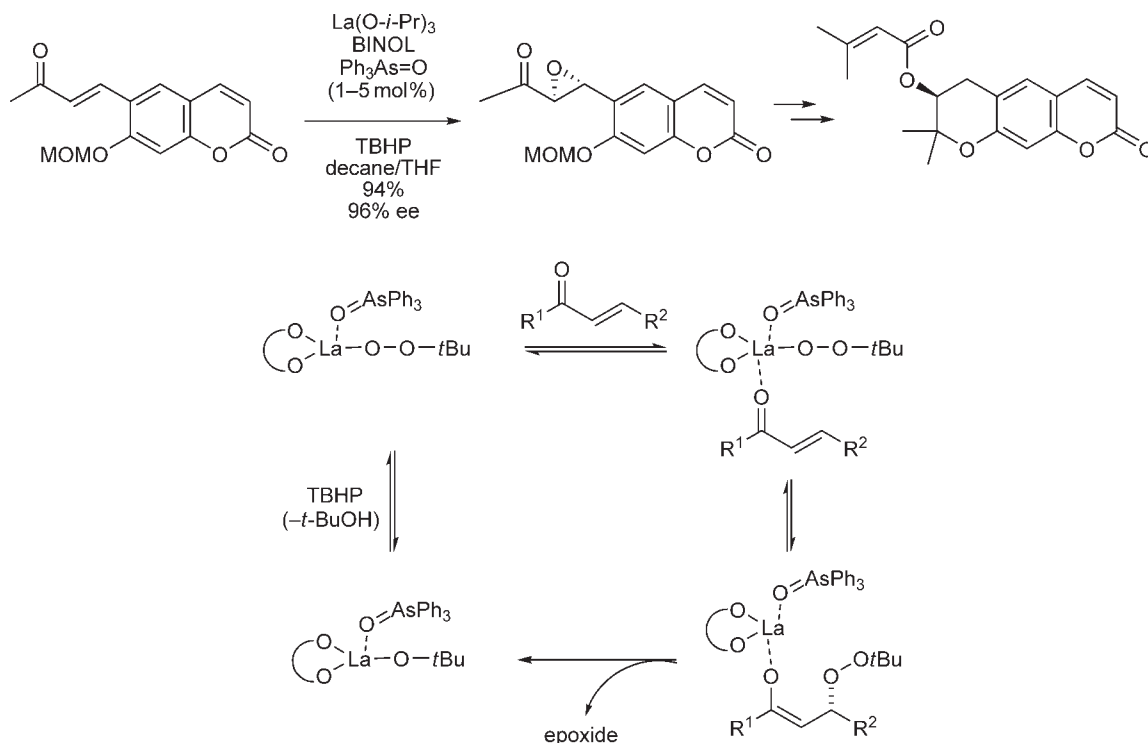
Scheme 27

A novel multifunctional catalyst derived from lanthanum(III) isopropoxide, BINOL, and triphenylarsine oxide can, in the presence of organic peroxides, produce α,β -epoxy-carbonyl compounds in very high ee's <1997JA2329, 2001JA2725>. As an example, lanthanum catalyst promoted epoxidation of enone in the presence of TBHP with excellent enantioselectivity (Scheme 28). The resultant epoxide was used as a key intermediate in the total asymmetric synthesis of (+)-decursin <2003T6889>. As yet, examination of the kinetics of this epoxidation system has not provided conclusive results regarding the number of lanthanum species required at the transition state, although the relationship between the enantioselectivity and the reaction solvent has lead to the proposal that a single La center is involved. Carboxylic acid imidazolides undergo reaction much faster than the corresponding esters, and the epoxy peroxyester products could be converted to alkyl esters using mild conditions <2001JA9474>.

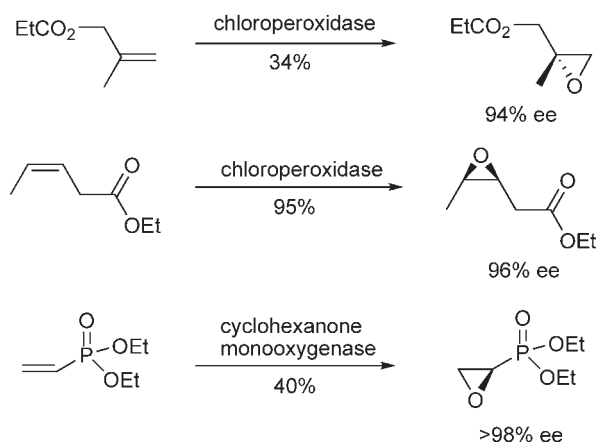
A chiral ytterbium complex formed from $\text{Yb}(\text{O}-i\text{-Pr})_3$ and 6,6'-diphenyl-BINOL catalyzed the asymmetric epoxidation of chalcone in 91% yield and 97% ee <2001TL6919>. A related reaction proceeds efficiently using enoates <2005JA8962>.

1.03.4.3.6 Enzyme-catalyzed epoxidation

Epoxide formation using biocatalysis is a useful process for the formation of chiral oxiranes (Scheme 29). The synthesis of enantioenriched epoxides using enzymes has been reviewed <1995BCSF769>. Chloroperoxidase has been examined for the oxidation of 2-methyl-1-alkenes, among other alkenes. The yields in some cases can be low, but the enantioselectivities can be high <1995JA6412, 1997JA443>. This enzyme has been used in a synthesis of



Scheme 28



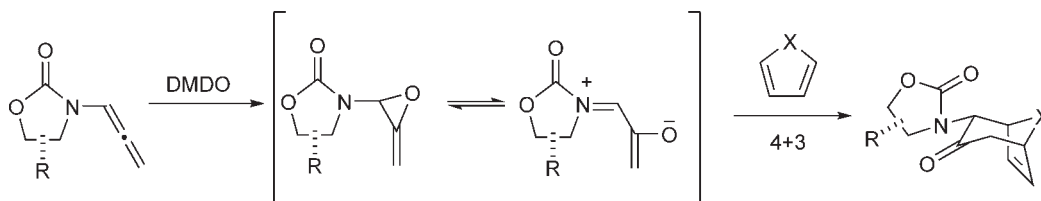
Scheme 29

mevalonolactone [<1996JOC3923>](#). A modified cytochrome P450 BM-3 was engineered for the enantioselective epoxidation of terminal alkenes [<2006CEJ1216>](#).

Cyclohexanone monooxygenase has been used for the epoxidation of substrates such as vinyl phosphonates [<2002TL1797>](#).

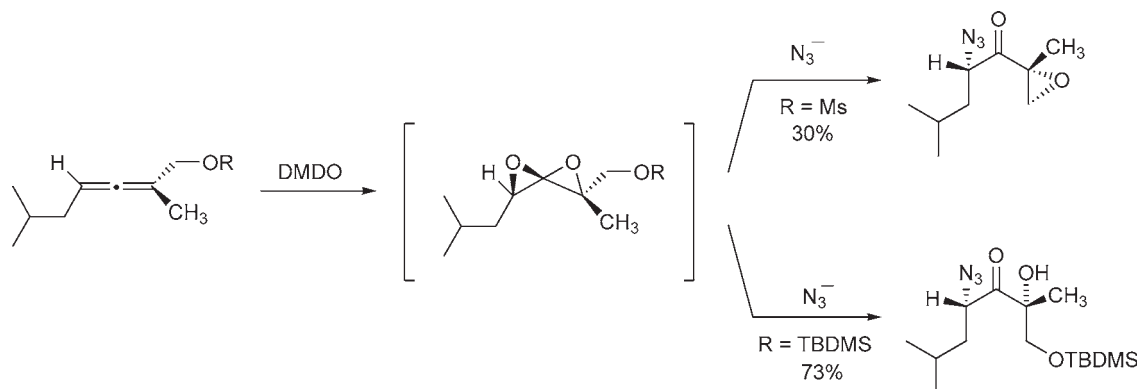
1.03.5 Allene Mono- and Bis-Oxiranes

Allenamides have been used as precursors for oxidation reactions [<2002JOC1339>](#). The allene oxide products that are produced are useful oxyallyl cation equivalents for cycloaddition chemistry ([Scheme 30](#)) [<2001JA7174, 2003JA12694>](#).



Scheme 30

Williams has used a spirodiepoxide derived from epoxidation of an allene to be a versatile electrophile for the formation of highly functionalized ketone-containing fragments. Reaction of a spiroepoxide formed *in situ* with a nucleophile such as azide ion initiates a cascade process. This strategy for the formation of highly functionalized fragments was highlighted in an epoxomicin synthesis (Scheme 31) <2004JA15348>.



Scheme 31

1.03.6 Oxiranes: Biological Aspects, Occurrence

The question of oxidative cyclization versus a 'polyepoxide cascade' in the biosynthesis of polyether natural products has been reviewed <1995AGE298>. Enzymatic domino reactions involving epoxide intermediates have been reviewed <2001CSR332>. The DNA-damaging activity of epoxides and other oxidized species has been examined using chemical models <1995ACR289>.

The oxirane fragment is a common functional group. As such, a large number of compounds isolated from biological sources contain acyclic epoxide moieties <2001TL687, 2001JAN149, 2002JP11581, 2003JAN630, 2004JAN537, 2006EJO582, 2002T6685, 2001TL7379, 2005OL3893, 2006JOC2510>. The structural complexity of compounds isolated from nature that contain an epoxide fragment can range from very simple dialkyl-substituted epoxides (usually pheromones) to stereochemically complex macrolides (Figure 11) <1995ACR289, 2000OL3249>.

1.03.7 Oxirenes

Work regarding oxirenes, a highly strained class of antiaromatic heterocycles, appears to have been largely focused on studies within the realms of physical organic, physical, and theoretical chemistry. The chemistry of oxirenes has been reviewed <B-2001MI1>. AMI and *ab initio* studies have determined that 'push-pull' substitution does not stabilize the oxirene system <1997JMT39>. Sung has examined substituent effects on the stability of oxiranes, oxirenes, and dioxiranes <2000CJC562>. The ability of DFT to correctly predict the oxirene stationary point has been evaluated <2003JMT263>.

The photochemical reaction between ozone and dimethylacetylene has been examined using both matrix isolation and *ab initio* methods <1999PSA7280>. The photolysis of hexafluoro-2-butyne and ozone forming oxirene

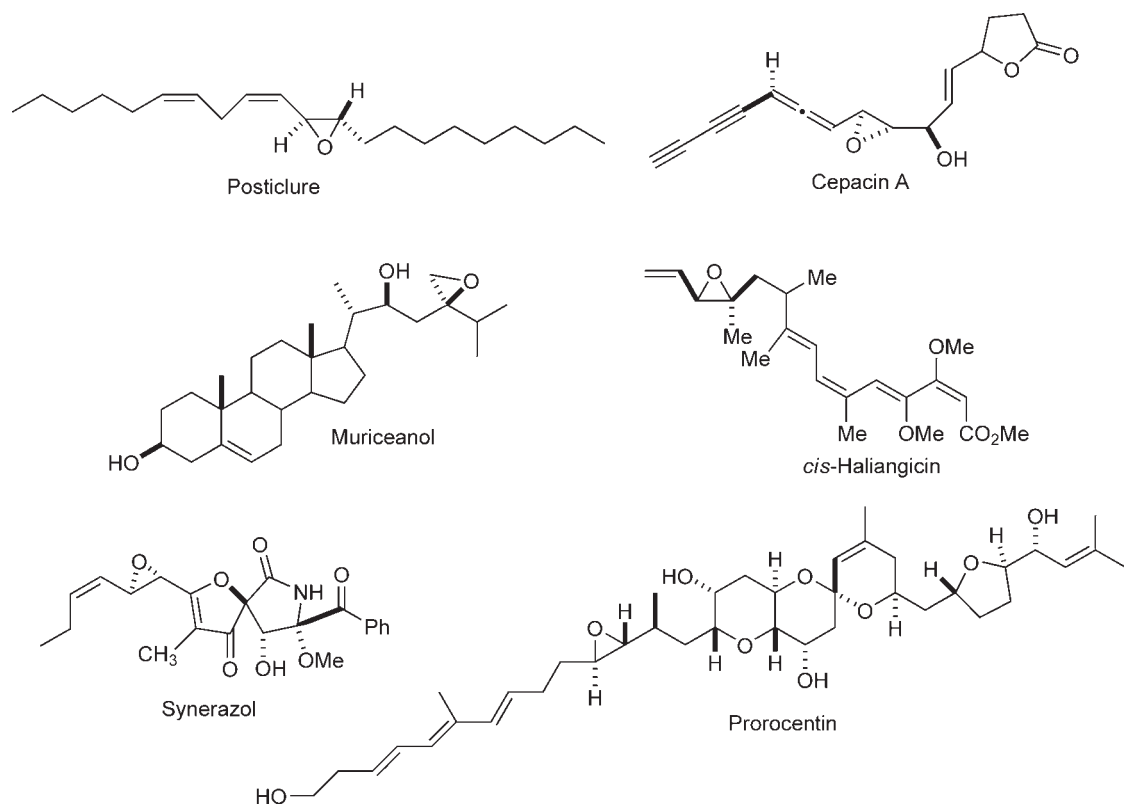


Figure 11

intermediates has been carried out [\[2000JA9078\]](#). The ozonolysis of acetylene has been examined by theoretical methods [\[2001JA6127\]](#). The oxidative cleavage of carbon–carbon triple bonds has been the subject of a recent review [\[2003JIC1129\]](#). Alkynes can be oxidized by ruthenium complexes [\[2000JA11380\]](#).

A computational study regarding the generation of oxirenes by retro-Diels–Alder reactions has been carried out [\[2002CJC94\]](#). Oxirenes can be generated by Wolff rearrangements, the photochemical or thermal dinitrogenation of α -diazoketones. This process has been the subject of a recent review [\[2004MI291\]](#). The Wolff rearrangement of 3-diazo-1,1,1-trifluoro-2-oxopropane has recently been reexamined [\[2003OBC2556\]](#). The question of conformational control versus structural constraints has been examined in Wolff rearrangement chemistry [\[2005CJC1382\]](#).

1.03.8 Further Developments

1.03.8.1 Theory

The effectiveness of density functional theory in theoretical analyses of protonated epoxides has been examined [\[2006JOC1592, 2007JOC295\]](#).

1.03.8.2 Reactions

Epoxides were regioselectively opened using reactions between reactive hydride reagents and aminoepoxides [\[2006JOC6420\]](#). The intramolecular addition reactions of alcohols to epoxides forming either substituted tetrahydrofuran or tetrahydropyran derivatives displayed a remarkable regiochemical preference on the activator that was utilized [\[2006AGE810\]](#). Strong Bronsted acids generated products of 5-exo closure, while trialkylsilyl triflate activators gave products resulting from 6-endo closure. A novel set of mung bean epoxide hydrolases have been used for the hydrolysis of styrene epoxides [\[2006OL1737\]](#).

Chiral titanocene complexes (Kagan's complex) have been used to open epoxides in a regiodivergent manner, in which the chirality of the catalyst dictates the selectivity of the ring opening reaction <2007JA3484>. The mechanism of the opening of epoxides by titanocenes has been examined by voltammetric, kinetic, computational and synthetic methods <2007JA1359, 2006AGE2041>. Radicals derived from xanthates add to vinyl epoxides, enabling a new construction of quaternary carbon centers <2007AGE6520>.

A Lewis acid promoted epoxide rearrangement reaction was used in the synthesis of (–)-aristolochene <2006JOC4929>. A full report describing the chemistry of intramolecular cyclopropanation process using unsaturated terminal epoxides as starting materials has been disclosed <2007JA4456>. Hodgson has written two reviews summarizing his group's recent work using lithiated epoxides as carbene equivalents <2006SL1, 2007PAC269>.

Vinyl oxiranes were shown to undergo rearrangement to substituted dihydrofurans using copper salts <2006JA16054>. These products should be useful platforms for the formation of either substituted tetrahydrofurans or substituted furans. Butadiene monoepoxide acts as an ambiphilic allylation reagent with aldehydes using palladium catalysis <2007JA4122>. In a full paper, epoxides were demonstrated to undergo a useful double carbonylation reaction to succinic anhydrides using the bimetallic catalyst $[(\text{CITPP})\text{Al}(\text{THF})_2]^+[\text{Co}(\text{CO})_4]^-$ (CITPP = *meso*-tetra(4-chlorophenyl)porphyrinato; THF = tetrahydrofuran) <2007JA4948>. The same group also reported a practical synthesis of β -lactones through the carbonylation of epoxides using an achiral chromium-containing bimetallic catalyst <2006OL3709>. This catalyst system allows this reaction to take place using 1 atm of carbon monoxide.

A review by Darensbourg outlining the use of metal–salen complexes as catalysts for the formation of polymeric materials using epoxides as starting materials was published in 2007 <2007CRV2388>.

1.03.8.3 Synthesis

A Mitsunobu dehydration process forming epoxides from diols was observed to have an interesting stereochemical dependence on the phosphine used in the process <2007OL635>. Triphenylphosphine and tributylphosphine give complementary results. Electron rich phosphines favor products of inversion of configuration while electron poor phosphines result in epoxides resulting from a process proceeding with overall retention of configuration. Bromomandelation of alkenes provides a route to chiral epoxides <2007JOC431>.

The epoxidation of alkenes is accelerated in fluorinated alcohol solvents; the factors responsible for this rate acceleration have been examined <2006JA8421, 2006JA13412>. Chiral dioxiranes can now be used in a catalytic sense for the synthesis of vinyl *cis*-epoxides <2006AGE4475>.

The factors underpinning the construction of chiral vinyl epoxides using camphor-derived sulfur ylides has been described in a full paper <2006JA9730>.

Novel chiral vanadium–bishydroxamic acid complexes have been used to catalyze the enantioselective epoxidation of homoallylic alcohols <2007JA286>. Yields and enantioselectivities are excellent.

Platinum complexes ligated to chiral fluorinated ligands are active enough to catalyze the formation of terminal epoxides using hydrogen peroxide with good enantioselectivities <2006JA14006>.

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Biographical Sketch



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1.04

Oxiranes and Oxirenes: Fused-ring Derivatives

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1.04.1 Introduction

The oxirane (epoxide) functional group is arguably the most synthetically useful small-ring heterocycle due to its ease of synthesis and wide-ranging ring-opening reactions, which usually occur with predictable regioselectivity and stereospecificity. As such the chemistry of oxiranes fused to other ring systems pervades the literature.

Oxirenes are not of as much interest as their saturated analogs, due to the lability of the former; recent progress will be reviewed at the end of this chapter.

The reader is directed to Chapter 1.03 for advances in the chemistry of monocyclic oxiranes and oxirenes, and to CHEC(1984) and CHEC-II(1996) for additional background information <1996CHEC-II(1)145, 1984CHEC(5)95>.

1.04.2 Fused-Ring Oxiranes

1.04.2.1 Introduction

As in CHEC-II(1996), emphasis will be placed on epoxides fused to small rings or other systems with unusual structural features. Methods of generation will focus on chiral oxiranes and those methods which allow access to

highly labile small-ring-fused epoxides. Reactivity aspects will concentrate on processes specific to such systems that are not exhibited by their nonfused analogs.

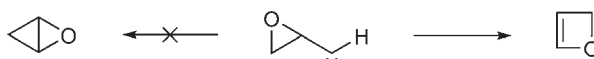
1.04.2.2 Advances in Theoretical Methods

Since the publication of CHEC-II(1996), there has been little advance, with respect to ring-fused oxiranes, in experimental structural methods (e.g., nuclear magnetic resonance (NMR), ultraviolet (UV), and Raman spectroscopy). However, there has been considerable interest in the use of theoretical computational studies to probe structural and reactivity issues, particularly with regard to highly labile oxiranes fused to small rings.

Inagaki *et al.* have investigated the origin of the inverted tetrahedral configurations of the bridgehead carbons in bicyclo[1.1.0]butane in a theoretical manner. Inverted and normal tetrahedral bridgehead configurations in the bicyclo[1.1.0]butane frameworks (including 2,4-dioxabicyclobutane) were designed by controlling the geminal delocalization and confirmed by *ab initio* molecular orbital calculations. The delocalization of σ -electrons between the central C(1)–C(3) bond and the side C(1)–C(2) bonds was found to be bonding to relax the angle strains, while the delocalization between the geminal C–C bonds is antibonding in propane and cyclopropane, etc. The bonding property of the geminal delocalization was shown to be related to the inversion of the configurations. Electronegative atoms (i.e., O, as in 2,4-dioxabicyclobutane) in the bridges decrease the bonding property of the geminal delocalization, relative to bicyclo[1.1.0]butane. Geometry optimization of 2,4-dioxabicyclobutane shows a normal configuration ($\theta < 0^\circ$) and an inversion angle of $\theta = -14.9^\circ$ <1996JPC9615>.

Vijay and Narahari Sastry employed hybrid density functional theory (DFT) and post-SCF (SCF = self-consistent field) *ab initio* calculations to explore the isomers of glyoxal, $C_2O_2H_2$ (including 2,4-dioxabicyclo[1.1.0]butane), along with the corresponding cation and anion radicals. The dependence of relative energies with respect to the methods and quality of basis set was critically analyzed, all the way up to cc-pV5Z. Principal geometries and relative energies were obtained using various methods and compared, and bond stretch isomerism values were calculated <2005JST(714)199>.

Mück-Lichtenfeld has carried out *ab initio* studies on the experimentally uncharacterized 2-oxiranylcabene at B3LYP/6-31G(d) and CCSD(T)/6-31G(d,p)//MP2/6-31G(d,p) levels of theory. Of the possible rearrangement pathways, β -C–H insertion leading to oxabicyclo[1.1.0]butane (Scheme 1) was considered to be an insignificant side reaction ($\Delta H^\ddagger > 35 \text{ kcal mol}^{-1}$). Natural bond orbital (NBO) analyses show that the donor–acceptor interactions between the carbene frontier orbitals and σ -bond orbitals in the oxiranyl ring destabilize the compound kinetically. 2-Oxiranylcabenenes with a fixed *cis*- (or *exo*)-conformation are rather predicted to rearrange to the hetero-analog derivatives of cyclobutene <2000JOC1366>.



Scheme 1

Leszczynski and co-workers carried out a high-level quantum-chemical study into the proposed fragmentation of 2-oxabicyclo[1.1.0]butane to acrolein. The predicted activation energies for unimolecular and acid-catalyzed fragmentation of the fused oxirane are found to be high enough to rule out nonobservable oxabicyclobutane intermediates in various thermal, photochemical, and chemical reactions (see Section 1.04.2.3). Indeed, they find that 2-oxabicyclobutane is so stable that there should be an alternative mechanism of formation of carbonyl compounds in the above-mentioned reactions, and suggest an alternative pathway for the observed formation of acrolein in cyclopropene oxidations <2001T1509>.

Calculations in terms of the self-consistent finite perturbation theory (SCPT) and analysis of contributions of localized molecular orbitals in terms of the polarization propagator theory (CLOPPA), conducted by Krivdin and Kuznetsova, indicate additivity of ^{13}C – ^{13}C coupling constants in saturated, sterically strained heterocycles. Their fused derivatives (especially those containing third period elements) show considerable deviations of the calculated coupling constants from the additive values <2003RJO698>.

NBO analysis was performed by Deyhimi and co-workers in an investigation of the relative stability and the nature of the highly strained central bond in [1.1.1]propellane and some [1.1.1]heteropropellane compounds (**Figure 1**), using the 6-31G(d,p) basis set on previously DFT-optimized structural molecular geometries. The results explained how the p character of the natural atomic hybrid orbital on C-1 and C-3 (central bond) is increased by the substitution of the bridge CH₂ groups by O (or NH, S) and also the resulting bent of the carbon natural hybrid orbitals (NHOs) of the σ_{CX} and σ_{CZ} bond orbital from the lines of C–X and C–Z centers, in these compounds. The NBO analysis of donor–acceptor (bond–antibond) interactions resulted in decreasing occupancy of the localized $\sigma_{C(1)-C(3)}$ -orbital of the idealized Lewis structure, increasing occupancy of $\sigma^*_{C(1)-C(3)}$ of the non-Lewis orbital, and also their subsequent impact on molecular stability and geometry (bond length) along with the resulting p character of the corresponding carbon NHO of σ -bond orbital. The results suggested that in these compounds, the C(1)–C(3) bond lengths are closely controlled by the p character of these hybrid orbitals and also by the nature of the CX bonds. The magnitude of the molecular stabilization energy associated with delocalization from $\sigma_{C(1)-C(3)}$ and to $\sigma^*_{C(1)-C(3)}$ p bond orbitals were also quantitatively determined <2003JST(626)223>.



Figure 1

Okovityi *et al.* have calculated the strain in epoxycycloalkanes (including epoxycyclobutene) using the MM2MX procedure. Opening of the oxirane ring in these compounds by alkaline methanolysis was simulated by the PM3 method. The calculations were performed both for the gas phase and with account taken of solvent effect in macroscopic and supermolecular approximations. A model was developed, which takes into consideration contributions of electronic and steric factors in the supermolecular approximation. The calculated values of $\Delta H^\ddagger$ showed a good agreement with the experimentally determined rate constants <2001RJO345>.

Kuznetsova *et al.* calculated the ¹³C–¹³C spin–spin coupling constants and orbital hybridization of the bridging bond in bicyclo[2.1.0]pentane heteroanalogues and their unsaturated derivatives (**Figure 2**) in terms of SCPT intermediate neglect of differential overlap (INDO). The results showed that the bridging C–C bond in all the examined compounds has an anomalously low s character <2002RJO394>.

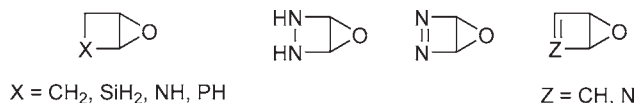


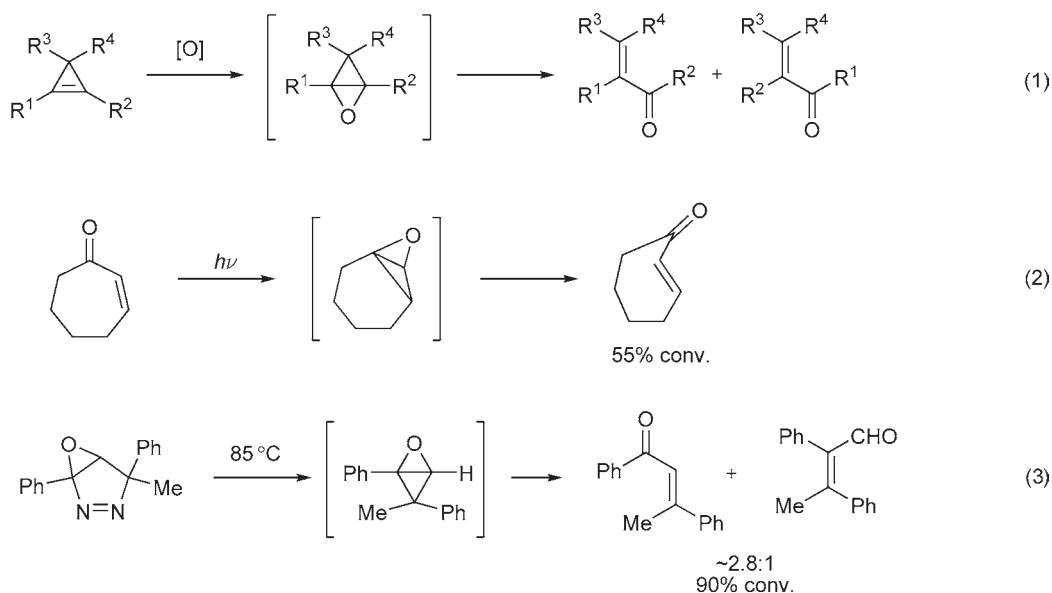
Figure 2

1.04.2.3 Fusion to Three-Membered Rings

Oxiranes fused to a three-membered ring, that is, containing the 2-oxabicyclo[1.1.0]butane skeleton, are formally derived from cyclopropenes via oxygen atom transfer. To date, no members of this class of compounds have been characterized, all attempts to isolate or even spectroscopically detect oxabicyclobutanes being unsuccessful. The lack of experimental observation is usually ascribed to the significant strain present in this framework, as well as facile rearrangement under the conditions under which they are speculated to be generated. Since the mid-1960s, derivatives of 2-oxabicyclo[1.1.0]butane have been postulated as intermediates to explain the formation of carbonyl compounds from various chemical (oxidation of cyclopropenes (**Scheme 2**, Equation 1) both by peracids <1971JA4902, 1978JOC604, 1978JOC1323> and dimethyldioxirane (DMDO) <1994JOC6874>), photochemical (*cis/trans*-double-bond isomerization of 2-cycloalkenones under irradiation (**Scheme 2**, Equation 2) <1965JA205>), and thermal (extrusion of nitrogen from bicyclic azo epoxides (**Scheme 2**, Equation 3) <1978JOC34>) reactions.

1.04.2.4 Fusion to Four-Membered Rings

Unlike for oxirane fusion to three-membered rings, oxiranes fused to four-membered rings (5-oxabicyclo[2.1.0]pentanes, cyclobutene oxides) are well known.



Scheme 2

Huet and co-workers have prepared several 5-oxabicyclo[2.1.0]pentanes by oxidation of the corresponding cyclobutenes (Figure 3). Compounds **2–4** gave mainly the *cis*-epoxides using *m*-chloroperbenzoic acid (MCPBA), while **1** and **5** gave mainly the *trans*-isomers. The result for **4** was reversed using Payne's reagent (PhCN and 30% H₂O₂) <1996T15103>. Interest in these compounds stems from subsequent transformation of the epoxides into novel nucleoside analogs <1997T5797, 2000T2995, 2000TL3057, 2000EJO2717>.

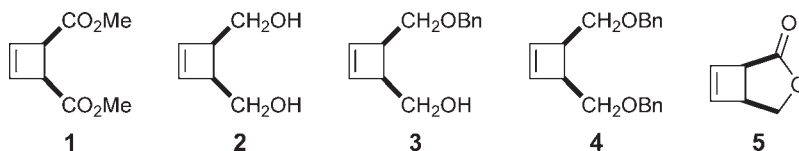
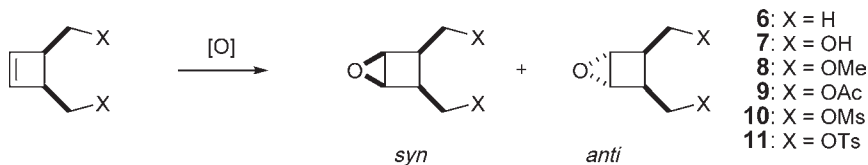


Figure 3

The epoxidation reactions of a series of *cis*-3,4-disubstituted-(CH₂X)-cyclobutenes **6–11** with DMDO and MCPBA have been investigated by Freccero *et al.* <1999T11309>. A remarkable *syn*-diastereoselectivity in the formation of the epoxide has been observed for substrates bearing electron-withdrawing substituents. Transition structures for epoxidations of 3,4-dimethylcyclobutene **6** and 3,4-bis(mesyloxymethyl)-1-cyclobutene **11** with dioxirane and peroxyformic acid have been located with the B3LYP/6-31G* method (Table 1).

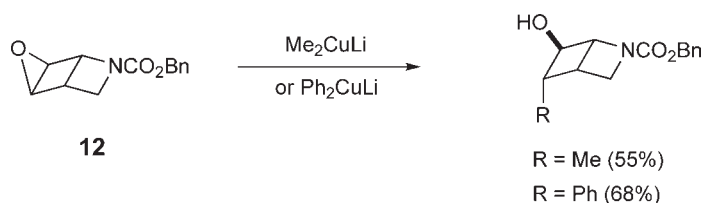
Syn-selectivity in the epoxidation reactions with MCPBA was higher than 80% with substrates **7**, **10**, and **11**, while for cyclobutenes **8** and **9**, although lower, was still significant (≥69%). Epoxidation of *cis*-3,4-dimethylcyclobutene **6** in CDCl₃ afforded an equimolar mixture of *syn*- and *anti*-epoxides, but in benzene a slight preference for *syn*-attack (60:40) was observed. The *syn:anti* ratio for the epoxidation reactions using DMDO and MCPBA with the same substrate is almost identical. The latter is particularly true when selectivities in solvents with similar dielectric constant (CCl₄/acetone (9:1) for DMDO vs. benzene or CH₂Cl₂ for MCPBA) are compared; the only exception to this was alkene **7**, where the peroxyacid reaction showed a higher *syn*-facial selectivity. Experimentally observed dominant *syn*-facial selectivity is rationalized mostly as a result of an electrostatic attractive interaction involving the peroxo oxygens of the oxidizing reagents and the positively charged homoallylic hydrogens of the olefins.

Interest in the rearrangement of the 2-azabicyclo[2.2.0]hexane skeleton to 2-azabicyclo[2.1.1]hexanes led Krow *et al.* to investigate the ring opening of *exo*-cyclobutene oxide **12** (prepared in three steps from pyridine); reaction with organocopper reagents gives *endo*-addition products (Scheme 3) <2001JOC1811, 2004OL1669>.

Table 1 Oxidation of *cis*-3,4-disubstituted-(CH₂X)-cyclobutenes

[O] Method A: DMD, acetone; method B: DMD, CCl₄/acetone (9:1); method C: MCPBA, CH₂Cl₂; method D: MCPBA, benzene

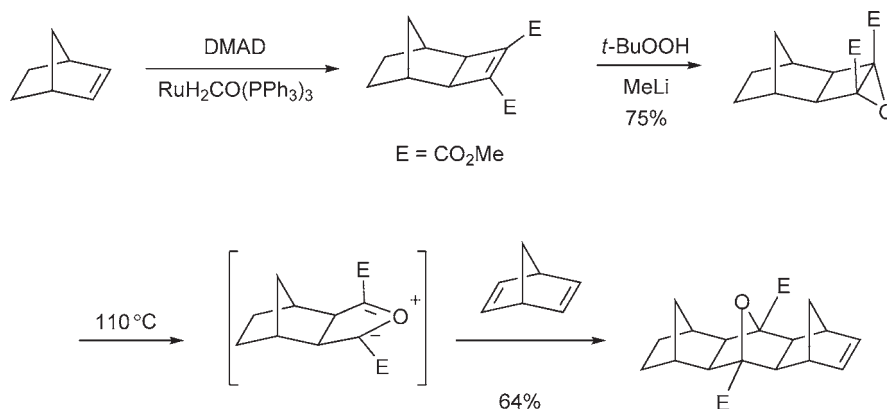
Substrate	[O] Method	Yield (%)	<i>syn:anti</i>
6	A	99	44:56
6	B	99	55:55
6	C (CDCl ₃)	99	49:51
6	D (C ₆ D ₆)	99	60:40
7	A	70	57:43
7	B	80	67:33
7	C	55	82:18
7	D	58	81:19
8	A	99	49:51
8	B	99	62:38
8	D	45	76:24
9	A	69	72:28
9	B	99	68:32
9	C	64	69:31
10	A	85	79:21
10	B	99	90:10
10	C	69	87:13
10	D	60	88:12
11	A	97	63:37
11	B	99	82:18
11	D	70	80:20

**Scheme 3**

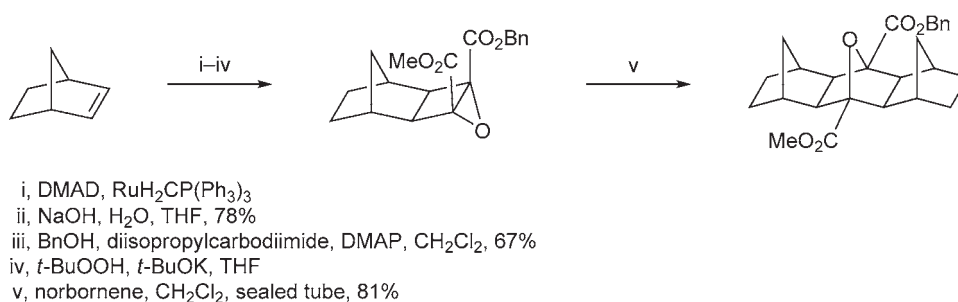
In 1997, Warrener *et al.* reported initial studies utilizing the ACE (alkene plus cyclobutene epoxide) reaction to construct structures of defined geometry, typically based on a norbornene skeleton. The thermal ring opening of the epoxides (derived from the cycloaddition products of DMAD and norbornenes) gives the corresponding carbonyl ylides, which, in the presence of further norbornene compounds, undergo subsequent 1,3-dipolar cycloaddition reaction <1997CC1023> (**Scheme 4**).

In nearly a decade of further work in this area, Warrener *et al.* have used this technology to synthesize numerous structures of defined geometry, incorporating such diverse functionality as crown ethers, aromatic rings, porphyrins, pyrimidines, and polynorbornenes <1998JOC4218, 1998TL4721, 1998TL5277, 1999OL199, 1999OL203, 1999TL4111, 2000AJC561, 2000OL4003, 2000TL4671, 2001CEJ3406, 2001T571, 2001TL465, 2002T3445, 2003AJC269>.

Pfeffer and co-workers have prepared several related oxiranes and examined their reaction with norbornenes. This group's particular area of interest is the differentiation of the two ester functions about the cyclobutene epoxide (**Scheme 5**) <2002J(P1)2680, 2003OBC1845, 2005OL5357>.

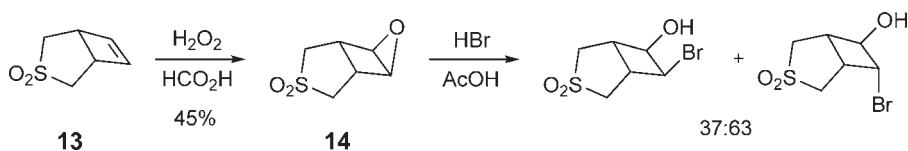


Scheme 4



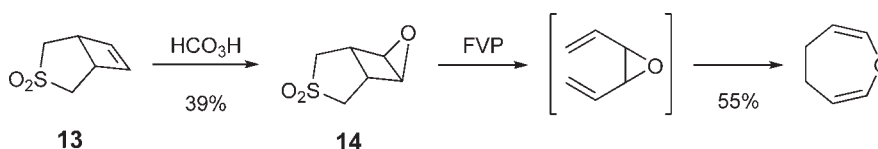
Scheme 5

Cadogan *et al.* have prepared epoxide **14** from bicyclic sulfone **13**. Acid-catalyzed ring opening gives a mixture of *exo,exo*- and *exo,endo*-bromohydrins (Scheme 6) <1996J(P2)2309>.



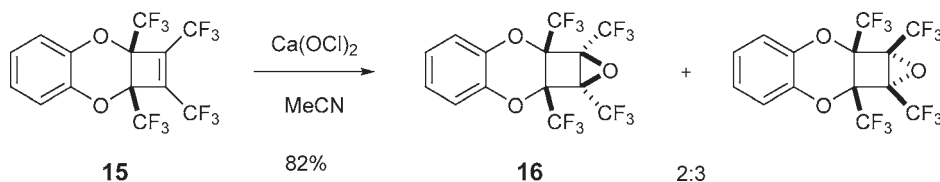
Scheme 6

Aitken *et al.* have also oxidized bicyclic sulfone **13** (performic acid; 39% yield). Flash vacuum pyrolysis of epoxide **14** (580 °C) gives a 55% yield of 4,5-dihydrooxepine, identified by comparison of its ^1H and ^{13}C NMR data with the literature values. The dihydrooxepine presumably results from initial extrusion of SO_2 to give *cis*-2,3-divinyloxirane, which then undergoes a Cope rearrangement (Scheme 7) <1999J(P1)605>.



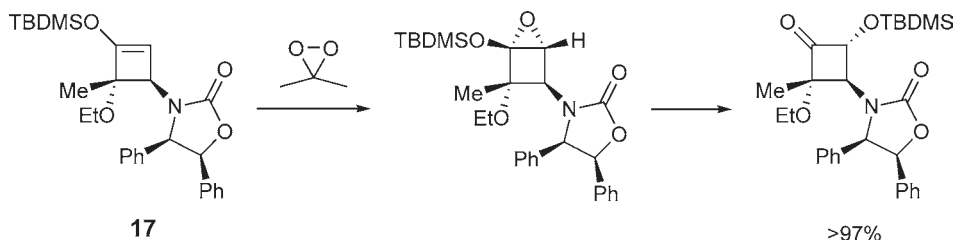
Scheme 7

Chambers *et al.* epoxidized bis(trifluoromethyl)-substituted cyclobutene **15** and obtained a mixture of stereoisomers (Scheme 8). This is surprising, since the two ring-junction CF₃ groups in the cyclobutene might have been expected to exert a high degree of facial control in the epoxidation. Thus, the *cis,trans*-isomer **16**, with CF₃···CF₃ interactions minimized, might have been expected to be formed almost exclusively. The reason both diastereoisomers are formed is thought to be due to a competing destabilizing effect of eclipsing of the trifluoromethyl groups with the epoxide oxygen atom in **16** <1997J(P1)1457>.



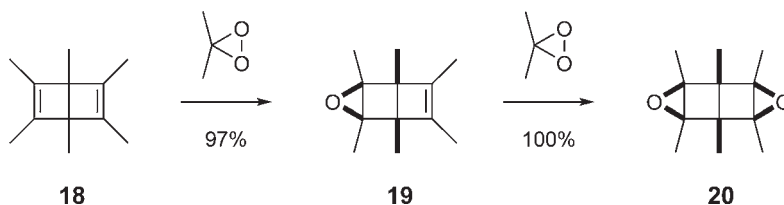
Scheme 8

Hegedus and co-workers isolated a cyclobutane-fused epoxide intermediate in the Rubottom oxidation of silyl enol ether **17** (Scheme 9) <1998JOC4691>.



Scheme 9

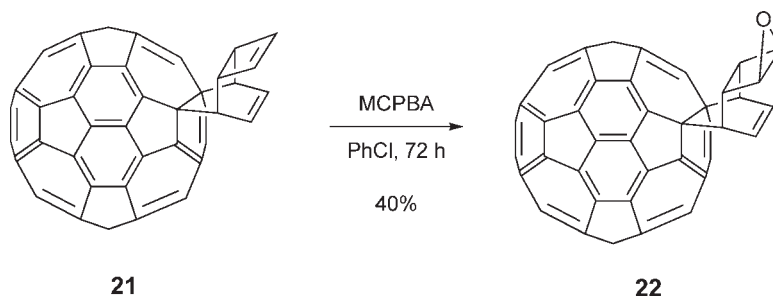
Asouti and Hadjirapoglou have examined the DMDO epoxidation of hexamethyl Dewar benzene **18**, which yields a mixture of the monoepoxide **19** and bis-epoxide **20** (Scheme 10). The ratio of the products depends on the amount of dioxirane employed: surprisingly, with 1 equiv of DMDO, epoxide **19** was isolated in 97% yield, while with excess of DMDO the bis-epoxide **20** was quantitatively isolated. Epoxide **19** had been previously postulated <1988OSC(VI)39> as a labile intermediate (not even detected due to rapid acid hydrolysis) in the peracid epoxidation of **18** <2000TL539>.



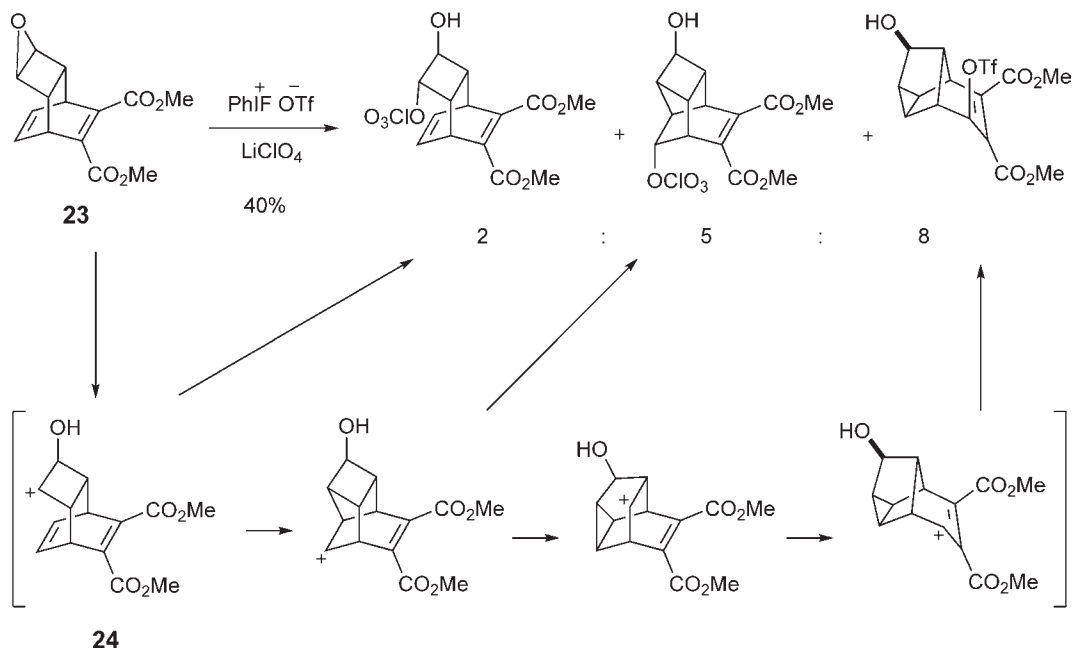
Scheme 10

Ohno and co-workers found that cyclooctatriene underwent reaction with C₆₀-fullerene to give product **21**, which could be epoxidized, giving cyclobutene oxide **22** in 40% yield (Scheme 11) <2000TL9839>.

Pirkuliev *et al.* examined the reaction of cyclobutene oxide **23** with a hypervalent iodine reagent and isolated a mixture of products consistent with the initial formation of cation **24** which can rearrange to give precursors to the other products (Scheme 12) <2002RJO1066>.

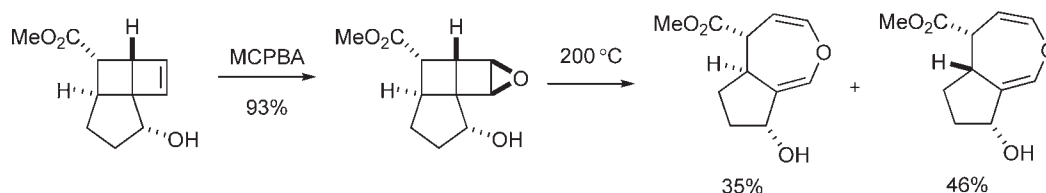


Scheme 11



Scheme 12

Leyhane and Snapper have epoxidized a series of fused cyclobutenes, and the adducts were subject to thermal rearrangement leading to oxepine-containing bicyclo[5.3.0] ring systems (e.g., [Scheme 13](#)) <2006OL5183>.

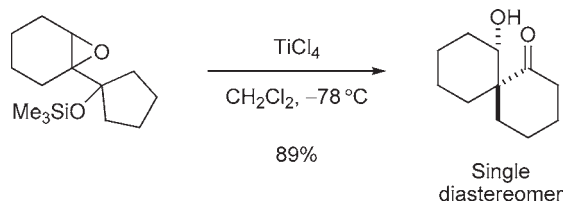


Scheme 13

1.04.2.5 Fusion to Ordinary and Large Rings

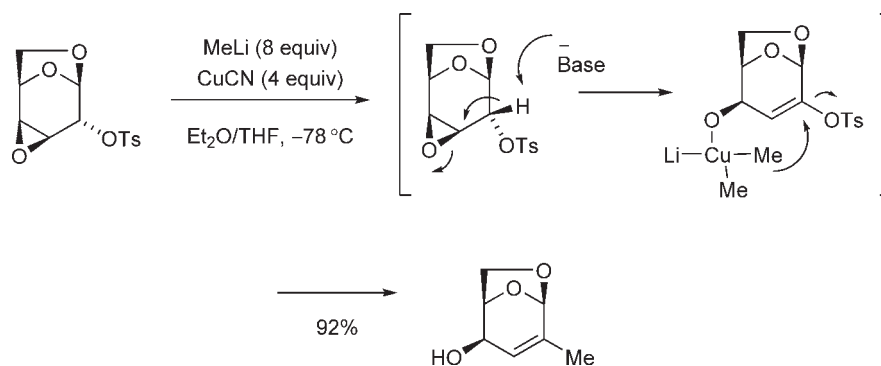
The synthesis and reactivity of oxiranes fused to five-membered and larger rings in many cases mirror that of acyclic epoxides and the reader is directed to Chapter 1.03 for standard methods in this area. A few specific examples and exemptions are considered below; also see [Section 1.04.2.8](#) for a discussion of the reactivity of ring-fused oxiranes.

Dake *et al.* have developed a siloxy-epoxide semipinacol ring expansion process that yields spirocyclic cycloalkanones (e.g., **Scheme 14**) <2004JOC5676>.



Scheme 14

Epoxides derived from 1,6-anhydro- β -D-glucopyranose undergo a rearrangement to generate allylic alcohols on treatment with MeLi and CuCN (e.g., **Scheme 15**) <2005EJO2841, 2005EJO4557>.



Scheme 15

In their synthesis of (+)-narciclasine **26**, Elango and Yan performed a stereocontrolled epoxide formation via the bromohydrins **25**. Following concomitant ring closure and N-piperonylation, treatment with catalytic SnCl_4 affected intramolecular arene-epoxide coupling (**Scheme 16**) <2002JOC6954>.

Boyd and co-workers' interest in the properties of arene oxide metabolites has led them to undertake investigations into the synthesis and isomerization of such compounds (e.g., dibenz[*a,h*]anthracene 3,4-oxide **27**, phenanthrene 3,4-oxide **28**, triphenylene 1,2-oxide **29**, and dibenz[*a,c*]anthracene 1,2-oxide **30** (**Figure 4**)) <2001J(P1)1091>.

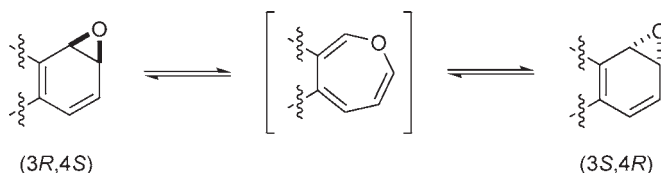
Enantiopure epoxides (3*R*,4*S*)-dibenz[*a,h*]anthracene 3,4-oxide and (3*R*,4*S*)-phenanthrene 3,4-oxide were synthesized via involved routes and were observed to spontaneously racemize. This racemization of arene oxides is in accordance with perturbation molecular orbital predictions based on resonance energy considerations, and presumably occurs via an electrocyclic rearrangement to the corresponding (undetected) oxepine tautomer (**Scheme 17**) <2001J(P1)1091>.

Guanti's interest in the chemical and biological properties of artificial enediynes has led to the rational design of two new classes of such compounds; a decade of work in this area was the subject of a recent account <2006ARK261>. One of these new classes of enediynes comprises analogues of dynemicin A (**Figure 5**), in which an epoxide is fused across a *cis*-decalin-type ring system, which is itself bridged by a 10-membered enediyne ring.

During the synthesis of such compounds, the epoxide is often installed at an early stage; for example, dihydroquinoline **31** (**Scheme 18**) is readily epoxidized with MCPBA, and subsequent formation of the bis-alkynyl iodides followed by bis-intramolecular Stille coupling occurs with complete chemoselectivity <2006ARK261>.



Parrain and co-workers examined the epoxidation and subsequent reactivity of 1,4,7,10-cyclododecatetraene **32** [<2003JOC3319>](#); fourfold oxidation with either MCPBA (75% yield) or DMO (98% yield) gave exclusively the *exo,exo,exo,endo*-diastereomer **33** out of eight possibilities (**Scheme 19**). Studies into the sequential epoxidation of the



Scheme 17

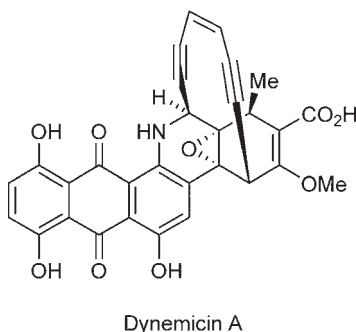
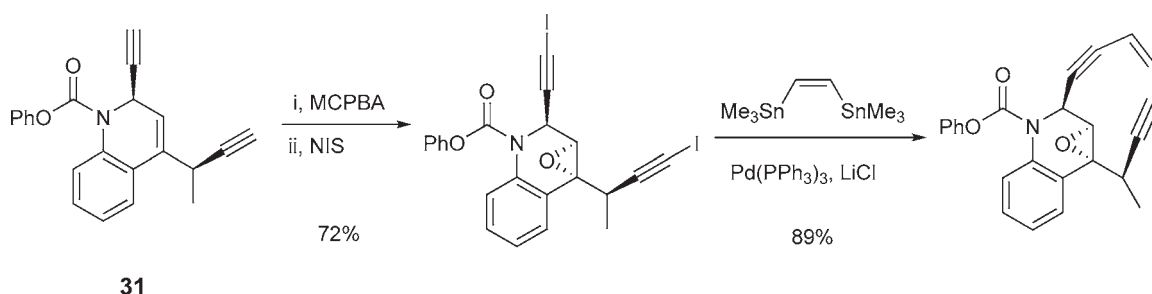


Figure 5



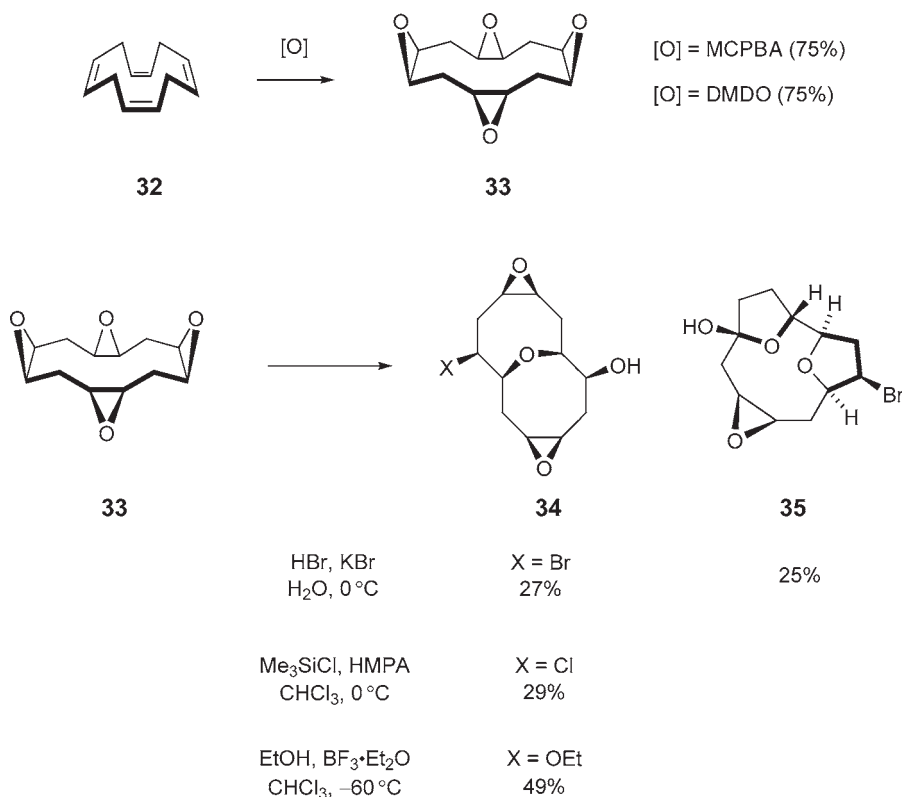
Scheme 18

tetrene revealed that the first two oxidations occur exclusively from the *exo*-face, the third oxidation with 70% *exo*-selectivity, and the fourth oxidation from the opposite face to the third. Treatment of the tetraepoxide **33** with HBr/KBr yielded two products from ring opening; oxabicyclo[5.5.1]tridecanol **34** (X = Br; 27% yield) and bis-THF-containing epoxide **35** (25% yield). Exposure of tetraepoxide **33** to Me₃SiCl in the presence of catalytic hexamethylphosphoramide (HMPA) also gave **34** (X = Cl; 29% yield, 35% conversion), while EtOH in the presence of BF₃·Et₂O gave **34** (X = OEt; 49% yield) (Scheme 19) <2003JOC3319>.

1.04.2.6 Synthesis of Chiral Ring-Fused Oxiranes

As with several other sections in this chapter, when discussing the synthesis of ring-fused oxiranes there are obvious overlaps with Chapter 1.03. While attempting to give a comprehensive overview of such methods, leading references and specific examples will only be given relating to ring-fused oxiranes.

A general review of the advances in homogeneous and heterogeneous catalytic asymmetric epoxidation covering Sharpless, porphyrin, *N,N'*-bis(salicylaldehyde)ethylenediamine (salen), and 1,1'-bi-2-naphthol (BINOL) systems, carbonyl-derived dioxiranes and iminium species, as well as their supported counterparts, has recently been published <2005CRV1603>.



Scheme 19

Sello *et al.* have reviewed recent developments in oxirane preparation including metal- and ketone-mediated methods, the synthesis of epoxides from carbonyls, and enzymatic reactions [<2006CSY457>](#).

1.04.2.6.1 Metallosalen-catalyzed (Jacobsen–Katsuki) epoxidation

The body of work that constitutes the metallosalen-catalyzed (Jacobsen–Katsuki) asymmetric epoxidation reaction is far too extensive to be detailed here; however, it has been comprehensively reviewed [<1996JMO87, B-1999MI\(II\)649, B-2000MI287, 2001COR663, 2005CRV1563>](#). Rather, after some introductory remarks, we will highlight examples in which ring-fused oxiranes are produced.

The report by Kochi and co-workers in 1986 that a (salen)manganese(III) complex (Mn(salen) complex) was an efficient epoxidation catalyst for simple olefins [<1986JA2309>](#) quickly led to independent reports from the groups of Jacobsen [<1990JA2801>](#) and Katsuki [<1990TL7345>](#) that chiral Mn(salen) complexes could catalyze asymmetric epoxidation reactions. The reaction requires the use of a stoichiometric oxidant; initially iodosylarenes were utilized, but it was quickly found that NaOCl was also successful.

The series of catalysts (so-called ‘first-generation’ catalysts ([Figure 6](#))) subsequently developed by both groups proved to be efficient moderators of the asymmetric epoxidation of numerous cycloalkenes, with enantioselectivities ranging from moderate to excellent [<1990JA2801, 1990TL7345, 1991JA7063, 1991TL1055, 1993SL261, 1994JOC4378, 1995TL5457>](#).

The prevalence of 2,2-dimethylchromene derivatives (arising biosynthetically via addition of an isoprene unit to phenols) in a variety of natural products led to extensive examination of the asymmetric epoxidation of numerous such substrates, the yields and enantioselectivities of the thus-obtained fused oxiranes typically being good to excellent [<1991JA7063, 1991TL5055, 1993SL261, 1995TL5457>](#).

A second-generation catalyst ([36](#), [Figure 7](#)) was developed by Katsuki and co-workers following consideration of the factors that influenced the trajectory and the orientation of the olefin as it approaches the reactive site. By intensifying perceived steric and π – π -antibonding interactions, they were able to achieve excellent level of enantioselectivity in the epoxidation of *cis*-di- and trisubstituted olefins [<1994SL356, 1994T11827, 1995SL197>](#), and in the monoepoxidation of cyclic dienes [<1995SL827>](#).

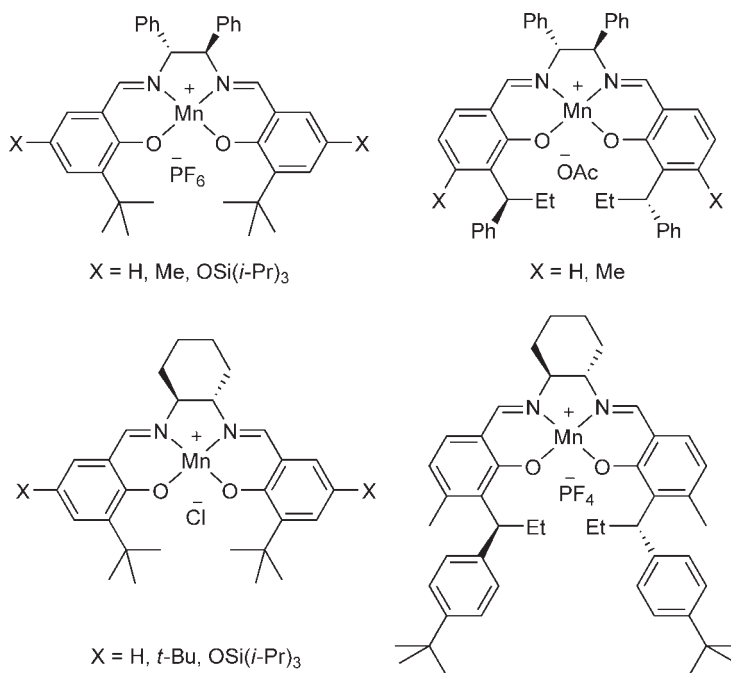


Figure 6

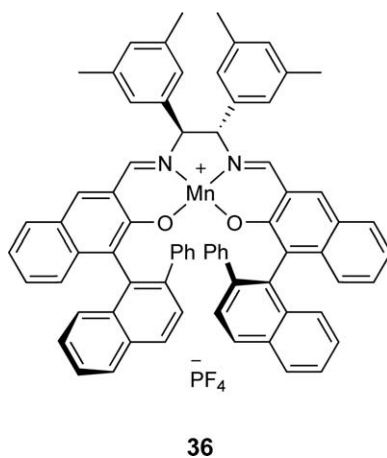


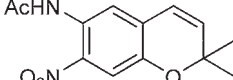
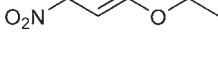
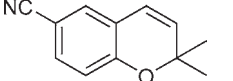
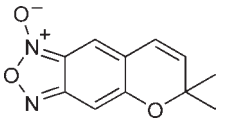
Figure 7

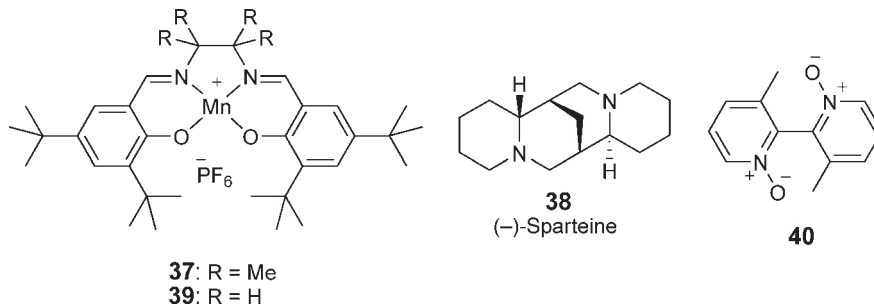
In recent years, the focus in this area has been on further catalyst development, and it has been pursued by several research groups.

Katsuki and co-workers have investigated asymmetric epoxidation reactions mediated by achiral Mn(salen) complexes in the presence of chiral additives; the combination of tetramethyl diamine-derived complex **37** and (–)-sparteine **38** can mediate the oxidation of chromenes with up to 73% ee (Table 2, entry 1); however, the yields were low [1997T9541]. More successful was ethylene diamine-derived complex **39**, which promoted the asymmetric epoxidation of several chromenes in good to excellent yields and good levels of ee in combination with chiral

N,N'-dioxide **40** (Table 2, entries 2–4) <1999SL783>. Although not as efficient, particularly in terms of ee, as the corresponding reactions mediated by first- or second-generation catalysts, such results demonstrate the possibility of moving away from the need for such complex chiral catalysts (e.g., **36**).

Table 2 Chromene oxidations in the presence of chiral additives

Chromene		complex, additive PhIO		Chromene oxide	
Entry	Chromene	Complex	Additive	Yield (%)	ee (%)
1		37	(–)-Sparteine (38)	6	73
2		39	(+)- 40	90	83
3		39	(+)- 40	59	77
4		39	(+)- 40	60	78



The group of Kureshy has synthesized novel homochiral dimeric Mn(salen) complexes **41–43** (Figure 8), and examined them as asymmetric epoxidation catalysts in the reaction of indene and several chromenes (Table 3) <2001TA433, 2003JMO69, 2004JCT229>. They have also prepared analogous polymeric species **44** and **45** (Figure 8), which give equally good results that are in both cases typically better than those observed with first- or second-generation complexes (Table 3) <2004JMO141>.

Related dimeric Mn(salen) complexes have also been examined by the group of Ning; 6-cyano-2,2-dimethylchromene was epoxidized in 92–93% yield and 92–94% ee <2004JMO353>.

Ahn *et al.* examined a number of novel sterically hindered Mn(salen) complexes prepared from an aldehyde derived from BINOL. These complexes efficiently catalyzed the asymmetric epoxidation of several cycloalkenes (Table 4; Figure 9) <2001TL2485>.

Murahashi *et al.*'s strategy of generating an oxo-manganese species in a cage led them to develop an Mn(salen) complex for asymmetric epoxidation reactions bearing a chiral binaphthyl strapping unit (**48**, Figure 9); 2,2-dimethylchromene was epoxidized in 50% yield and 93% ee <2004ASC195>.

The group of Wang has prepared a series of Mn(salen) complexes containing a pyrrolidine backbone (**49**, Figure 9); 6-nitro- and 6-cyano-2,2-dimethylchromene are epoxidized in 86–99% yield and 86–96% ee <2006JCT248>.

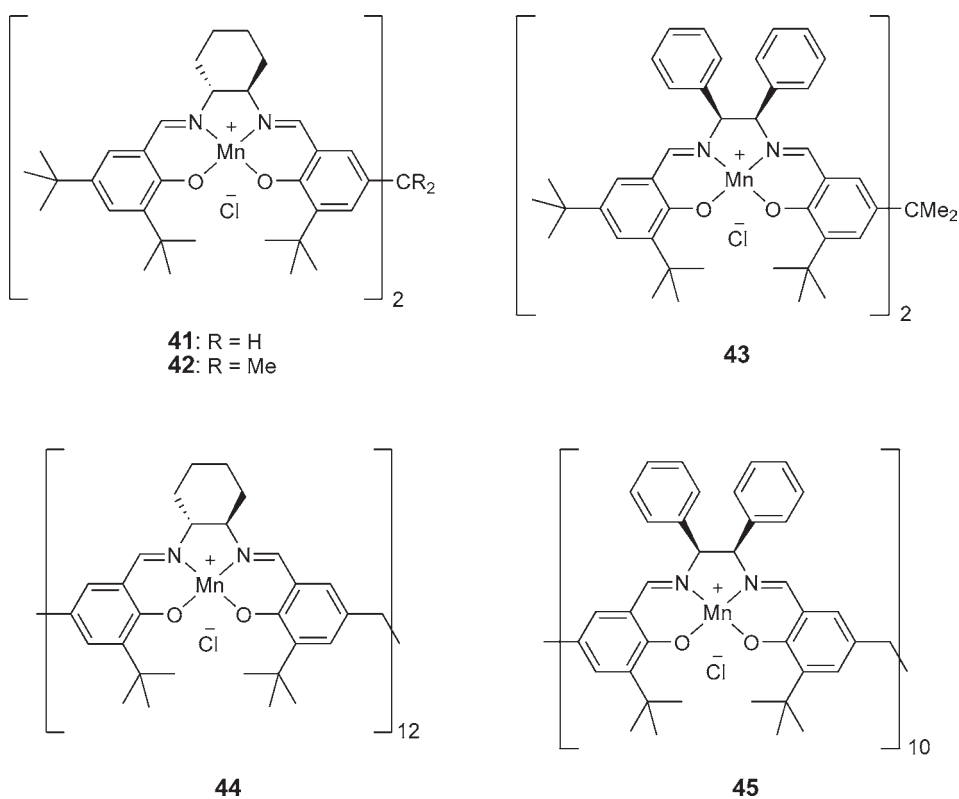
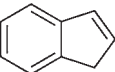
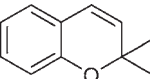
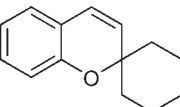


Figure 8

Table 3 Indene and chromene oxidations with homochiral Mn(salen) complexes

		complex			
Alkene		oxidant, PyNO	Epoxide		
<i>Alkene</i>	<i>Complex</i>	<i>Oxidant</i>	<i>Yield (%)</i>	<i>ee (%)</i>	
	41	Oxone	95	78	
	42	NaOCl	>99	77	
	43	NaOCl	>99	66	
	44	NaOCl	>99	79	
	45	NaOCl	>99	78	
	41	Oxone	99	71	
	42	NaOCl	>99	83	
	43	NaOCl	>99	88	
	44	NaOCl	>99	77	
	45	NaOCl	>99	72	
	41	Oxone	99	91	
	42	NaOCl	>99	91	
	43	NaOCl	96	96	
	44	NaOCl	61	82	
	45	NaOCl	50	78	

(Continued)

Table 3 (Continued)

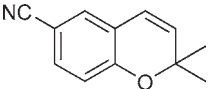
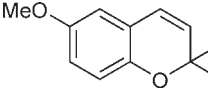
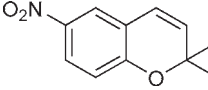
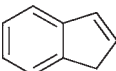
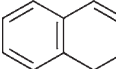
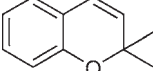
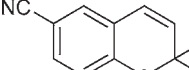
<i>Alkene</i>	<i>Complex</i>	<i>Oxidant</i>	<i>Yield (%)</i>	<i>ee (%)</i>
	41	Oxone	99	99
	42	NaOCl	>99	99
	43	NaOCl	>99	99
	44	NaOCl	>99	99
	45	NaOCl	>99	99
	41	Oxone	99	71
	42	NaOCl	>99	99
	43	NaOCl	>99	99
	44	NaOCl	>99	89
	45	NaOCl	>99	82
	41	Oxone	>99	99
	44	NaOCl	>99	99
	45	NaOCl	>99	99

Table 4 Mn(salen)-catalyzed asymmetric epoxidation of cycloalkenes

<i>Alkene</i>	<i>Complex</i>	<i>Yield (%)</i>	<i>ee (%)</i>
	(<i>R,S</i>)- 46	55	88
	(<i>R,R</i>)- 46	57	94
	(<i>R,R</i>)- 47	63	90
	(<i>R,S</i>)- 46	60	87
	(<i>R,R</i>)- 46	65	95
	(<i>R,R</i>)- 47	62	95
	(<i>R,S</i>)- 46	80	99
	(<i>R,R</i>)- 46	60	85
	(<i>R,R</i>)- 47	62	98
	(<i>R,S</i>)- 46	87	92
	(<i>R,R</i>)- 46	77	78

1.04.2.6.2 Chiral dioxirane-mediated asymmetric epoxidation

The use of dioxiranes (typically DMDO or methyl(trifluoromethyl)dioxirane) as the oxygen-transfer source in epoxidations provides a commonly used and powerful alternative to peracids. The dioxiranes are prepared from the corresponding ketones via reaction with an oxygen-transfer source, usually Oxone[®] (KHSO₅) or hydrogen peroxide, the ketone in principle being a catalytic species.

Since the pioneering report of Curci in 1984 that a chiral ketone can catalyze asymmetric epoxidation reactions (methylenecyclohexene oxide produced with up to 12% ee using (+)-isopinocampheol/KHSO₅) <1984CC155>, this area has attracted considerable interest with particular advances being achieved in the past decade by numerous research groups.

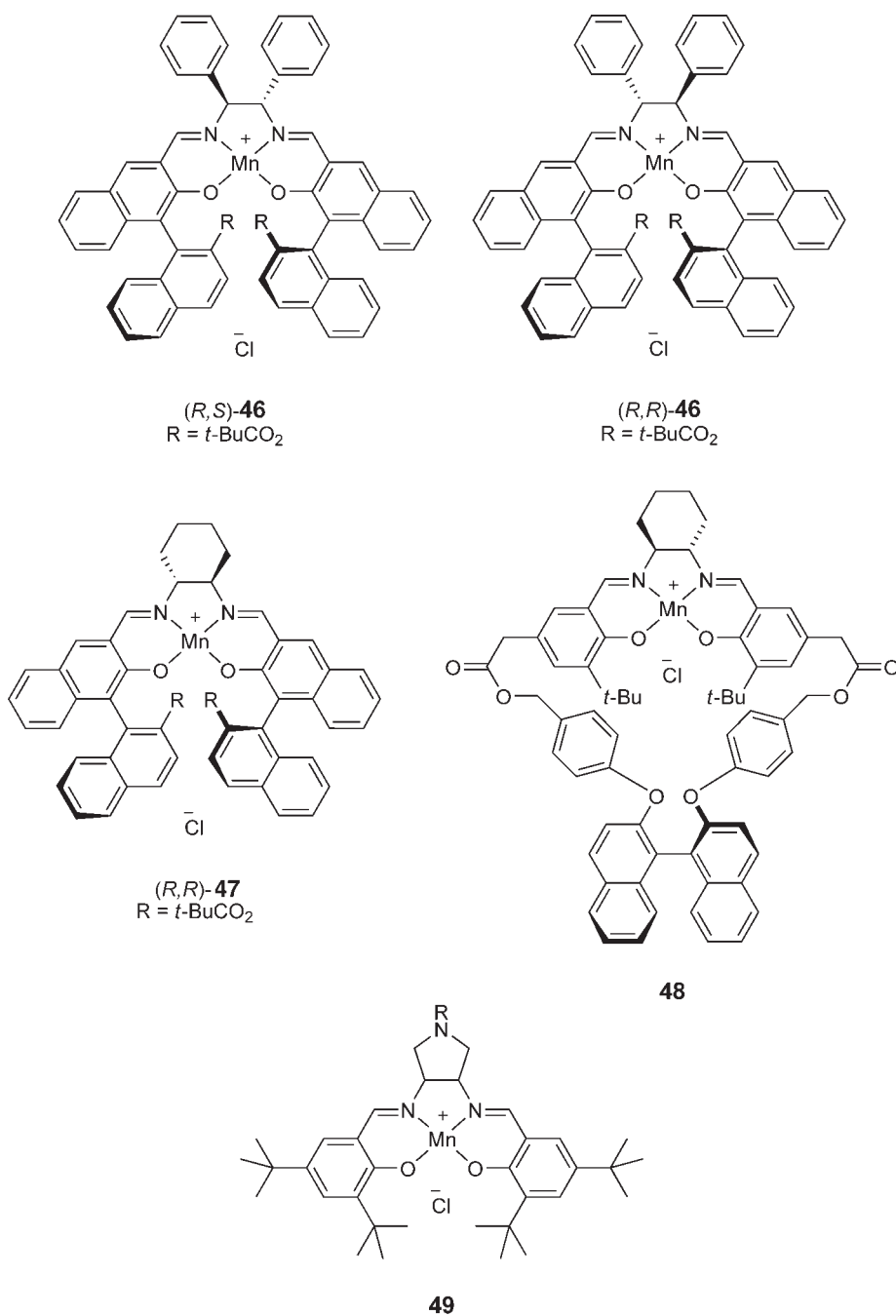


Figure 9

Since 1996, Shi has introduced a range of chiral cyclic ketones as asymmetric epoxidation catalysts (Figure 10) <2004ACR488>.

D-Fructose-derived ketone **50** (also available in its enantiomeric form from L-sorbose) was introduced as a catalyst for the asymmetric epoxidation of *trans*- and trisubstituted olefins, and as such was successful in the preparation of enantioenriched substituted cycloalkene oxides (Table 5, entries 1–5) <1996JA9806, 1997JA11224, 2001T5213>.

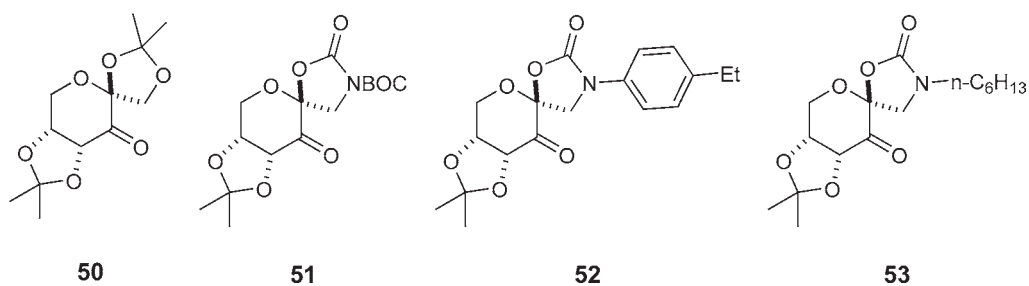


Figure 10

Table 5 Shi asymmetric epoxidation of cycloalkenes

Entry	Alkene	Catalyst	Yield (%)	ee (%)
1		50	77	81
2		50	94	98
3		50	41	97
4		50	98	91
5		50	75	96
6		51	88	83
7		51	88	84
8		51	77	91
9		51	61	91
10		51	47	96
11		51	61	97
12		51	88	94

Chiral ketone **51** (derived from glucose, and therefore available as either enantiomer) was introduced in 2000 as an asymmetric epoxidation catalyst specifically for *cis*-olefins, giving good results for a range of unsubstituted cycloalkenes (**Table 5**, entries 6–12) <2000JA11551, 2002JOC2435>.

Recently, Wong and Shi have examined the effect of substitution in the 6- or 8-position in the asymmetric epoxidation of chromenes by chiral dioxiranes derived from ketones **52** and **53**. Up to 93% ee was achieved, with higher ee's obtained when substrates are substituted at the 6-position <2006JOC3973>.

A further series of ketone catalysts containing spiro ethers and lactones have been examined in the asymmetric epoxidation of phenylcyclohexene (cf. **Table 5**, entry 2; 94% yield, 98% ee) (**Figure 11**). The substituents on the spiro ring appeared to effect enantioselectivity both sterically and electronically <2005T6409>.

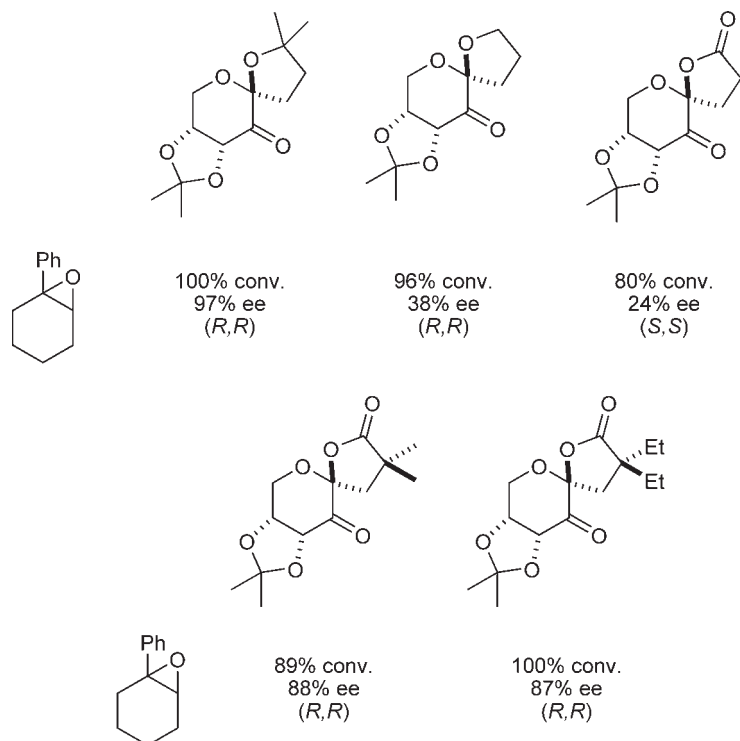


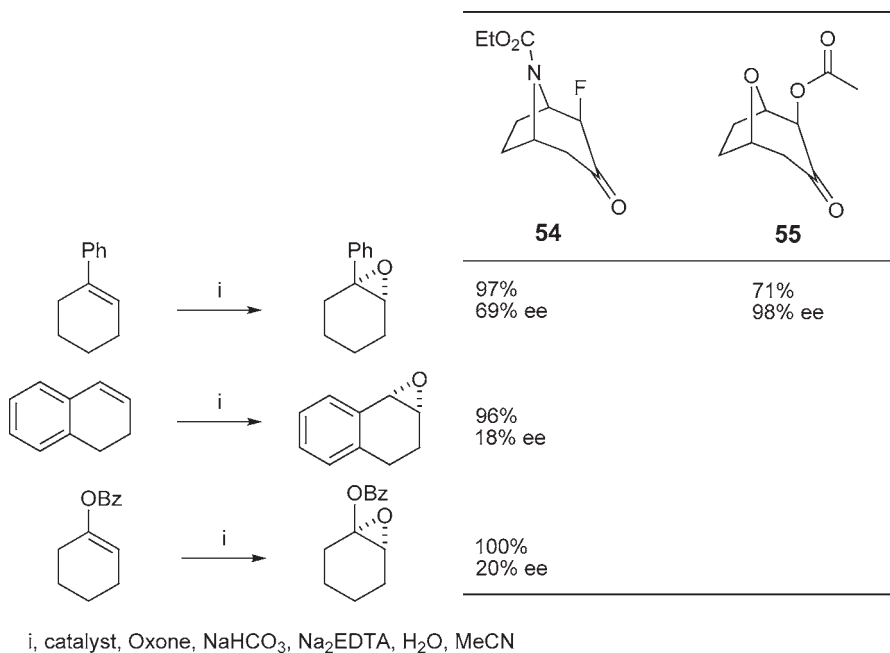
Figure 11

Armstrong has developed α -fluoro-*N*-ethoxycarbonyltropinone **54** as an asymmetric catalyst for the enantioselective epoxidation reaction; 1-phenylcyclohexene oxide is produced in 97% yield and 69% ee (**Scheme 20**) <1998CC621>. Analogously, the use of α -acetoxy-8-oxabicyclo[3.2.1]octan-3-one **55** results in 71% yield and 98% ee (**Scheme 20**) <2001TA2779>. Tropinone catalyst **54** gives only low levels of enantioselectivity in the asymmetric epoxidation of dihydronaphthalene and an enol benzoate (**Scheme 20**) <2002JOC8610>.

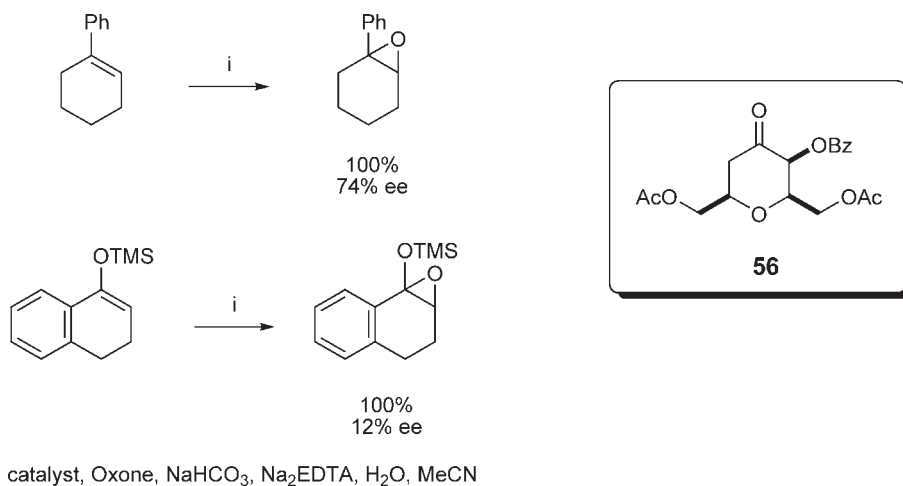
Recently, Armstrong and Tsuchiya have prepared the chiral tetrahydropyranone **56** and examined its use in asymmetric epoxidation reactions. Phenylcyclohexene oxide was formed in excellent yield and high ee; however, low enantioselectivity was observed with a trimethylsilyl enol ether (**Scheme 21**) <2006T257>.

Denmark and Matsuhashi achieved only moderate success in the asymmetric epoxidation of phenylcyclohexene and indene catalyzed by novel chiral α -fluoroketones **57** and **58** (**Scheme 22**) <2002JOC3479>.

Matsumoto and Tomioka examined chiral ketone **59** containing the 1-aza-7-oxabicyclo[3.5.0]decane skeleton and its C_2 -symmetric analog **60** as catalysts in the asymmetric epoxidation of phenylcyclohexene and phenyldihydronaphthalene (**Scheme 23**); in both cases, excellent yields of the oxiranes were obtained with good ee's <2002TL631>.



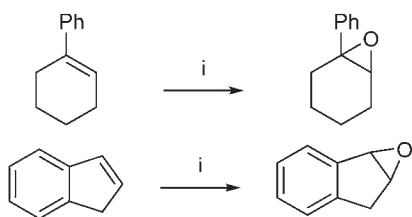
Scheme 20



Scheme 21

Shing *et al.* have prepared a number of arabinose (commercially available in both enantiomeric forms) derived 4-uloses and examined their potential as chiral dioxirane precursors. The most successful of these ketones was found to epoxidize phenylcyclohexene in 92% yield and 85% ee (**Scheme 24**) <2003TL9225>.

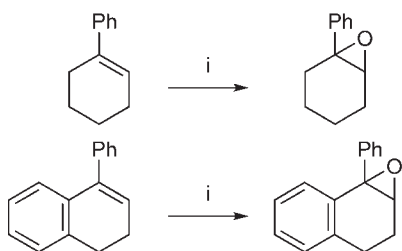
Yang *et al.* have investigated a series of *C*₂-symmetric chiral ketones based on the 2,2-bis(diphenyl-phosphanyl)-1,1'-binaphthyl (BINAP) skeleton. The asymmetric epoxidation of phenylcyclohexene (and in one example dihydronaphthalene) was achieved in good yields and levels of enantioselectivity (**Figure 12**) <1996JA491, 1998JA5943, 2004ACR497>.



i, catalyst, Oxone, NaHCO₃, Na₂EDTA, H₂O, MeCN

57	58
93% 7% ee	78% 59% ee
78% 14% ee	67% 12% ee

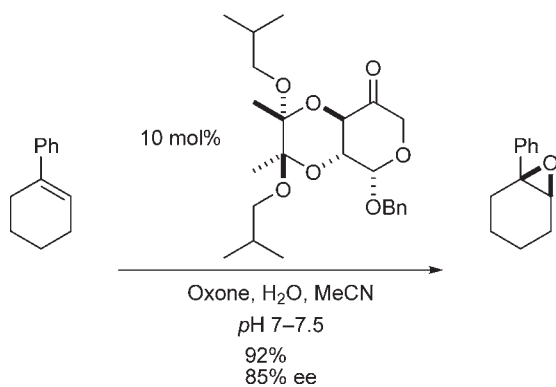
Scheme 22



i, catalyst, Oxone, Bu₄NHSO₅, EDTA, H₂O, MeCN, (MeO)₂CH₂

59	60
99% 75% ee	99% 61% ee
99% 71% ee	99% 75% ee

Scheme 23



Scheme 24

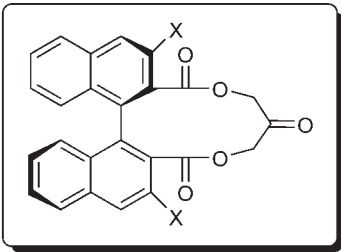
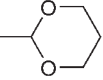
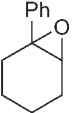
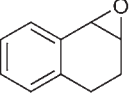
					
X = H X = CH₂OMe X =  X = Cl X = Br					
	90%	80%	90%	75%	81%
	83% ee	67% ee	71% ee	65% ee	64% ee
	80%				
	85% ee				

Figure 12

1.04.2.6.3 Chiral iminium salts and amine catalysis

The first use of an enantiomerically pure oxaziridinium salt to catalyze asymmetric epoxidation (*trans*-stilbene oxide produced with 33% ee using **61** (Figure 13)) was reported by Lusinchi and co-workers in 1993 <1993TL7271>. Subsequently, it was reported that phenylcyclohexene is converted to the corresponding epoxide with just 5% ee using stoichiometric quantities of **61** <1999T141>.

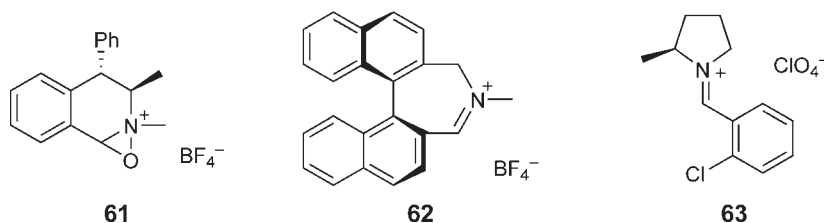


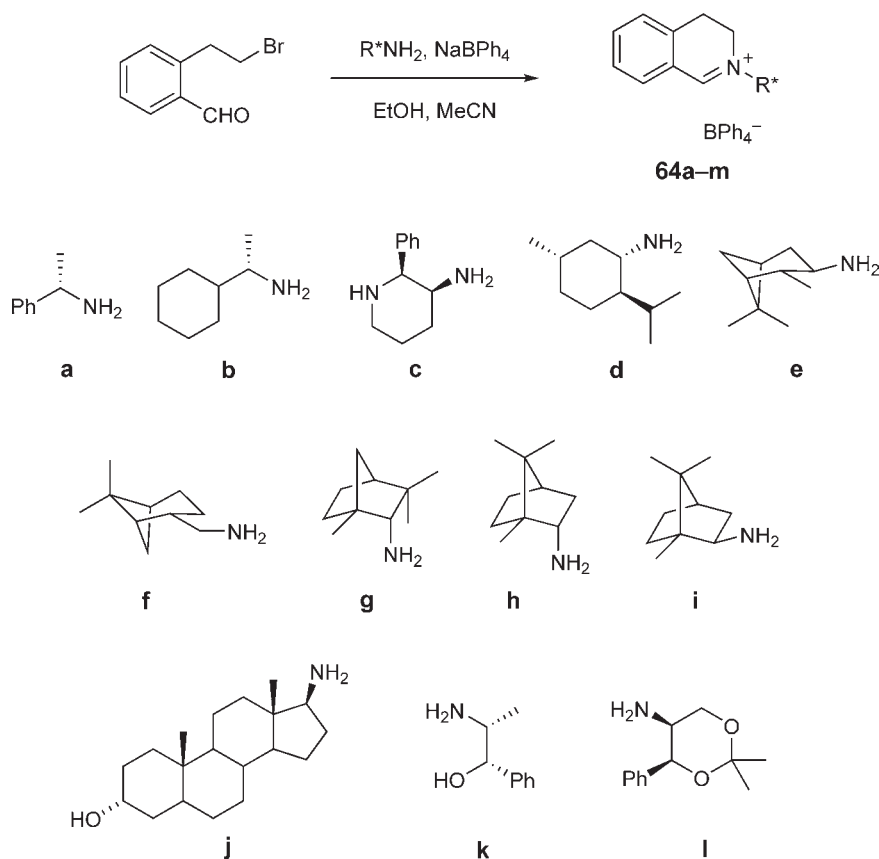
Figure 13

This remains a developing area for the synthesis of chiral oxiranes and has attracted interest from several research groups. As with the use of dioxiranes (above), it is not necessary to form the reactive oxaziridinium salt; rather, the epoxidation reaction can be mediated by the corresponding iminium salt and Oxone.

Aggarwal and Wang have investigated binaphthyl-based iminium salt **62** (Figure 13); 5 mol% of the catalyst is sufficient to mediate the asymmetric epoxidation of phenylcyclohexene (80% yield, 71% ee), whereas the induction was not as efficient for methylcyclohexene (80% yield, 39% ee) <1996CC191>.

Armstrong *et al.* found that stoichiometric use of chiral pyrrolidine-derived iminium salt **63** (Figure 13; could only be isolated in impure form) in the asymmetric epoxidation of phenylcyclohexene gave the oxirane with 22% ee <1999T2341>.

Bulman Page *et al.*'s approach has been to prepare a series of chiral iminium salts (**64a–l**), formally derived from dihydroisoquinoline and a primary amine, but chiral at the exocyclic nitrogen substituent, by condensation of 2-(2-bromoethyl)benzaldehyde with a number of chiral amines in the presence of sodium tetraphenylborate (Scheme 25). These asymmetric catalysts were initially screened in the epoxidation of phenylcyclohexene, with the more promising candidates then examined against phenyldihydronaphthalene and indene (Figure 14) <1998JOC2774, 2000J(P1)3325, 2001JOC6926>.



Scheme 25

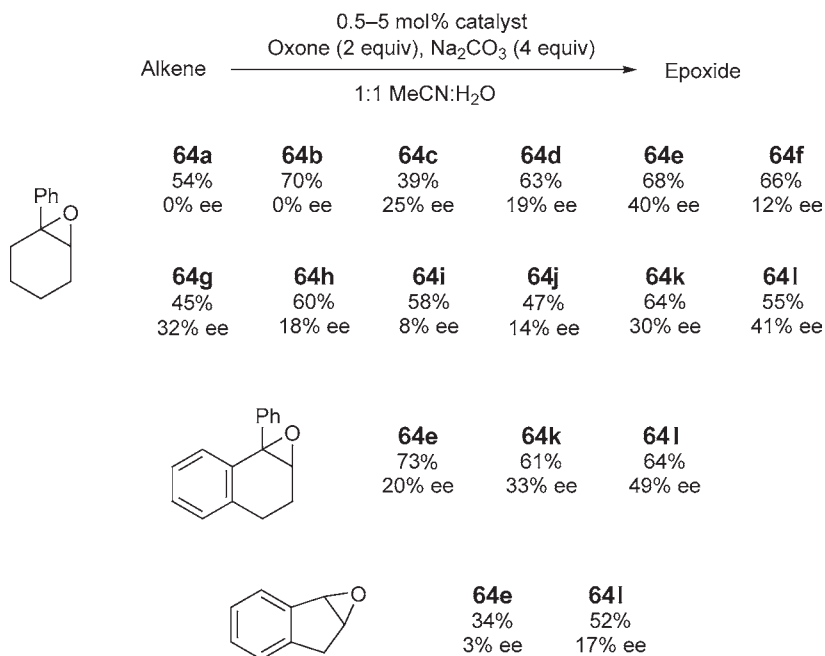


Figure 14

In 2002, Bulman Page *et al.* reported the dibenzazepinium salt analogs of catalysts **64e** and **64l**, **65** and **66**, respectively. These were examined in the asymmetric epoxidation reactions of phenylcyclohexene, phenyldihydronaphthalene, and indene, with very similar results being observed with **65** and **66** as with **64e** and **64l** (Figure 15) <2002SL580>.

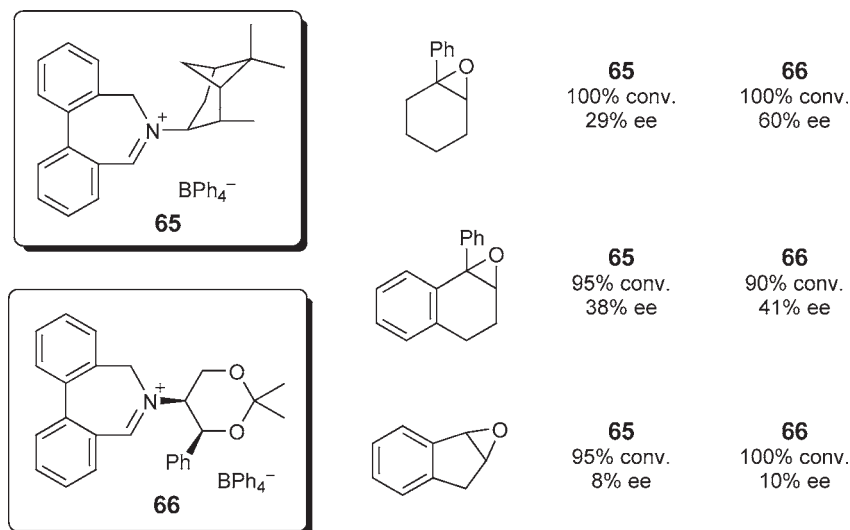
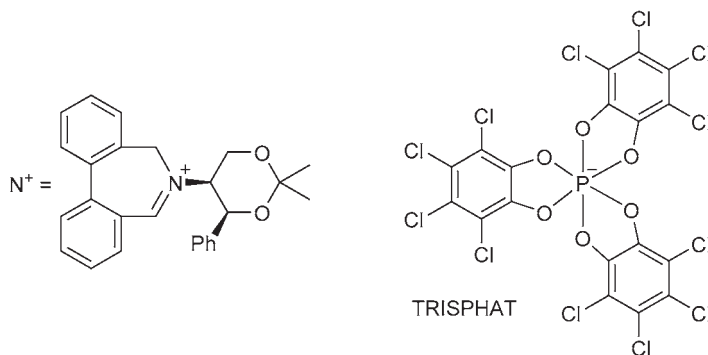
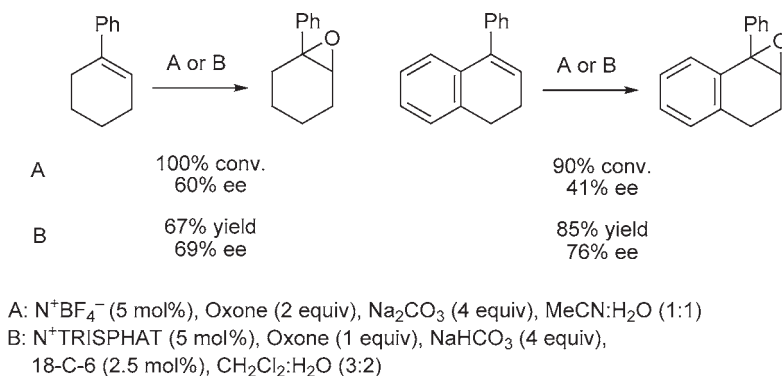


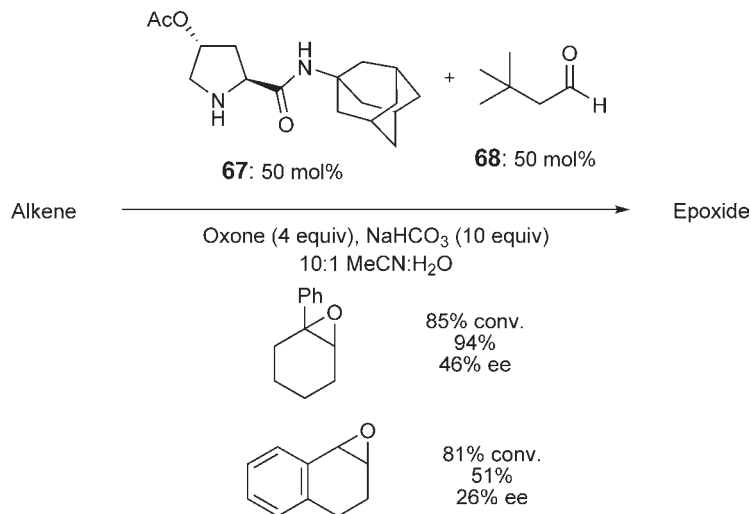
Figure 15

Lacour *et al.* have shown that the ion pairing of Bulman Page's iminium cation **66** with a tris(tetrachlorobenzenediolato)phosphate(v) (TRISPHAT) anion allows the use of strict biphasic conditions leading to higher enantioselectivities when compared to a tetraphenylborate counterion (Scheme 26) <2002TL8257>.



Scheme 26

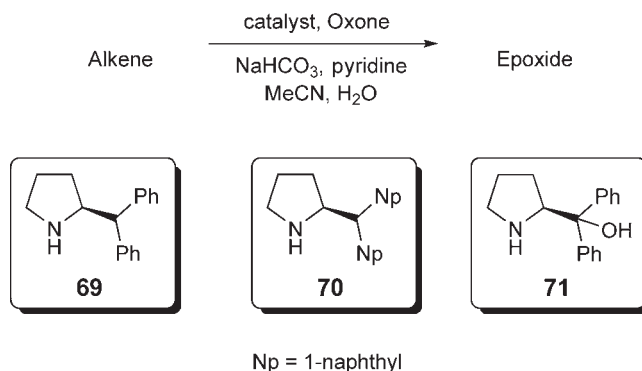
Yang and co-workers have suggested that the inherent difficulties in the preparation/isolation of unstable exocyclic iminium salts can be overcome by *in situ* formation of the catalytic species from chiral pyrrolidines and aldehydes. The catalytic asymmetric epoxidation of phenylcyclohexene and dihydronaphthalene mediated by the iminium salt derived from pyrrolidine **67** and aldehyde **68** has been examined (Scheme 27) <2001OL2587>.



Scheme 27

The use of amines to catalyze (asymmetric) epoxidation reactions was introduced by Aggarwal and co-workers in 2000 <2000JA8317>. (*S*)-2-(Diphenylmethyl)pyrrolidine **69** was examined in the asymmetric epoxidation of a number of cycloalkenes (Table 6). Subsequently it was found that more consistent and reproducible results were obtained when

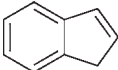
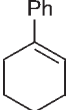
Table 6 Pyrrolidine catalysts for asymmetric epoxidation of cycloalkenes



Alkene	Catalyst	Time	Yield (%)	ee (%)
	69	4 h	90	15
	69	4 h	93	ND

(Continued)

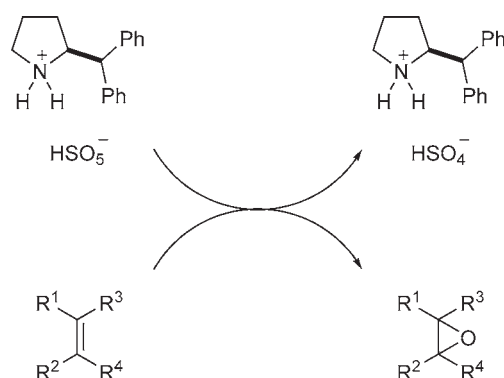
Table 6 (Continued)

Alkene	Catalyst	Time	Yield (%)	ee (%)
	69	4 h	20 (31% conv.)	25
	69	4 h	74 (80% conv.)	ND
	69	4 h	96	32
	69 ·HCl	20 min	93	46
	70 ·HCl	1 h	89	59
	71 ·HCl	2 h	79	54

ND = not determined.

the amine HCl salt was used in the epoxidation of phenylcyclohexene and that moderately improved results were obtained with 2-substituted pyrrolidine catalysts **70** and **71** (Table 6) <2000JA8317, 2003JA7596>.

It has been proposed that the reaction proceeds via a mechanism in which the amine salts most likely function as a phase-transfer catalyst and Oxone activator (Scheme 28) <2003JA7596, 2004AGE1460>.

**Scheme 28**

Yang and co-workers have screened a number of 2-substituted pyrrolidines in the asymmetric epoxidation of phenylcyclohexene and observed that an electronegative fluorine atom β to the nitrogen improved the efficiency of the catalyst (Table 7). Run under slightly different reaction conditions to Aggarwal's procedure (i.e., acidic), they found no benefit in using the corresponding ammonium salts <2005JOC898>.

1.04.2.6.4 Other synthetic methods

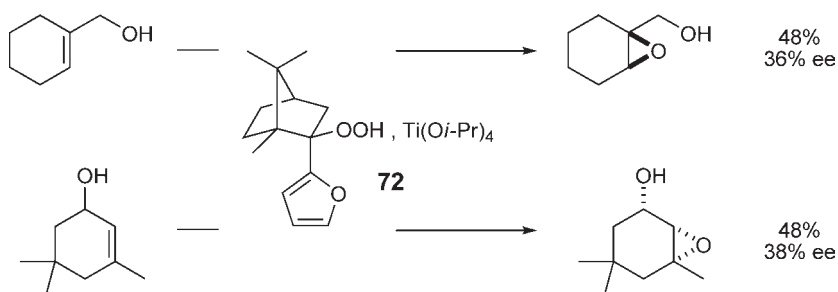
The synthesis of enantiopure epoxides through biocatalytic approaches (including enzymatic approaches to oxirane precursors in addition to direct olefin oxidation) has been reviewed <1997ARM491>.

The asymmetric epoxidation of electron-deficient olefins, particularly α,β -enones, including the use of chiral metal hydroperoxides, asymmetric phase-transfer methods, polyamino acid catalysts, and the chiral dioxiranes, has been reviewed <2000CC1215>.

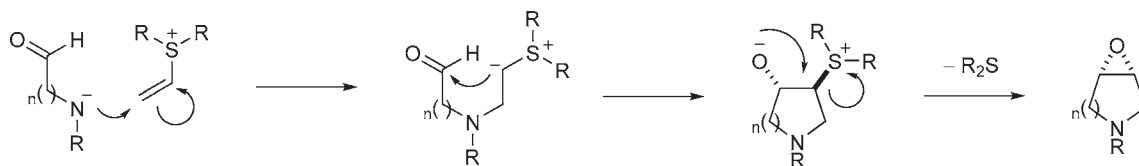
Lattanzi *et al.* have developed a renewable camphor-derived hydroperoxide **72** (Scheme 29) that mediates the asymmetric epoxidation of allylic alcohols resulting in moderate levels of ee <2003CC1440>.

Table 7 Optimization of phenylcyclohexene epoxidation catalyzed by 2-substituted pyrrolidines

<i>Catalyst</i>	<i>Conv. (%)</i>	<i>Yield (%)</i>	<i>ee (%)</i>	
	X = H	100	73	31
	X = OH	58	41	43
	X = OMe	100	83	43
	X = F	100	87	50
	Ar =	100	76	52
	Ar =	96	79	45
	Ar =	94	82	45
	Ar =	100	66	46
	Ar =	43	86	33

**Scheme 29**

Aggarwal and co-workers have developed a new epoxy-annulation method for converting α -, β -, and γ -aminoaldehydes and -ketones into racemic five-, six-, and seven-membered epoxide-fused azacycles via reaction with a vinyl sulfonium salt (**Scheme 30**) <2006AGE7066>.



Scheme 30

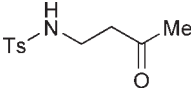
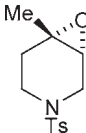
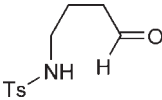
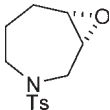
The achiral reaction with diphenyl vinyl sulfonium triflate **73** (**Table 8**) has been extended to an asymmetric process in the synthesis of five- and six-membered rings, using the chiral vinyl sulfonium salt **74**, with very good levels of asymmetric induction being achieved (**Table 8**) <2006AGE7066>.

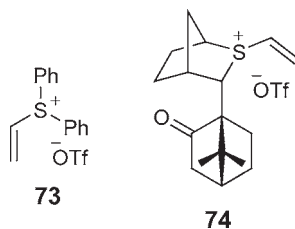
Table 8 Asymmetric epoxy-annulation reaction

<i>Aminocarbonyl</i>	<i>Epoxide</i>	<i>Method</i>	<i>Yield (%)</i>	<i>ee (%)</i>
		A	90	97
		B	76	
		A	90	99
		B	65	
		A	96	92
		B	80	
		A	67	98
		B	67	
		A	50	88
		B	50	

(Continued)

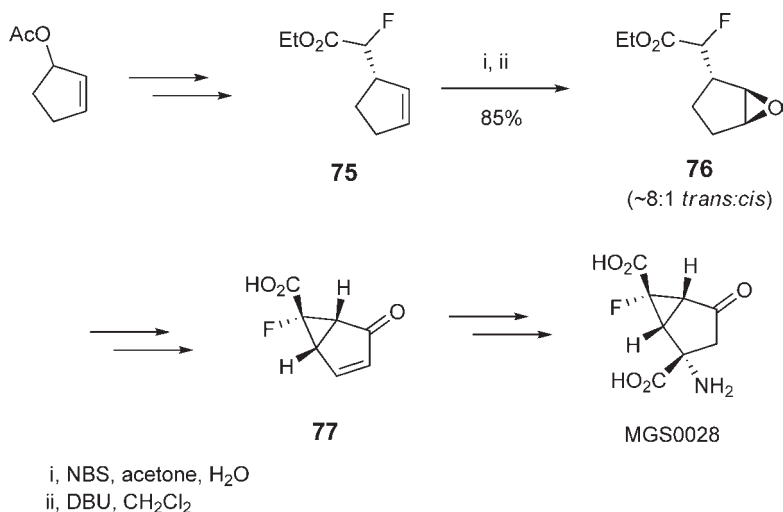
Table 8 (Continued)

<i>Aminocarbonyl</i>	<i>Epoxide</i>	<i>Method</i>	<i>Yield (%)</i>	<i>ee (%)</i>
		A	77	86
		B	30	
		A	62	

Method A: **73** (1.2 equiv), DBU (2 equiv), CH₂Cl₂, 0 °C, 2–4 hMethod B: **74** (1 equiv), DBU (2 equiv), CH₂Cl₂, –20 °C, 2–5 d

1.04.2.7 Miscellaneous Achiral Epoxidation Methods

Zhang *et al.* at Merck have developed an approach involving diastereoselective epoxidation via bromohydrin formation toward the densely functionalized fluorocyclopropane **77** (Scheme 31), a key intermediate in the synthesis of mGluR2 receptor agonist MGS0028 <2004OL3775>. This synthesis required stereoselective formation of *trans*-epoxide **76** from alkene **75**, that would be typically expected to undergo selective epoxidation from the *cis*-face via neighboring group direction by the carbonyl. It was found that formation of the bromohydrin of cyclopentene **75** followed by elimination gave an approximately 8:1 mixture of *trans*- and *cis*-epoxides (Scheme 31) <2004OL3775>.

**Scheme 31**

The stoichiometric epoxidation of norbornene (73–99% yield) (and other alkenes) with sterically encumbered *trans*-dioxoruthenium(VI) porphyrins (e.g., **78**; Figure 16) has been the subject of a mechanistic investigation by the group of Yu <1999JOC7365>. Manganese(II) complex **79** (Figure 16) has been utilized by Stack and coworkers as a catalyst in the efficient epoxidation of a number of olefins (including electron-deficient ones) by peracetic acid; cyclohexene (85% yield), cyclooctene (90% yield), cyclohexenone (88% yield), and (–)-carvone (8,9-monoepoxide (91% yield) with 1 equiv peracid, diepoxide (88% yield) with 3 equiv) are all readily oxidized. Little or no diastereo- or enantioselectivity was observed <2003JA5250>.

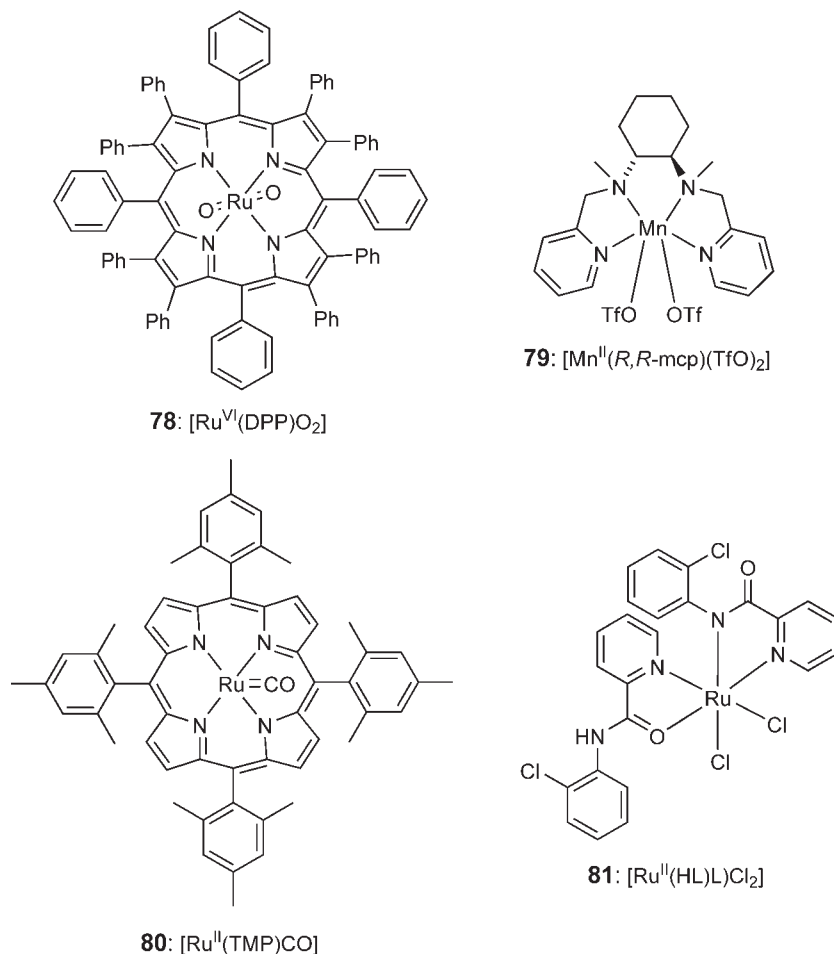


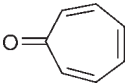
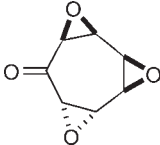
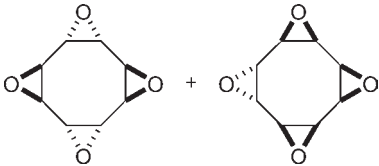
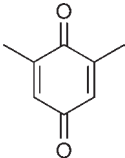
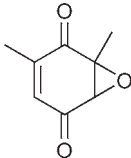
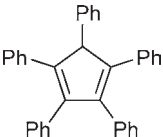
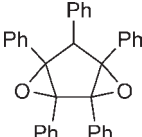
Figure 16

Inoue and co-workers have used ruthenium(II) porphyrin **80** (Figure 16) to mediate the photochemical epoxidation of several alkenes with excellent selectivity over the formation of other oxidation products, including cyclohexene (up to 97% selectivity), norbornene (up to 99.7% selectivity), and cyclooctene (up to 99.9% selectivity) <2003JA5734>.

Chan and co-workers have developed a novel ruthenium complex (**81**, Figure 16) which catalyses the epoxidation of cyclic alkenes with molecular oxygen in excellent yield under mild reaction conditions. Cyclopentene (90% yield), cyclohexene (up to 90% yield), methylcyclohexene (90% yield), phenylcyclohexene (78% yield), and cyclooctene (97% yield) are all readily epoxidized <2003CC1058>.

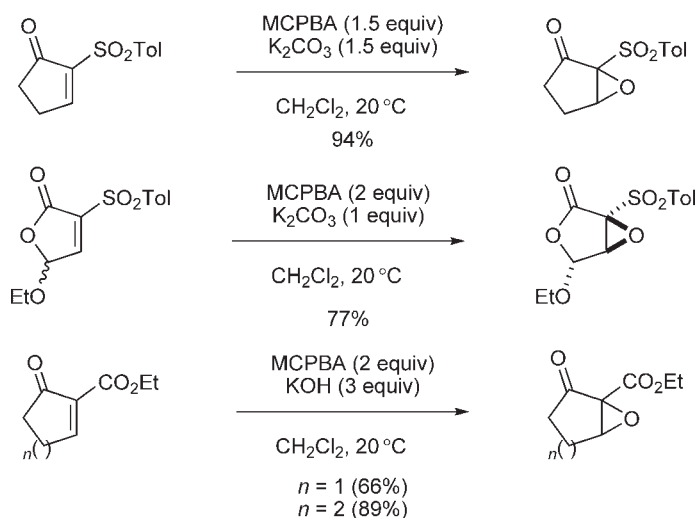
Rozen and co-workers have obtained impressive results using the efficient oxygen-transfer reagent $\text{HOF} \cdot \text{MeCN}$ with normally difficult to epoxidize olefins (Table 9) <2004TL3397>.

Table 9 Epoxidations with HOF-MeCN

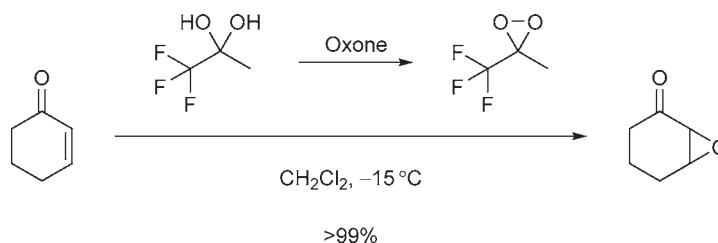
Alkene	Time	Epoxide	Yield (%)
	15 min		82
	30 s		97
	5 min		97
	15 min		72

The epoxidation of alkenes using hydrogen peroxide as an environmentally friendly oxidant has been reviewed [<2003GC1>](#). Hydrogen peroxide can be used in the presence of a homogeneous metal catalyst based on tungsten, manganese, iron, or rhenium, or through addition of stoichiometric amounts of auxiliaries, or in the presence of heterogeneous catalysts such as mixed oxides, redox zeolites, layered materials, and supported metal catalysts. Heterogeneous catalysts, however, suffer generally from lower activity and stability compared to homogeneous catalysts.

The group of García Ruano has found that the *m*-chloroperoxybenzoate anion (generated from MCPBA and bases such as K_2CO_3 or KOH) is a highly efficient nucleophilic epoxidizing agent for strongly deactivated olefins containing two electron-withdrawing groups at the same carbon (e.g., [Scheme 32](#)) [<2005JOC4300>](#).

**Scheme 32**

Recently, Mello *et al.* have disclosed a simple and robust protocol for the generation of methyl(trifluoromethyl)dioxirane from an aqueous solution of 1,1,1-trifluoroacetone hydrate, sodium bicarbonate, and peroxomonosulfate on a 'preparative scale' (typically <2 g; the authors suggest multiple iterations for larger scales). The methyl(trifluoromethyl)dioxirane is removed from the reaction mixture by the evolved gases (O_2 , CO_2) and has been applied to the oxidation of substrates in a second reaction zone (e.g., the epoxidation of cyclohexenone; [Scheme 33](#)) [<2007S47>](#).



Scheme 33

1.04.2.8 Reactivity of Ring-Fused Oxiranes

As with other sections in this chapter, the discussion of oxirane reactivity is limited to cases where the bicyclic nature of the ring-fused epoxide plays an important role in the outcome of the reaction. The reader is directed to Chapter 1.03 for more general discussion of oxirane reactivity.

1.04.2.8.1 Ring-opening reactions

Perhaps the most familiar reaction of epoxides is their propensity to undergo ring opening with various nucleophiles, and as such the ring-opening reaction of oxiranes (even when limited to ring-fused examples) represents a vast body of work. However, a number of highly specialized reviews already exist in this area, and, after directing the reader to the available literature, we will provide highlights from the ongoing development of new methodologies in this area.

Enzyme-catalyzed epoxide ring opening including discussion of convergent families of epoxide hydrolases, the catalytic mechanism of microsomal epoxide hydrolases, epoxide hydrolases in metabolism, and the synthesis, structure, and mechanism of leukotriene A₄ hydrolase, and glutathione transferase has been reviewed by Armstrong [<1999CONAP\(5\)51>](#).

In addition to being highly efficient catalysts for the preparation of asymmetric oxiranes (see [Section 1.04.2.6.1](#)), chiral metal-salen complexes can mediate the enantioselective nucleophilic ring opening of epoxides; Jacobsen reviewed this area in 2000 [<2000ACR421>](#).

The use of glycal and *exo*-glycal-derived epoxides (and episulfonium and iodonium ions) in the preparation of *C*-glycosides has been reviewed by Smoliakova [<2000COR589>](#). The opening of glycal epoxides with diverse organometallics (cuprates, Grignards, lithiums, sodio malonates, and allylsilanes) has found application in the stereoselective synthesis of both α - and β -*C*-glycosides. Furthermore, the resulting C(2)-hydroxyl groups can be removed in a two step process to afford 2-deoxy-*C*-glycosides.

The well-known base-mediated rearrangement of epoxides into allylic alcohols was first reported as an enantioselective process using a chiral base in 1980. Since then, the reaction has received much attention, mostly due to the significance of chiral allylic alcohols in organic synthesis. Major breakthroughs in the area include the use of a substoichiometric amount of chiral base and the development of chiral bases for a true catalytic reaction protocol. Andersson and co-workers have reviewed this area from 1980 to 2001, with emphasis on the period 1997–2001 [<2002CSR223>](#).

Gansäuer and Narayan have reviewed the use of epoxides as substrates for radical reactions via electron transfer [<2002ASC465>](#). The discussion focuses on recent developments in the use of titanocene(III) reagents as stoichiometric reagents, and the catalytic use of cyclopentadienyl ligands in reagent-controlled radical reactions.

Recent advances in the synthesis of *trans*-fused polycyclic ethers by hydroxy epoxide cyclization reactions via monocyclic epoxonium ion intermediates and ether ring expansion reactions via bicyclic epoxonium ion intermediates are described in a review by Fujiwara and Murai. Natural *trans*-fused polycyclic ethers (e.g., brevetoxin A and ciguatoxin), produced by marine sources such as dinoflagellates, are hypothesized to be constructed from the corresponding polyepoxide precursors by a cascade of ring-closure reactions, which has prompted much work in the development of new methods for the construction of cyclic ethers from epoxides <2004BCJ2129>.

Haufe has reviewed the regio- and stereoselective synthesis of vicinal fluorohydrins, including the ring opening of epoxides with hydrofluorinating reagents (e.g., KF and CsF, KHF₂, Alk₄NF, Bu₄N⁺H₂F₃[−], Bu₄PF·HF, SiF₄ and BF₃·OEt₂, and various amine–HF adducts) <2004JFC(125)875>.

Copper-catalyzed enantioselective allylic alkylation ring-opening reactions of oxiranes (and aziridines) with alkyl metals (e.g., dialkylzincs) has been reviewed by Pineschi <2004NJC657>.

The ring opening of ring-fused oxiranes by nitrogen nucleophiles (e.g., amines, azides, and hydrazines) has been reviewed <2004RJO1>, as has intramolecular participation of oxygen in ring opening <2005RJO186>.

The asymmetric ring opening of oxiranes (and aziridines) with carbon nucleophiles has been reviewed by Pineschi <2006EJO4979>.

The metal-promoted asymmetric ring opening of achiral epoxides using achiral carbon-, nitrogen-, oxygen-, sulfur-, and halogen-containing nucleophiles, the synthesis of chiral allylic alcohols via asymmetric deprotonation of achiral epoxides with chiral bases, and the kinetic resolution of racemic epoxides using chiral metal complexes has recently been reviewed by Pastor and Yus <2005COR1>. Similarly, advances in the development of metal- and enzyme-catalyzed, enantioselective ring-opening reactions of *meso*-epoxides and racemic epoxides with various hetero- and carbon nucleophiles has been reviewed by Schneider <2006S3919>.

The enantioselective cleavage of strained ethers (epoxides and oxetanes) by organolithiums, mediated by chiral, nonracemic ligands (as well as additions to aldehydes and ketones), has been reviewed by Goldfuss <2005S2271>.

Mizuno and Shioiri have developed a regio- and stereoselective ring-opening reaction of epoxides with diphenyl phosphorazidate in the presence of 4-dimethylaminopyridine (DMAP) and lithium perchlorate. In addition to obtaining *O*-diphenylphosphoryl vicinal azidohydrins from the ring opening of epoxides, α -azidovinyl ketones are obtained directly from the corresponding α,β -epoxy ketones (Table 10) <1999TL7105>.

Table 10 Ring opening of epoxides with diphenyl phosphorazidate

$\text{Epoxide} \xrightarrow[\text{DMF or MeCN, 50 } ^\circ\text{C}]{\begin{array}{c} \text{O} \\ \parallel \\ (\text{PhO})_2\text{P}-\text{N}_3, \text{ DMAP, LiClO}_4 \end{array}} \text{Product}$			
Epoxide	Time (h)	Product	Yield (%)
	72		60
	84		73
	96		36 (+37 sm)

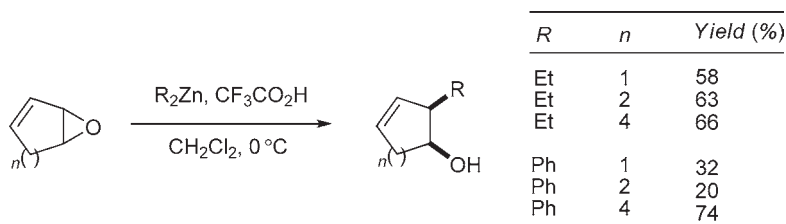
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Table 10 (Continued)

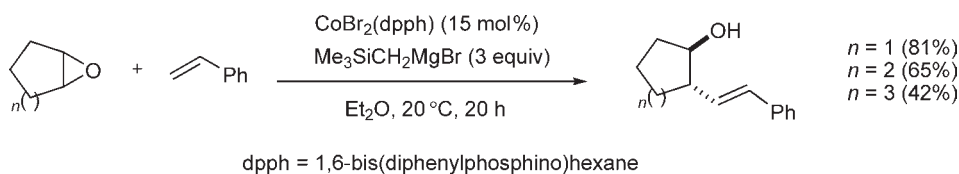
Epoxide	Time (h)	Product	Yield (%)
	84		52
	3		88
	12		68
	96		70

sm = starting material.

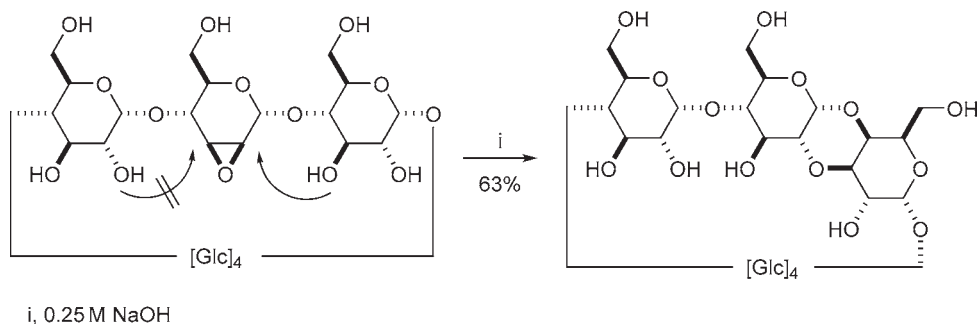
Xue *et al.* have found that organozinc reagents (ZnEt_2 , ZnPh_2) react with cyclic 1,3-diene monoepoxides in the presence of CF_3COOH to give the *cis*-addition products (**Scheme 34**) <2002OL905>.

**Scheme 34**

Oshima and coworkers have developed a new epoxide ring-opening methodology; treatment of a mixture of epoxide and styrene with trimethylsilylmethylmagnesium bromide in the presence of a cobalt–phosphine complex afforded the corresponding homocinnamyl alcohols in good yield (**Scheme 35**) <2004ASC1631>.

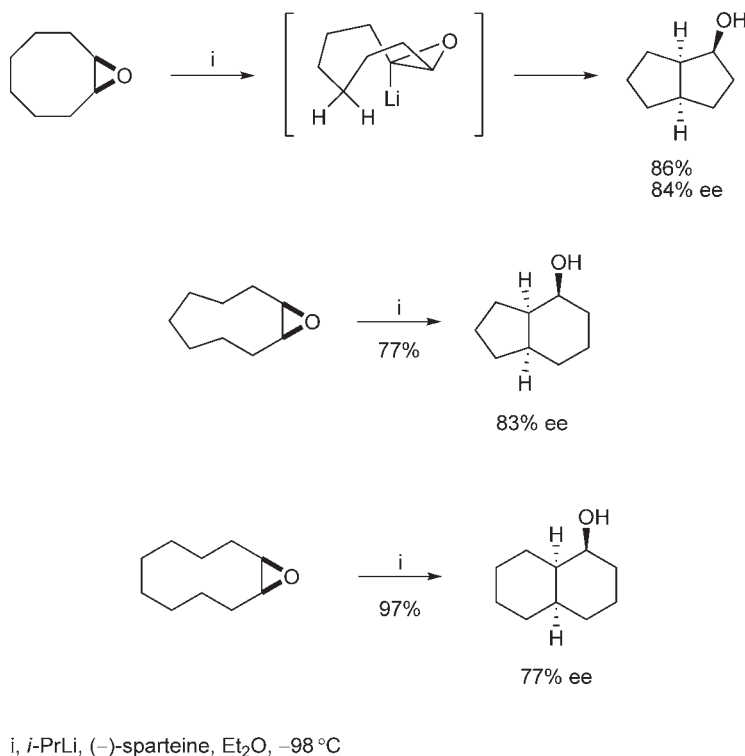
**Scheme 35**

Fujita *et al.* have observed an unusual pathway in the intramolecular ring-opening reaction of cyclodextrin epoxide rings (e.g., **Scheme 36**), the product being that arising via *trans*-diequatorial ring opening <2004EJO3113>.

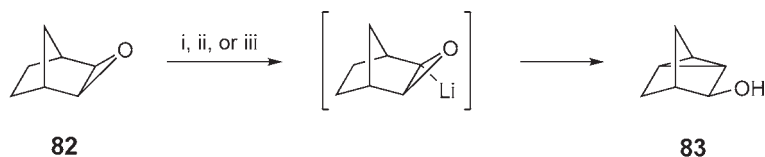
**Scheme 36**

1.04.2.8.2 Chemistry of lithiated epoxides

Following early efforts in the area of asymmetric epoxide ring opening with chiral lithium amide bases, the group of Hodgson became interested in enantioselective rearrangements which proceed specifically via metallation of an epoxide ring; this work has been reviewed [<1996T14361, 2002S1625, B-2003MI217, B-2005MI145, 2006SL1, 2007PAC269>](#). Hodgson and Lee achieved enantioselective α -deprotonation rearrangement of medium-sized (eight-, nine- and ten-membered) cycloalkene-derived epoxides using organolithiums in the presence of (–)-sparteine, to give bicyclic alcohols in good yields and enantioselectivities (**Scheme 37**) [<1996CC1015, 1997TA2303, 1998J\(P1\)2151>](#).

**Scheme 37**

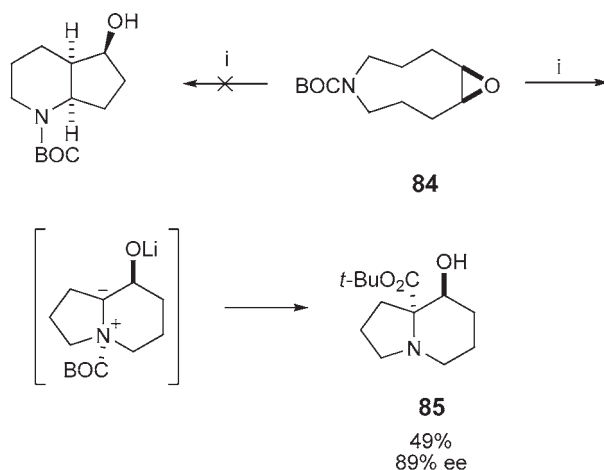
The classical isomerization of *exo*-norbornene oxide **82** to nortricyclanol **83** [<1964JOC2830>](#) was next examined (**Scheme 38**); chiral lithium amides or organolithium/(–)-sparteine complexes effected this transformation, with up to 52% ee [<1996TA1275>](#).



i, LiNEt_2 , Et_2O , reflux, 48 h (55%)
 ii, $s\text{-BuLi}$ (1.4 equiv), (–)-sparteine (1.45 equiv), pentane, -78°C , (73%, 52% ee)
 iii, Lithium (S,S)-bis(1-phenyl)ethylamide (1.8 equiv), Et_2O , 0°C , (73%, 49% ee)

Scheme 38

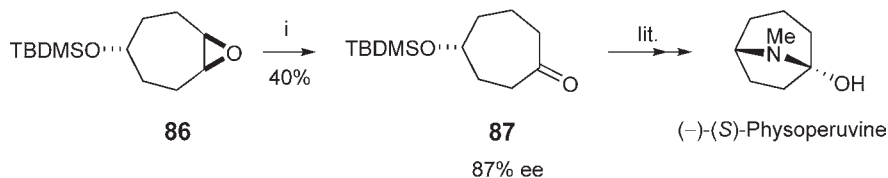
Moving away from rearrangements of known compounds, Hodgson and Robinson investigated the lithiation rearrangement of azacyclic epoxide **84** (Scheme 39). Analogous methodology to above was anticipated to result in a carbenoid C–H insertion α to the carbamate nitrogen. In fact, the observed indolizidinol product appears to arise via nitrogen trapping of the α -lithiated epoxide, the thus-formed transient ylide subsequently undergoing a Stevens rearrangement to give azabicyclo[4.3.0]nonanol **85** (Scheme 39) <1999CC309, 2001J(P1)2161>.



i, $i\text{-PrLi}$ (2.4 equiv), (–)-sparteine (2.45 equiv), Et_2O , -98°C , 18 h

Scheme 39

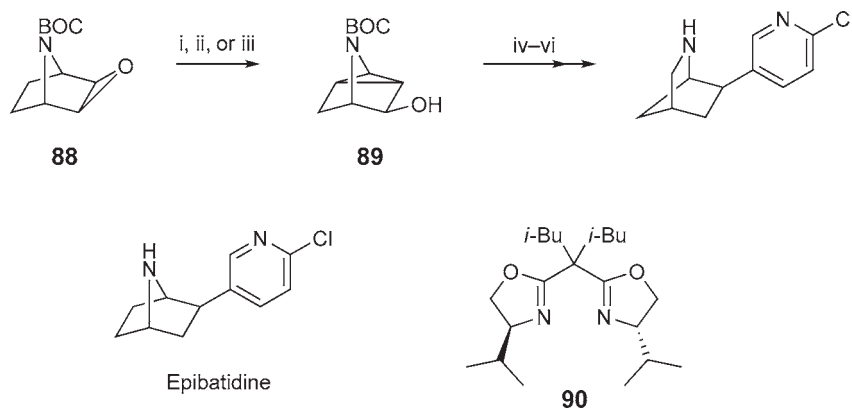
α -Lithiation/elimination of 5-silyloxycycloheptene oxide **86** gives 4-silyloxycycloheptanone **87**, an intermediate in the synthesis of the alkaloid (–)-(*S*)-physoperuvine, with 87% ee (Scheme 40) <1999TL8637>.



i, $i\text{-PrLi}$ (2.4 equiv), (–)- α -isosparteine (2.4 equiv), Et_2O , -98°C

Scheme 40

α -Lithiation/transannular carbenoid insertion of 7-azabicyclic epoxide **88** gave azanortricyclanol **89** (Scheme 41), which was converted to an analog of the potent nicotine acetylcholine receptor agonist epibatidine <1998SL1349, 2001J(P1)3150>. The epoxide transformation has been examined as an asymmetric process: a 2-tolyl lithium/(–)-sparteine combination gives the azanortricyclanol **89** in 61% yield and 77% ee, while use of bisoxazoline ligand **90** increased the ee to 87% (51% yield) <1999TA1847>.



- i, LDA (1.6 equiv), Et₂O, 0 °C, 5 min (52%)
 ii, 2-tolyl lithium (3 equiv), (–)-sparteine (3 equiv), Et₂O, –78 °C (61%, 77% ee)
 iii, PhLi, **90**, Et₂O, –78 °C (51%, 87% ee)
 iv, Swern oxidation, then 6-chloropyridin-3-yl lithium, THF–Et₂O, –78 to 25 °C, 1 h (60%)
 v, ClCOCO₂Me, DMAP, MeCN, 25 °C, 30 min, then Bu₃SnH, AIBN, PhMe, 100 °C, 45 min (61%)
 vi, H₂ (1 atm), 10% Pd/C, EtOAc, 25 °C, 3 h, then TFA, CH₂Cl₂, 25 °C, 2 h (89%)

Scheme 41

The rearrangement of epoxides of more highly substituted medium-ring cycloalkenes was investigated by Hodgson and Cameron. Diastereomeric *meso*-epoxides **91** and **94**, containing a protected 1,4-diol unit, and epoxide **96**, containing a 1,2-diol unit, all underwent enantioselective transannular desymmetrization to give the corresponding substituted bicyclo[3.3.0]octanol compounds **92**, **95**, and **97**. In the case of **91**, cyclooctenol **93**, likely arising via β -elimination, was also observed under certain conditions (Scheme 42) <2001OL441, 2001J(P1)2161>.

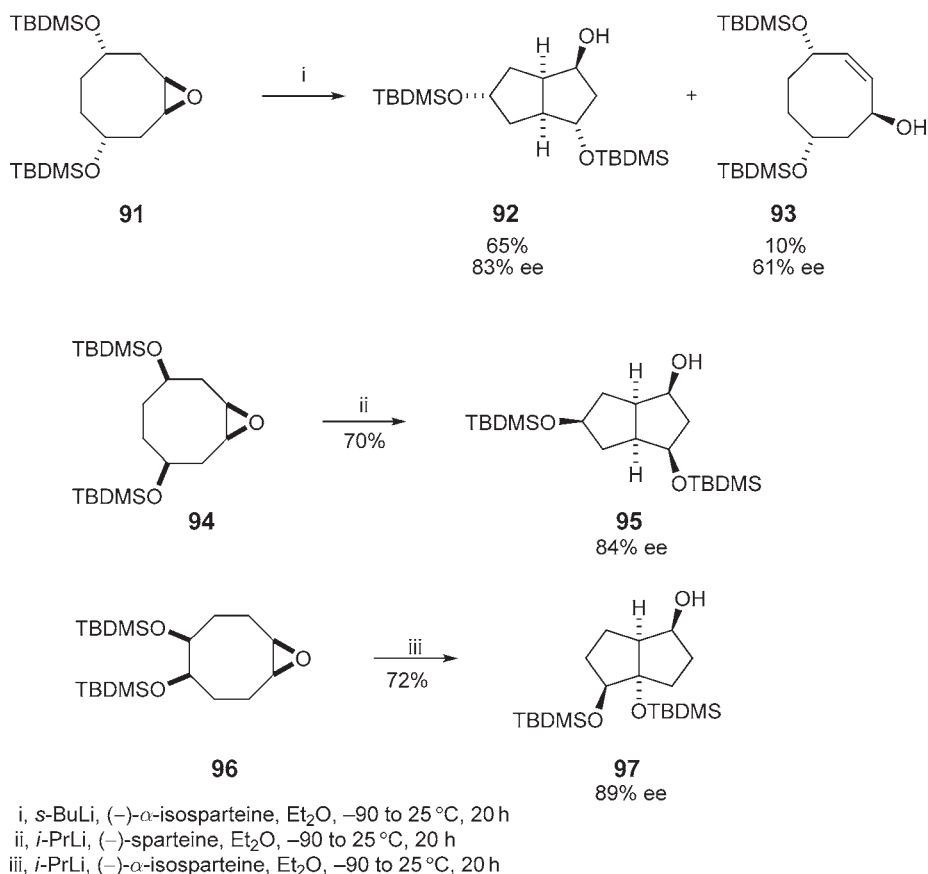
Bicyclic alcohol **97** was utilized in a total synthesis of the natural product (–)-xialenon A (Scheme 43) <2002CC2436, 2003T9719>.

In 1995, Mioskowski and co-workers reported a new carbenoid 1,2-alkyl rearrangement of α -hydroxy-substituted cyclopentene and cyclohexene oxides; treatment of such systems with 3 equiv of an organolithium resulted in the formation of two products, as exemplified by the synthesis of dihydrojasnone and its regioisomer **99** (Scheme 44) <1995JA12700>.

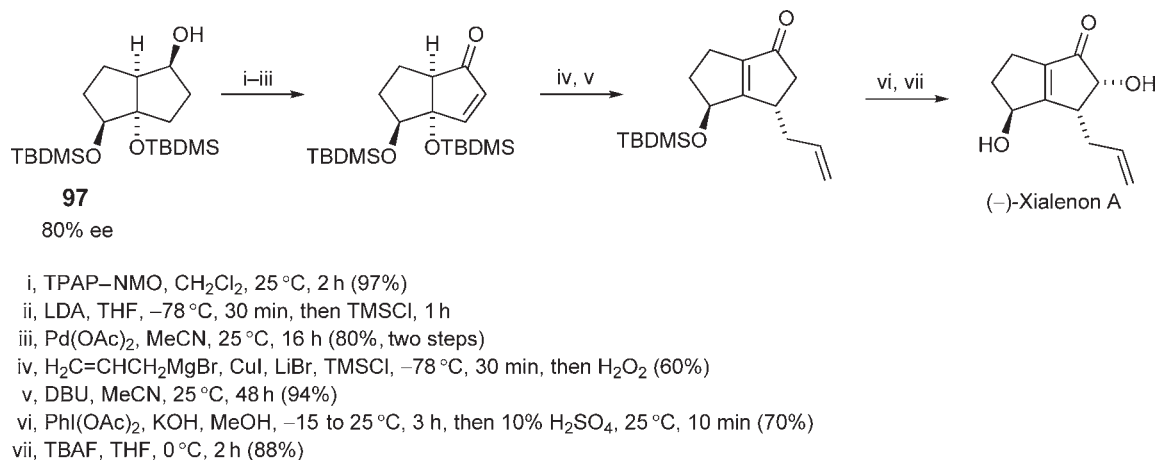
The suggested mechanistic pathway for this transformation implicates carbenoid **98** as a key intermediate, generated by α -elimination of the metallated oxirane. The highly reactive carbenoid undergoes intramolecular insertion rearrangement via either route A or B to yield dilithiated alkoxy enolate intermediates which, after usual workup, furnish the α,β -unsaturated ketones, via H₂O elimination <1995JA12700>.

Evidence for the generation of a carbenoid intermediate was obtained by the intramolecular trapping [2+1] cycloaddition reaction (20% yield) of butenyl-substituted system **100** (Scheme 45) <1995JA12700>.

The migratory aptitude of the alkyl substituents was investigated by reaction of a series of analogs <1995JA12700>, and it was subsequently found that the regiochemical outcome of the reaction was strongly affected by the nature of the solvent <1998JOC3808>. While the reaction was successfully extended to cyclohexene-derived epoxides, two observations are of note. First, an acyclic example failed to give the analogous product; rather, classical β -elimination was observed (Scheme 46, Equation 4). Second, a methoxy-substituted system also failed to give the expected product, with instead a cyclopentenol being isolated (Scheme 46, Equation 5) <1995JA12700, 1998SL337>.

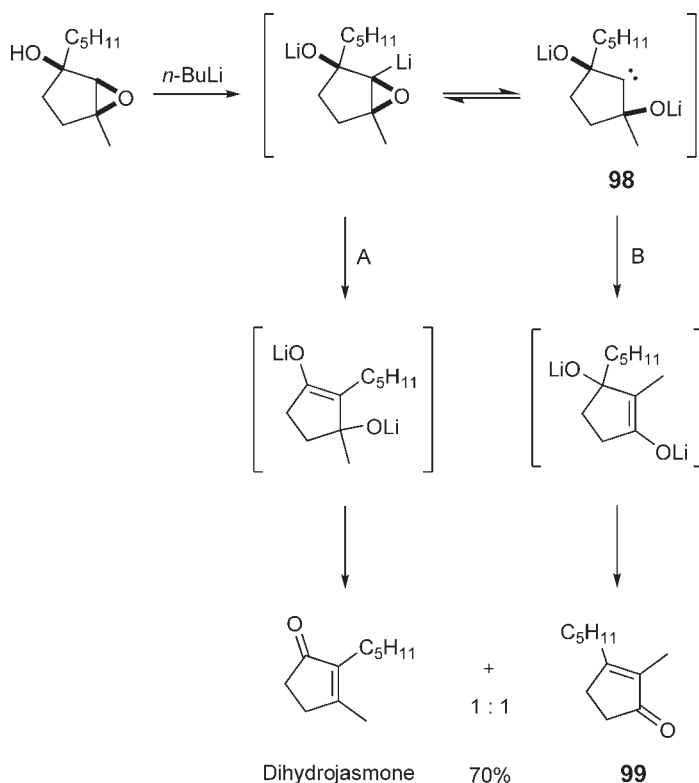


Scheme 42

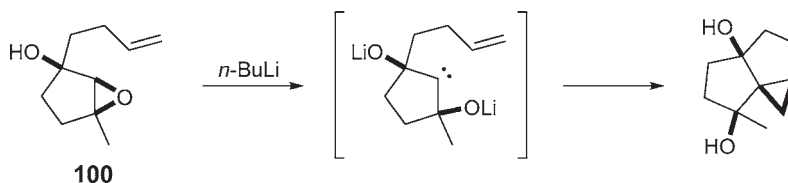


Scheme 43

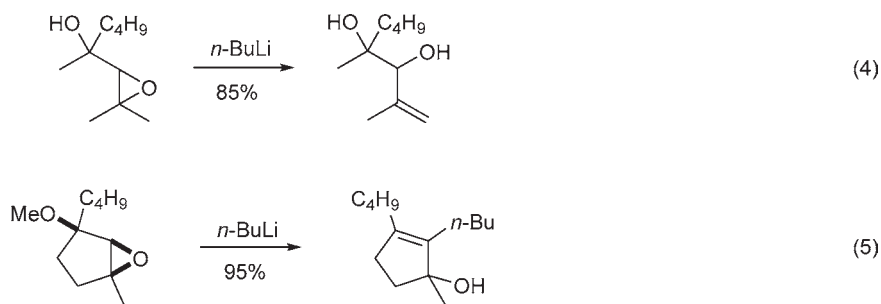
In 1996, Mioskowski and co-workers expanded on this second observation to advance the classical ‘reductive alkylation’ chemistry of epoxides first reported by Crandall and Lin in 1967 ([Scheme 47, Equation 6](#)) <1967JA4526, 1967JA4527, 1983OR345>. Mioskowski and co-workers proposed a similar pathway for the formation of cyclopentenol **102** from methoxy-substituted cyclopentene oxide **101**: lithiation, carbenoid formation, insertion into the excess organolithium, followed, in this case, by LiOMe elimination (rather than Li₂O) ([Scheme 47, Equation 7](#)) <1996CC549>.



Scheme 44

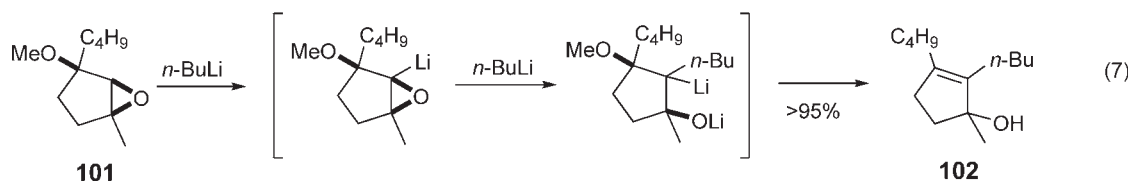
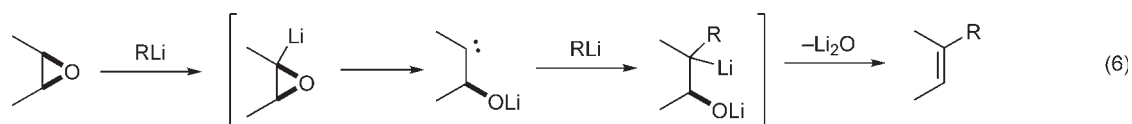


Scheme 45



Scheme 46

The methodology was successful with a range of organolithiums (primary, secondary, tertiary, and aryl), the intermediacy of a carbenoid was again demonstrated by intramolecular [2+1] cycloaddition trapping of a butenyl group (15% of the product mixture, 85% reductive alkylation), and cyclohexene-derived epoxides were also included (acyclic examples again underwent β -elimination) (Table 11) <1996CC549, 1998SL337>.

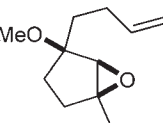
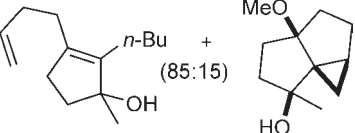
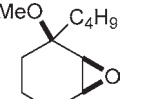
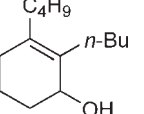
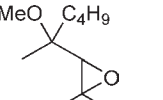
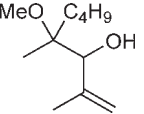


Scheme 47

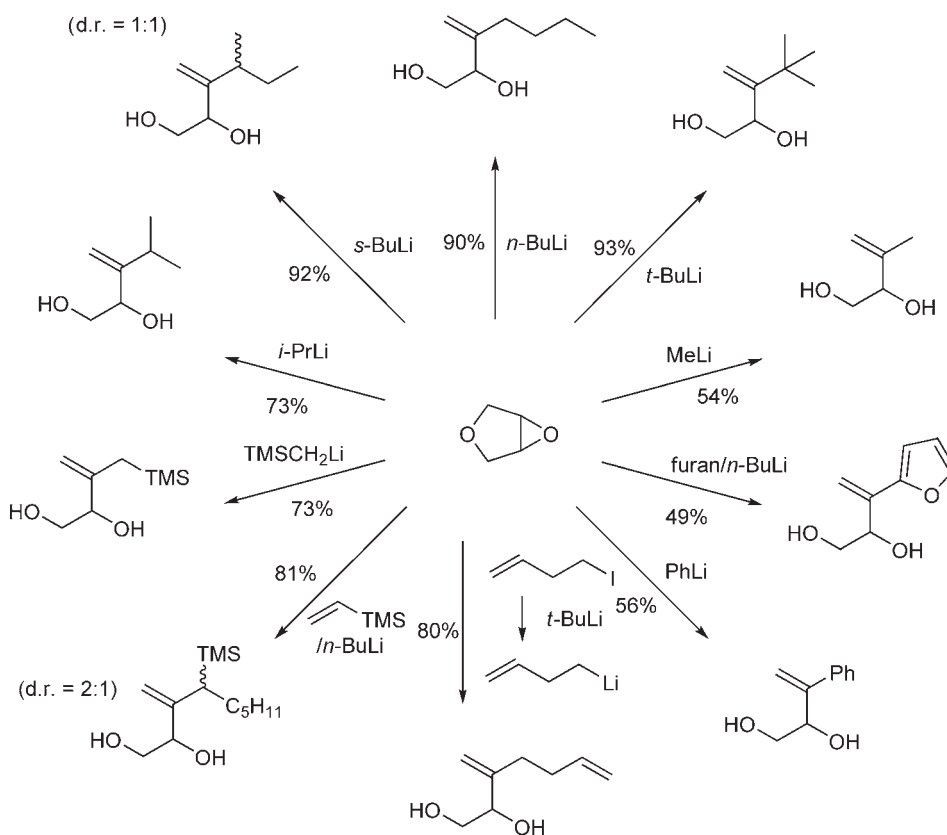
Table 11 Alkylative ring opening of cyclopentene and cyclohexene oxides

<i>Epoxide</i>	<i>RLi</i>	<i>Products</i>	<i>Yield (%)</i>
	<i>n</i> -BuLi		95
	MeLi		83
	<i>s</i> -BuLi		95
	<i>t</i> -BuLi		95
	PhLi		79
	<i>n</i> -BuLi		88
	<i>n</i> -BuLi		85

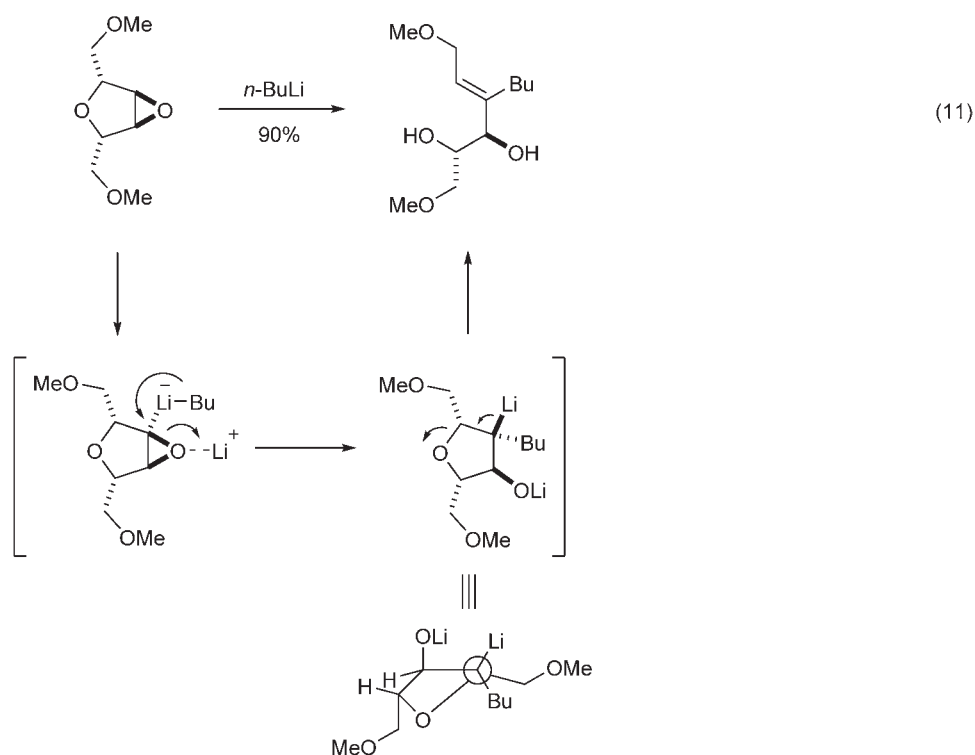
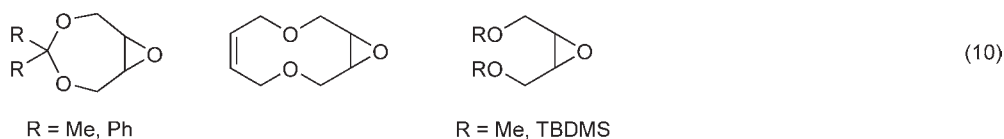
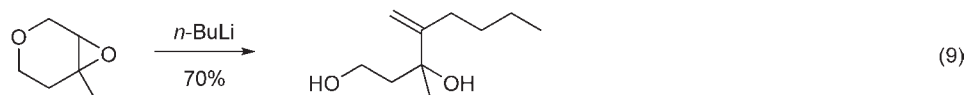
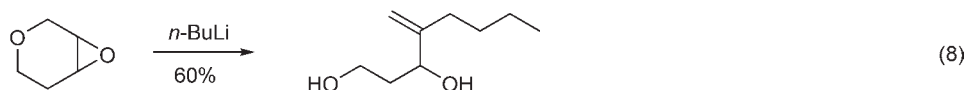
(Continued)

<i>Epoxide</i>	<i>RLi</i>	<i>Products</i>	<i>Yield (%)</i>
	<i>n</i> -BuLi		91
	<i>n</i> -BuLi		76
	<i>n</i> -BuLi		89

Scheme 48

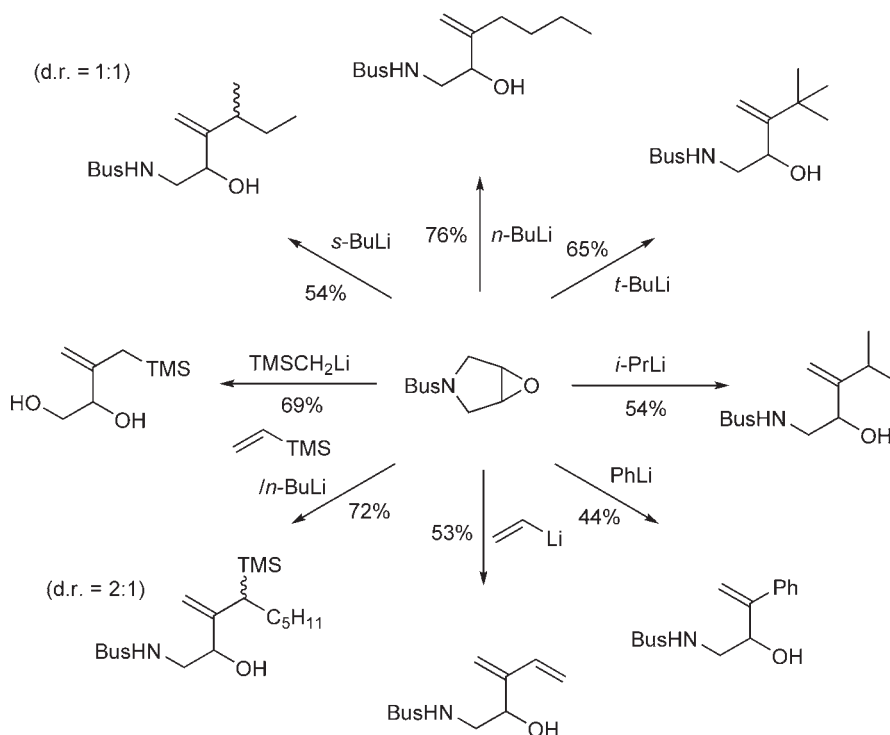


The reaction was further extended to trisubstituted epoxides and epoxides derived from dihydropyrans (Scheme 49, Equations 8 and 9), but failed for larger ring systems and acyclic examples (Scheme 49, Equation 10). Examination of the double bond geometry arising from reaction of 2,5-disubstituted-3,4-epoxytetrahydrofurans indicated a stereospecific elimination pathway for which a 1,2-metallate rearrangement [\[2001CRV697\]](#) mechanism was suggested (Scheme 49, Equation 11) [\[2001OL3401, 2002S1145\]](#).



Scheme 49

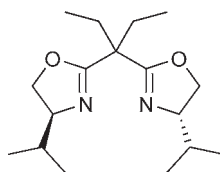
The methodology was also successful for epoxides derived from *N*-Bus protected (Bus = *tert*-butylsulfonyl) 2,5-dihydropyrroles, the successful formation of the corresponding substituted aminoalcohols being highly dependent on the nature of the nitrogen protecting group (Scheme 50) [\[2002SL310, 2003T9729\]](#).



Scheme 50

In line with its interest in asymmetric transformations of lithiated epoxides, the Hodgson group extended this new alkylative ring-opening reaction of epoxides fused to five- and six-membered rings by conducting the reaction in the presence of chiral ligands thus affecting an enantioselective deprotonation.

Examination with both (–)-sparteine and bisoxazoline **103** (Figure 17) as chiral ligands revealed that, while moderate yields/enantioselectivities could be achieved in the reactions of dihydrofuran- and dihydropyrrole-derived epoxides, the process gave better overall results with epoxides derived from 7-oxa- and azabicyclo[2.2.1]hept-2-enes and 8-oxa- and azabicyclo[3.2.1]oct-2-enes (Tables 12 and 13) <2002AGE4313, 2003OBC1139, 2004T3611, 2004T5185>.



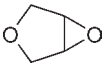
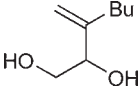
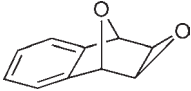
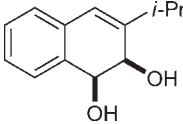
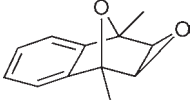
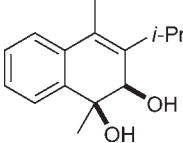
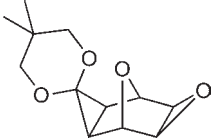
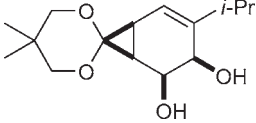
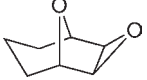
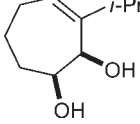
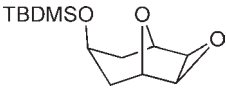
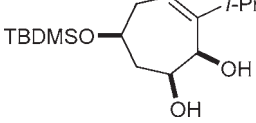
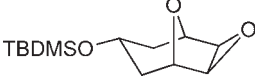
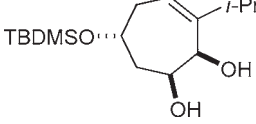
103

Figure 17

Mioskowski and co-workers continued their work in the area of lithiation of ring-fused epoxides by developing a stereospecific intramolecular cyclopropanation of β,γ -unsaturated carbenoids, leading to highly strained tricyclo[4.1.0.0^{1,5}]heptane intermediates whose hydrolysis leads to α -ketocyclopropanols. This methodology is exemplified below in the case of ketone **104** (Scheme 51) <1997TL4071>.

The use of phenyllithium restricted competing reaction pathways (i.e., reductive alkylation as discussed above) and the stereospecificity was demonstrated by the use of different geometries of the reactive double bond, while the hydrolysis of the tricyclic intermediates proceeds with retention of configuration (Scheme 52) <1997TL4071, 2001EJO4107>.

Table 12 Asymmetric alkylative ring opening of epoxides of oxacycles

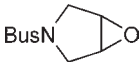
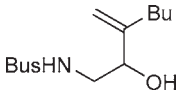
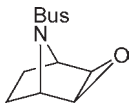
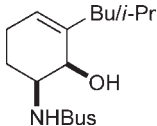
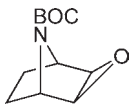
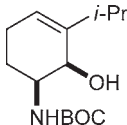
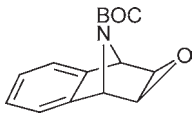
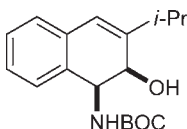
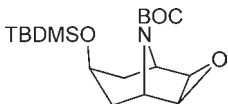
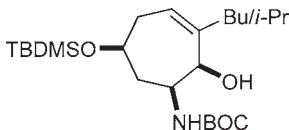
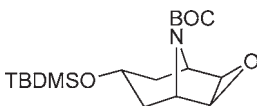
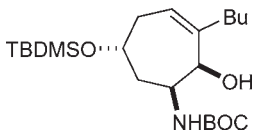
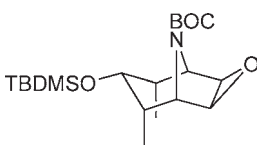
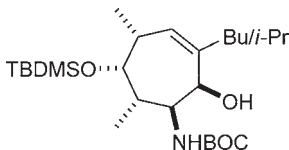
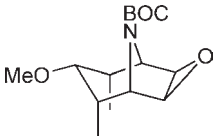
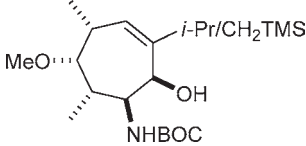
Epoxide	RLi	Ligand	Product	Yield (%)	ee (%)
	<i>n</i> -BuLi	Sparteine		16	43
		103		44	−42 ^a
	<i>i</i> -PrLi	Sparteine		44	77
	<i>i</i> -PrLi	Sparteine		42	56
	<i>i</i> -PrLi	Sparteine		49	59
	<i>i</i> -PrLi	Sparteine		58	73
	<i>i</i> -PrLi	Sparteine		58	66
	<i>i</i> -PrLi	Sparteine		54	84

^aBisoxazoline **103** gives the opposite sense of asymmetric induction to (−)-sparteine.

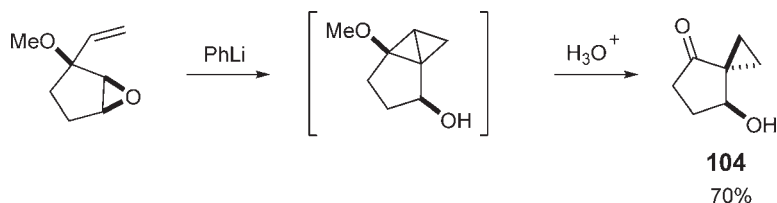
In addition to cyclopropane formation arising via carbenoid-trapping [2+1] cycloaddition reactions with adjacent unsaturation, Mioskowski and co-workers have also observed cyclopropanation via carbenoid insertion into an adjacent C–H bond (**Scheme 53**); optimization of this pathway has proved only moderately successful <1999JOC9279, 2003T9701>.

In a further development of the chemistry of lithiated epoxides, Hodgson and co-workers have recently shown that oxiranyl anions derived from cycloalkenes can act as nucleophiles. The possibility of metal–hydrogen exchange for the generation of nonstabilized (i.e., H- or alkyl-substituted) oxiranyl anions, previously thought to be unlikely <1996CRV3303>, was suggested by the observation of low-temperature deuterium trapping of the lithiated epoxide derived from cyclooctene oxide **96** during studies regarding the pathway of the transformation of **96** into bicyclic alcohol **97** (**Scheme 54**).

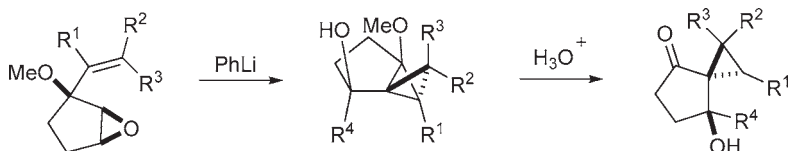
Table 13 Asymmetric alkylative ring opening of epoxides of azacycles

<i>Epoxide</i>	<i>RLi</i>	<i>Ligand</i>	<i>Product</i>	<i>Yield (%)</i>	<i>ee^a (%)</i>
	<i>n</i> -BuLi	Sparteine		69	24
		103		79	—45
	<i>n</i> -BuLi <i>i</i> -PrLi	Sparteine		52 42	40
	<i>i</i> -PrLi	Sparteine		78	87
	<i>i</i> -PrLi	Sparteine		44	71
	<i>n</i> -BuLi <i>n</i> -BuLi <i>i</i> -PrLi	Sparteine 103 Sparteine		83 60 59	41 —67 65
	<i>n</i> -BuLi	Sparteine		68	79
	<i>n</i> -BuLi <i>n</i> -BuLi <i>i</i> -PrLi <i>i</i> -PrLi	Sparteine 103 Sparteine 103		84 71 85 72	66 —67 71 —75
	<i>i</i> -PrLi TMSCH ₂ Li	Sparteine Sparteine		69 61	82 57

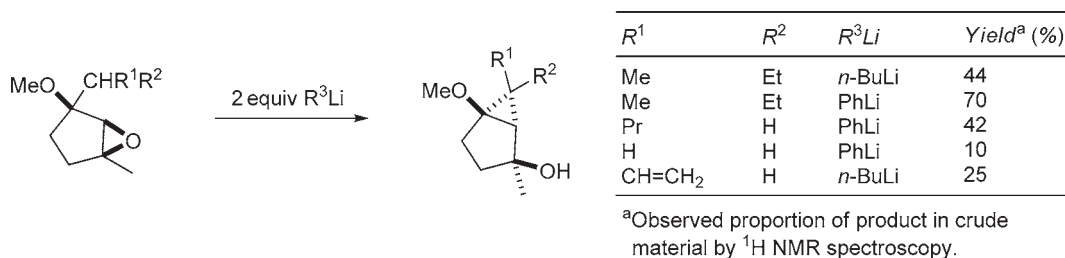
^aBisoxazoline **103** gives the opposite sense of asymmetric induction to (–)-sparteine.



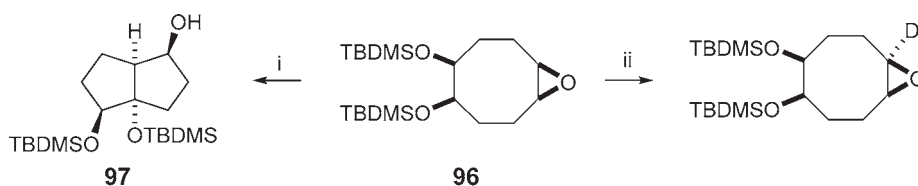
Scheme 51



Scheme 52



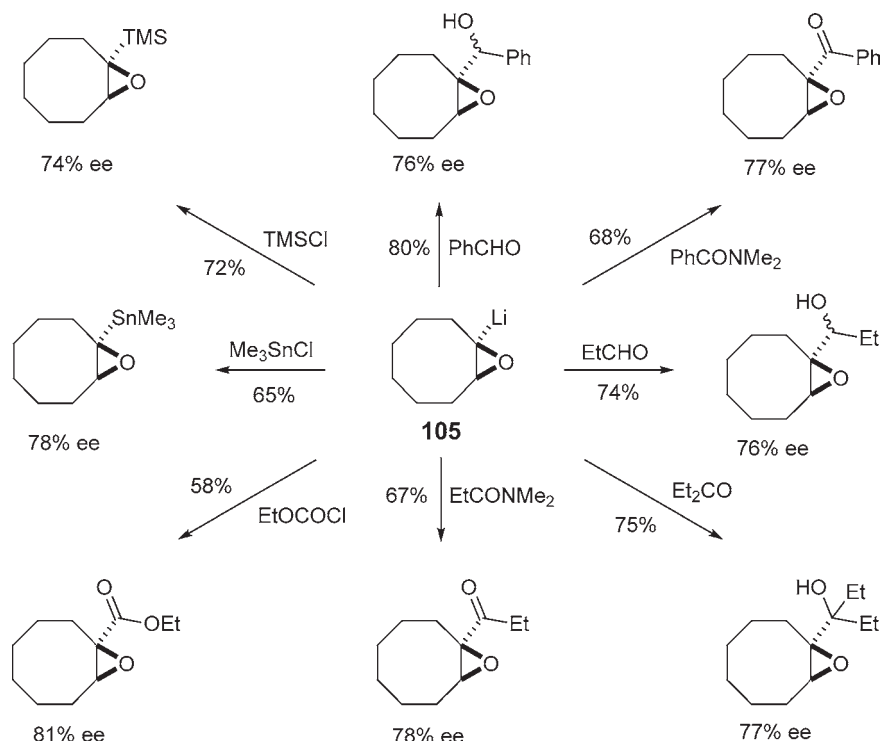
Scheme 53



i, *i*-PrLi, (–)-α-isosparteine, Et₂O, –90 to 25 °C, 20 h (72%, 89% ee)
 ii, *s*-BuLi, (–)-sparteine, Et₂O, –90 °C, 5 h, then D₂O (84%)

Scheme 54

Speculating that the role of the ligand was vital in this transformation, both in accelerating the deprotonation and in stabilizing the thus-formed oxiranyl anion, an examination of the chemistry of α-lithiated cyclooctene oxide **105** was conducted. The lithiated epoxide was generated with *s*-BuLi in the presence of (–)-sparteine and then quenched at low temperature with a range of electrophiles, the corresponding substituted epoxides being obtained in good yield and ee (Scheme 55) <2002AGE2376, 2003OBC4293>.



Scheme 55

While this methodology could be extended to more-substituted cyclooctene oxides (Scheme 56, Equation 12), examination of cycloheptene oxide (Scheme 56, Equation 13) revealed the need for considerably longer reaction times, leading to reduced yields due to competing carbenoid-insertion pathways (cycloheptanone formation and reductive alkylation) <2002AGE2376, 2003OBC4293>.

The reactivity of oxiranes with organolithium reagents, including deprotonation, ring cleavage, and the preparation and reactivity of lithiooxiranes, has been reviewed by Chemla and Vrancken <B-2004MI(2)1165>.

1.04.2.8.3 Other reactivity

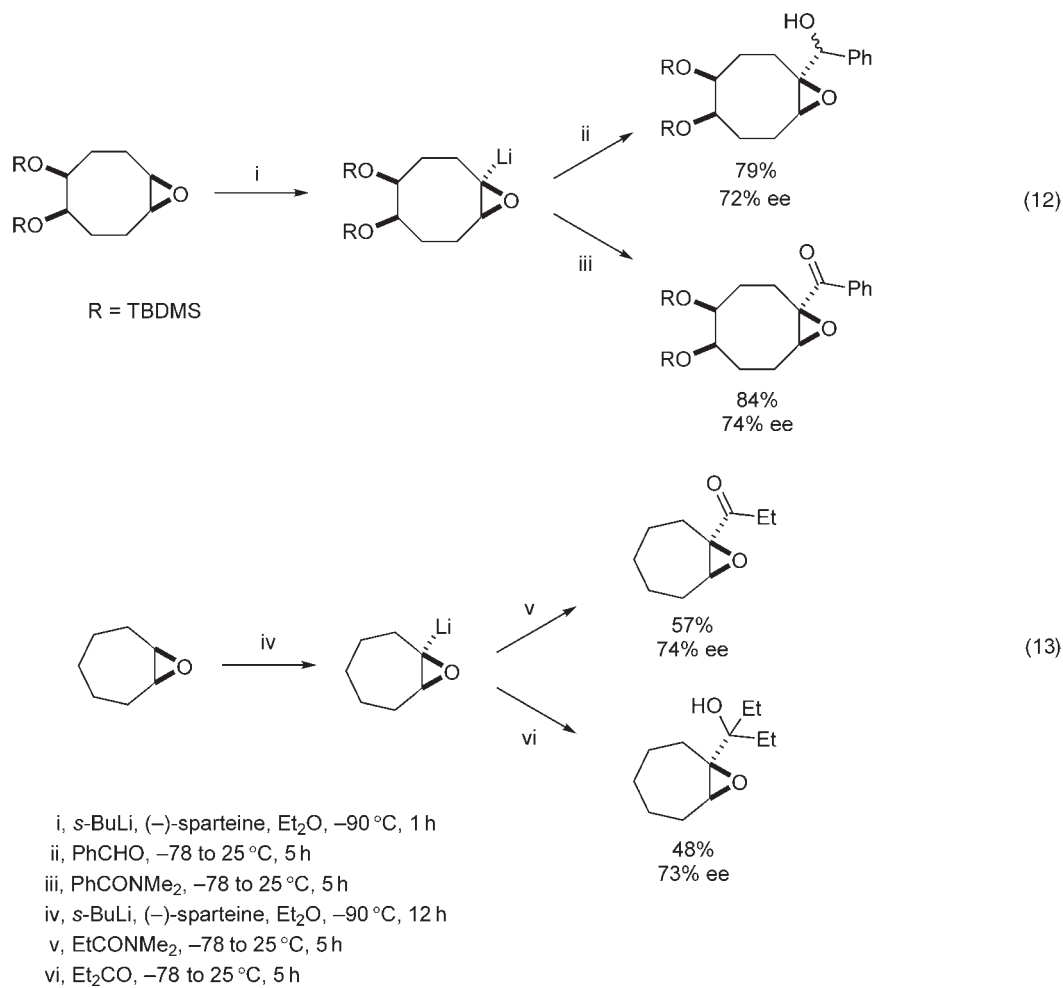
Mal and co-workers have reported that the deoxygenation of cyclic α,β -epoxy ketones (and acyclic α,β -epoxy esters) is accomplished in high yields under mild and neutral conditions by the use of $\text{Mo}(\text{CO})_6$ (Table 14) <2003TL2355>.

Antonioti and Duñach have reviewed the stoichiometric and catalytic oxidation of epoxides and their scope in organic synthesis, with particular focus on the Bi/O_2 -catalyzed oxidation developed in their group. Such reactions can lead to either the oxidative cleavage of the epoxy carbon–carbon bond (giving carbonyl compounds or carboxylic acids (Scheme 57, Equation 14) or alternatively the formation of α -functionalized ketones when the C–C bond of the epoxide remains uncleaved (Scheme 57, Equation 15) <2003S2753>.

The rearrangement reaction of α,β -epoxy acylates in bicyclic systems has been studied by Kita *et al.* (Table 15). Treatment of *cis*-derivatives with a Lewis acid afforded rearranged products via the regioselective β -cleavage of the oxirane ring, due to the electron-withdrawing nature of the acyloxy group; *trans*-derivatives (e.g., entry 2) suffered from enhanced neighboring group participation to yield only a small amount of rearranged products. The stereochemical integrity of chiral substrates was maintained (e.g., entry 5) <1997JOC4991>.

This rearrangement reaction was extended to *cis*-epoxy acylates derived from monocyclic alkenes (Table 16) <1997JOC4991>.

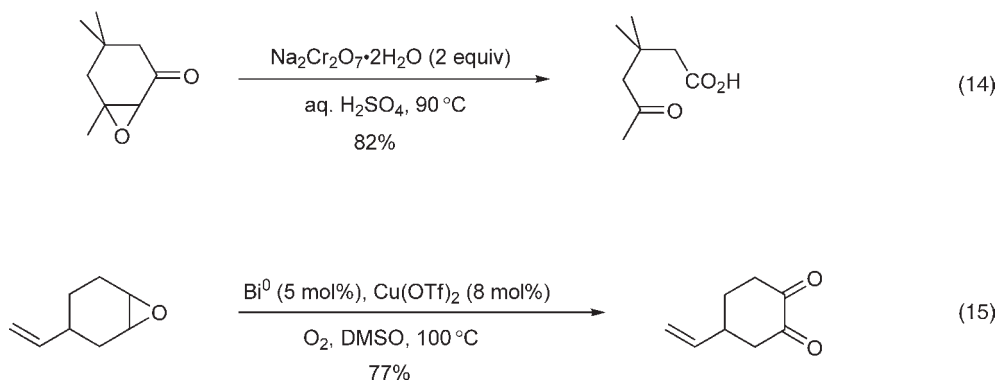
Grée and co-workers have found that bicyclic epoxy alcohols when treated with diethylamino sulfur trifluoride (DAST) can undergo a ring expansion via C–C bond cleavage of the oxirane ring to provide fluorinated cyclic vinyl ethers (Table 17) <2002OL451>.



Scheme 56

Table 14 Deoxygenation of cyclic α,β -epoxy ketones

Epoxide $\xrightarrow[\text{toluene, reflux}]{\text{Mo(CO)}_6 \text{ (1 equiv)}}$ Alkene			
Epoxide	Alkene	Time (h)	Yield (%)
		7.5	95
		4	90
		4	96



Scheme 57

Table 15 Rearrangement of bicyclic α,β -epoxy acylates

Entry	Substrate	Product	Yield (%)
1			80
2			18
3			58
4	$R = R^1 = \text{Me}$	$R = R^1 = \text{Me}$	95
5	$R = R^1 = \text{Me}$ (91% ee)	$R = R^1 = \text{Me}$ (91% ee)	95
6			99
7			55
8			41

Table 16 Rearrangement of *cis*-epoxy acylates of monocyclic alkenes

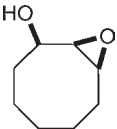
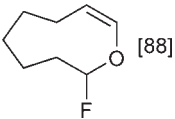
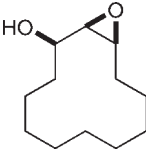
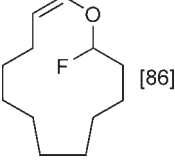
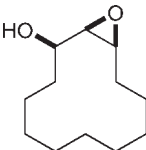
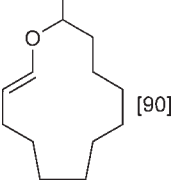
Substrate	Product [Yield (%)]
 X = Bz X = PNB	 [81] [79]
 X = Bz X = PNB	 [61] [71]
 X = Bz X = PNB	 [37] [34] and [32] [24]

Table 17 Reaction of bicyclic epoxy alcohols with DAST

Substrate	Product(s) [Yield (%)]
	 [73] (<i>syn:anti</i> = 2:1)
	 [70]
	 [44] and [19]
	 [20] and [46]

(Continued)

Table 17 (Continued)

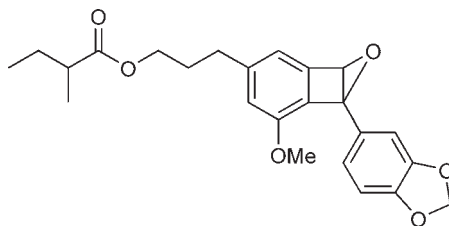
Substrate	Product(s) [Yield (%)]
	 [88]
	 [86]
	 [90]

The transformation of oxiranes into other oxygen-containing heterocyclic systems (e.g., cyclic ethers, dioxolanes, orthoesters, lactones, and cyclic carbonates), via a variety of heterolytic, homolytic, enzymatic, and single-electron transfer processes, has been reviewed [<2004RJO1227>](#).

1.04.2.9 Natural Products

There are numerous examples of natural products containing epoxides fused to other ring systems; the examples presented here are representative.

Akgul and Anil have reported the isolation of the novel benzofuran, 4-[3''-(1c-methylbutanoyloxy)propyl]-2-methoxy-(3',4'-methylenedioxyphenyl)-1a,5b-dihydrobenzo-[3,4]-cyclobutaoxirene (**Figure 18**) from the hexane extract of the seeds of *Styrax officinalis* [<2003P939>](#).

**Figure 18**

Cyclopentene oxide containing natural products include a highly diverse range of structures: for example, citrifolinoside A [<2006OL5337>](#), turrapubesin B (a maleimide-bearing limonoid isolated from the twigs and leaves of *Turraea pubescens* [<2006OL3845>](#)), (1*R*,2*S*)-1,2-epoxyneomajcin (isolated from the poisonous shrub *Illicium micranthum*) [<2006HCA983>](#), kongensin A (an *ent*-8,9-secokaurane diterpene isolated from the aerial parts of *Croton kongensis*) [<2006HCA537>](#), micrandilactone B (a highly oxygenated nortriterpenoid isolated from *Schisandra micrantha*) [<2005CC2936>](#), corianlactone (a cytotoxic sesquiterpene isolated from *Coriaria nepalensis* Wall) [<2004OL1593>](#), dysoxylumic acid A (a limonoid isolated

from the bark of *Dysoxylum hainanense* Merr., which exhibited significant antifeeding activity against *Pieris rapae* L.) <2002T7797>, hodgsonox (an insecticidal sesquiterpene isolated from the New Zealand liverwort *Lepidolaena hodgsoniae*) <2001JOC2818>, antirrhinoside (isolated from *Antirrhinum majus* (Scrophulariaceae)) <1998EJO1665>, pentenocin A (an interleukin-1 β -converting enzyme inhibitor) <1999JAN754>, and agardhilactone (isolated from the marine red alga *Agardhiella subulata*) <1996TL4635> (Figure 19).

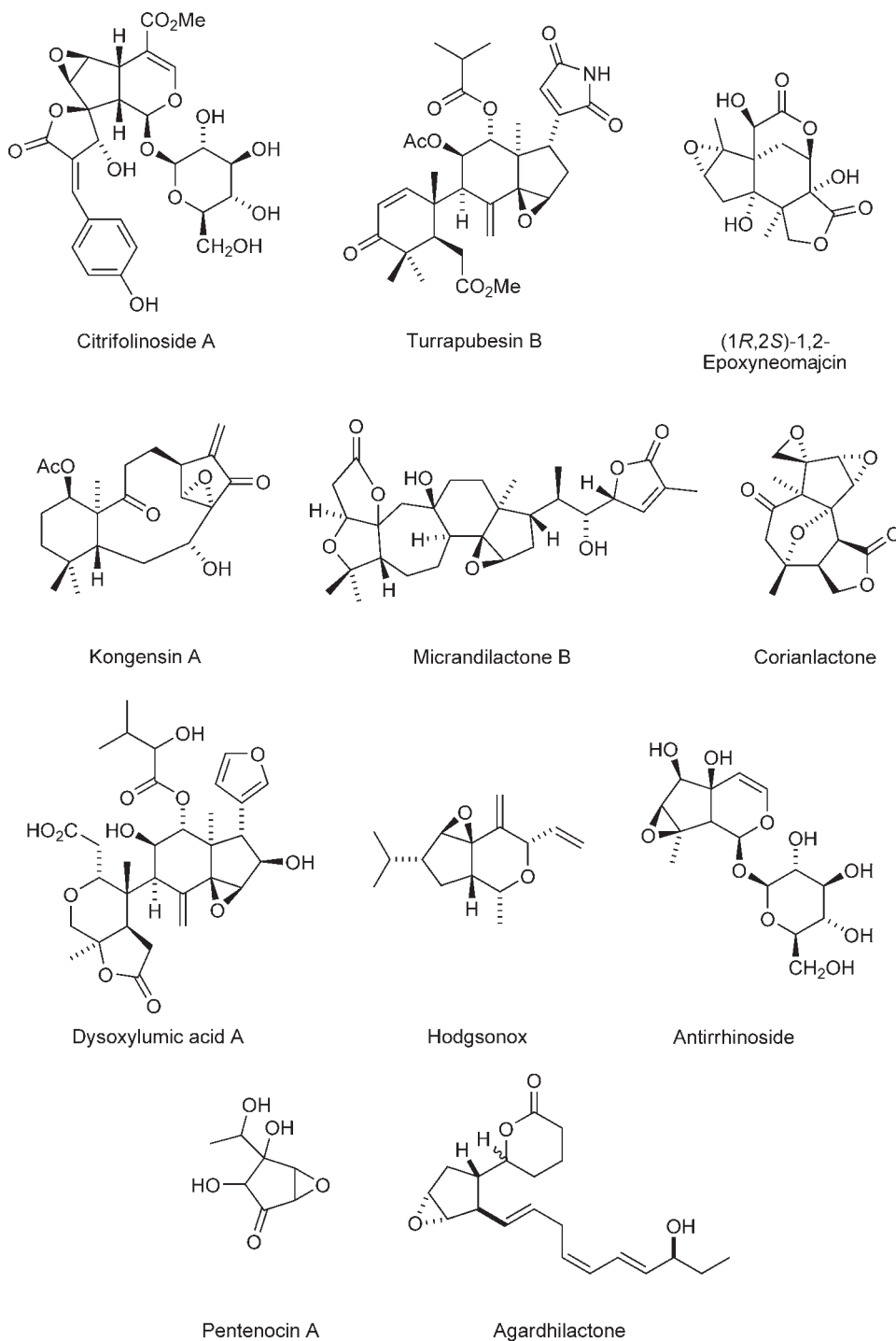


Figure 19

The frequent natural occurrence of cyclohexene epoxides, coupled with the wide range of interesting biological activities that they display, has made these compounds of considerable interest to biologists, pharmacologists, and synthetic chemists. A recent review detailed efforts in the total synthesis of such complex naturally occurring cyclohexene fused-oxiranes as anticapsin, eutypoxide B, paniculides A–C, crotepoxide, boesenoxide, β -senepoxide, pipoxide, tingtanoxide, and aranorosin (Figure 20). Naturally occurring cyclohexene fused-epoxides also include numerous quinone monoepoxides (e.g., eupenoxide, phyllostine, cycloepoxydon, and jesterone) and several 2-amino-epoxyquinones (e.g., LL-C10037 α and epoxyquinomycin B) (Figure 21) <2004CRV2857>. The synthesis of naturally occurring epoxyquinones has itself been reviewed <2005CRV4515>.

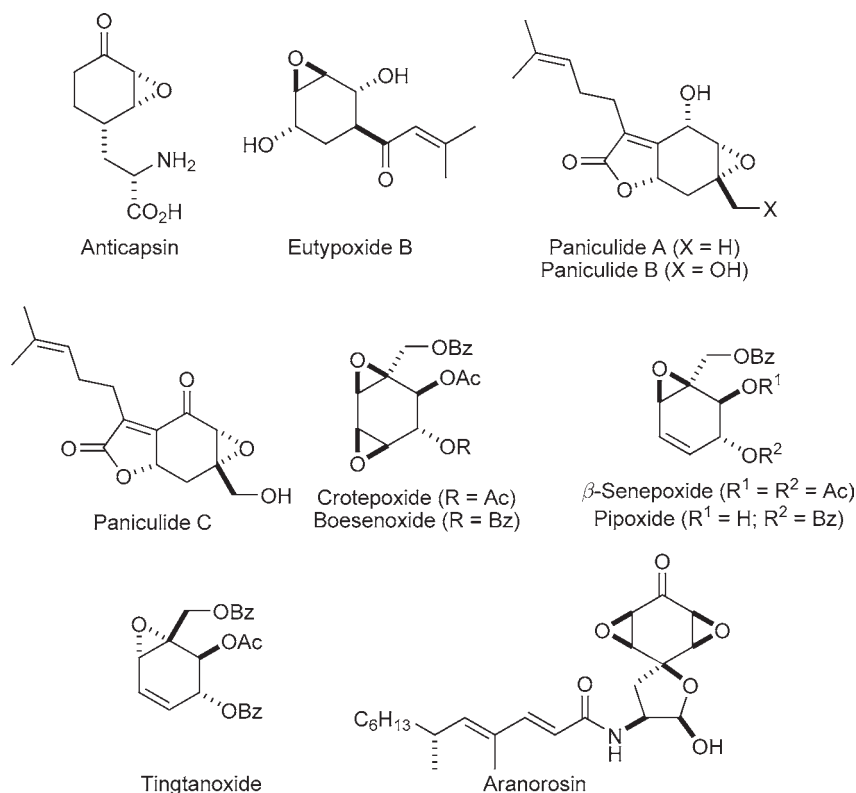


Figure 20

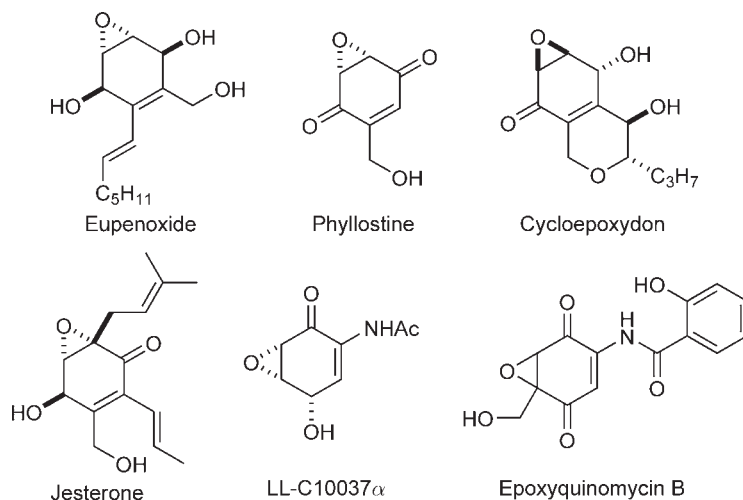


Figure 21

Other examples of natural products containing the cyclohexene oxide moiety include **106** (a bisabolene epoxide isolated from the flower buds of *Tussilago farfara*, which has shown inhibition of nitric oxide synthesis in lipopolysaccharide-activated macrophages) <1999JNP1437>, **107** (taxinine A 11,12-epoxide; isolated from the needles of the Japanese yew, *Taxus cuspidate*) <1999P1577>, steroids **108** and **109** (isolated from the marine sponge *Polymastia tenax* and showing antiproliferative activity) <2002JNP1161>, the palmarumycins (e.g., palmarumycin C₂) <2002JOC2735>, the withanolides (e.g., **110** and **111**, isolated from the whole plant of *Withania somnifera* and displaying inhibitory potential against butyrylcholinesterase) <2004CPB1358>, (+)-cyclophellitol (a potent β -glucosidase inhibitor) <2005JOC10139>, and the spiroisoxazoline (+)-calafianin (analogs of which have been shown to inhibit *Mycobacterium tuberculosis*) <2006OL927> (Figure 22).

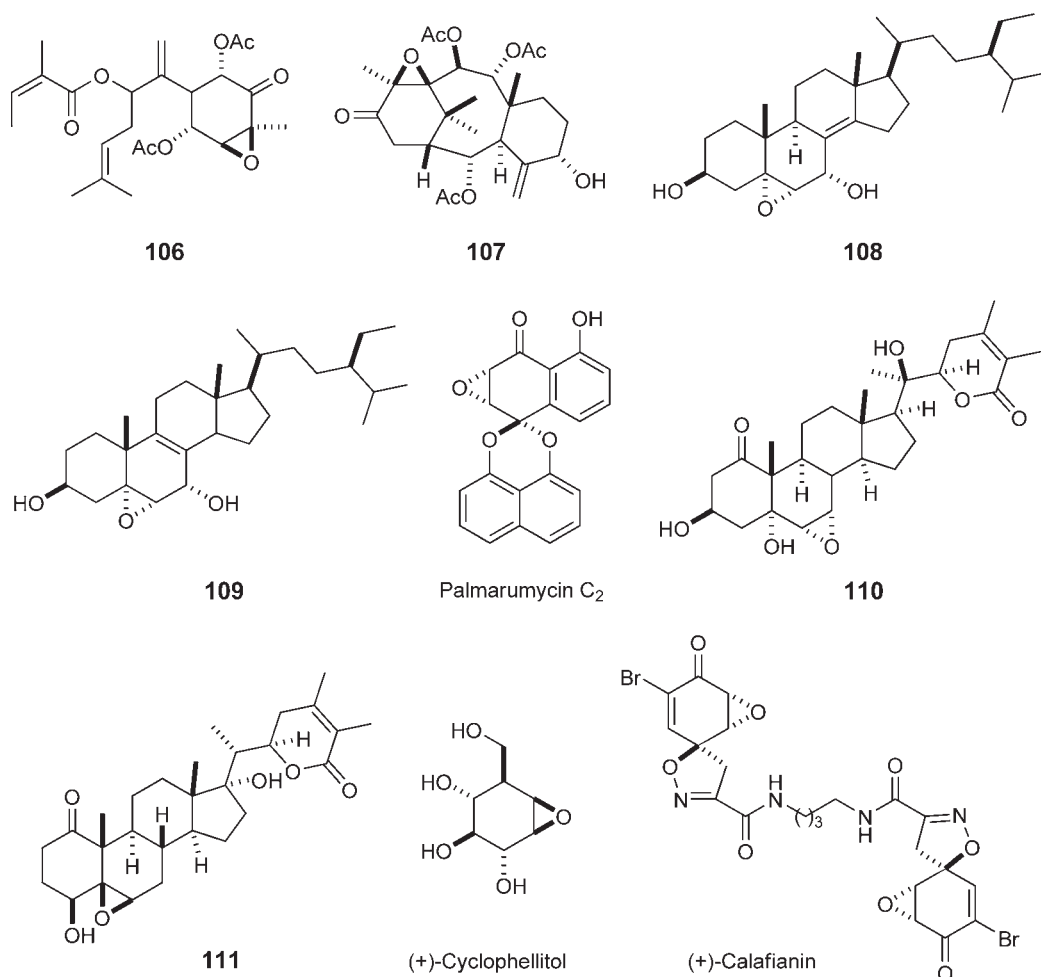


Figure 22

A few examples of naturally occurring cycloheptene oxides have been reported in the period under review, including diterpenoid **112** (isolated from the aerial parts of *Azorella compacta*) <1998P1091>, aspergilloxide (a sesterterpene epoxide-diol, isolated from the extract of a cultured marine-derived fungus (strain CNM-713)) <2002OL1583>, and sesquiterpene **113** (isolated from *Piper cubeba*) <2005JNP64> (Figure 23).

There are a few recent examples of naturally occurring compounds containing oxiranes fused to large rings, including sesquiterpenoids **114** and **115** (isolated from *Abies nordmanniana* ssp. *bornmuelleriana* (Pinaceae) leaves and unripe cones) <1999FIT103> and germacranolide **116** (isolated from the aerial parts of *Artemisia pallens*) <2000FIT590> (Figure 24).

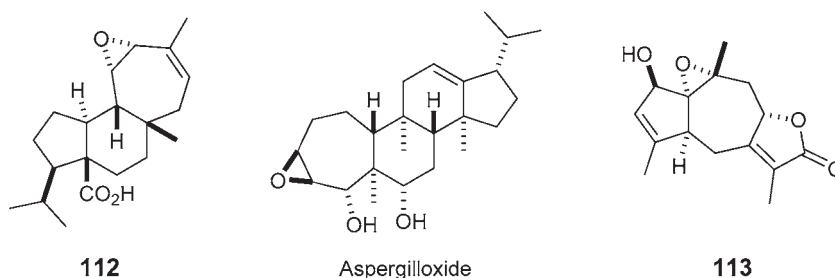


Figure 23

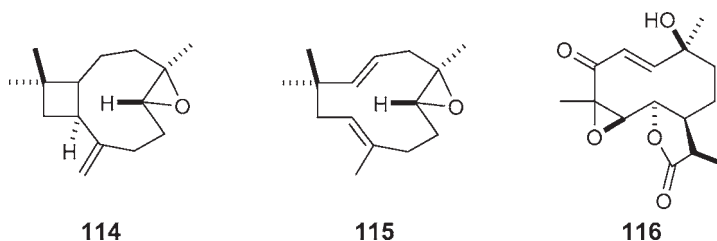


Figure 24

The chromophore portion of neocarzinostatin (**Figure 25**) contains an extremely strained nine-membered epoxide fused enediyne motif. Isolated in 1965 [\[1965JAN68\]](#), the structure of neocarzinostatin was elucidated in 1985 [\[1985TL331\]](#). Consisting of a 1:1 complex of protein and chromophore, the potent cytotoxicity of neocarzinostatin is derived entirely from the chromophore. The neocarzinostatin chromophore has been the subject of synthetic studies by several groups, including those of Myers [\[1996JA10006\]](#), Magnus [\[1996T6283\]](#), Pale [\[1997TL8193\]](#), and Caddick [\[2007OL45\]](#), and has been successfully synthesized by Myers *et al.* [\[1998JA5319\]](#) and Kobayashi *et al.* [\[2006JOC636\]](#).

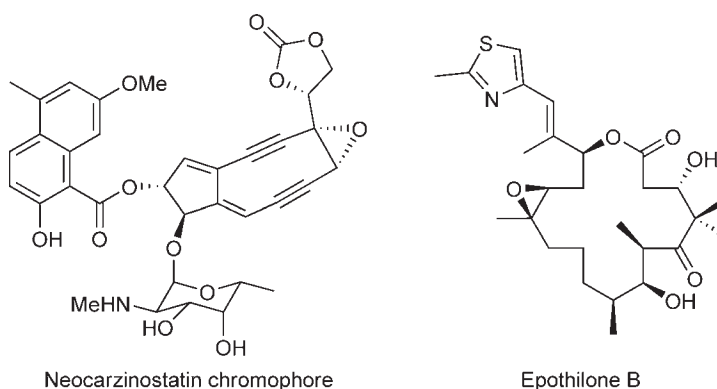


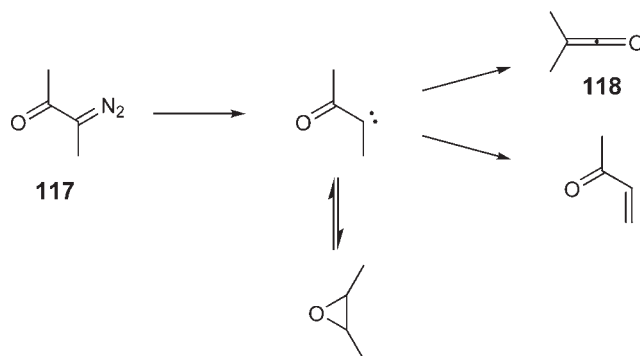
Figure 25

Epothilone B (**Figure 25**) is a 16-membered lactone to which an oxirane is fused; highly cytotoxic with activity against multidrug resistant cell lines, it has been the subject of total syntheses by Danishefsky [\[1997AGE757\]](#), Nicolaou [\[1997NAT268\]](#), and Avery [\[2001OL3607\]](#).

1.04.3 Fused-Ring Oxirenes

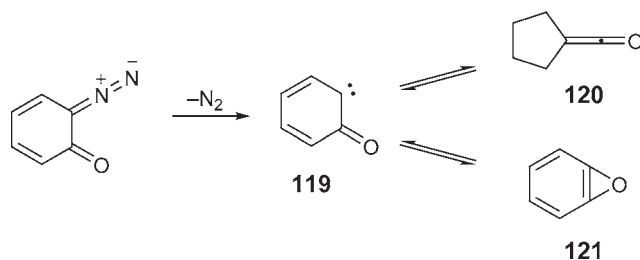
Background information on the chemistry of oxirenes is presented in Chapter 1.03, and this area has been reviewed by Zeller [\[2002SOS\(9\)19\]](#). The potential antiaromatic character of oxirenes, the strain of the unsaturated three-membered ring, and the possible involvement in important reactions (e.g., oxidation of alkynes, Wolff rearrangement)

have made these species significant objects of study with both theoretical and experimental interest. The extreme elusiveness of oxirenes is mainly based on the ease with which they rearrange to α -oxocarbenes followed by further isomerization to ketenes or α,β -unsaturated carbonyl compounds (Scheme 58). Oxirene participation in the photochemical Wolff rearrangement (Scheme 58; α -diazo ketone **117** to ketene **118**) has also recently been reviewed by Zeller *et al.* <2004RMC291>.



Scheme 58

Ab initio calculations of the geometry, and reactivity of 1,2-ketocarbene C_6H_4O (**119**; Scheme 59) as an intermediate in organic reactions, were performed using the second-order Møller–Plesset (MP2) perturbation theory in the 6-311G* basis set. Only the singlet state of the intermediate was considered. Fused-oxirene **121** and ketene **120** were localized on the potential energy surface. Attempts to locate a quinone-type structure characteristic of aliphatic ketocarbenes failed. The energy of structure **120** is $-70 \text{ kcal mol}^{-1}$ lower than that of structure **121**. Harmonic frequencies and intensities of normal vibrations in the IR spectra of **121** and **120** were calculated. The activation energy of the Wolff rearrangement **121** $\rightarrow$ **120** was estimated at $12.5 \text{ kcal mol}^{-1}$ <1999RCB1642>.

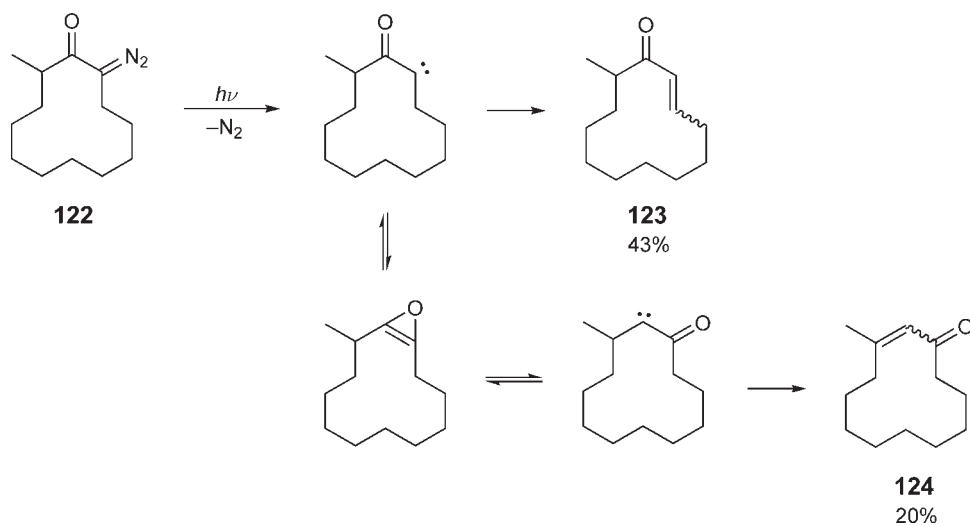


Scheme 59

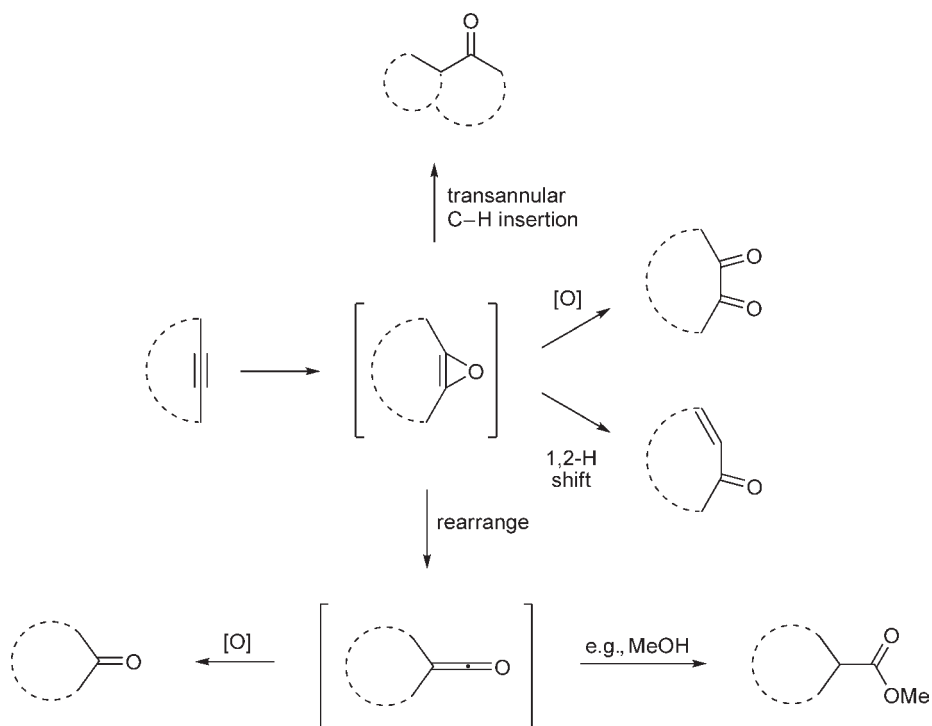
The photolysis of 1-diazo-3-methyl-2-oxocyclododecane **122** appears to involve oxirene participation as indicated by the formation of regioisomeric enones **123** and **124** (Scheme 60) <1978CB1549, 2004RMC291>.

Oxirenes arising out of cycloalkyne oxidations have been implemented in several transformations (Scheme 61), ultimately resulting in bicyclic ketones, α -dicarbonyls, α,β -unsaturated ketones, and ring-contracted products via Wolff rearrangement.

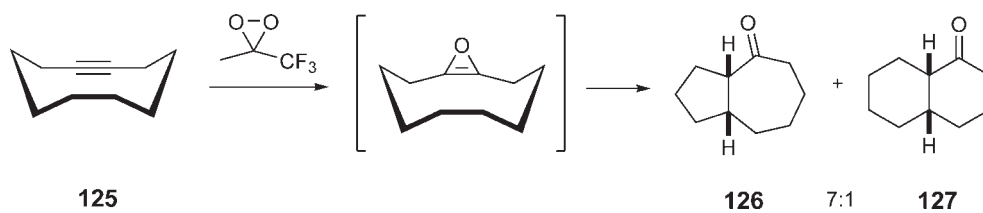
Curci *et al.* subjected cyclodecyne **125** to epoxidation with methyl(trifluoromethyl)dioxirane and observed a mixture (7:1) of *cis*-bicyclo[5.3.0]decan-2-one **126** and *cis*-bicyclo[4.4.0]decan-2-one **127**, these products presumably arising via respective 1,5- and 1,6-transannular insertion pathways into the intermediate oxirene (Scheme 62) <1992TL7929, 1996CHEC-II(1)145>. Prior to this report, Concannon and Ciabattini had observed the product profiles arising from the oxidation of several cycloalkynes with MCPBA (Table 18) <1973JA3284>.



Scheme 60

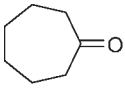
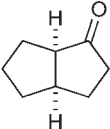
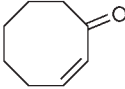
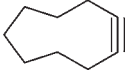
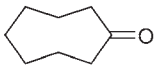
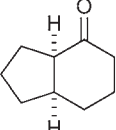
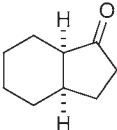
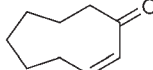
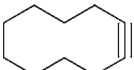
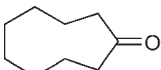
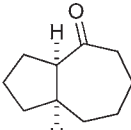
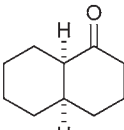
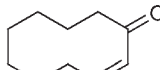
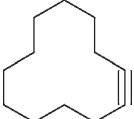
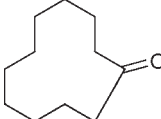
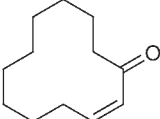
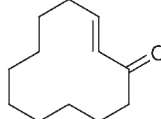


Scheme 61



Scheme 62

Table 18 Products arising from cycloalkyne oxidations

<i>Cycloalkyne</i>	<i>Oxidation products</i>			
	 22%	 29%	 49%	
	 1%	 68%	 16%	 15%
	 <1%	 67%	 12%	 21%
	 15%	 66%	 19%	

1.04.4 Conclusion

Advances in the chemistry of ring-fused oxiranes during the period under review (1995–2007) principally involve new or expanded methods of asymmetric synthesis including metallosalen-catalyzed, and chiral dioxirane- and iminium salt-mediated processes. Developments in the reactivity of such species include extensive work in the area of epoxide ring opening and advances in the chemistry of lithiated epoxides.

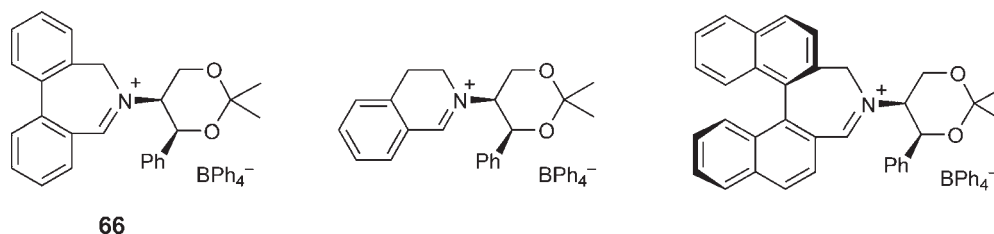
In contrast, there has been little work in the area of ring-fused oxirenes.

1.04.5 Further Developments

In the field of catalytic asymmetric epoxidation several groups have made advances in the development of processes utilizing aqueous hydrogen peroxide as the terminal oxidant. Shitama and Tsutomu have developed novel chiral Mn(salen) complexes bearing a non-coordinating and a coordinating substituent at the ethylenediamine moiety; 2,2-dimethylchromene is epoxidized in up to 98% ee <2007CEJ4849>. Shi and coworkers have demonstrated that their *N*-arylsubstituted oxazolidinone-containing ketone (dioxirane precursor) **52** (Figure 10) can mediate the epoxidation of 2,2,6-trimethylchromene in up to 91% ee <2007JOC6320>.

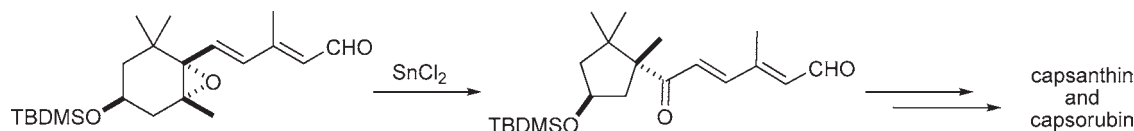
Bulman Page and coworkers have optimized conditions for the use of their 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane derived iminium salt catalyst **66**, and introduced two new analogues (Figure 26) for asymmetric epoxidation. 1-Phenyl cyclohexene and 1-phenyl 3,4-dihydronaphthalene are epoxidized in up to 89% ee <2007JOC4424, 2007T5386>.

Yamano and Ito have used the SnCl₂ mediated regio- and stereoselective rearrangement of a cyclohexene oxide to produce a precursor to the natural products capsanthin and capsorubin (Scheme 63) <2007OBC3207>.



66

Figure 26



Scheme 63

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Biographical Sketch



David Hodgson obtained his first degree in chemistry at Bath University. After a Ph.D. at Southampton University in the field of natural product synthesis (with P. J. Parsons) and a research position at Schering, he was appointed in 1990 to a lectureship at Reading University. In 1995, he moved to the Chemistry Department at Oxford University, where he is now a professor of chemistry. He received a Glaxo Wellcome Award for Innovative Organic Chemistry in 1999, a Pfizer Academic Award and an AstraZeneca Research Award in Organic Chemistry in 2000, the Liebig Lectureship of the German Chemical Society for 2001, and the 2006 Royal Society of Chemistry Bader Award. His research interests are broadly in the development and application of synthetic methods, particularly asymmetric generation and transformations of carbenoids.



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1.05

Thiiranes and Thiirenes: Monocyclic

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1.05.1 Introduction

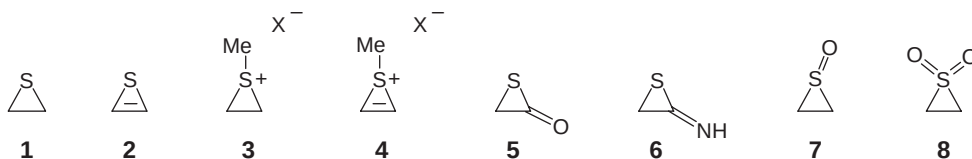
A major previous review on thiiranes, thiirenes, and monocyclic derivatives, such as ethylene sulfoxides and ethylene sulfones, covering material through early 1995, was published in 1996 <1996CHEC-II(1)174>. Reviews of thiiranes and thiirenes also appeared regularly in subsequent and previous years, often mixed in with other heterocycles. They are listed below in order of the year of appearance from 2005 to 1995 in the format of keywords <review reference>: synthesis thiiranes <2005NKNP35>; microwave synthesis <2005AHC1>; heterocycles via benzyne <2005YKG791>; literature heterocycles <2004AHC2>; 1,2,3-thiadiazoles <2004HOU253>; synthesis thiiranes <2004CRV251>; fluorinated thiiranes <2004AHC129>; toxicity of haloalkanes <2004MI583>; toxicity <2004CRT942>; matrix photochemistry <B-2004MI15-1>; sulfur heterocycles, thiocarbonyl compounds <2003SCM38>; sulfur, important element <2003SR191>; sulfanyl chlorides <2003SR255>; cysteine protease inhibitors <2003MRMC585>; thiiranium ions <2003MI1>, <2002SCM24>; polymerization chloromethyl thiirane <2002CHJC299>; mechanism sulfanyl migration <2002AGE2462>; three-membered rings <2002HOU43>; thiocarbonyl ylides <B-2002MI271>, <B-2002MI265>, <2002HC315>; 2002 literature heterocycles <2001AHC201>; sulfur ylides <2001RCR655>; optical resins <2001YH342>; catalytic macrocyclizations from thiiranes <2000ACR171>; synthesis from thiirane <2000ADCA39>; thiiranes to cyclic disulfides <2000POL521>; *C*-glycosylic compounds <2000COR589>; thiocarbonyl ylides <2000PJC1503>; heterocyclic chemistry <2000ARB157>; recyclization <1999MI138>; Ramberg-Bäcklund episulfone <1999CC217>; three-membered heterocycles <1999SR49>; sulfur electrophiles <1999PS235>; thiiranium ions <1997SL11>; thiiranes <1997RCC1>; episulfides <1997SR1>; small-ring heterocycles <1997SR173>; thiiranium/thiirenium ions <1997G177>; enzyme inhibitors <1997TCC187>; ring-opening polymerization <1997PE223>; thiiranes; episulfones <1997PS197>; polymer resins <1997MI3>; fused-ring thiiranes/thiirenes <1996CHEC-II(1A)241>; polymerization thiiranes <1996VS(AB)392>; matrix isolation <1995ASOC1>; thiiranium ions <B-1995MI89>; research in sulfur chemistry <1995SR299>; thermodynamic properties <1995MI1351>.

This chapter review attempts to cover much material published from 1996 through early 2006, including some papers from 1995. The authors realize that individual contributions made during that period cannot possibly be covered in the detail that those contributions deserve, and they apologize to authors whose work may appear to have been slighted or missed altogether. In order to stay within defined limits of length, it was necessary to limit coverage, and the references cited are generally meant to include references to background material discussed or cited by a particular author or group. The present authors used the Beilstein (DP), Gmellin (DP), Scopus (DP), and Scifinder (JW) databases to locate papers published in the past decade that concern thiiranes, thiirenes, and their monocyclic derivatives. It is clear that such a search depends critically on keywords and that some relevant material could be missed.

A scientific review is basically a survey of the literature meant to save scientists much time by citing the work that has been reported, in enough detail to whet some readers' appetites to look at the original papers. We hope to have achieved that goal, at least in some cases.

1.05.1.1 Nomenclature

Neutral, saturated three-membered rings with one sulfur atom in the ring are called thiiranes (**1**), while neutral, unsaturated, three-membered rings with one sulfur atom in the ring are called thiirenes (**2**). Alternative nomenclatures for **1** are 'name of alkene + sulfide' or 'name of alkene + episulfide' for **1** and 'name of alkyne + sulfide' or 'name of alkyne + episulfide' for **2**. 2-Methyl thiirane is sometimes called epithiopropene or propene sulfide or propylene sulfide. Positively charged analogs are thiiranium ions **3** or thiirenium ions **4**. There can be only one α -thiolactone isomer (thiiranone, **5**) but both (*E*)- and (*Z*)-thiiranimines **6** are possible. Derivatives of thiiranes and thiirenes are named according to the functional group present by prefixing the name(s) of the functional group(s) with appropriate numbers. Numbering begins with sulfur as number 1. If the oxidation state of the sulfur atom in a neutral thiirane is higher than two, the compounds are called thiirane-1-oxide (thiirane *S*-oxide; ethylene sulfoxide; ethylene episulfoxide) **7** or thiirane-1,1-dioxide (thiirane *S,S*-dioxide; ethylene sulfone; ethylene episulfone) **8**. Some of the examples are illustrated.



1.05.2 Theoretical Methods

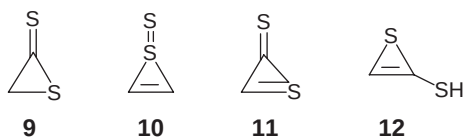
1.05.2.1 Introduction

In the last 10 years, large advances in computer technology, including those in hardware and software, have made it possible for scientists to carry out computational studies on quite large systems with a reasonable investment of money and time. Chemists have carried out computational studies in order to clarify or support experimental results with respect to structure, energetics, and mechanism, for example. They have also used computation in a predictive sense to discover the properties of molecules that are unknown or so short-lived as to make experimental study very difficult. The section that follows includes both purely computational results and computational results used to support conclusions based on experimental work. The selection as to which computational papers should appear in this section and which should appear in another section is somewhat arbitrary.

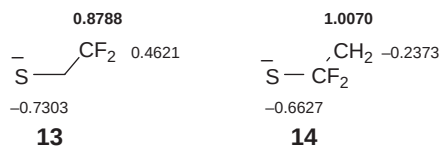
1.05.2.2 Structure and Mechanism

Gronert and Lee investigated substitution and elimination reactions of methylthiirane with HO^- and HS^- by means of *ab initio* calculations <1995JOC4488>. With HS^- , the barrier to elimination was high, and only substitutions at carbon and sulfur were feasible. Substitution at C-2 with HO^- was found to occur with a $2.8 \text{ kcal mol}^{-1}$ lower activation energy than attack at C-1, and the transition states were early on the reaction coordinate, with only about 15% cleavage of the CS bond. In spite of the early transition state, much of the strain relief of the three-membered ring was realized. Attack by HO^- at sulfur led to a stable hypervalent intermediate.

Vijay and Sastry examined the basis set dependence of the calculated energies of $\text{C}_2\text{S}_2\text{H}_2$ isomers, including thiirane-2-thione **9** and thiirenes **10–12** <2005JST71>. Quantum-mechanical calculations were carried out at the Hartree–Fock (HF), Møller–Plesset second-order perturbation (MP2), CCSD(T), and B3LYP levels with basis sets such as 6-31G*, 6-311G**, and cc-pVTZ. Single-point calculations at the B3LYP, MP2, and CCSD(T) levels, with basis sets ranging from double to quintuple ζ quality, were carried out to illustrate the effects of electron correlation and basis set on the results. It was found that the basis set requirements are much higher than affordable for molecules of medium size because of slow convergence.



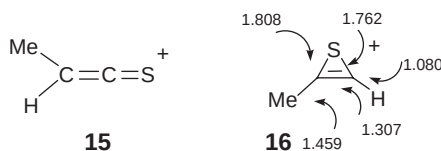
Sevin *et al.* carried out a theoretical study of the formation of stable anions from electron capture by thiirane, 2,2-difluorothiirane, and 2,2,3,3-tetrafluorothiirane <1996JMT69>. Emphasis was placed on the ability of those substrates to accommodate an extra electron vertically in their lowest-energy antibonding molecular orbitals (MOs). For thiirane itself, the vertical electron affinity (EA) calculated was -3.39 eV , and for the difluoro and tetrafluoro compounds the absolute value was computed to be lower, -2.07 and -1.89 eV , respectively. Fluorine substitution lowered the absolute value of the EA. A good correlation was found between those values (and corresponding values for oxiranes and aziridines) and the energy of the singly occupied molecular orbital (SOMO) (a.u.). The anions were found to open to radical anions **13** and **14** with the spin density (bold) and charge density at the terminal atoms as shown for the different senses of opening of the unsymmetrical thiirane.



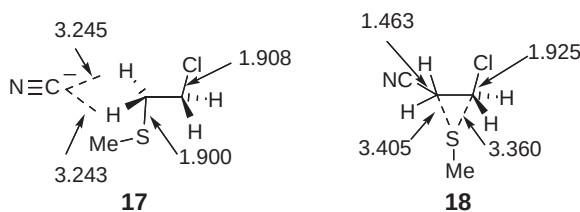
Modena and co-workers examined the relevance of the symmetry of the lowest unoccupied molecular orbital (LUMO) of the electrophile in substitutions at vinyl carbon of thiirene <1995JA2297>. The computational levels included 3-21G**//3-21G*, 6-31G**//3-21G*, and 6-311G**//3-21G*. In attack at the vinyl carbon of a thiirenium ion, for example, the thiirenium ion is the electrophile and the attacking nucleophile is a neutral species with a lone pair, or an anion. It was found that in cases where the first vacant σ - and π -levels differ in energy by more than 0.01 hartree, there is a good correspondence between the symmetry of the lowest unoccupied orbital and the stereochemical

outcome of substitution. If the lowest orbital is of π -symmetry, the nucleophile attacks in a plane orthogonal to the molecule (Ad_N -E mechanism), leading to retention of configuration or stereochemical convergence. If it has σ -symmetry, the nucleophile approaches in the molecular plane ($\text{S}_\text{N}2$ -Vin mechanism) with the consequence of inversion. There are few confirmed $\text{S}_\text{N}2$ -Vin mechanisms, one of the more recent ones being the internal nucleophilic displacement that converts di-*t*-butyl thiirenium ions to thietium ions <1993JA4527, 2003ARK38>. For thiirenium ion itself, the LUMO at the carbons has σ -symmetry with energy -0.1046 hartree.

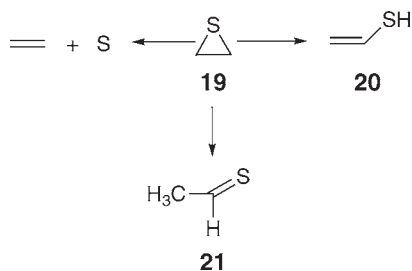
Gómez and Flores studied the entire SC_3H_4^+ system by means of *ab initio* and density functional theory (DFT) <2003PCA914>. Those species are of astrophysical significance as the products of reaction of S^+ with propyne (CH_3CCH). The species at the absolute energy minimum was the methylthioketene cation **15** but methylthiirene cation **16** and several others were very close together. The calculated bond lengths (Å) of **16** are shown.



AM1 and *ab initio* calculations, with the 3-21G(+) basis set, were used to study the $\text{S}_\text{N}2$ mechanism of nucleophilic substitution on 2-methylthio-1-chloroethane by cyanide ion <1999RJO1135>. The reaction was described as involving a pre-reaction ion dipole complex **17** leading over a transition state to a thiiranium-like intermediate **18**, containing both the entering and the leaving groups. Calculated bond lengths (Å) are indicated in the drawings. The intermediate then passes over a second transition state to a postreaction ion dipole complex (not shown). Overall, the reaction was described as a double inversion with the transfer of the methylthio group from the β - to the α -carbon with cyanide at the former β -position.



Simulated annealing calculations were performed to acquire the mechanisms of thermolysis of thiirane and thiiranium cation <2002JMT71>. The AMPAC 6.55 package along with AIM1 and SAM1 methods were used to estimate structures, which were then used as starting points for further *ab initio* calculations. Critical points were confirmed by calculation of the vibrational frequencies. The primary reactions thiirane **19** $\rightarrow$ S + ethene, thiirane $\rightarrow$ vinyl thiol **20**, and thiirane $\rightarrow$ ethanethial (thioacetaldehyde) **21** were examined for thermolysis of thiirane Scheme 1. Many secondary reactions were also examined. The simulated annealing method was predicted to be very useful in the future for the study of competing chemical reactions.



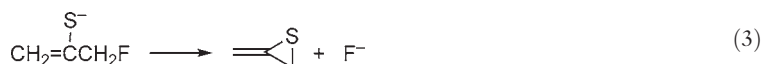
Scheme 1

Anders and co-workers proposed α -thiolactones (thiiranones) as intermediates in the cysteine conjugate, β -lyase-catalyzed bioactivation of bromine-containing cysteine S-conjugates <1995JA9590>. The proposed intermediates

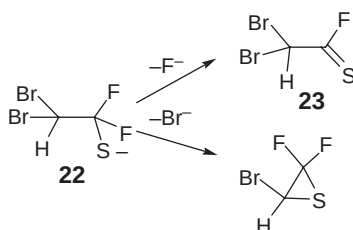
could arise from an intramolecular displacement of bromide by a thiolate anion (Equation 1). Evidence for the proposal was presented by the authors.



Intramolecular nucleophilic substitution to form thiiranes was studied by means of *ab initio* MO computations based on the 6-31G* basis set <1997JCC1773>. Systems studied included the anions $^-\text{SCH}_2\text{CH}_2\text{F}$ and $^-\text{CH}_2\text{C}(\text{=S})\text{CH}_2\text{F}$ which would afford thiirane and 2-methylenethiirane, respectively (Equations 2 and 3). It was important to include electron correlation which was done with the frozen-core approximation at the second-order Møller–Plesset perturbation level. Optimized structures were confirmed by means of vibrational frequency calculations. The main conclusions were that electron correlation is important in lowering ΔG and ΔG^0 , that the displacements are enthalpy controlled, and that reaction energies are strongly dependent on reactant stabilities.



Two plausible routes for bioactivation of *S*-(1,1-difluoro-2,2-dihaloethyl)-L-cysteine conjugates were examined by means of *ab initio* theory <1997CRT103>. It was found that 2,2-dibromo compounds, modeled with **22**, which are mutagenic in the Ames test, preferred a thiirane pathway energetically rather than a thionoacyl fluoride **23** pathway, in conflict with a recently proposed mechanism <1995JA9590> but in agreement with a subsequent study <1996CRT227>.

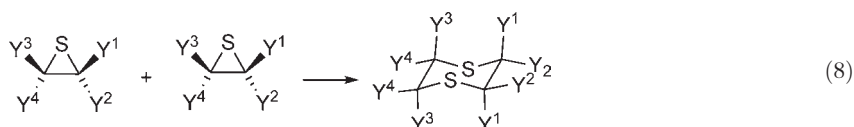
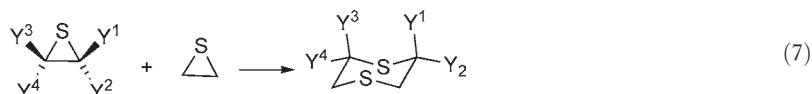
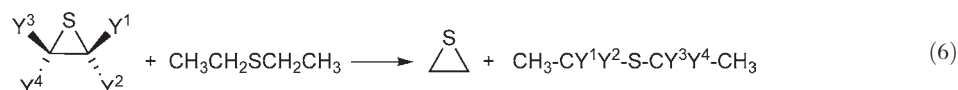
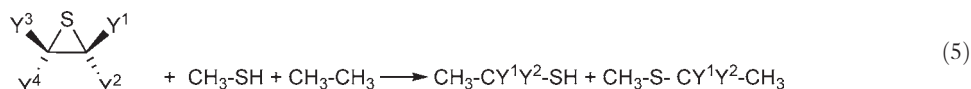
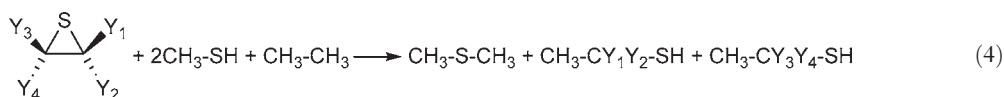


Transfer of sulfur from thiirane to ER_3 ($\text{E} = \text{As}, \text{P}$; $\text{R} = \text{Me}, \text{Ph}$) was studied with G2 and G3 *ab initio* calculations and isodesmic exchange reactions <2005IC8426>. The authors present a detailed analysis of various computational methods. Best estimates for the enthalpies of transfer of a sulfur atom from 2-methylthiirane to phosphines and arsines are: Me_3P (−26.6), Me_3As (−8.2), Ph_3P (−21.5), Ph_3As (−7.1) kcal mol^{-1} , respectively. Best estimates for the $\text{P}=\text{S}$ and $\text{As}=\text{S}$ bond strengths are: for $\text{H}_3\text{P}=\text{S}$ (63.7), $\text{H}_3\text{As}=\text{S}$ (48.3), $\text{Me}_3\text{P}=\text{S}$ (87.5), $\text{Me}_3\text{As}=\text{S}$ (69.5), $\text{Ph}_3\text{P}=\text{S}$ (82.4), $\text{Ph}_3\text{As}=\text{S}$ (68.4) kcal mol^{-1} . For triphenylarsine, the agreement was fine, but for triphenylphosphine the calculated value was ca. 6 kcal too low. Estimated $\text{X}=\text{S}$ bond orders are: for $\text{Me}_3\text{P}=\text{S}$ (1.55), $\text{Me}_3\text{As}=\text{S}$ (1.42), $\text{Ph}_3\text{P}=\text{S}$ (1.52), $\text{Ph}_3\text{As}=\text{S}$ (1.38).

Chiu *et al.* used *ab initio* Gaussian-2 (G2++) to study energies, structures, and reactions of thiirane anions and other isomers of $\text{C}_2\text{H}_3\text{S}^-$ <2004JMT221>. The heat of formation of the anion of thiirane was $\Delta H_f(298) = 198.9 \text{ kJ mol}^{-1}$, in good agreement with the experimental value of $192.2 \text{ kJ mol}^{-1}$ and the calculated proton affinity was $1642.2 \text{ kJ mol}^{-1}$. The barrier for ring opening of thiirane anion to $\text{CH}_2=\text{CHS}^-$ was computed to be $182.2 \text{ kJ mol}^{-1}$.

The electronic structures and the strain energies of oxirane and thiirane, as well as their partially and fully fluorinated derivatives, were studied with QTAIM theory <2005CPL440>. The effect of progressive fluorination of thiirane was to decrease the $\text{C}(2)\text{--}\text{S}(1)$ bond length from 1.824 in thiirane to 1.803 in 2-fluorothiirane to 1.789 Å in 2,2-difluorothiirane. At the same time, $\text{C}(3)\text{--}\text{S}(1)$ bond lengths increased from 1.824 to 1.837 to 1.861 Å. *trans*-2,3-Difluorothiirane ($\text{C}\text{--}\text{S} = 1.811 \text{ Å}$) was calculated to be more stable than the *cis*-isomer by 8.6 kJ mol^{-1} . Reaction energies for some homodesmic processes, usually used to estimate strain energies (Equations 4–8), were computed at the B3LYP/6-311++G(3d2f,3p2d) level. Those energies for thiirane depended significantly on the equation used, ranging from 57.7 (Equation 4) to 61.1 (Equation 5) to $155.6 \text{ kcal mol}^{-1}$ (Equation 6) but they showed a good linear relationship to one another and to the larger diagonal reaction energies (Equation 7). Ultradagonal reaction energies

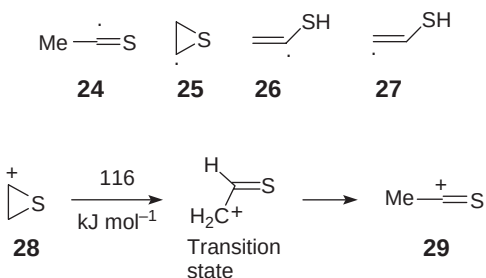
(Equation 8), however, appeared to be particularly erratic. Variations found were attributed to the combined effects of bond path distortion and σ -delocalization. Reaction energies computed as above were considered to be unsuitable measures of strain.



An *ab initio* study at the MP2/6-31+G**//MP2/6-31+G* level was used to study the potential energy surface of the ring closure of $\text{HSCH}_2\text{CH}_2\text{S}^-$ to thiirane and HS^- [\[1995JOC6731\]](#). The barrier for the reaction was computed to be $19.2 \text{ kcal mol}^{-1}$, a value smaller than that for formation of analogous four- and five-membered rings and smaller than the barrier ($25.0 \text{ kcal mol}^{-1}$) for the $\text{S}_{\text{N}}2$ reaction $\text{CH}_3\text{S}^- + \text{CH}_3\text{CH}_2\text{SH} \rightarrow \text{CH}_3\text{CH}_2\text{SCH}_3 + \text{HS}^-$. That is, the more endothermic process leading to the more strained product has the lower barrier. The result was rationalized in terms of starting material destabilization (a proximity effect) in the case of formation of the three-membered ring and minimization of angle strain in forming thiirane because the transition state for ring closure does not involve much of the strain of the product.

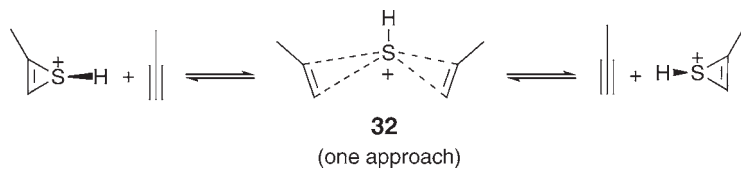
Ab initio MO calculations based on Gaussian-3 were used to study $\text{C}_3\text{H}_6\text{S}$ isomers and dissociation channels of diradical $\cdot\text{CH}_2\text{CH}_2\text{SCH}_2\cdot$ and radical cation $\cdot\text{CH}_2\text{CH}_2\text{SCH}_2^+$ [\[2003JMT237\]](#). Thioacetone, with $\Delta H_{\text{R}(298)} = 26.7 \text{ kJ mol}^{-1}$, was the most stable isomer, and propene sulfide (2-methylthiirane) was found to be less stable by 17.2 kJ mol^{-1} . Some bond lengths ($\text{\AA}$) calculated for 2-methylthiirane are listed: S–C(2) (1.822), C(2)–C(3) (1.479), C(3)–S (1.818), C(2)–Me (1.505).

Chiu *et al.* conducted a modified Gaussian-2 *ab initio* study of structures, energies, and reactions of thiiranyl radicals ($\text{C}_2\text{H}_3\text{S}^\cdot$) and cations ($\text{C}_2\text{H}_3\text{S}^+$) and other isomers of $\text{C}_2\text{H}_3\text{S}$ [\[2000PCA3028\]](#). Isomers of the $\text{C}_2\text{H}_3\text{S}$ radical are the thioacetyl radical **24**, the thiiranyl radical **25**, the 1-thiovinyl radical **26**, and the 2-thiovinyl radical **27**, with H°_{f} values of 251, 301, 314, and $342\text{--}347 \text{ kJ mol}^{-1}$, respectively. On the $[\text{C}_2\text{H}_3\text{S}]^+$ surface, they found that the thiiranyl cation **28** rearranges to the thioacetyl cation **29** (Scheme 2). Cation **28** rearranges, through a transition structure resembling the thiomethylformyl cation, to the thioacetyl cation **29** over a barrier of 116 kJ mol^{-1} . Barriers for other reactions were computed.



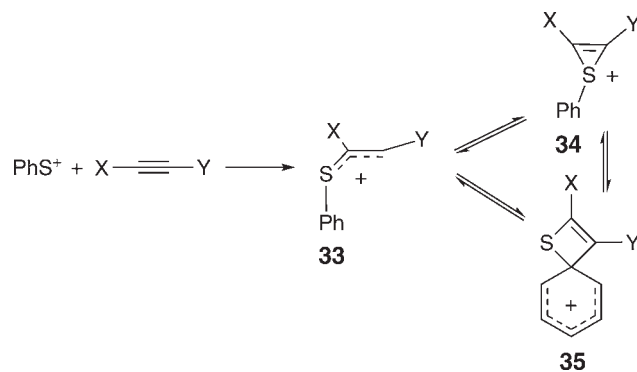
Scheme 2

Radom and co-workers used *ab initio* computations to determine that π -ligand exchange reactions of thiiranium and thiirenium ions, in which an alkene or alkyne abstracts the SH group, are feasible <1999CEJ509>. Analogous exchanges have been observed with phosphiranium ions. An identity exchange reaction between ethylene and thiiranium ion **30** proceeds through a complex with C_S symmetry with a binding energy of 25.6 kJ mol^{-1} relative to the energies of the reactants (Equation 9). The complex proceeds through a transition structure with C_{2V} symmetry and energy 46.6 kJ mol^{-1} . Thiirenium ion **31** exchanges with ethylene in an exothermic process (53.0 kJ mol^{-1}) that involves a C_S complex that lies 28.7 kJ mol^{-1} above the reactants (Equation 10). In the reverse reaction, alkyne and thiiranium ion **30** form a C_S complex with a binding energy of 35.8 kJ mol^{-1} and the complex proceeds, over a barrier of 19.8 kJ mol^{-1} , to thiirenium ion **31** and ethylene. The identity reaction of **31** with ethyne was also examined (Equation 11). Insertion to afford a five-membered ring was not competitive in either exchange. All exchanges were found to occur through a complex **32** that leaves the stereochemistry at sulfur unchanged (Scheme 3). A second exchange mechanism, not discussed here, was also examined.



Scheme 3

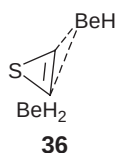
Nesterenko and Staninets used quantum-chemical methods to examine the reaction of the phenylsulfenium ion (PhS^+) with alkynes XCCY ($\text{X}, \text{Y} = \text{H}, \text{Me}, \text{Ph}, \text{CN}$) <2004TEC77>. Reaction was found to occur in two steps in general, forming first an acyclic cation **33** that could close to a thiirenium cation **34** or to a four-membered ring cation **35** (Scheme 4). The thiirenium ion **34** could rearrange to cation **35**. All steps were described as reversible.



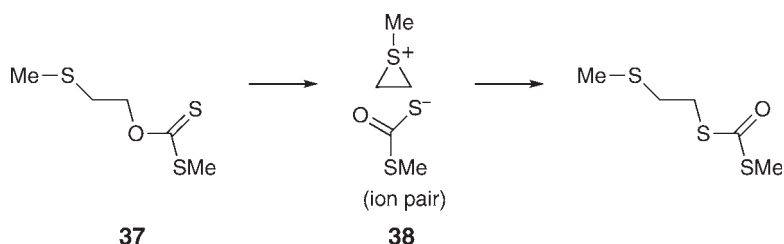
Scheme 4

Veszpremi and co-workers used *ab initio* calculations at various levels to compute the structures of thiirene with electropositive substituents such as BeH and BeH_2 <1997PCA8565>. Structure **36**, with one electropositive

substituent lying over the π -bond of the thiirene and the other on the opposite side, was found to describe the data best.



Neighboring group participation in the thione-to-thiol rearrangement of xanthates **37** (illustrated below) was studied by Harano and co-workers by means of MO calculations based on the conductor-like screening model (COSMO) <2001CPB1433>. There is an ion pair intermediate **38**, formed by anchimeric assistance to afford a thiiranium ion, as one component of the pair (Scheme 5). In polar solvents, the negative charge in the anion is largely localized on sulfur. Solvents studied included cyclohexane, acetone, acetonitrile, and water. Fully optimized geometries obtained by the PM3 or AM1 methods were used as starting points for *ab initio* and DFT calculations of the gas-phase reactions.

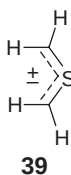


Scheme 5

A Russian group studied the stability of α -halogen dithiols ($\text{RC}(\text{SH})_2\text{CH}_2\text{X}$; $\text{R} = \text{Me}, \text{Ph}$; $\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$) by quantum-chemical methods <2005RCB566>. Four stable rotamers differing in the mutual orientations of the thiol and halogen groups were located. Kinetic and thermodynamic parameters for the thermolysis were computed. Thermolysis of aliphatic chloro and bromo derivatives in aprotic media gave thiirane derivatives. In water, elimination of H_2S with formation of thiones predominated.

In 1997, Fabian published a theoretical study of some nonclassical compounds with dicoordinate sulfur, including thioformaldehyde *S*-methylide **39** (H_2CSCH_2), a thiocarbonyl ylide <1997JM411>. The MP2, QCISD, and QCISD(T) levels were used, and triplets were optimized by *ab initio* open-shell methods. The C–S bond length in the ylide was calculated at the B3LYP level of theory to be 1.642 Å. The calculated adiabatic S_0/T_1 gap, about 30 kcal mol^{−1}, was taken to indicate that the ylide has some diradical character. However, the charge separation indicated that the species is strongly ylidic. The positive charge at sulfur ranged from +0.42 to +0.72 depending on the method used to determine it. The ylide undergoes exothermic, conrotatory electrocyclicization to thiirane, the exothermicity ranging from −36.3 to −38.9 kcal mol^{−1}. The calculated energy of activation ranged from 15.0 to 15.5 kcal mol^{−1} depending on the type of computation.

Formation of thiirane by ring closure of the corresponding thiocarbonyl ylide **39** was also studied by another group. Sustmann *et al.* used the (U)BL3LPY/6-31G* level to calculate the transition-state geometry for the expected conrotatory closure and obtained an HC–SC dihedral angle of 57°, a CS bond length of 1.73 Å, and a CASPT2 barrier height of 14.5 kcal mol^{−1} <2003CEJ2245>. The transition state has 35% biradical character. The calculations gave for the product, thiirane, a C–C bond length of 1.48 Å, a C–S bond length of 1.84 Å, and a CSC bond angle of 48°, in excellent agreement with the other results.



White and Banks conducted an *ab initio* study of gas-phase reactions of amines with thiirane. The amines included ammonia, methyl, ethyl, isopropyl, and *t*-butyl amine as well as aniline <2000ARK153>. Calculations were done with Gaussian 94 and HF/6-31G* to identify a transition state and to determine its geometry and thermodynamic parameters. Transition-state theory was then applied to estimate relative reaction rates. The *anti*-mode of approach, in which the alkyl group of the amine and the CC bond of the thiirane are roughly collinear, was favored. Relative rates were reported with a factor less than 20 separating the slowest from the fastest alkyl amines. Ethyl amine was calculated to be most reactive, probably a result of high nucleophilicity and relatively low steric requirements. Both ammonia and aniline reacted slowly, the former about 380-fold slower and the latter slower by about 21 000-fold than ethyl amine. The fact that the transition states are more polar than the starting materials must be kept in mind when computed gas-phase reaction rates are compared to reactions in solution.

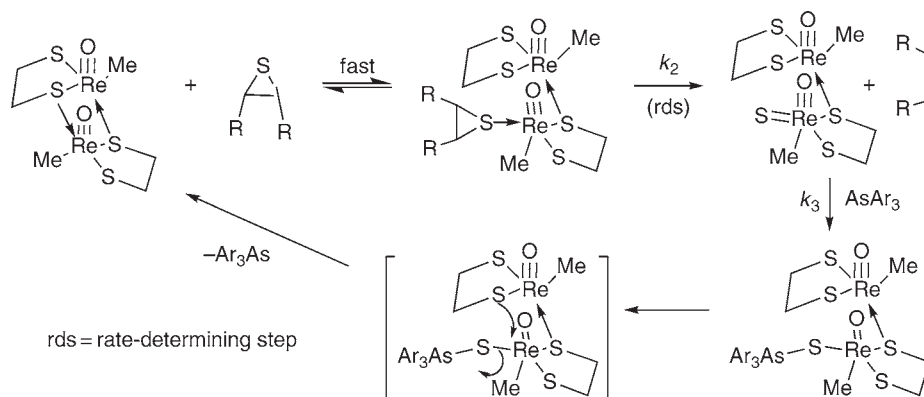
Subsequently, Banks and White reported a gas-phase study of the reactions of thiiranes with ammonia and secondary amines <2001JOC5981>. B3LYP/6-31+G(d) and HF/6-31G(d) computations and transition-state theory were used, and the reactivity of a thiirane with a secondary amine was ascribed to the net effect of steric hindrance and polarizability. 2-Fluorothiirane was calculated to react with ammonia more than 10^6 times as fast as thiirane. Reaction at C-2 was calculated to be slower by a factor of 2.4×10^7 than reaction at C-1. 2-Methylthiirane reacts more slowly than thiirane and the regioselectivity in favor of C-1 was 12.8. In 2,2-dimethylthiirane, the analogous regioselectivity rose to 124.

Jenks *et al.* studied the effects of conjugation and aromaticity on the sulfoxide bond by means of *ab initio* computation <1996JOC1275>. They calculated S–O bond dissociation energies (BDEs) and found that, in a formally aromatic system such as thiophene sulfoxide, the SO BDE is decreased by as much as 25 kcal mol^{−1} relative to the BDE of DMSO. Although the BDE of the formally antiaromatic thiirene sulfoxide increased by about 15 kcal mol^{−1}, the authors concluded, on the basis of calculated geometries and isodesmic reactions with pure hydrocarbons, that cyclic unsaturated sulfoxides are neither significantly aromatic nor antiaromatic.

Dreizler and co-workers used quantum-chemical calculations at the MP4(SDQ) level to compute the nuclear quadrupole coupling tensor of ³³S in a series of molecules to compare them to values obtained from rotational spectra <1997ZNA297>. Improved values for thiirane ³³S are: *caa* = −329425(78), *cbb* = −16.402(14), and *ccc* = 49.345(14) MHz, respectively.

An *ab initio* and DFT study of the stereochemistry of desulfurization of *cis*- and *trans*-2,3-dimethylthiirane isomers by trimethyl phosphate was reported by Kalaiselvan and Venuvanalingam <2006JMT1>. In keeping with experimental results, their calculations indicated that the exothermic reaction is concerted and occurs by attack at sulfur. The completely stereospecific desulfurizations had activation energies of 28.6 and 26.7 kcal mol^{−1} for the *cis*- and *trans*-isomers, respectively, at the B3LYP/6-31G(d) level of theory.

The kinetics and mechanism of rhenium-catalyzed desulfurization of thiiranes was studied experimentally and by means of computation <2006IC5351>. The oxorhenium dimer MeReO(edt)₂ (X), where edt = 1,2-ethanedithiolate, was found to catalyze the transfer of S from thiiranes to triarylphosphines and triarylsines. In the case of phosphines, catalysis was less effective because they converted the dimer catalyst rapidly to MeReO(edt)PAr₃, a less effective catalyst. The rate law for AsAr₃, which did not transform the catalyst, was $v = k[\text{thiirane}][X]$ with $k = 5.581 \text{ mol}^{-1} \text{ s}^{-1}$ at 25 °C in CDCl₃, for X = cyclohexene sulfide. The value of $\Delta H^\ddagger$ was $10.0 \pm 0.9 \text{ kcal mol}^{-1}$, while $\Delta S^\ddagger$ was $-21 \pm 3 \text{ cal K}^{-1} \text{ mol}^{-1}$. The proposed mechanism is shown in Scheme 6.



Scheme 6

A theoretical study of desulfurization of thiirene and methyl thiirene on the molybdenum catalysts MoS_3H_3^+ and MoS_4H_4 was reported to involve hydrogenation of the double bond in the first step <2003BCSE75>. The extended Hückel technique was used to determine the orientation of thiirene adsorbed on vacant sites of MoS_3H_3^+ . The molecule is adsorbed preferentially in the vertical sense through the sulfur atom <2000JSOA127>.

Some effort has gone into prediction and verification of structural parameters of complexes from interaction of HX with thiirane <2004SAA1883>. By means of *ab initio* MO and B3LYP DFT at the 6-311++(d,p) level, Araújo and co-workers obtained structural and electronic parameters for HF and HCl complexes with thiirane. The complexes have C_s symmetry with the HX unit lying in a plane perpendicular to the plane of the thiirane ring. The MP2 distance between H of HF and the thiirane sulfur was 2.164 Å, in good agreement with the experimental distance, 2.193 Å.

Later, the same group performed *ab initio* calculations at the MP2/631++G(d,p) and DFT/B3LYP/6-311++G(d,p) levels of theory to obtain geometries, H-bond energies, and harmonic infrared (IR) vibrational frequencies for some HX–thiirane complexes, including one between thiirane and HCN <2005SAA491>. The H-bond lengths calculated at the DFT/B3LYP level were closer to experimental values than those calculated with MP2. Several interesting features were found including an intermolecular stretching mode.

Alkylation of aziridine-, oxirane-, and thiirane-based cysteine protease inhibitors were examined by means of model calculations about the influence of environment on inhibition potency <2004PCA7691>. Changes in the mechanism, the thermodynamics, and the kinetics of inhibition were studied as a function of environment. Methyl thiolate anion was used to mimic the role of cysteine, while water molecules were used to model environments with weak proton donor ability. Either NH_4^+ or HCO_2H were used to mimic environments with stronger proton-donating abilities. The pH dependence (lower pH-caused catalysis) was small for thiiranes and oxiranes but large for aziridines. Thiiranes are less potent inhibitors than analogous aziridines. A rough model, 40, of the transition state for ring opening of thiirane by methyl thiolate in the presence of formic acid is shown in Figure 1.

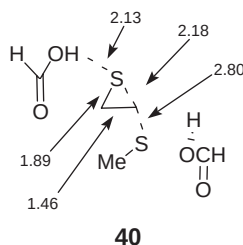


Figure 1 Bond lengths (Å) for the transition state of thiirane opening by MeS^- in the presence of HCO_2H .

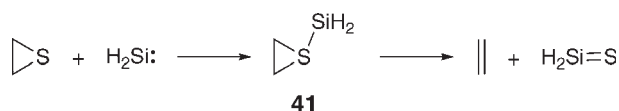
Later, the same authors computed the effects of ring substituents (H, ester, and carboxyl) on nucleophilic ring opening (by CH_3S^-) of the three-membered heterocycles aziridines, oxiranes, and thiiranes with the TORBOMOLE or Gaussian packages <2005JOC233>. Such ring-opening substitutions are believed to be important processes in cysteine protease inhibition. Free carboxyl substituents can impart very high inhibition potencies compared to ester functional groups. The model studies permitted the authors to rationalize the experimentally observed dependence of inhibitor potencies on structure of the three-membered heterocycle and its substituents. Aziridine ring opening is strongly catalyzed by a water-mediated intramolecular acid catalysis which is aided by a free intramolecular carboxyl group. Corresponding oxiranes and thiiranes do not show that effect. Therefore the high inhibition potency of carboxylic acids, compared to corresponding esters, was attributed to an interaction of a histidinium moiety in the active site of the proteases with the negatively-charged carboxyl group.

Fang *et al.* used DFT to study deoxygenation of oxirane and desulfurization of thiirane by singlet germylenes $\text{R}^1\text{R}^2\text{Ge}$ ($\text{R}^1 = \text{R}^2 = \text{Me}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$; $\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Br}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Cl}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{F}$; $\text{R}^1 = \text{R}^2 = \text{Br}$; $\text{R}^1 = \text{R}^2 = \text{Cl}$; $\text{R}^1 = \text{R}^2 = \text{F}$) <2006JMT53>. Those reactions proceed through an ylidic complex formed by interaction of a lone pair at sulfur with the formally empty p - π orbital at germanium. The bond between germanium and sulfur is long and the C–S bonds are little affected by the complexation. At the transition state for abstraction of sulfur, those bonds are longer by 12.3% for GeMe_2 to 22.7% for GeF_2 . Barrier heights follow the same trend, being 8.99 kcal mol^{-1} for Me_2Ge and 32.75 kcal mol^{-1} for GeF_2 . The findings are in accord with the Hammond postulate, transition states of higher energy coming later along the reaction coordinate.

Geng *et al.* used DFT to examine abstraction of sulfur from thiirane by alkylidene carbenes <2005HX1402>. The greater the electronegativity of the carbene substituents ($\text{XYC}=\text{C}$), the lower the activation energy for abstraction. Electronic factors were found to be much more important than steric factors.

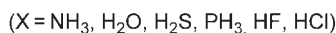
Su and Chu examined abstraction of oxygen from oxirane and sulfur from thiirane by six carbenes with substituents ranging from dimethyl to dimethoxy <2000CEJ3777>. DFT (B3LYP/6-31G*), including zero-point corrections, showed that all abstractions involve initial formation of a loose complex followed by the heteroatom shift. Complexation energies, barriers, and enthalpies were compared to arrive at the reactivity order cyclobutylidene > dimethylcarbene or cyclohexylidene > phenylchlorocarbene > methoxyphenylcarbene or dimethoxycarbene. Donor-substituted carbenes are predicted to be less reactive than alkyl-substituted carbenes in agreement with the experimental results reported in Section 1.05.6.3.2 <1998JA8681>.

Apeloig and Sklenak used high-level *ab initio* computation (QCISD/6-31G**) to determine the mechanism of a sulfur-transfer reaction between silylene (H₂Si:) and thiirane <2000CJC1496>. A complex **41**, formed in the first step over a barrier of 7.4 kcal mol⁻¹, was predicted to be observable in a matrix because the barrier to subsequent abstraction of S in a single step is higher at 14.9 kcal mol⁻¹ (Scheme 7). Other studies of abstraction of sulfur from thiirane by carbenes are discussed under Section 1.05.6.3.2.



Scheme 7

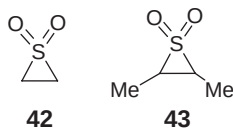
Solling and Radom investigated ligand exchange between monoadducts of the sulfenium ion (HSX⁺) and either unsaturated hydrocarbons or lone pair donors computationally with a modified form of G2 theory (Equations 12 and 13) <2001CEJ1516>. In all cases involving ethylene, except for HS-PH₃⁺, the reaction was exothermic and without a significant barrier. In the exceptional case, there was a transition state lying at 35.8 kJ mol⁻¹ above the reactants and at 11.6 kJ mol⁻¹ above the products. In the case of ethyne, reactions were exothermic except for the cases of HS-NH₃⁺, HS-PH₃⁺, and HS-SH₂⁺. The other substitutions were barrierless. A process involving frontside attack on the three-membered ring of the thiiranium ion (the reverse reaction) was found but the gas-phase barrier was very high. Many geometric parameters are included in the paper. The conclusion was that monoadducts of HS⁺ react with lone pair donors, ethyne or ethylene, to form a thiirenium or thiiranium ion without a barrier, in general, through a collinear or nearly collinear approach.



Steudel and co-workers <2002CEJ217> have reported *ab initio* calculations on the mechanism of decomposition of thiirane. Standard *ab initio* calculations used the Gaussian 98 programs. Energies of various equilibrium structures and transition states of *c*-C₂H₄S were examined with the G3(MP2) level of theory. Spin-restricted and spin-unrestricted calculations were used for closed-shell and open-shell systems, respectively. Products of thermolysis of thiirane, which are ethene and sulfur, do not come from an excited state of thiirane but involve the intermediacy of thiirane-1-sulfide, an analog of ethylene episulfoxide. Thiirane-1-sulfide is probably formed by transfer of a sulfur atom from one thiirane molecule to another. Thiirane-1-sulfide can react unimolecularly to afford ethene and S₂ in its excited singlet state or, by means of spin crossover, S₂ in its triplet ground state. Alternatively, it can react with itself to afford thiirane-1,1-disulfide (sulfone analog) and ethene. The 1,1-disulfide can decompose to ethene and S₃. Thiirane-1-sulfide can also react with itself in a strongly exothermic reaction to afford two molecules of ethene and S₄ whose geometry was obtained at the QCISD/6-31G* level. The findings agree with experimental data. Radicals, zwitterions, and thiirane-1-persulfide were considered to be unlikely intermediates in the thermal decomposition of thiiranes. The calculated C-C, C-S, and C-H bond lengths of thiirane came to 1.479, 1.817, and 1.084 Å, respectively, at the MP2/6-311+G(2df,p) level in good agreement with experimental numbers. Angles were CSC (48.0°), CCS (66.0°), HCH (115.5°), HCC (118.1°), and HCS (115.0°), respectively. The calculated dipole moment of thiirane came to 1.93 D at the same level of computation, close to the experimental value of 1.84 D for gaseous thiirane.

The nature of bonding in the sulfonyl group was studied at the B3LYP/6-311+G(d,p) level in the atoms-in-molecules (AIM) approach <2004JCC734>. For thiirane-oxide and thiirane-1,1-dioxide, Chesnut and Quin found delocalization indexes of 1.44 and 1.28, respectively. Bond distances (SO) were 1.509 for thiirane oxide and 1.466 Å for thiirane dioxide. The oxygen-to-sulfur bond is strongly polarized toward oxygen, and the latter's lone pairs provide significant backbonding to create the short, strong S–O bonds.

Suarez *et al.* studied the mechanism of decomposition of ethene episulfone **42** and 2-butene episulfones **43** to SO₂ and the appropriate ethene by means of *ab initio* computation <1996JPC13462>. Decomposition of the episulfones was stereospecific involving an asynchronous, chelotropic transition state. For ethene episulfone, the barrier to reach the transition state was between 28.68 and 32.52 kcal mol^{−1}, and the exothermicity was between −29.03 and −33.23 kcal mol^{−1}, depending on the computation method. The fact that the *cis*-2-butene episulfone lost SO₂ more rapidly than the *trans*-isomer, according to the calculations, was attributed to the dominance of attractive over repulsive dispersion forces between *cis*-methyl groups.



DFT (B3LYP/6-311G-(d)) and single-point calculations at the QCISD level were used to explore the potential energy surfaces for the reactions of silylene and substituted silylenes with oxirane and thiirane <2002JA12335>. The silylenes investigated were SiH₂, SiMe₂, Si(NH₂)₂, Si(OH)₂, and SiF₂, all of which have singlet ground states. The value of Δ*E*_{ST} depends a little on the level of theory but was about 19, 26, 56, 63, and 73 kcal mol^{−1} for the five silylenes. The calculations indicated that, for abstraction of oxygen from oxirane and sulfur from thiirane, a weak complex is formed first by interaction of an oxygen or sulfur lone pair (**44**) with a vacant p-π orbital of the silylene **45**. Some of those complexes are probably too weakly bound to be observed experimentally. Complexes of silylenes and thiirane then decay to the products through transition states with different degrees of Si–S bond formation. For the silylenes listed above, the extents of Si–S bond formation at the transition state were 10%, 11%, 35%, 25%, and 20%, respectively. Barriers, enthalpies, complexation energies, and bond lengths/angles were calculated for starting materials, complexes, transition states, and products. Abstraction by alkyl-substituted silylenes is more favorable than abstraction by donor-substituted silylenes.

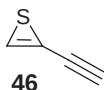


Fang *et al.* used DFT at the B3LYP/6-31++G (d,p) level to study sulfur abstraction from thiirane by germylene (H₂Ge:) and substituted germylenes <2005WHX1331>. The abstraction occurs in two steps through complex formation in a barrierless, exothermic process followed by separation of the complexes to form products. The stronger the π-donor substituents at Ge or the greater their electronegativity, the higher was the activation energy for abstraction of sulfur.

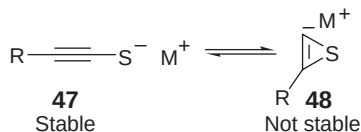
In a Russian study, it was found that good agreement with experimental results could be obtained by adding electron correlation effects and by using correlation-consistent basis sets and additional functions <2003RJO1618>.

Low-lying states of thiirene (and other small ring compounds) were examined with configuration interaction (CI) calculations using the SINDO1 method <1996T4709>. The ground state of thiirene was found to be planar and moderately antiaromatic with C–C bond length 1.295 Å and C–S bond length 1.814 Å. The first singlet excited state was found to be moderately aromatic with a longer C–C bond (1.329 Å), as expected for a bond that is no longer a plain double bond, and shorter C–S bonds at 1.745 Å.

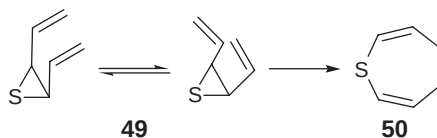
One of the potential products of rearrangement of C₄H₂S isomers is ethynylthiirene. Kim and McMahon used coupled cluster theory and DFT to compute properties of highly unsaturated molecules such as ethynylthiirene **46** that might be detected spectroscopically in the interstellar medium <2005JOC8171>. C–S bond lengths were calculated as 1.823 and 1.892 Å. The computed IR spectrum was devoid of any strong characteristic peak but the large dipole moment (2.07 D) holds promise for the detection of the thiirene by rotational spectroscopy. Rotational constants are listed.



Petrov and Belyakov, based on a DFT study of acetylenic alkali metal thiolates **47** and their thiirene anion isomers **48**, investigated the influence of Li, Na, and K cations as well as acetylenic substituent on geometry and electronic structure <2005RJOC1142>. Infrared and ^{13}C nuclear magnetic resonance (NMR) spectra were computed and the authors concluded that only the acyclic isomer is stable. Kass and co-workers studied the opening of saturated analogs, including thiirane anions, by means of theory <1999JOC7395> (Section 1.05.2.3).



Zora used a DFT computation to compare the Cope rearrangements of *cis*-2,3-divinylcyclopropane with analogous rearrangements of the corresponding aziridine, oxirane, phosphirane, and thiirane **49** <2005JOC6018>. All undergo the expected sigmatropic rearrangement which, in the last case, affords 4,5-dihydrothiepine **50**, the known seven-membered ring. Activation energies were predicted to increase in the order (atom in the three-membered ring) $\text{C} < \text{N} < \text{O} < \text{P} < \text{S}$ and the exothermicities to decrease in the order $\text{N} > \text{O} > \text{C} > \text{P} > \text{S}$. The thiirane analogs rearrange at temperatures of about 60 °C or less, while the thiirane itself, under nitrogen, rearranges at 90 °C to afford an array of products that include 4,5-dihydrothiepine **50**, 2,7-dihydrothiepine, and polymerization products from 1,3,5-hexatrienes. The 2,7-dihydrothiepine is believed to be the result of a radical process that competes with sigmatropic rearrangement. Control experiments showed that 2,7-dihydrothiepine does not come from 4,5-dihydrothiepine. The polymers were attributed to desulfurization of the parent thiirane to produce 1,3,5-hexatrienes.



1.05.2.3 Ring Strain

Strain in three-membered ring molecules was investigated by Naruse *et al.* who examined σ - and π -relaxation of ring strain by delocalization of electron density between geminal ring bonds and of lone pairs to neighboring σ -bonds <2003PCA2860>. The conclusion drawn was that σ -delocalization is significant in $(\text{CH}_2)_2\text{X}$, $(\text{NH})_2\text{X}$, and $(\text{SiH}_2)_2\text{X}$ where $\text{X} = \text{SiH}_2$, PH , and S but lone pair delocalization does not contribute significantly to the π -relaxation of ring strain, except in $(\text{SiH}_2)_2\text{S}$.

Hoz and co-workers used the Marcus equation and theory at the HF/6-31G* level to determine that the strain relief contribution to ring opening of thiirane by MeS^- is 8.5 kcal mol $^{-1}$ <2001JOC915>. There is an additional contribution to the lowering of the activation energy, relative to that for the unstrained model ($\text{MeS}^- + \text{MeSMe}$) of 13.3 kcal mol $^{-1}$. The additional factor was not identified.

Three-membered rings react at exceptionally large rates in nucleophilic substitutions. Banks used computation, based on the MP2(Full)/6-31+G(d) level, to determine that the reactivity of thiirane and oxirane is not due to relief of strain only <2003JOC2639>. Although the reactivity of four-membered rings could be largely explained in terms of strain relief, three-membered rings were at least 10^6 times as reactive as one would expect if relief of strain were the only factor. Calculation of atomic charges by the Mulliken, AIM, CHELPG, and natural bond orbital (NBO) methods indicated that positive charge at the reaction center was significantly lower for three-membered rings than for larger rings. The unique topological ability of a three-membered ring, to lower the positive charge in the ring by putting it onto the partially negative sulfur or oxygen, was held responsible. A similar study, in which nucleophilicity of the attacking agent was highlighted, was described earlier <2000ARK153>.

Strain in three-membered rings such as thiirane and disilathiirane $(\text{H}_2\text{Si})_2\text{S}$ was examined in terms of σ - and π -delocalization <2003PCA2860>. Those terms denote the relief of strain by electron delocalization from a doubly

occupied σ -bond to a neighboring unoccupied π -bond and from lone pairs of heteroatoms to neighboring σ -bonds, respectively. The σ -relaxation by delocalization between ring bonds was found to be significant, but the π -delocalization was generally not significant except in the case of $(\text{H}_2\text{Si})_2\text{S}$. Strains were calculated by means of the RHF/6-31G* method with zero-point energy corrections. The strain energy of thiirane was estimated to be $17.3 \text{ kcal mol}^{-1}$. Liebman and co-workers estimated it at $20.4 \text{ kcal mol}^{-1}$ <1999JOC9328>.

1.05.2.4 Proton Affinity

The proton affinities of thiirane and other neutrals were calculated with the Gaussian and Gamess programs <2000JA10133>. For thiirane, the computed proton affinity value was 192.44 compared to the literature value of $193 \text{ kcal mol}^{-1}$ and proton transfer from protonated thiirane to methylthioethane was calculated to be exothermic by $9.3 \text{ kcal mol}^{-1}$ (Equation 14) <1998JPCRD413>.



In a gas-phase study involving ion molecule reactions, Kass and co-workers examined the proton affinities of some three-membered, heterocyclic ring anions by both experimental and high-level, *ab initio* theoretical means <1999JOC7395>. Gas-phase experimental studies involved a variable-temperature flowing afterglow apparatus or a Fourier transform (FT) mass spectrometer. The proton affinity of thiirane anion was found to be $392 \pm 5 \text{ kcal mol}^{-1}$ and that of thiirane *S,S*-dioxide was $365 \pm 2 \text{ kcal mol}^{-1}$. Ring opening of the anion of thiirane, which affords vinyl thiolate, was computed to be exothermic by $49.1 \text{ kcal mol}^{-1}$ with activation energy (E_a) of $10.8 \text{ kcal mol}^{-1}$. Similarly, ring opening of the dioxide anion is exothermic ($48.7 \text{ kcal mol}^{-1}$), and the barrier for that process (to form $\text{CH}_2=\text{CHSO}_2^-$) was computed to be $20.7 \text{ kcal mol}^{-1}$. The proton affinity of the anion of thiirane *S*-oxide could not be determined experimentally because the anion undergoes ring opening very easily to vinyl sulfenate ($\text{CH}_2=\text{CHSO}^-$). The anion, which has C_s symmetry, can have the lone pair electrons at carbon in an orbital that is either *cis* or *trans* to the sulfoxide oxygen. At the G2+ level of theory, the barriers to ring opening were computed to be $11.5 \text{ kcal mol}^{-1}$ for the *trans*-species and $3.7 \text{ kcal mol}^{-1}$ for the *cis*-ion. Moreover, the barrier for isomerization of the two ions is only $5.5 \text{ kcal mol}^{-1}$. Thus, the low barriers and the exothermicity of ring opening combine to make the lifetime of the anion of thiirane *S*-oxide very short. Structures of starting materials and transition states for various reactions were included in the study.

1.05.2.5 Heats of Hydrogenation, Ionization Potential, Net Charge, and Dipole Moment

The period 1996–2006 did not appear to have papers concerned with heats of hydrogenation, ionization potential, or net charge of thiiranes or thiirenes.

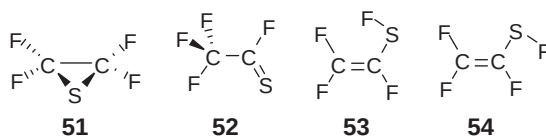
The calculated dipole moment of thiirane was reported by Steudel and co-workers to be 1.93 D <2002CEJ217> (Section 1.05.2.2), close to the experimental value of 1.84 D for gaseous thiirane.

The electric dipole moment of methylthiirane was determined experimentally by Dreizler and coworkers who measured the rotational spectrum of three isotopomers <1997JF11863>. They obtained $\mu_a = 1.6139(25) \text{ D}$, $\mu_b = 1.1620(36) \text{ D}$, and $\mu_c = 0.2714(23) \text{ D}$ from Stark effect measurements. They also determined the rotational barrier of the methyl group in the gas phase: $13.49(11) \text{ kJ mol}^{-1}$.

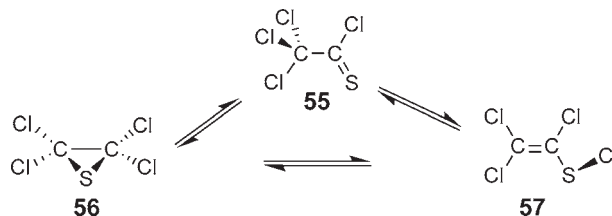
Values of the dipole moments of sulfones, including ethylene episulfone, were computed by Rozas at different computational levels (HF 6-31G* and MP2 6-31G* HF-6 31G*) and different methods of charge estimation <1997IJQ477>. Numbers ranged from 5.946 to 3.901 D . The experimental value of the dipole moment is 4.41 D .

1.05.2.6 Structures and Energies of Isomers

Senning and co-workers investigated tetrafluorothiirane and isomers by means of *ab initio* computations <2003JFC99>. They concluded that the thiirane **51**, which is known, should interconvert with its isomers, trifluorothioacetyl fluoride **52** (also known) and trifluoroethenesulfenyl fluoride **53**. The latter could exist as two conformers **53** and **54** with a calculated rotation barrier of about 37 kJ mol^{-1} . The authors determined likely mechanisms for interconversions of the isomers.



Senning and co-workers also conducted *ab initio* calculations by Hartree–Fock, MP2, and Gaussian-3 theories of, *inter alia*, equilibria between the isomers trichlorothioacetyl chloride **55**, tetrachlorothiirane **56**, and trichloroethene-sulfenyl chloride **57** [\[2004JSC111\]](#). None of the isomerizations that were computed have been observed experimentally, although the calculations indicate that they are feasible. For tetrachlorothiirane **56**, the Gibbs energy (ΔG_{298}) was calculated to be 22 kJ mol^{−1} relative to zero for trichlorothioacetyl chloride **55**.



1.05.3 Experimental Structural Methods

1.05.3.1 Bond Angles and Bond Lengths

A very accurate structure of thiirane, based on millimeter wave spectra of the ground state, was reported in 2001 [\[2001JSP148\]](#). Bond lengths are: C–C = 1.48396(5), C–S = 1.81740(4), and C–H = 1.08523(8) Å, respectively. Bond angles reported are: CSC = 48.192°, HCH = 114.55(2)°, and Φ = 152.55(2)°, where Φ is the dihedral angle between the HCH plane and the C–C bond.

It was shown that vibrational spectra contain explicit information about the electronic structure and bonding in a molecule [\[1999JST385\]](#). Adiabatic stretching frequencies from experimental vibrational spectra were used to estimate CH and CC bond lengths in thiirane. For CH bonds, it was shown that adiabatic stretching frequencies can be used to define a CH bond dissociation energy that is free from radical stabilization energies included in experimental bond dissociation energies. For thiirane, the ideal CH bond dissociation energy (D_e^{ideal}) is given as 117.9 kcal mol^{−1} and the CH and CC bond lengths as 1.086 and 1.481 Å. There is not an experimental value of the bond dissociation energy but the experimental CH and CC bond lengths are 1.08523(8) and 1.48396(5) Å [\[2001JSP148\]](#).

Ground-state rotational spectra of three isotopomers of a complex between thiirane and HCl, (CH₂)₂³²S⋯H³⁵Cl, (CH₂)₂³²S⋯H³⁷Cl, and (CH₂)₂³⁴S⋯H³⁵Cl, were observed by means of pulsed nozzle, Fourier transform spectroscopy [\[1995CPH119\]](#). The complex has *C_s* symmetry, with the angle between the thiirane *C₂* axis and the S⋯H bond direction at 85.5(20)° and the S⋯H distance at 2.329(28) Å, with the deviation of the S⋯H–Cl bonds from collinearity at 20.0(5)°.

Fourier transform IR spectra and band contour analysis of the deuterium fluoride (DF) stretching region were also measured in a similar system for the thiirane–DF complex [\[2004JCP7784\]](#). Analysis of the spectra between 50 and 250 K showed three low-frequency H-bond modes ($\nu_{\delta 1}$, $\nu_{\delta 2}$, ν_{σ}) strongly coupled to the DF stretching mode with anharmonic coupling constants, indicating a strengthening of the H-bond upon vibrational excitation of DF. A lower bound for the predissociation lifetime of the complex was set at 10^{−10} s.

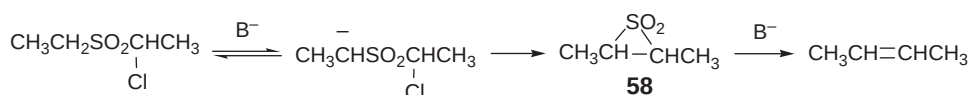
Coupled anharmonic vibrational analysis of the coupled high-frequency HF stretching vibrations and low-frequency intermolecular modes was also reported in 2004 [\[2004SWC291\]](#). The physically correct treatment of H-bond-induced vibrational red shifts requires a sophisticated vibrational treatment far beyond the customary one dimensional approach. That sophisticated treatment is not described here.

Scaled quantum mechanics computations of vibrational spectra of small molecules, including thiirane, were performed by Katsyuba and Vandyukova [\[2003CPL658\]](#). With 13 scaling factors, applied to B3LYP force fields, they were able to compute stretching and bending frequencies for 26 molecules with a total standard deviation of about 11 cm^{−1} for 6-31G* and 6-31+G* basis sets. The latter basis set was recommended for Raman spectra.

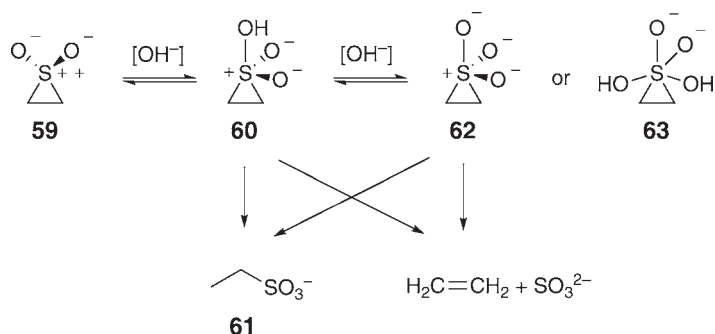
A fast-mixing nozzle in an FT microwave spectrometer was used to measure rotational constants, centrifugal distortion constants, Cl-nuclear quadrupole- and spin-rotational coupling constants for the isotopomers $(\text{CH}_2)_2\text{S}-^{35}\text{ClF}$ and $(\text{CH}_2)_2\text{S}-^{37}\text{ClF}$ <1996CPL119>. The complex, with C_s symmetry, has an arrangement of the S-ClF nuclei that is about 3.5° off collinearity. The Cl-F axis makes an angle of 95° with thiirane's C-2 axis.

The sulfur K-shell spectra and electron transmission spectra of polymethylene sulfides, including thiirane, were studied by Tronc and co-workers <2001CPH105>. The spectra were dominated by similar broad resonances with trapping of the impinging (or K-shell-excited) electron in $\sigma^*(\text{S}-\text{C})$ or $\pi^*(\text{CH}_2)$ orbitals. Calculation of the electron affinity with the DFT/B3LYP approach gave good agreement with experimental results and confirmed the role of molecular strain in lowering the $\sigma^*(\text{S}-\text{C})$ level in thiirane and thietane.

The Ramberg-Bäcklund reaction involves a thiirane-1,1-dioxide intermediate **58** as shown in Scheme 8. King *et al.* determined the mechanisms of reaction of thiirane-1,1-dioxide **59** with hydroxide ion in water <1996PAC825>. Two pathways were identified, the one first order and the other second order in hydroxide. The first step is formation of a trigonal bipyramidal mono-anion **60** formed by attack of OH^- at S of the sulfone. That anion then reacts with water to afford ethane sulfonate anion **61** or with a second OH^- to afford ethene and sulfite anion via **62** or **63** (Scheme 9). Some rate constants and equilibrium constants were determined.

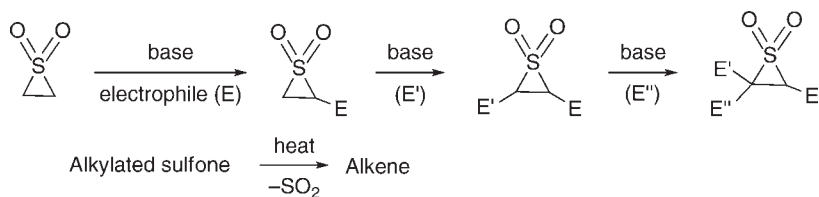


Scheme 8



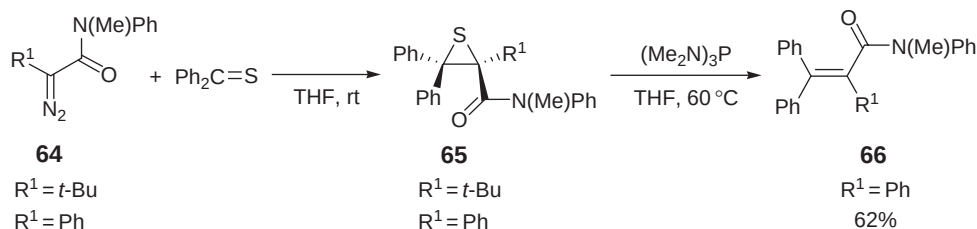
Scheme 9

At about the same time, Simpkins and co-workers studied the reaction of episulfones with bases and electrophiles in the hope that carbanions could be sequentially alkylated and lead, eventually, by thermal stereospecific extrusion of SO_2 , to substituted alkenes (Scheme 10) <1997JP1323>. This topic is also discussed in Section 1.05.6.5.



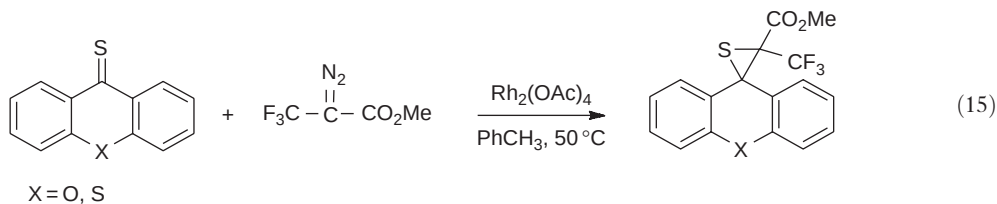
Scheme 10

Heimgartner and co-workers treated α -diazoketones and α -diazamides **64** with thiones, with and without a catalyst such as $\text{Rh}(\text{OAc})_2$ present (1998HCA285). The products were substituted thiiranes **65** and/or substituted 1,3-oxathioles. In all cases, a thiocarbonyl ylide intermediate, which could undergo either a 1,3- or a 1,5-electrocyclization, was held responsible. The ylide could arise either from addition of a carbene or a carbenoid to S of the thiocarbonyl compound or by loss of N_2 from a primary cycloadduct between the diazo and the thiocarbonyl compounds. In one case, such a primary adduct was isolated. The thiirane carboxamides could be desulfurized with $(\text{Me}_2\text{N})_3\text{P}$ in tetrahydrofuran (THF) at 60°C to afford acrylamides **66** (Scheme 11).

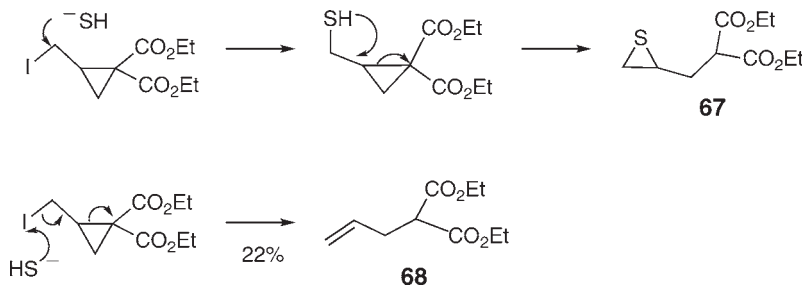


Scheme 11

Diazo compounds had also been used earlier as sources of carbenoids to react with thiocarbonyl compounds <1996HCA1537>. In toluene at 50°C , in the presence of a catalytic amount of $\text{Rh}_2(\text{OAc})_4$, 9*H*-xanthene-9-thione and 9*H*-thioxanthene-9-thione reacted with methyl 2-diazo-3,3,3-trifluoropropionate to afford the appropriate thiiranes in good yield (Equation 15).



Sodium hydrosulfide was found to afford a thiirane **67** upon reaction with 2-iodomethylcyclopropane-1,1-dicarboxylic acid diethyl ester <2005TL469>. In addition, 2-allyl malonic ester **68** was obtained. Scheme 12 shows the reasonable mechanisms proposed by the authors.



Scheme 12

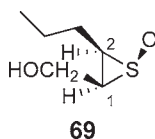
1.05.3.2 NMR Spectra

Regression formulas for calculating ^1H and ^{13}C magnetic shielding constants that were used to calculate chemical shifts were reported <2005MI175>. *Ab initio* and density functional calculations were used. For thiirane, the shift

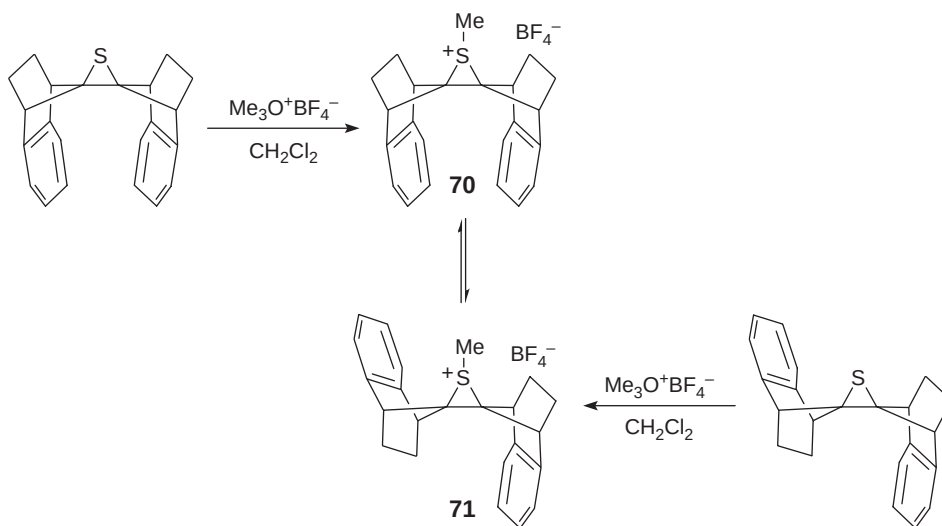
numbers (δ , rel. to trimethylsilane (TMS) in CDCl_3) are: for ^{13}C 18.9 found versus 20.63 predicted; for ^1H 2.30 found versus 2.28 predicted. Values for many other compounds are included.

Unusual downfield shifts reported in ^{31}S NMR spectra of an *S*-methylthiolanium iodide led Chesnut to reexamine the structure and bonding in the F, Cl, and Br *S*-methylsulfonium salts <2005HAC263>. A combination of DFT, AIM, and electron localization function (ELF) theoretical studies and NMR data supported the conclusion that the computations were reliable and the experimental data in error. In the gas phase, the binding in *S*-methylthiiranium halides is largely ionic, with only a small degree of covalency. Geometries for both 'front side' and 'back side' ion pairs are given, 'front side' referring to the position of the halide opposite to the methyl group.

Carlier *et al.* determined the proton NMR spectra of thiirane-1-oxides **69** prepared by diastereoselective oxidation of *cis*-1-hydroxymethyl-2-propylthiirane and derivatives <1997PS223>. They found that the β -hydroxyl directing effect, which normally leads to a preponderance of the *syn*-isomer, was absent. The steric effect of the propyl group was sufficient, apparently, to overcome the anticipated directing effect of the hydroxyl group. The unstable *syn*-isomers, for which NMR spectra were run *in situ* at low temperature, had downfield shifts for β -hydrogens *syn* to the sulfoxide oxygen, relative to shifts in the spectra of the starting thiirane. Moreover, the value of the coupling constant ($J_{1,2}$) was roughly 11 Hz in both the *syn*- and *anti*-sulfoxides, versus ca. 6.5 Hz in the corresponding thiirane.

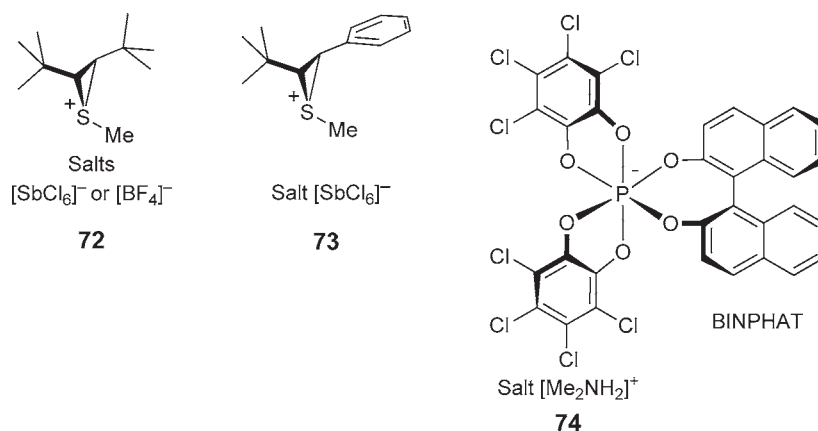


A dynamic ^1H NMR investigation of the first-order isomerization of 9,9'-bibenzonorbornenyldene episulfonium salts **70** and **71**, by Nakayama and co-workers, gave $\Delta E^\ddagger = 108 \text{ kJ mol}^{-1}$, $\Delta H^\ddagger = 106 \text{ kJ mol}^{-1}$, and $\Delta S^\ddagger = 20.9$ (*syn* to *anti*) $\text{J K}^{-1} \text{ mol}^{-1}$ <2001CL980>. The range of temperatures studied was 25–40 °C. For the *anti*- to *syn*-isomerization, the entropy of activation obtained was $8.8 \text{ J K}^{-1} \text{ mol}^{-1}$. Other thermodynamic properties were determined.

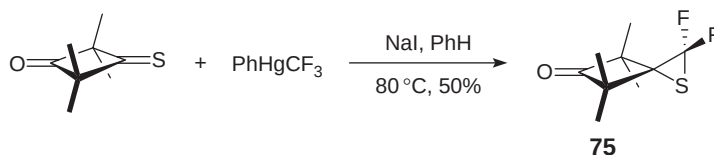


Proton NMR spectra of a number of benzylic thiiranes were measured at 60 MHz in CCl_4 <2002RJOC1620>. The chemical shifts of the benzylic protons were in the range 2.60–2.75 δ except in the case of α -naphthylmethyl where it was 3.20 δ .

Pasquato *et al.* differentiated enantiomeric thiiranium cations **72** and **73** by ^1H NMR spectroscopy using chiral hexacoordinated phosphate anions <2002TL5517>. Results obtained with BINPHAT **74** were best. Structures of the cations and BINPHAT are shown below.



Mloston *et al.* found a through-space coupling of methyl group hydrogens to *cis*-fluorines in 2,2-difluoro-4,4,6,6-tetramethyl-1-thiaspiro[2.3]hexan-5-one **75** <1999H(50)403>. In the ¹H NMR spectrum, the *cis*-methyl groups gave a triplet signal (*J* = ca. 1 Hz) at 1.39 ppm. In the ¹³C NMR spectrum, the C-2 signal was also a triplet with *J*_{CF} = 307.8 Hz. Similar spectra were observed in related sterically hindered difluorothiiranes.



Dahn and Van Toan measured the ¹⁷O NMR spectra of various sulfoxides including thiirene-1-oxide <1998MRC137>. The ¹⁷O chemical shift is only slightly dependent on electron donor substituents in the sulfoxide. Diphenyl thiirene-1-oxide has δ ¹⁷O = 18.0 ppm, relative to δ ¹⁷O = 0 for H₂O. In diphenyl cyclopropenone, there is a large aromaticity effect, but the effect of interaction between the double bond and the SO group in thiirene-1-oxide is small. The results are in accord with the conclusion that thiirene-1-oxide is not antiaromatic. The same conclusion was reached by another group <1996JOC1275>.

Krivdin and Kuznetsova used ¹³C–¹³C coupling constants to study strained, saturated heterocycles in an approach based on self-consistent, finite perturbation theory (SCPT) <2003RJO698>. They calculated ¹*J*_{CC} = 36 Hz for thiirane, which is very close to the values for open-chain compounds. The agreement between the calculated coupling constant in thiirane with coupling constants in acyclic compounds, such as ethanol, was taken to indicate that thiirane is not very strained. ¹³C–¹³C coupling constants are probably not a very sensitive criterion of strain, which has been estimated by other methods to be about 85.6 kJ mol⁻¹ (20.4 kcal mol⁻¹); see Section 1.05.2.3.

¹¹³Cd NMR spectroscopy was used by Darensbourg *et al.* to study complexation of propylene sulfide (and other bases) to cadmium of [Tp^{Ph}]₂Cd^{II}(acetate)·THF, where [Tp^{Ph}] is tris(3-phenylpyrazolyl)hydroborate <1997IC2426>. The Cd-to-acetate bond lengths were 2.307 and 2.342 Å, respectively, for equatorial and axial oxygens. Propylene sulfide and other ethers or thioethers displace THF from the complex although THF binds more strongly. By measuring the ¹¹³Cd chemical shifts at different temperatures in competition experiments they were able to determine the binding orders THF > dioxane > propylene sulfide > cyclohexane oxide ≥ propylene oxide. Various thermodynamic parameters, for the reaction [Tp^{Ph}]₂Cd^{II}(acetate) + ether (or thioethers) ⇌ [Tp^{Ph}]₂Cd^{II}(acetate)·ether (or thioether), were determined. The complexes are models for the initiation step in the copolymerization of epoxides with carbon dioxide catalyzed by metal carboxylates.

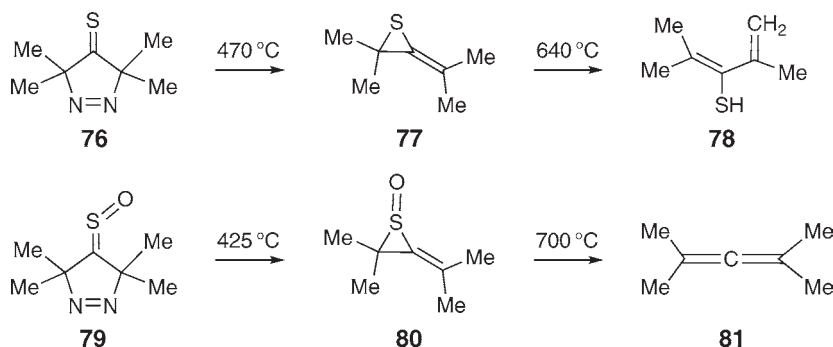
1.05.3.3 Mass Spectra, Photoelectron Spectra, and Other Spectra

Dreizler's group <1996ZNA1096> used natural abundance ³³S in methylthiirane to determine the ³³S quadrupole coupling in the rotational spectrum. The rotational and quadrupole coupling constants are: *A* = 11599.0976(18) MHz, *B* = 4815.6822(6) MHz, *C* = 3909.1318(5) MHz, *c*_{aa} = -12.7731(82) MHz, *c*_{bb} = -20.3366(118) MHz, *c*_{cc} = 33.1097(273) MHz.

Dissociation of energy-selected thiiranium ions ($\text{C}_2\text{H}_4\text{S}^+$) was studied by Fang *et al.* by means of a threshold photoelectron-photoion coincidence technique and quantum-chemical calculations <2005JCP1>. The equilibrium structures were optimized at the MP2(full)/631G(d) level, and single-point G3 energy calculations were performed at various high levels of theory. All stable structures had only real vibrational frequencies and all transition structures had one imaginary vibrational frequency. Well-resolved time-of-flight peaks in coincidence mass spectra gave information about branching ratios and average releases of kinetic energy for formation of $\epsilon\text{-C}_2\text{H}_4\text{S}^+$, CH_3CS^+ , and HCS^+ , for example. Gaussian-3 (G3) calculations, used to establish dissociation mechanisms, predicted that $\epsilon\text{-C}_2\text{H}_4\text{S}^+$ isomerizes to CH_3CHS^+ prior to formation of CHS^+ and CH_3 . A large release of kinetic energy for the channel $\text{CH}_3\text{S}^+ + \text{H}$ was tentatively attributed to a dissociation mechanism, which has $\epsilon\text{-C}_2\text{H}_4\text{S}^+$ isomerizing to a local minimum CH_3CSH^+ which then dissociates to $\text{CH}_3\text{CS}^+ + \text{H}$.

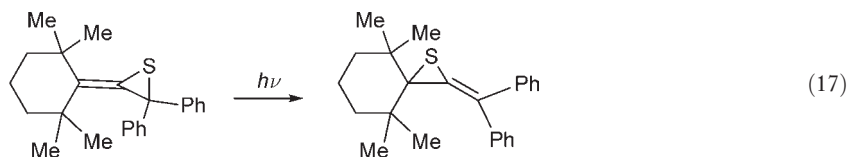
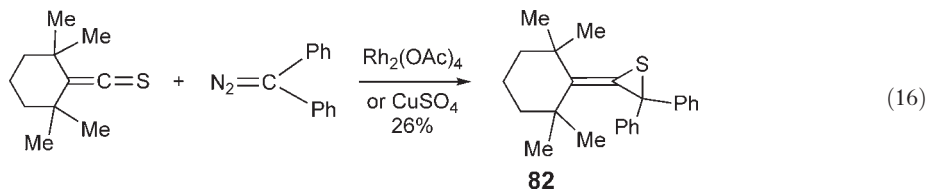
Subsequently, Chiang and Fang examined the photoionization of thiirane by means of photoionization mass spectrometry and Gaussian-3 calculations <2005JES223>. They reported that the adiabatic ionization energy is 9.051 eV, and that energies of formation of ring-opened isomers CH_3CHS^+ , CH_2CHSH^+ , and $\text{CH}_2\text{SCH}_2^+$ are 8.85, 8.91, and 9.37 eV, respectively. Major fragment ions had appearance energies of 10.71, 13.07, 11.13, 11.96, and 12.58 eV. Six dissociation channels were established for the cation $\epsilon\text{-C}_2\text{H}_4\text{S}^+$: $\epsilon\text{-C}_2\text{H}_4\text{S}^+ \rightarrow \text{CH}_3\text{CS}^+ + \text{H}$, $\text{CH}_3 + \text{HCS}^+$, $\text{H}_2\text{S}^+ + \text{C}_2\text{H}_2$, $\text{C}_2\text{H}_3^+ + \text{HS}$, $\text{CH}_2\text{CS}^+ + \text{H}_2$, and $\text{CHCSH}^+ + \text{H}_2$.

Rademacher and co-workers studied the gas-phase thermolysis of 4-substituted 3,3,5,5-tetramethyl-3,5-dihydro-4*H* pyrazoles by photoelectron spectroscopy <1996T1695>. Among the systems investigated was **76**, which afforded **77** at 470 °C. The alkylidene thiirane rearranged at 640 °C to thiol **78**. Thermolysis of **79** at 425 °C gave alkylidenethiirane **80**, which lost SO at 700 °C to yield allene **81** (Scheme 13).

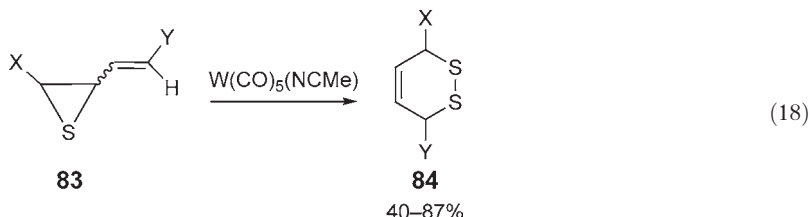


Scheme 13

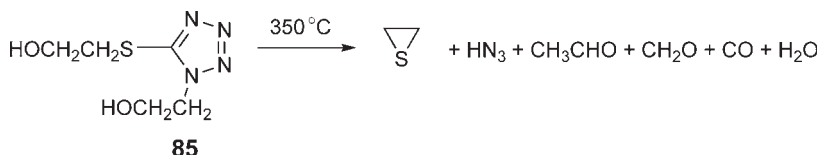
A series of alkylidene thiiranes were also generated by reaction of dialkylthioketenes with carbenes/carbeneoids <1997LA1295>. The carbenes/carbeneoids were generated by treatment of diazo compounds with $\text{Rh}_2(\text{OAc})_4$ or CuSO_4 . An X-ray structure of **82** showed a longer $\text{C}(\text{sp}^3)\text{-S}$ ring bond (1.89 Å) than that of methylenethiirane (1.84 Å) and a small angle (139.7°) between the exocyclic $\text{C}=\text{C}$ and the C-S single bond of the ring (Equation 16). The thiirenes were photolabile, rearranging upon irradiation to isomeric methylenethiirenes (Equation 17). They are analogs of allene episulfide, which is discussed under Section 1.05.7.1.1.



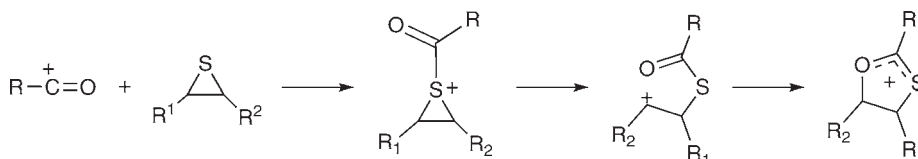
Vinylthiiranes **83** react catalytically with tungsten pentacarbonyl monoacetonitrile to afford 3,6-dihydro-1,2-dithins **84** (Equation 18). Adams *et al.* had discovered the reaction and established many features of the mechanism <2000ADCA39, 2000POL521, 1999JA3984, 1998JA1922, 1997OM1430, 1996JA10674>. Lupton and Taylor prepared eight of the relatively unstable vinylthiiranes (X = H, Me, aryl, vinyl; Y = H, Me, Ph) **83** and subjected them to the rearrangement conditions in order to provide additional mechanistic information <2002T4517>. They determined, *inter alia*, that the rate-determining step is coordination to the tungsten of the catalyst, that some products inhibit catalytic activity, that the reaction is sensitive to steric hindrance, and that a zwitterionic intermediate is not involved.



Rademacher and co-workers also studied the gas-phase thermolysis of tetrazoles by photoelectron spectroscopy and PM3 as well as *ab initio* theory <1997JHC113>. The tetrazole **85** began to decompose at 350 °C, forming thiirane among other products. Although the thiirane obviously comes from the 2-hydroxyethylthio group, 2-mercaptoethanol did not afford thiirane at temperatures up to 950 °C.

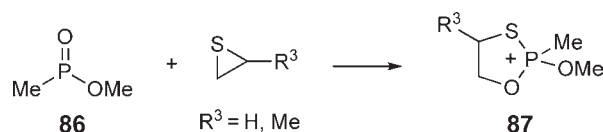


Meurer and Eberlin reported that the Meerwein reaction (Scheme 14) occurs efficiently at atmospheric pressure in a mass spectrometer in electrospray ionization (ESI) and chemical ionization experiments <2006JMP470>. The technique permits the analysis of high molecular weight thiiranes whose volatility is too low to fill the chamber under normal vacuum conditions. The acylium ion used was Me₂NCO⁺, formed from the dopant tetramethylurea. An earlier study on the Meerwein reaction in a mass spectrometer was reported <2004JAM398>.



Scheme 14

Cooks *et al.* used a miniature mass spectrometer to carry out ion/molecule reactions including the Meerwein reaction of the cation CH₃P(O)OCH₃⁺, from dimethyl phosphonate **86**, and the benzoyl cation (not shown) with thiirane and 2-methylthiirane <2003AN1112>. The latter afforded the appropriate 2-methoxy-2-methyl-1,3,2-oxathiaphospholanium ion **87**. Similar ions have been reported earlier <2000CEJ897, 1999AGE386, 1999JOC3213>.

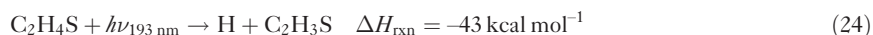
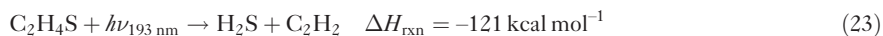
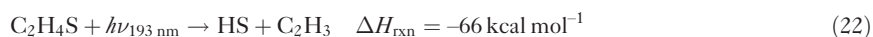


Organophosphorus compounds have agricultural and industrial applications and some are potent chemical warfare agents. Gas-phase reactions in a mass spectrometer are excellent for rapid detection and quantification of such compounds. In the gas phase, phosphonium ions were shown to undergo a Meerwein reaction with thiiranes to form oxathiaphospholanium ions (**87** and analogs) that undergo collision-induced dissociation (CID) to afford the

appropriate oxirane, thus replacing oxygen of the phosphonium ion by sulfur <2004JAM398>. The Meerwein reaction is believed to proceed by phosphonium ion addition to the sulfur center, followed by intramolecular nucleophilic attack with ring expansion to yield the 1,3,2-oxathiophospholanium ion such as **87**. The enhanced S–P orbital overlap was credited, in part, for successful competition of the Meerwein reaction with proton transfer and hydride abstraction. Product ion structures were investigated by CID tandem mass spectrometry (MS2) experiments and corroborated with DFT/HF calculations. The mechanism of the gas-phase Meerwein reaction had been studied earlier by the same group <2000CEJ897>.

Tunable synchrotron radiation, photofragment translational spectroscopy, and *ab initio* calculations were used to study the reaction products resulting for the photodissociation of thiirane at 193 nm <2001JA148>. Singlet and triplet sulfur atoms are among the products formed in some of the photodissociation channels. Branching between the channels to $S(^1D) + C_2H_4(^1A_g)$ and $S(^3P) + C_2H_4(^1A_g)$ was about equal. Most of the ground-state sulfur atoms came from a spin-forbidden process. The second peak of the ground-state sulfur atoms was tentatively assigned to the excited state of triplet ethylene ($^3B_{1u}$) with heat of formation $70 \pm 3 \text{ kcal mol}^{-1}$. Other dissociation channels were identified, and *ab initio* calculations were used to support and elaborate experimental results.

The photodissociation dynamics of a variety of cyclic sulfides, including thiirane and methylthiirane, at 193 nm were probed with tunable synchrotron radiation and photofragment spectroscopy <2001JES127>. Photodissociation of thiirane affords ethene and sulfur. The technique has several advantages over electron impact ionization, including the photoion yield spectra of the products and the ability to distinguish easily the ground state (S^3P) and the first excited state (S^1D) of sulfur. Six primary dissociation channels of thiirane that were observed are shown as Equations (19)–(24), together with the reaction energies. The products included radicals such as C_2H_3 .

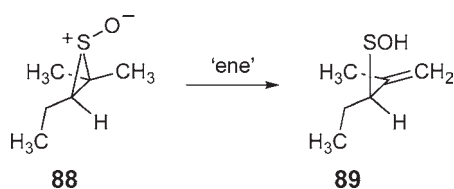


Methylthiirane had analogous channels except for the last one (Equation 24), the channel producing H.

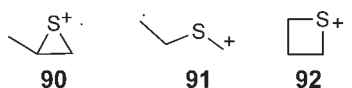
Photodissociation of propylene sulfide (2-methylthiirane) at 193 nm was studied with the Gaussian-3 method <2002PCA11025>. Three channels, affording the sulfur-containing products C_2H_3S , HS, and H_2S , were identified as well as two channels affording the sulfur atom. The reactions and the corresponding ΔE values (kcal mol^{-1}) are: $C_3H_6S \rightarrow CH_3 + C_2H_3S$ (111); $C_3H_6S \rightarrow HS + C_3H_5$ (74.5); $C_3H_6S \rightarrow H_2S + C_3H_4$ (44); $C_3H_6S \rightarrow C_3H_6 + S(^1D)$ (98, 110, 126 (three experimental values)); and $C_3H_6S \rightarrow C_3H_6 + S(^3P)$ (73).

The photoinitiated reactions of ground state $Cl(^2P_{3/2})$ atoms with thiirane were studied by means of resonance-enhanced, multiphoton ionization in a time-of-flight mass spectrometer <2005MP1785>. Rotationally cold, nascent HCl molecules were produced, with rotational energies of $0.31 \pm 0.02 \text{ kcal mol}^{-1}$. *Ab initio* calculations at the G2//MP2/6-31G(d,p) level permitted the authors to characterize transition states and molecular complexes involved in the H-abstractions. The reaction was found to be barrierless and weak pre- and postreaction complexes were located on the potential energy surface.

Foote *et al.* reported fast atom bombardment (FAB) mass spectrometry and NMR identification of episulfoxides **88** having β -hydrogen in a group *syn* to the sulfoxide oxygen <1999JOC1432>. Such sulfoxides undergo an intramolecular ‘ene’ reaction to afford an unsaturated sulfenic acid **89** at temperatures as low as -50°C . The authors succeeded in identifying the isomeric *syn*- (not shown) and *anti*-2-methyl-2-pentene episulfoxides at a low temperature by means of mass spectrometry and both ^1H and ^{13}C NMR spectroscopy.



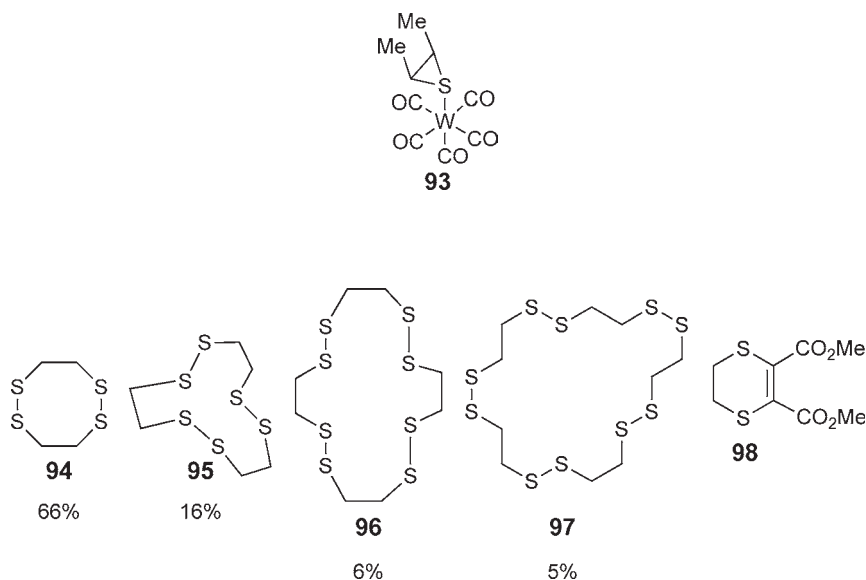
Radical ions, including that from 2-methylthiirane, were studied by mass spectrometry [<1996RCM235>](#). Ion $\text{C}_3\text{H}_6\text{S}^+$ (**90**) loses more $\text{CH}_3\cdot$ to afford an ion with m/z 59 and it also affords more $\text{CH}_3\cdot$ than isomers **91** and **92**. The major dissociation product of **90** was C_3H_5^+ . The neutralization/reionization spectrum of **90** showed a large recovery peak, as expected, indicating that the intermediate, propylene sulfide, is a stable molecule. The neutralization/reionization spectrum of the radical anion of propylene episulfide did not give a $\text{C}_3\text{H}_6\text{S}^-$ recovery peak, indicating that the anion of propylene episulfide is unstable.



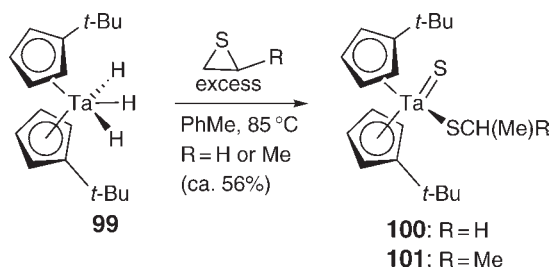
Supersonic gas chromatograph–mass spectrometry (GC–MS) apparently has several advantages over standard GS–MS methods for the detection of thermally unstable molecules [<2004JCH233>](#). A GC and MS are interfaced with a supersonic molecular beam (SMB), and activation of cold compounds in the SMB occurs by electron ionization or cluster chemical ionization. The gas flow rate is very high, permitting the elution of compounds that would normally be degraded. Ethylene sulfone was one of the analytes for which the technique was demonstrated.

1.05.3.4 X-Ray Structures

Adams *et al.* used crystallography to determine the structures of some complexes of thiirane and *cis*- and *trans*-2,3-dimethylthiirane with pentacarbonyl tungsten [<1997OM1430>](#). The structure was found to contain an S-coordinated *cis*-dimethylthiirane ligand with a pyramidal sulfur ligand coordinated to the $\text{W}(\text{CO})_5$ group **93**. The W–S distance was 2.560(2) Å and the S–C and C–C bond lengths were: S–C 1.841(7) and 1.835(7) Å; C–C 1.45(1) Å. The geometry about sulfur was pyramidal (W–S–C = 115°). A minor isomer was presumed to have *endo*-methyl groups. A similar complex of $\text{W}(\text{CO})_5$ and thiirane in CH_2Cl_2 acted as a catalyst to convert excess thiirane to the polysulfides **94–97** and ethene. Control experiments established that the tungsten complex was responsible for the catalytic activity. In the presence of excess dimethyl acetylenedicarboxylate (DMAD), an intermediate of the type $\text{SCH}_2\text{CH}_2\text{S}$ was trapped to afford dimethyl 3,6-dithiacyclohexene-1,2-dicarboxylate **98**. Much additional information was provided.

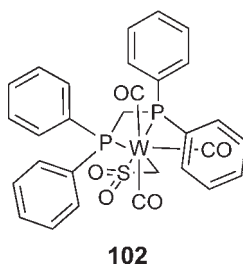
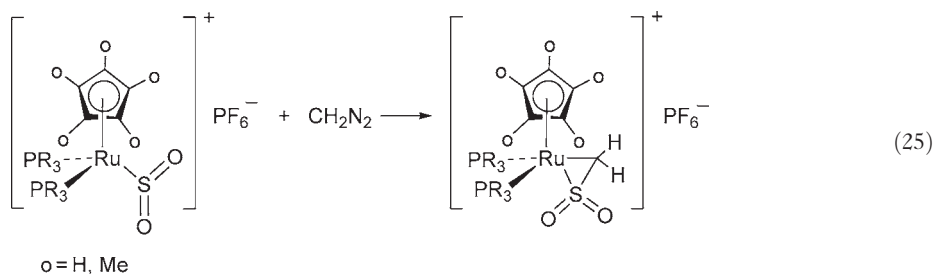


Leblanc and co-workers studied ring opening of thiiranes induced by tantalocene trihydride complexes **99** <1999JOM278>. Reaction was found to proceed via sulfur transfer and regioselective ring opening to yield tantalocene sulfide-thiolato complexes **100** and **101**, as shown in **Scheme 15**. An X-ray structure showed that there were two independent molecules of **101** in the unit cell and that the single Ta–SCH(Me)₂ bond length was 2.492(4) Å in one and 2.465 Å in the other. The Ta=S bond lengths were 2.235(4) and 2.222(4) Å.



Scheme 15

An organometallic complex, which had been prepared by means of the reaction of **Equation (25)** <1993CB679>, was used to model the preparation of analogous molybdenum and tungsten complexes, the latter shown as **102** <2002IC1079>. The structure of **102** was established by means of X-ray crystallography.

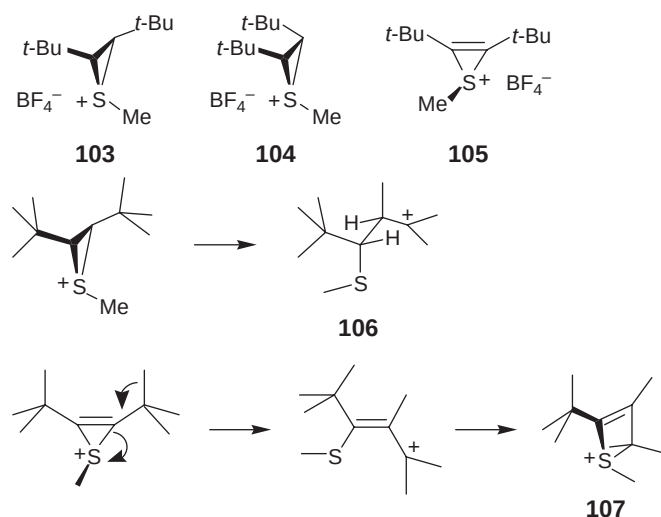


Poliakoff and co-workers reported that X-ray absorption spectra of cyclic polymethylene sulfides (C_nH_{2n}S; *n* = 2 and higher) in the continuum above the sulfur K-edge showed a shift to higher energy and a broadening with increasing ring size <2003JCP4399>. Although shifts generally depend on bond lengths too, a correlation with bond lengths was not observed.

X-ray structures of *cis*- and *trans*-di-*t*-butyl-*S*-methylthiiranium **103** and **104** and of di-*t*-butyl-*S*-methylthiirene-nium ions **105** were determined by Pasquato *et al.* <2000JOC3367, 1999PS235>. Although many differences were found, the main ones are described here. Relief of steric hindrance between the *cis*-*t*-butyl groups of the *cis*-thiiranium salt **104** caused stretching of the C(2)–C(3) bond by 0.048 Å and increased the C(2)–C(3)–C(5) and C(3)–C(2)–C(4) bond angles by about 10°, compared to the analogous *trans* salt. The thiirene-nium ion **105** had a shorter C(2)–C(3) double bond (1.278 Å) than cyclopropene (1.294 Å). Endocyclic C–S bonds were also shortened by 0.02–0.03 Å, relative to those in the saturated thiiranium ions. The *trans* ion and the thiirene-nium ion rearranged by methyl group migration to form **106** and **107**, respectively. **Table 1** lists some selected bond lengths.

Table 1 Bond lengths (Å) for structures **103–105** from X-ray data (bold) and from optimization at the RHF/3-21G**/RHF/3-21G* level of theory

	103	104	105
MeS	1.807 1.817	1.791 1.820	1.802 1.820
C(2)–S	1.850 1.887	1.849 1.880	1.819 1.860
C(3)–S	1.868 1.907	1.849 1.891	1.820 1.860
C(2)–C(3)	1.455 1.467	1.498 1.492	1.277 1.270



Structures of thietanium tetrafluoroborate and hexachloroantimonate salts of **107**, formed by anionotropic rearrangement of corresponding thiiranium salts, were obtained by X-ray crystallography and by calculation at the RHF/6-31G**/RHF/6-31G* level <2001HCA860>.

A photonic three-dimensional (3-D) crystal-type structure of a brominated thiirane/iodonium salt/ coumarin resin showed that it has a 'woodpile' structure <2004JPST115>.

1.05.3.5 Electronic Spectra and Optical Rotary Dispersion

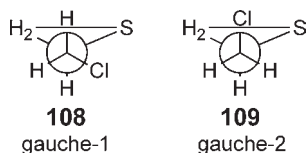
Contributions in these areas in the period 1996–2006 were not found.

1.05.3.6 IR, Raman, and Microwave Spectra

Complexes between thiirane and HF were studied by Asselin's group by means of Fourier transform infrared spectroscopy in a neon matrix at 4.5 K with a resolution of 0.1–0.5 cm^{-1} <2004JCP5241>. Corroborative calculations were carried out with the Gaussian 98 package, including electron correlation and complete optimization of geometries. A consistent picture emerged of significant coupling between the high-frequency HF stretching mode and all three H-bond modes that have been observed to date. Good agreement between experimental and calculated dissociation energies of the complex was achieved. A lower bound for the lifetime of the complex was estimated as 10 ps.

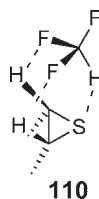
FT IR spectra of xenon solutions of chloromethylthiirane in the temperature range -55 to -150°C were used to determine its stable conformations <2001JST195>. Only gauche-1 **108** and gauche-2 **109** conformers were present in detectable amounts at ambient temperature. The enthalpy difference between the gauche-1 (38%) and the more

stable gauche-2 conformer (62%) is $1.26 \pm 0.18 \text{ kJ mol}^{-1}$ at ambient temperature. Experimental parameters were compared with MP2/631 G(d) computational values. Optimized geometries were also obtained with *ab initio* basis sets with full electron correlation up to MP2/6-311+G(2d,2p).

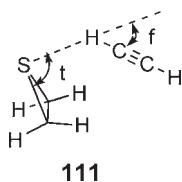


FT IR spectra and band contour analysis of the DF stretching region were also measured for the thiirane-DF complex <2004JCP7784>. Analysis of the spectra between 50 and 250 K showed three low frequency H-bond modes strongly coupled to the DF stretching mode with anharmonic coupling constants, indicating a strengthening of the H-bond upon vibrational excitation of DF.

Evidence of weak H-bonds was also seen by FT microwave spectroscopy when a mixture of thiirane and trifluoromethane was expanded in a supersonic jet <2005CPL4>. The spectra could be analyzed in terms of H-bonding by the acidic CH bond of trifluoromethane to sulfur and H-bonding of the two CH groups of thiirane to two fluorines, as in **110**.



The ethyne/thiirane complex was studied by Legon and co-workers with a microwave spectrometer <2003JCP7903>. They found that H of ethyne forms a hydrogen bond to S of thiirane. The complex **111** is nonlinear with r_0 geometry as follows: $r(\text{S} \cdots \text{H}) = 2.76(5) \text{ \AA}$, $t = 84.0(5)^\circ$, and $f = 42.9(2)^\circ$, where t is the angle made between the $\text{S} \cdots \text{H}$ bond and the C-2 axis of the thiirane ring and f is the angular deviation of the $\text{S} \cdots \text{H}-\text{C}$ nuclei from linearity. A calculated geometry at the MP2/6-31G** level of theory was very similar.



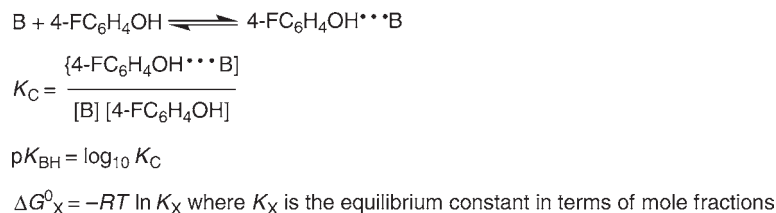
Diastereomers of 2-deuterothiirane-1-oxide were prepared and examined by IR spectroscopy. The SO chromophore has a strong absorption near 1114 and 1116 cm^{-1} for the *cis*- and *trans*-compounds, respectively. The authors were able to use a CO_2 laser for selective destruction of one diastereomer, by dissociating it to deuterated ethylene and SO, to achieve a small separation factor <1998CEJ441>.

FT microwave spectroscopy was used to measure and assign the ground-state rotational spectrum of *trans*-2,3-dimethylthiirane and to analyze the internal rotations of the methyl groups <1996ZNA1099>. The potential parameters obtained are $V_3 = 13.1678(21)$ and $V'_2 = -1.6678(25) \text{ kJ mol}^{-1}$. The measurement and assignment of the ^{13}C and ^{34}S isotopomers in the ground state allowed for determination of the molecular structure of the heavy atom frame, by using the r_s and r_0 methods. Use of methane as carrier gas, rather than rare gases, was shown to extend the range of observable transitions to those of higher rotational energy <1996ZNA1091>.

A Japanese group used surface-enhanced Raman scattering to study the reaction of methyl thiirane on a gold colloid <1999L7409>. The spectra suggested that the thiirane ring is opened on the gold surface, and the results are expected to clarify the interaction of the episulfide group with the surfaces of precious metals.

1.05.3.7 Thermodynamic Properties

The H-bond acceptor (HBA) strength of thiirane was measured, relative to those of other sulfur compounds and oxygen analogs, by analyzing the complexation of the compounds with *p*-fluorophenol in CCl₄ at 25 °C by NMR spectroscopy. The pK_{BH} scale is defined in [Scheme 16 <2005CJC138>](#).



Scheme 16

The pK_{BH} values of sulfur and oxygen compounds were found to depend on the heteroatom, oxygen bases being stronger than sulfur analogs and, for sulfur compounds, on the functionality of the sulfur atom in the sense phosphine sulfur > thioamide > thioketone > thioethers > thiol > isothiocyanate $\approx$ disulfide. There are also substituent effects depending on polarizability, inductive effects, and resonance effects. The ring size determines the percentage of s-character of the orbital that holds the lone pair of electrons. For example, the pK_{BH} of thiirane and 2-methylthiirane were 0.03 and 0.10 with corresponding ΔG_{298}^0 values of -5.92 and -6.47 kJ mol⁻¹. For ethyl methyl sulfide, pK_{BH} was 0.18 and ΔG_{298}^0 was -6.85 kJ mol⁻¹.

Dorofeeva and Gurvich evaluated the available structural parameters, fundamental frequencies, and enthalpies of formation of thiirane, thiirene, and other sulfur compounds as well as some other quantities [<1995JPCRD1351>](#). For thiirane, ideal gas values at 1 b and 300 K recommended in 1995 are: $C_p^0 = 53.603$, $S^0 = 255.569$ J K⁻¹ mol⁻¹, $\Delta_f H^0 = 81.917$ kJ mol⁻¹, and $\Delta_f G^0 = 96.897$. Analogous values for thiirene are: 54.929, 255.678, 299.973, and 275.665. The latter were all calculated because experimental numbers were not available. The situation does not appear to have changed since that time.

Gomes and Ribeiro da Silva used the B3LYP, CBS-Q, G3MP2B3, and G3 approaches to compute thermodynamic quantities for a large number of sulfur compounds, including thiirane and methyl thiirane [<2004PCA11684>](#). Calculated CS bond lengths were 1.824 and 1.827 Å for thiirane and methylthiirane, while CSC bond angles were 47.8° and 47.6°. The calculated gas-phase acidity of thiirane, to afford the C₂H₃S anion, was calculated to be ca. 1650 kJ mol⁻¹.

Calorimetric and computational studies were carried out on 1,4-dithiane as part of an effort to understand the strain energy of thiirane [<1999JOC9328>](#). The ultradiagonal strain energy of thiirane is defined as one half of the formal enthalpy of the following homodesmotic reaction: 1,4-*cyclo*-(CH₂)₄S₂ → 2 *cyclo*-(CH₂)₂S. The authors used only experimental numbers to arrive at 85.6 kJ mol⁻¹ (20.4 kcal mol⁻¹) as the strain energy of thiirane – significantly smaller than the strain energy of cyclopropane (115 kJ mol⁻¹) or that of oxirane (105.1 kJ mol⁻¹).

The diagonal method, in which thiirane is formally combined with cyclopropane to form pentamethylene sulfide, was used to estimate the value of the strain energy (18.9 kcal mol⁻¹) of thiirane [<2002JOC3884>](#). In a subsequent paper, Bach and Dmitrenko used *ab initio* computational methods to calculate the strain energy caused by introduction of a carbonyl group into three-membered ring compounds [<2006JA4598>](#). Although thiiranone was not included, the strain energy of thiirane, calculated using three-CH₂- equivalents at the CBS-Q level, was estimated as 17.2 kcal mol⁻¹. Based on formal reaction with cyclopropane, it was 19.6 kcal mol⁻¹.

1.05.3.8 Miscellaneous Properties

L. Richard reported the standard molal thermodynamic properties of more than 100 organic sulfur compounds, including cyclic sulfides [<2001GCA3827>](#). Regressions of experimental data and group additivity algorithms, combined with carbon number systematics, were used to obtain, for thiirane $T_{\text{m}} = 164$ K, $T_{\text{v}} = 328.09$ K, and $\Delta H_{\text{v}} = 6.98$ kcal mol⁻¹, where T_{m} is the melting temperature, T_{v} is the boiling point, and ΔH_{v} is the standard molal enthalpy of vaporization.

1.05.4 Thermodynamic Aspects

1.05.4.1 Physical Properties

Values of the physical properties of thiiranes or thiirenes, other than those given above, were not found.

1.05.4.2 Tautomerism

Recent references to tautomers of thiirane or thiirene were not found.

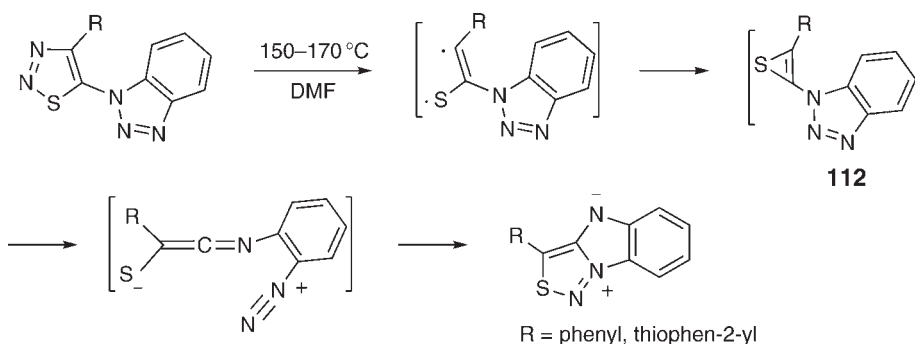
1.05.5 Reactivity of Fully Conjugated Rings – Thiirene, Thiirene-1-oxide, and Thiirene-1,1-dioxide

1.05.5.1 Introduction

The double bond in thiirene, thiirene-1-oxide, and thiirene-1,1-dioxide is expected to increase ring strain and lead, in general, to enhanced reactivity in any reactions that would lead to strain relief. Such relief would result from ring-opening reactions, extrusion of S, SO, or SO₂, or additions to the double bond that convert sp²- to sp³-carbon. Moreover, conjugation between the π -bond and sulfur, with its substituents, might be expected to lead to absorption of light and photochemical reactions.

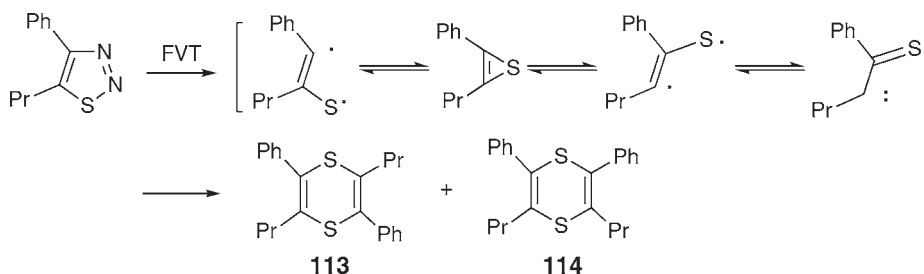
1.05.5.2 Thermal and Photochemical Reactions

Katritzky *et al.* postulated that thiirenes **112** are probable intermediates in the thermal conversion of 1,2,3-triazoles into zwitterionic benzimidazol-2-ium-4-ides (**Scheme 17**) <2002H(58)311>.



Scheme 17

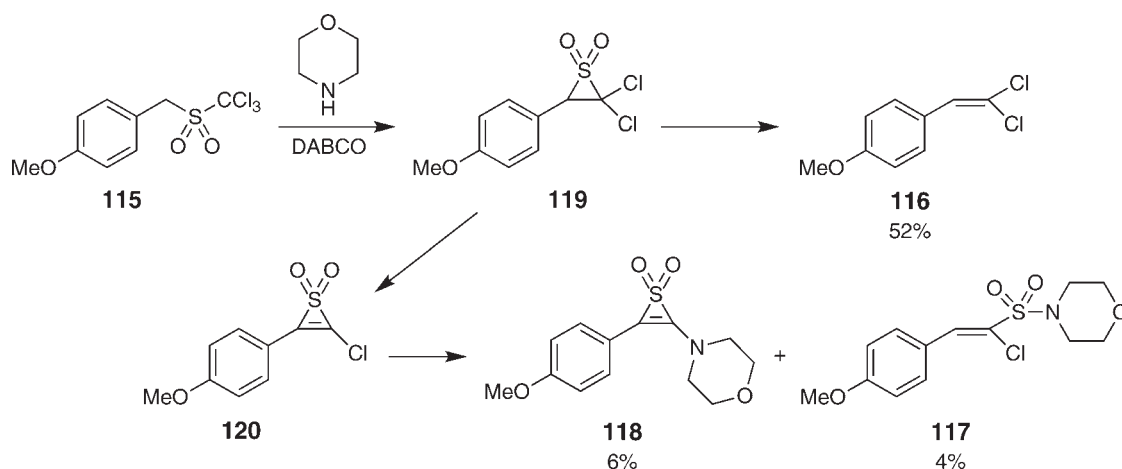
A similar reaction occurred as a result of flash vacuum thermolysis of 5-alkyl-4-phenyl-1,2,3-thiadiazoles <2004ARK61>. Thermolysis of 4-phenyl-5-propyl-1,2,3-triazole at 340 °C gave the two 1,4-dithiins **113** and **114** shown in **Scheme 18**. Diradicals, equilibrated with a thiirene and a carbene, were postulated intermediates.



Scheme 18

Photodissociation of ethylene episulfoxide was investigated with time-resolved laser-induced fluorescence spectroscopy <1996JA8417>. Photodissociation of ethylene episulfoxide at 193 and 248 nm produces SO in various vibrational states. Those states are inverted with maxima at $v'' = 1$. Franck-Condon and impulsive models failed to fit the experimental data with the cofragment (ethylene) in the ground state. When the models assumed that the cofragment was in its lowest energy triplet state, excellent agreement was obtained. A second channel suggested from the time dependence of the signal was ascribed to formation of $\text{SO}(\text{X}^3\Sigma^-)$ by relaxation of $\text{SO}(\text{a}^1\Delta)$.

Reaction of trichloromethyl *p*-methoxybenzyl sulfone **115** in refluxing toluene for 1.5 h with a mixture of 1,4-diazabicyclo[2.2.2]octane (DABCO) and morpholine gave a mixture of alkenes **116** and **117** and thiirene-1,1-dioxide **118** (Scheme 19) <1998T1901>. These products were formed from unstable 2,2-dichloro-3-(*p*-methoxyphenyl)thiirane-1,1-dioxide **119**, which loses SO_2 to give **116** in 52% yield or loses HCl to give chloro(*p*-methoxyphenyl)thiirene-1,1-dioxide **120**. Nucleophilic attack on the sulfur atom in **120** by morpholine gave styrylsulfonamide **117** in 4% yield, and nucleophilic substitution of halogen by morpholine gave isolable thiirene-1,1-dioxide **118** in 6% yield. Other trichloromethylsulfones in this reaction gave a mixture of alkenes and other products.



Scheme 19

1.05.5.3 Nucleophilic Attack at Sulfur

Nucleophilic attack at the sulfur atom was observed in reaction of chloro(4-methoxyphenyl)thiirene-1,1-dioxide with morpholine (for more details, see Section 1.05.5.2).

1.05.5.4 Nucleophilic Attack at Carbon

Papers on this subject, for the period 1996–2006, were not found.

1.05.5.5 Electrophilic Attack at Carbon

Papers on this subject, for the period 1996–2006, were not found.

1.05.5.6 Reactions Involving Cyclic Transition States – Dipolar Addition to Thiirene-1-Oxides and -1,1-Dioxides

Dipolar additions to thiirene-1-oxide or thiirene-1,1-dioxide, to produce monocyclic thiirane derivatives, were not found. A cycloaddition to a thiirene, to produce a bicyclic thiirane, was reported in 2002 <2002JA8316>.

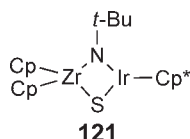
1.05.6 Reactivity of Nonconjugated Rings – Thiirane, Thiirane-1-oxide, and Thiirane-1,1-dioxide

1.05.6.1 Introduction

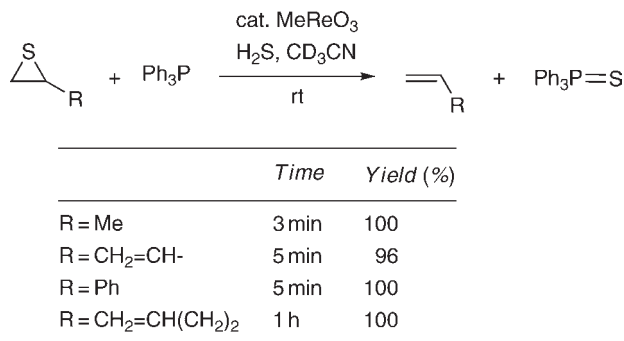
Ring-opening reactions of thiirane, thiirane-1-oxide, and thiirane-1,1-dioxide are to be expected, as such attacks could lead to relief of ring strain. Such attack could occur at carbon or at sulfur and the attacking species could be an electrophile, a nucleophile, or a radical. Deprotonation from a ring carbon is also to be expected, especially in the cases of the more acidic episulfoxides and episulfones.

1.05.6.2 Thermal and Photochemical Reactions

Very rapid desulfurization of thiiranes by a bimetallic complex was reported late in 1995. Bergman and co-workers found that $\text{Cp}_2\text{Zr}(\mu\text{-}N\text{-}t\text{-Bu})\text{IrCp}^*$, where Cp is cyclopentadienyl and Cp^* is pentamethylcyclopentadienyl, desulfurizes thiiranes via a bridging sulfido complex **121**, for which a crystal structure was obtained <1995JA10041>. Small substituent effects in the thiiranes and retention of substituent stereochemistry suggested that ring-opened intermediates are not involved and that the reaction rate might approach the diffusion-controlled limit.



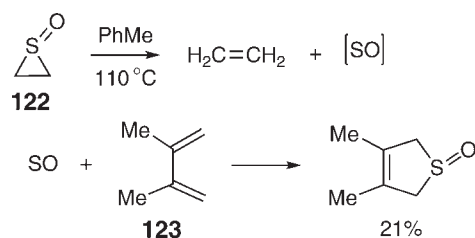
Thiiranes are rapidly desulfurized by reaction with triphenylphosphine and catalytic methyltrioxorhenium in the presence of H_2S in acetonitrile- d_3 at room temperature (Scheme 20) <1999CC1003>. H_2S reacts with MeReO_3 to form MeReO_2S , MeReOS_2 , and MeReS_3 , which are the reactive species in this reaction.



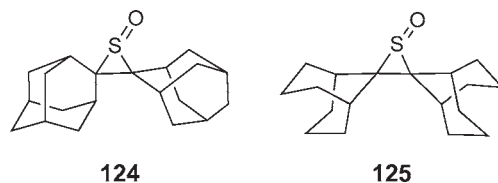
Scheme 20

The synthesis and chemistry of thiirane-1-oxides (episulfoxides) was reviewed in 1997 by Abu-Yousef and Harpp <1997SR1>. One of the many interesting processes discussed there is the thermolysis of thiirane-1-oxide **122**, at temperatures exceeding 100°C , to generate sulfur monoxide. The latter is very reactive and can be trapped by cycloaddition to 1,3-dienes such as 2,3-dimethyl-1,3-butadiene **123** (Scheme 21).

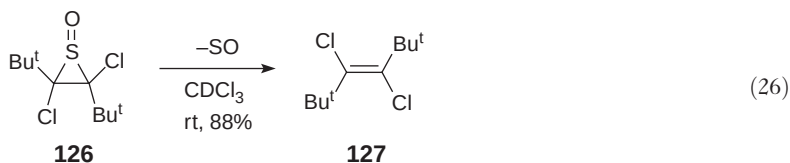
Abu-Yousef and Harpp also generated sulfur monoxide from the episulfoxides **124** and **125** <1997JOC8366>. The solvent and temperature choices were critical; best results were obtained in refluxing toluene. The yields of cycloadduct of SO, from **124**, to 2,3-dimethyl-1,3-butadiene reached 82%.



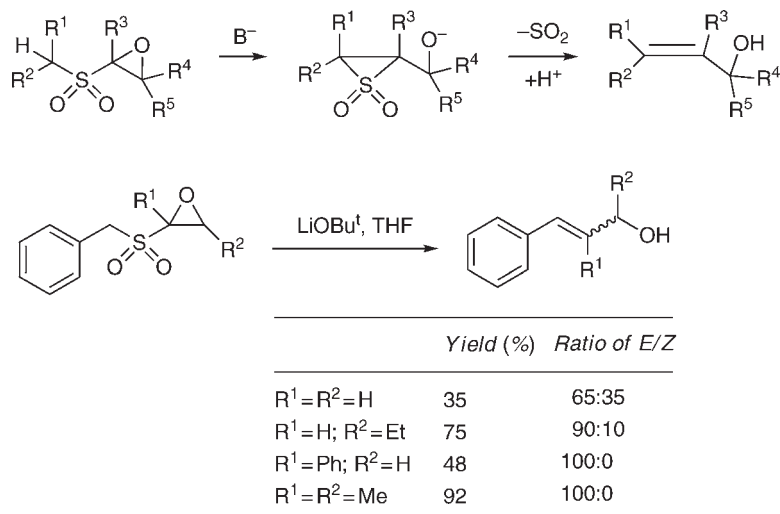
Scheme 21



Thiirane-1-oxide **126** was thermally labile and decomposed slowly at room temperature to give the alkene **127** in good yield (Equation 26) <2002HC424>.

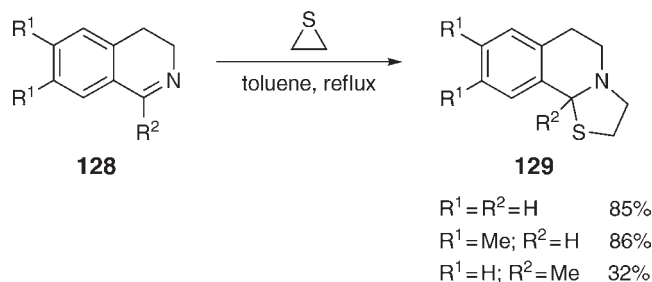


Treatment of α,β -epoxysulfones with bases, such as KO-*t*-Bu, lithium diisopropylamide (LDA), LiHMDS, or LiO-*t*-Bu in THF, led to the epoxy-Ramberg-Bäcklund reaction and gave allyl alcohols via thiirane 1,1-dioxides (HMDS = hexamethyldisilazide). The latter lose sulfur dioxide under the reaction conditions (Scheme 22) <1997TL3055>.



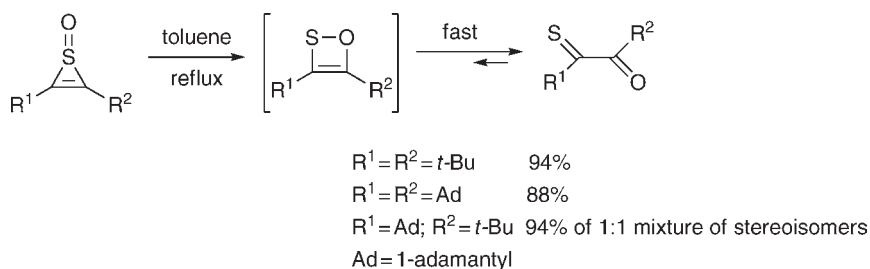
Scheme 22

Reactions of 3,4-dihydroisoquinolines **128** with thiirane in refluxing toluene for 30 h gave tetrahydrothiazolo[2,3-a]-isoquinolines **129** in moderate or good yields (Scheme 23) <2001T3499>.



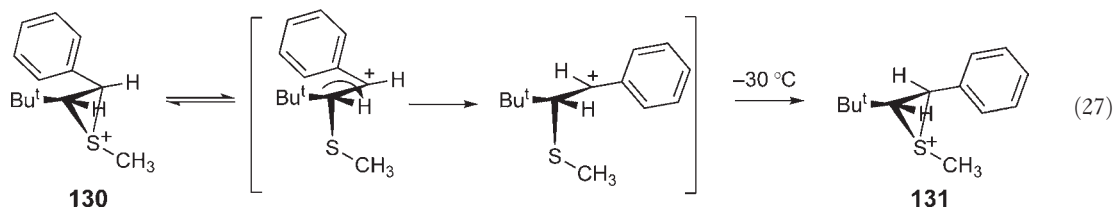
Scheme 23

It was reported that the diphenylthiirene-1-oxide, when heated in toluene, gave benzil, which is formed by air oxidation of an unstable oxothioketone <1996CHEC-II197>. 2,2'-Disubstituted thiirene-1-oxides, when heated in refluxing toluene, isomerized in high yields to corresponding α -oxothioketones (Scheme 24), which were air stable <2002HAC424>.



Scheme 24

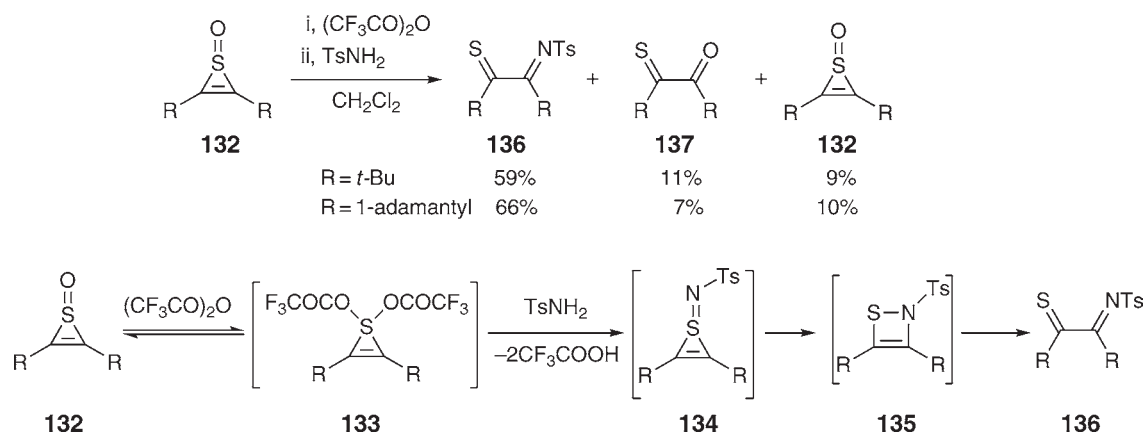
trans-2-*t*-Butyl-*trans*-3-phenyl-*r*-1-methylthiiranium hexachloroantimonate **130**, prepared prior to use from (*Z*)-3,3-dimethyl-1-phenylbut-1-ene and methylthio(bismethylthio)sulfonium hexachloroantimonate at -50°C for 30 min, isomerizes into the more stable *trans*-2-*t*-butyl-*cis*-3-phenyl-*r*-1-methylthiiranium hexachloroantimonate **131** (Equation 27) <1999CC1469>.



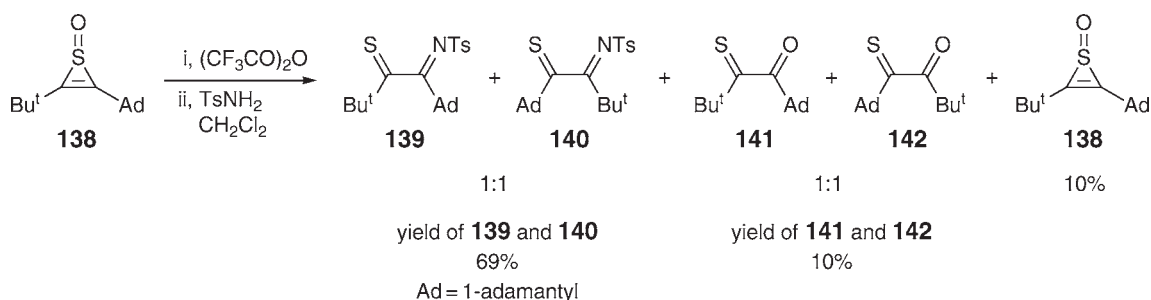
1.05.6.3 Electrophilic Attack at Sulfur

Thiirene-1-oxides **132**, substituted at the 2- and 3-positions, reacted with trifluoroacetic anhydride (TFAA) followed by *p*-toluenesulfonamide to give sulfilimines **133** via episulfurenes **134**. The latter undergo spontaneous ring expansion to form 1,2-thiazetes **135** that isomerize into α -iminoketones **136** and α -oxothioketones **137** (Scheme 25) <2002CL314>.

In reaction of asymmetrically substituted thiirene-1-oxides **138** ($\text{R} = t\text{-Bu}$, 1-adamantyl), 1:1 mixtures of **139** and **140** and of **141** and **142** were obtained in 69% and 10% yield, respectively, with recovery of 10% of starting **138** (Scheme 26).

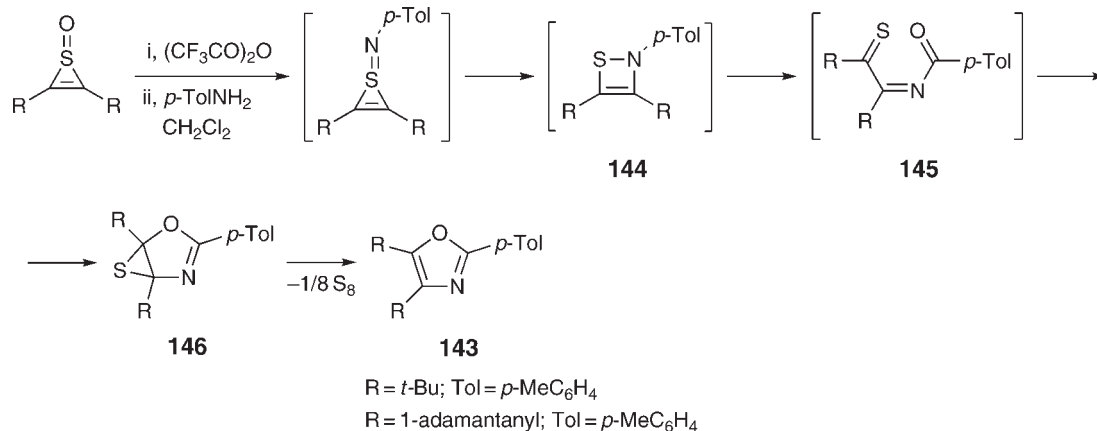


Scheme 25



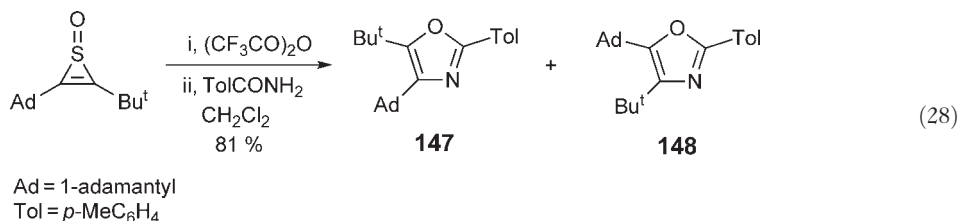
Scheme 26

When *p*-toluamide was used in place of *p*-toluenesulfonamide, the reactions led to surprising products, the oxazoles **143**. Formation of the unexpected products can be explained by assuming that the thiazetes **144**, formed in this reaction, undergo a ring opening to give **145**. An electrocyclicization of **145** leads to thiiranes **146**, which lose the sulfur to give oxazoles **143** (Scheme 27).

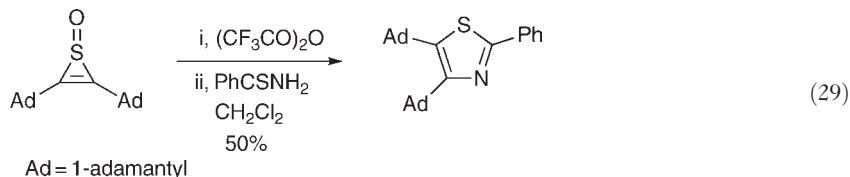


Scheme 27

When unsymmetrical thiirene-1-oxides were used in this reaction, 1:1 mixtures of both isomeric oxazoles **147** and **148** were formed in 81% yield (Equation 28).

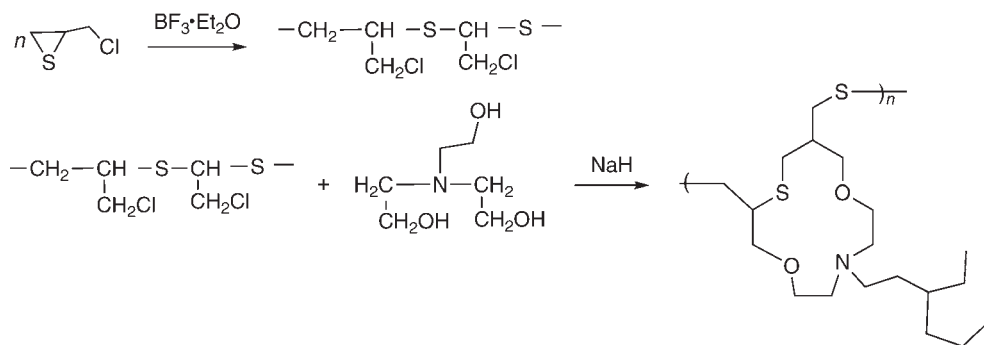


Use of thiobenzamide, instead of *p*-toluamide, in reaction with thiirene-1-oxide (R = 1-adamantyl) produced thiazole in 50% yield (Equation 29).



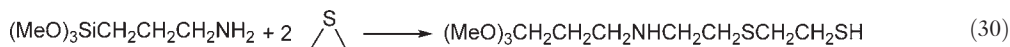
1.05.6.3.1 Lewis acids

Polymeric pseudocrown ether resins, containing azathiacrown and oxacrown ethers in 13- and 19-membered rings, were prepared as shown for the former in Scheme 28 <1997JAPS931>. The polymers adsorbed noble metals well. IR spectra of the polymeric azacrown ethers and photoelectron spectra of the uncomplexed and metal-complexed reagents were reported.



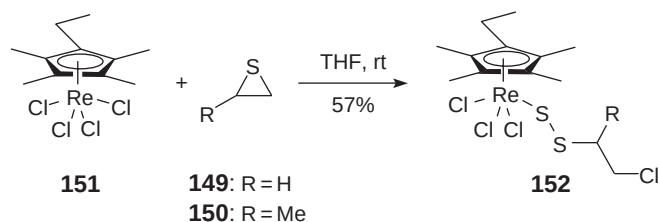
Scheme 28

Two moles of thiirane reacted with 3-aminopropyltrimethoxysilane to afford the expected product of substitution with ring opening (Equation 30) <2001POL929>. The product was then immobilized by reaction with silica gel. Removal of divalent cations (Cu, Co, Ni) from aqueous solution was demonstrated and thermodynamic parameters were determined.



Thiiranes are easily converted to β -chlorothioacetates in reaction with acid chlorides in dichloromethane at room temperature in the presence of catalytic amounts of a Lewis acid (CoCl₂, AlCl₃, FeCl₃, ZnCl₂). The best results were obtained when CoCl₂ was used as catalyst <2003SC2321>.

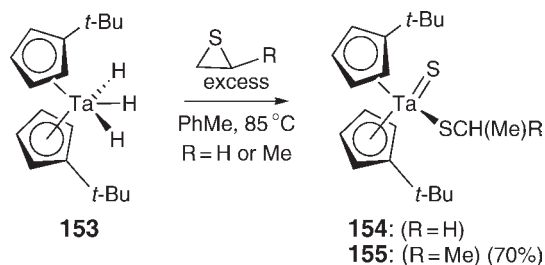
Thiirane **149** and 2-methylthiirane **150** react with rhenium complex **151** (Cp'ReCl₄; Cp' = EtMe₄C₅), at room temperature in THF solution, to form disulfide complex **152** (Scheme 29) <2000OM4925>.



Scheme 29

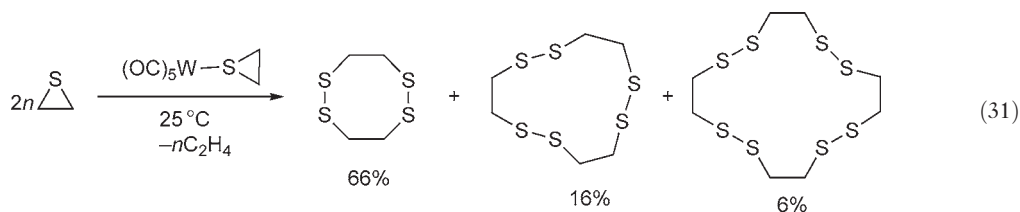
Thiirane reacted with $\text{Tp}'\text{ReO}_2$, generated *in situ* from $\text{Tp}'\text{ReO}_3$ and PPh_3 (Tp' = hydride-tris(3,5-dimethylpyrazolyl)borate), in THF at room temperature for 15 h to give a complex ($\text{Tp}'\text{ReO}_2(\text{SCH}_2\text{CH}_2\text{S})$) in 27% yield [<2004OM5268>](#).

Reactions of tantalocene trihydride complexes **153** with thiirane or 2-methylthiirane, in toluene at 85 °C for 7 h, gave new organometallic complexes **154** and **155** (Scheme 30) [<1999JOM278>](#).

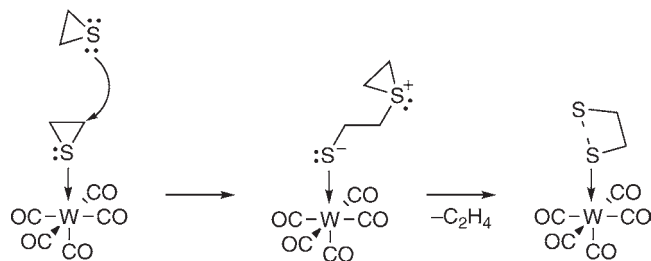


Scheme 30

Thiiranes undergo catalytic macrocyclizations in reaction with $\text{W}(\text{CO})_5$ (thiirane) to give a mixture of cyclic disulfides (Equation 31) [<1997OM1430, 2000POL521, 2000ACR171>](#).

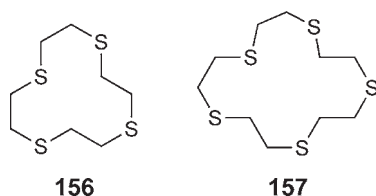


In this reaction, 2 equiv of thiirane is consumed in the formation of each disulfide group. One equivalent of alkene is also formed. The proposed mechanism of formation of cyclic disulfides from thiirane is shown in Scheme 31.

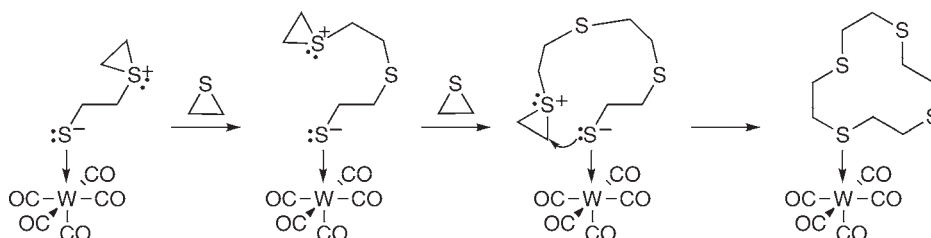


Scheme 31

First, the sulfur atom from a thiirane is added to one of the carbon atoms of the thiirane ligand of the complex, with formation of a zwitterionic intermediate. The zwitterionic intermediate undergoes elimination of ethylene to yield a reactive alkene disulfide tungsten complex. The dithietane ligands from two or more molecules, then combine to form the cyclic polysulfides. If the macrocyclization of thiirane catalyzed by $\text{W}(\text{CO})_5(\text{SC}_2\text{H}_4)$ is performed in the presence of DMAD, small quantities of polythioether macrocycles **156** and **157** are formed <1997OM1430>.



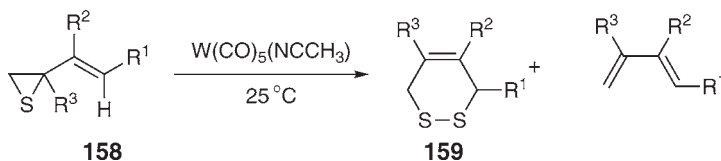
The formation of such products is easily explained by a series of ring-opening additions of thiirane to the thietanium group (Scheme 32).



Scheme 32

Carbonyl complexes of tungsten, molybdenum, chromium $\text{M}(\text{CO})_5(\text{NCCH}_3)$ ($\text{M} = \text{Mo}, \text{W}, \text{Cr}$) and $[\text{Mn}(\text{CO})_4(\text{NCCH}_3)\text{L}][\text{BPh}_4]$ ($\text{L} = \text{CO}, \text{PPh}_3, \text{PPh}_2\text{Me}, \text{PEt}_3$) were used as catalysts as well <2002JOM51, 1996JA10674, 2001ICC671>.

Vinyl thiiranes **158**, in a reaction catalyzed by $\text{W}(\text{CO})_4(\text{L})(\text{L}')$ ($\text{L} = \text{NCCH}_3, \text{L}' = \text{CO}$; $\text{L} = \text{NCCH}_3, \text{L}' = \text{PPh}_3$; $\text{L} = \text{NCCH}_3, \text{L}' = \text{PMe}_2\text{Ph}$), gave a mixture of 3,6-dihydro-1,2-dithiins **159** and 1,3-butadiene (Scheme 33; Table 2) <1998JA1922, 1999JA3984, 2000POL521, 2000ACR171>.

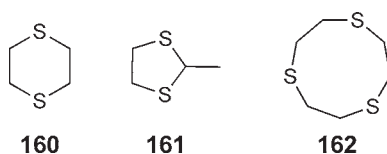


Scheme 33

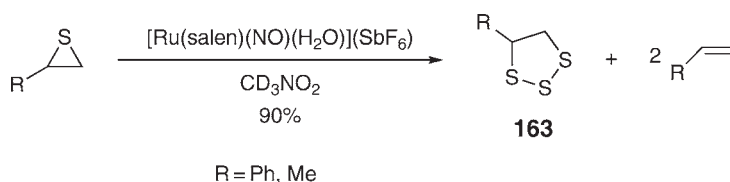
Table 2 Synthesis of 3,6-dihydro-1,2-dithiins from vinylthiiranes

R^1	R^2	R^3	Yield of 159 (%)
H	H	H	86
H	Me	H	84
Me	H	H	86
Me	Me	H	80
H	H	Me	34

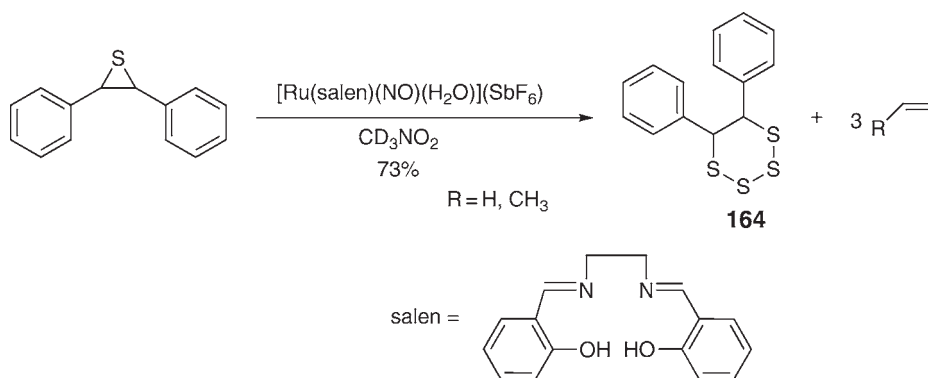
Acidic molecular sieves (HZSM-5, HY, and AIMCM-41) and alumina catalyzed the transformation of thiirane into a mixture of ethene, hydrogen sulfide, 1,4-dithiane **160**, 2-methyl-1,3-dithiolane **161**, and 1,4,7-trithiacyclononane **162** <2001CAL95>.



Ruthenium salen nitrosyl complexes react catalytically with thiiranes and convert them to olefins and 1,2,3-trithiolanes **163** (Scheme 34) or 1,2,3,4-tetrathianes **164** (Scheme 35) <2001JA4770>.



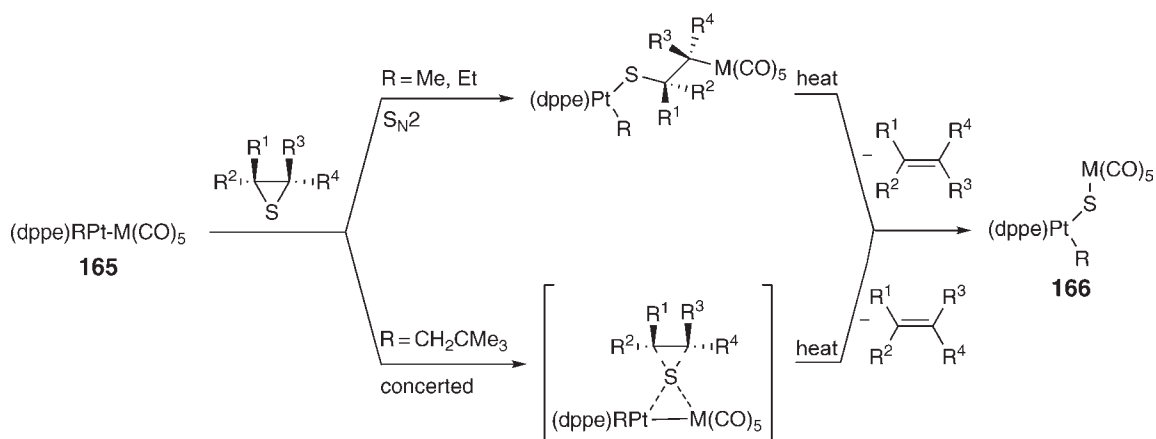
Scheme 34



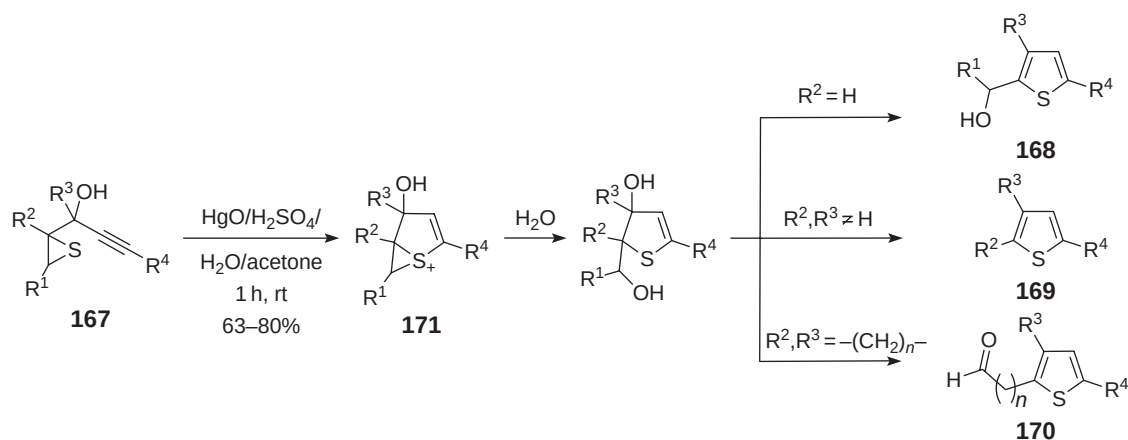
Scheme 35

Reactions of $\text{CpFeMn}(\text{CO})_7$ and $\text{Cp}^*\text{FeMn}(\text{CO})_7$ with thiirane yielded mixtures of metal disulfide complexes: $[\text{CpFeMn}(\text{CO})_5(\mu_3\text{-S}_2)]_2$ and $[\text{Cp}^*\text{FeMn}(\text{CO})_5(\mu_3\text{-S}_2)]_2$ <2004JOM1370>. Thiiranes undergo a highly regio- and stereocontrolled ring-opening reaction with organoplatinum–manganese (or rhenium) complexes $(\text{dppe})\text{RPtM}(\text{CO})_5$ **165** (M = Mn, R = Me, Et, CH_2CMe_3 ; M = Re, R = Me, Et; $\text{dppe} = \text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2$) giving heterodinuclear complexes. Thermolyses of these complexes gave mixtures of alkenes and a sulfur-bridged Pt–S–M complex **166** with retention of configuration (Scheme 36) <2000JA170>.

Mercury(II) catalyzed conversion of 2-(1-hydroxypropargyl)thiiranes **167** into thiophenes **168–170** (Scheme 37) has been reported <1997TL7785>. First, the episulfonium ions **171** are formed, followed by nucleophilic attack of water to generate the thiophenes.



Scheme 36



Scheme 37

Thiiranes such as 2-methylthiirane and epithiocyclohexane, catalyzed by rhenium complexes, are useful reagents for sulfurization of phosphorus(III) compounds (Equation (32); Table 3) <1997TL7701>. Mild reaction conditions and a short reaction time make this method of sulfurization of phosphorus(III) compounds most interesting. Possible mechanisms for the rhenium-catalyzed sulfurization of phosphorus(III) compounds are outlined in Scheme 38.

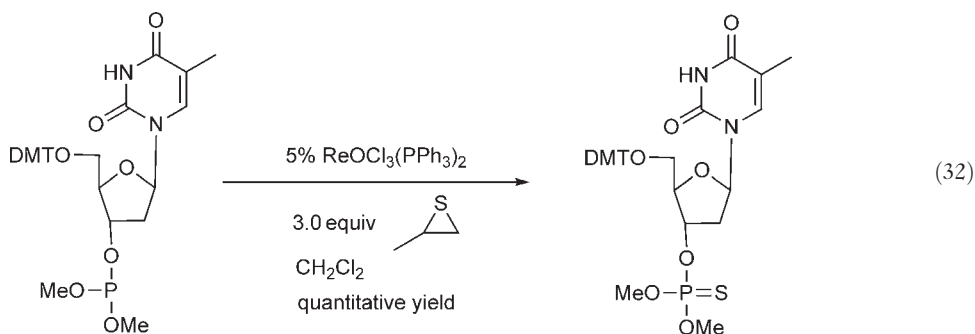
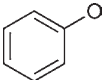
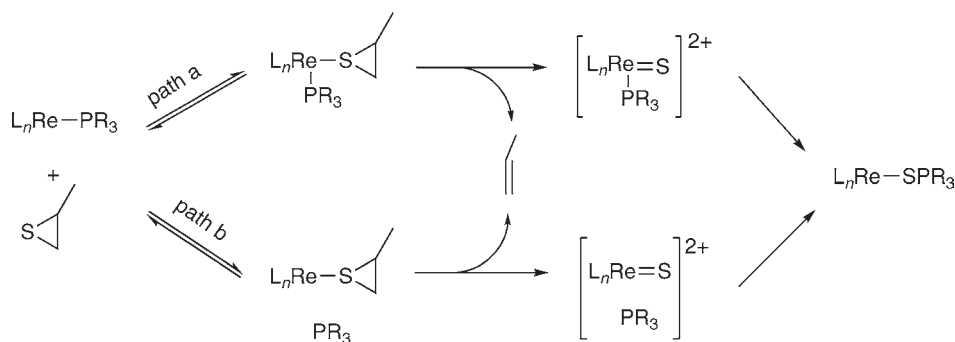


Table 3 Rhenium-catalyzed sulfurization of P(III) compounds with thiiranes
$$\text{R}_3\text{P} \xrightarrow[\text{thiirane, CH}_2\text{Cl}_2]{5\% \text{ ReOCl}_3(\text{PPh}_3)_2} \text{R}_3\text{P}=\text{S}$$

<i>R</i>	<i>Thiirane</i>	<i>Solvent</i>	<i>Time (min)</i>	<i>Yield (%)</i>
	2-Methylthiirane	CH ₂ Cl ₂	5	95
	2-Methylthiirane	CH ₃ CN	5	95
	Cyclohexene sulfide	CH ₂ Cl ₂	5	95
EtO-	2-Methylthiirane	CH ₂ Cl ₂	20	85
	2-Methylthiirane	CH ₂ Cl ₂	30	93
(CH ₃) ₂ N	2-Methylthiirane	CH ₂ Cl ₂	20	100

**Scheme 38**

1.05.6.3.2 Carbenes and related species

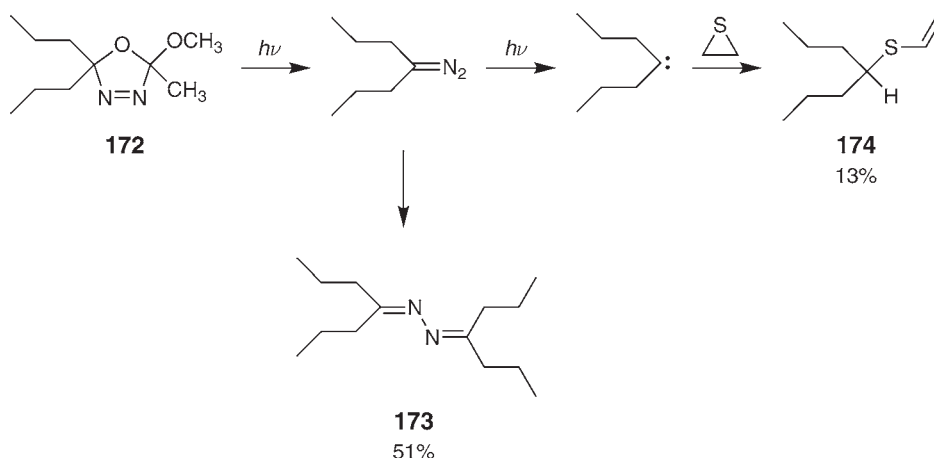
Work by Apeloig and Sklenak on reaction of thiirane with H₂Si: is discussed in [Section 1.05.2 <2000CJC1496>](#).

An earlier experimental study involved the generation of benzylchlorocarbene, phenylchlorocarbene, methoxyphenylcarbene, dimethylcarbene, cyclobutylidene, adamantylidene, and fluorenylidene by means of laser flash photolysis and their reactions with oxiranes and thiiranes [<1998JA8681>](#). Absolute rate constants ranging from 10⁴ to 10¹⁰ M⁻¹ s⁻¹ at 22 °C were measured in acetonitrile and cyclohexane. Thermally generated dimethoxycarbene was found to be inefficient at abstracting oxygen or sulfur from an oxirane or a thiirane.

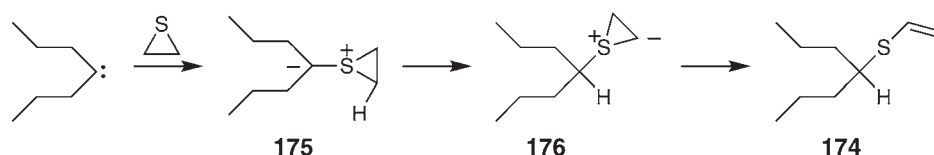
Photolysis of 2-methoxy-2-methyl-5,5-dipropyl-Δ³-1,3,4-oxadiazoline **172** with thiirane, in dichloromethane at 4 °C for 2 h, gave a mixture of azine **173** (51%), (*E*)- and (*Z*)-heptene (15%), 4-heptanone (11%), and vinyl sulfide **174** in 13% yield ([Scheme 39](#)) [<1999TL4921>](#). Formation of **174** can be explained by assuming formation of ylide **175** from dipropylcarbene and thiirane. The ylide undergoes a 1,2-proton shift to form a new ylide **176** which rearranges to vinyl sulfide **174** ([Scheme 40](#)).

1.05.6.3.3 Benzyne

The period 1996–2006 did not appear to contain papers concerned with reactions of thiiranes or thiirenes with benzyne.



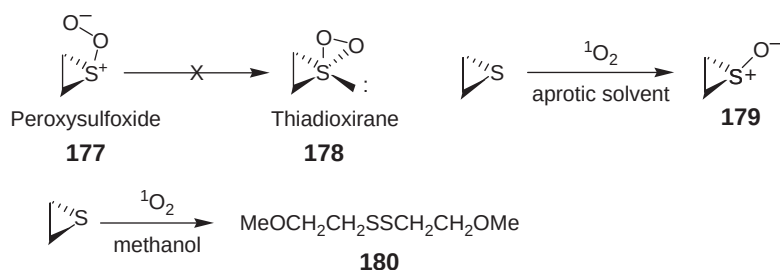
Scheme 39



Scheme 40

1.05.6.3.4 Singlet oxygen

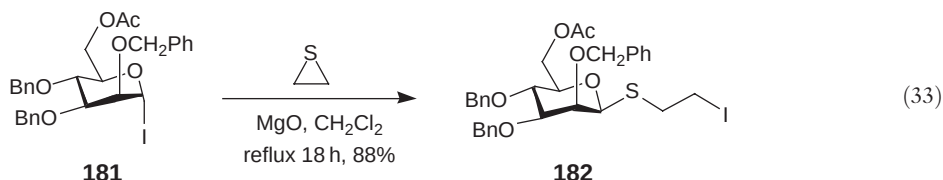
In a 1998 paper [<1998JA4439>](#), Jensen *et al.* revised a previously published theoretical study of the reactions of singlet oxygen with organic sulfides, including thiirane [<1996JOC4107>](#). In aprotic solvents, a weakly bound peroxysulfoxide **177** is formed first, with a small barrier caused by entropy. The peroxysulfoxide may decay back to triplet oxygen and thiirane or it may be trapped by sulfoxides. A thiadioxirane **178**, postulated previously, is not formed. In aprotic solvents, thiirane forms thiirane-1,1-dioxide **179**, but in methanol thiirane reacts with singlet oxygen to afford bis(2-methoxyethyl)disulfide **180**. The reaction is very complicated and most of the study concerns dialkyl sulfides.



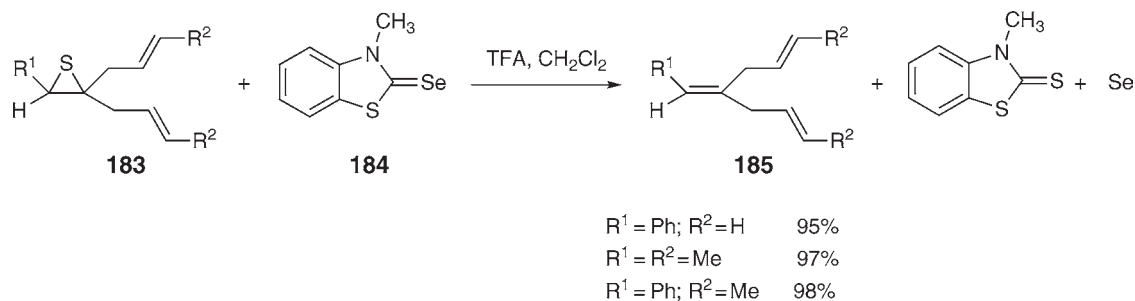
1.05.6.4 Nucleophilic Attack at Sulfur

Nucleophilic attack at sulfur of thiirane, thiirane-1-oxide, and thiirane-1,1-dioxide is to be expected, as such attacks (substitutions) relieve ring strain if attack is concerted with ring opening.

Glycosyl iodides **181** reacted with thiirane in dichloromethane at reflux for 18 h in the presence of magnesium oxide to give 2-iodoethylthio glycoside **182** in 88% yield (Equation 33) [<2004OL973>](#).

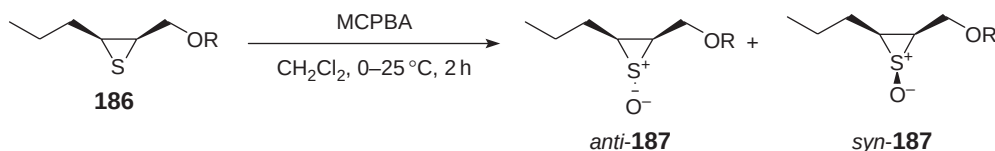


2,2-Bisallylthiiranes **183** undergo desulfurization in reaction with 3-methyl-2-selenoxabenzothiazole **184** in dichloromethane, or with triphenylphosphine in boiling THF, to afford corresponding trienes **185** in quantitative yield (Scheme 41) <1995TL171>.



Scheme 41

Oxidation of thiiranes **186** with *m*-chloroperbenzoic acid (MCPBA), in dichloromethane at 0–25 °C for 2 h, gave a mixture of *anti*- and *syn*-**187** (Scheme 42). The stable *anti*-**187** were isolated in satisfactory yield (Table 4) <1997PS223>.

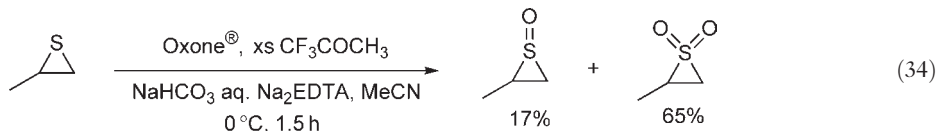


Scheme 42

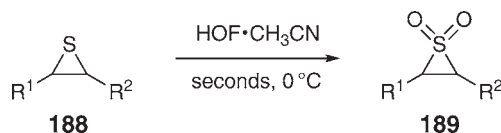
Table 4 Oxidation of thiiranes **186** with MCPBA

<i>R</i>	<i>Initial anti:syn ratio</i>	<i>Isolated yield of anti-187 (%)</i>
H	1.5:1	37
CO(CH ₂) ₂ COOH	4:1	70
	6:1	45
TBDMS	7.5:1	50
	3.5:1	64

Thiirane-1,1-dioxides are quite unstable and difficult compounds to make. The first stable thiirane-1,1-dioxides were synthesized by oxidation of thiiranes using a mixture of Oxone[®]/trifluoroacetone (Oxone[®] = 2KHSO₅·KHSO₄·K₂SO₄; Equation 34) <1997TL5873>. If thiiranes with long chains were used, the corresponding 1,1-dioxides were obtained in low yields (e.g., 2-decylthiirane gave the corresponding 1,1-dioxide in 32% yield).



Oxidation of thiiranes **188** to 1,1-dioxides **189** was carried out by HOF·CH₃CN under very mild conditions (Scheme 43; Table 5) <2006OL1213>. In this method, the 1,1-dioxides were formed in excellent yields in a few seconds.

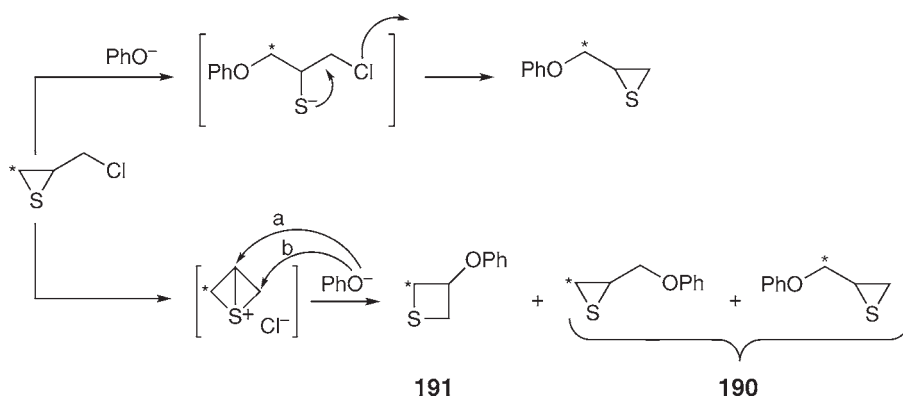


Scheme 43

Table 5 Oxidation of thiiranes **188** with HOF·CH₃CN

R^1	R^2	Yield of 189 (%)
H	H	90
H	Me	87
H	<i>n</i> -C ₁₀ H ₂₁	80
H	CH ₂ Cl	90
H	CH ₂ OPh	85
CH ₃	(CH ₃) ₂ CH	88
CH ₃	CH ₃ (CH ₂) ₃ CH ₂	95
Ph	Ph (<i>cis</i>)	80

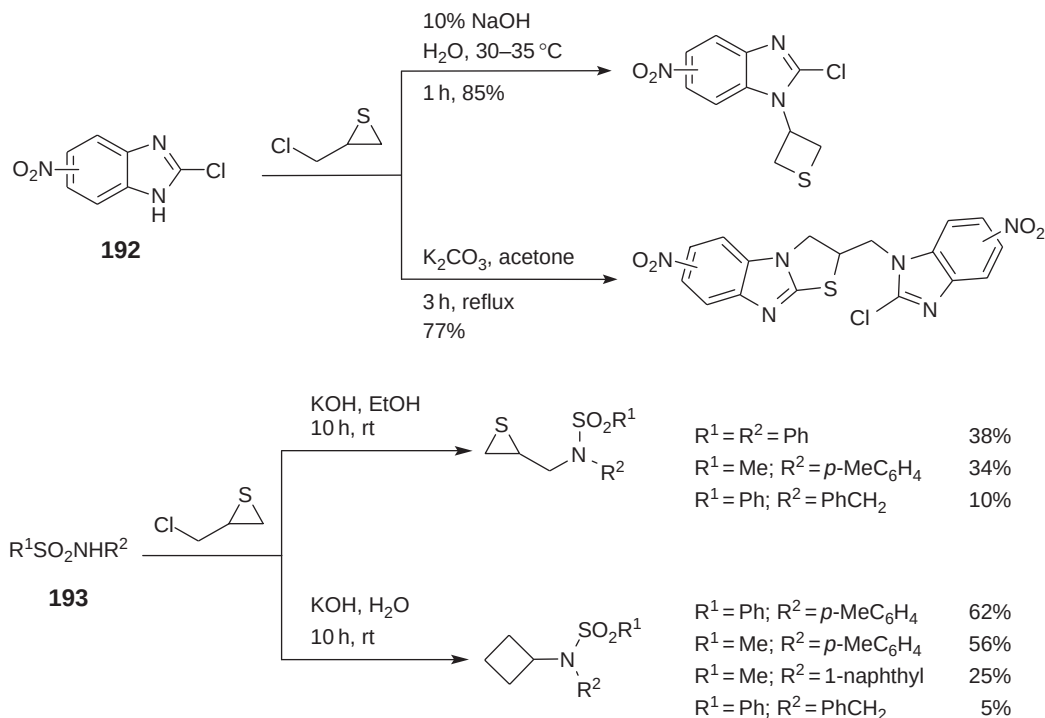
Reactions of (α-chloromethyl) thiiranes with sodium phenolate in various solvents were investigated <2003RJO226>. Reaction of 2-(chloromethyl) thiirane-3,3-*d*₂ with PhONa in 85% EtOH gave a mixture of the labeled (phenoxyethyl) thiiranes **190** and thietane **191** in 30% yield, as a 5:2 mixture of **190**:**191** (Scheme 44).



Scheme 44

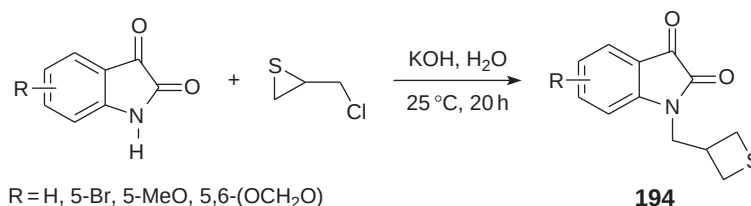
Increased polarity of the solvent favors the thiirane–thietane rearrangement. A similar study with various nucleophiles in aqueous sodium hydroxide has been reported <1999MI54>.

In reaction of (chloromethyl) thiirane with benzimidazole **192** or with sulfonamides **193**, the structures of the products formed depend on the solvent (**Scheme 45**) <2002RJO1507, 2005RJO1023>.



Scheme 45

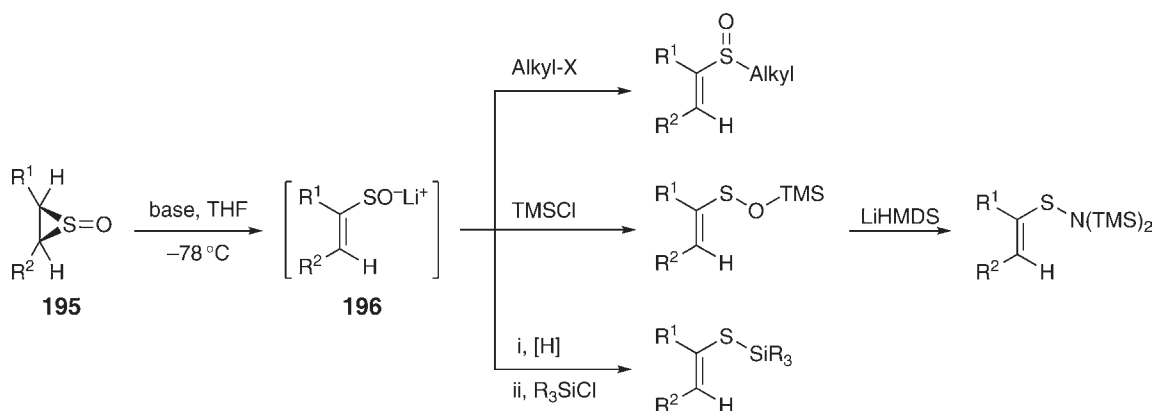
Butkevich *et al.* showed that reaction of chloromethylthiirane with N-unsubstituted isatins leads to *N*-(thietan-3-yl) isatins **194** in 22–34% yield (**Scheme 46**) <2006RJO1244>.



Scheme 46

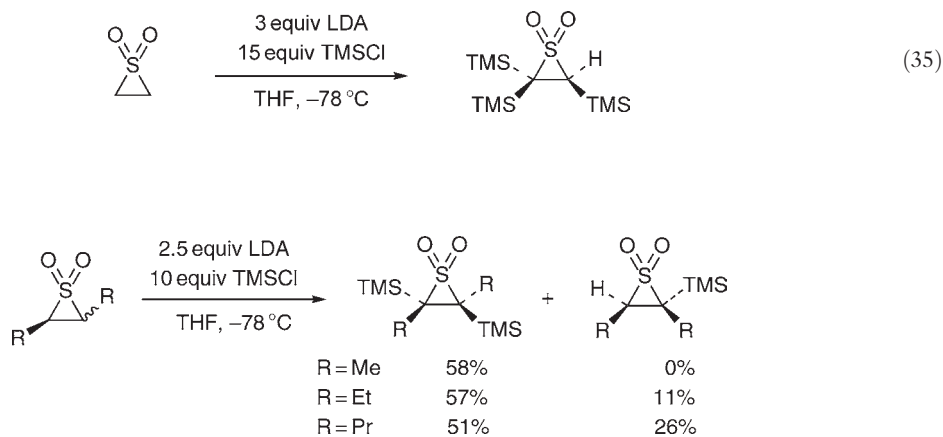
1.05.6.5 Nucleophilic Attack at Carbon

Thiirane-1-oxides **195** reacted with organolithium reagents (e.g., LDA, MN(TMS)₂ (M = Li, Na, K), RLi (R = *n*-butyl, CH₃, C₆H₅, (CH₃)₃C)) to give (*E*)-1-alkenesulfeneate anions **196** in 50–75% yield. The anions were trapped with an electrophilic reagent, (**Scheme 47**) <1995JA184, 1996JOC4232, 1998CJC213, 1998SL96, 2000SUL111, 1996T8387>.

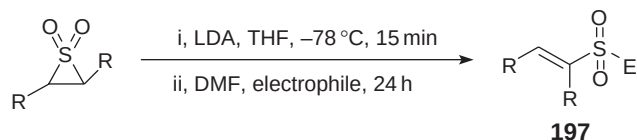


Scheme 47

Reaction of thiirane-1,1-dioxides with LDA followed by TMSCl at -78°C in THF gave, depending on the structure of the starting thiirane-1,1-dioxide, mono-, bis-, or tris-trimethylsilylthiirane-1,1-dioxides (Equation 35; Scheme 48) <1997JP1323>. When TMSCl was replaced by alkyl halides in dimethylformamide (DMF), the vinyl sulfones **197** were formed (Scheme 49; Table 6).



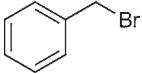
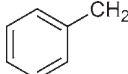
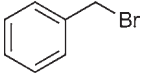
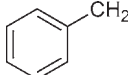
Scheme 48

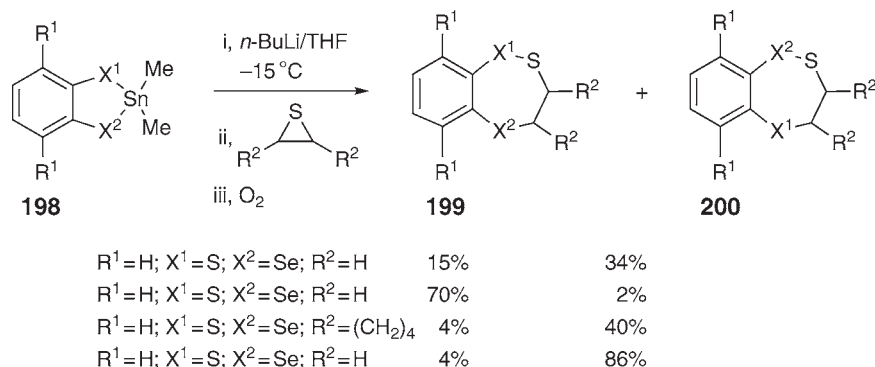


Scheme 49

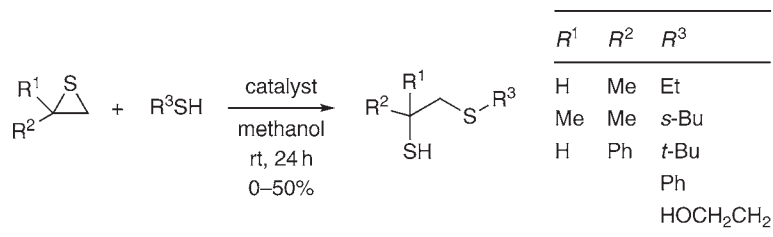
Reaction of 1,3,2-benzodichalcogenastannoles **198** with *n*-butyllithium was used to form a nucleophilic anion which reacted with thiiranes to give 1,2,5-benzotrichalcogenepins **199** and **200** in moderate to good yields (combined yields up to 90%; Scheme 50) <1997TL5821>.

Table 6 Synthesis of vinyl sulfones **197** from thiirane 1,1-dioxides

<i>R</i>	<i>Electrophile</i>	<i>E</i>	<i>Yield (%)</i>
H	CH ₃ I	CH ₃	41
Me	CH ₃ I	CH ₃	40
CH ₃ CH ₂	CH ₃ I	CH ₃	56
Me			62
Et			51
Me	H ₂ C=CHCH ₂ Br	H ₂ C=CHCH ₂	47
Et	H ₂ C=CHCH ₂ Br	H ₂ C=CHCH ₂	65
Me	ClCH ₂ COOC ₂ H ₅	CH ₂ COOC ₂ H ₅	41
Et	ClCH ₂ COOC ₂ H ₅	CH ₂ COOC ₂ H ₅	68

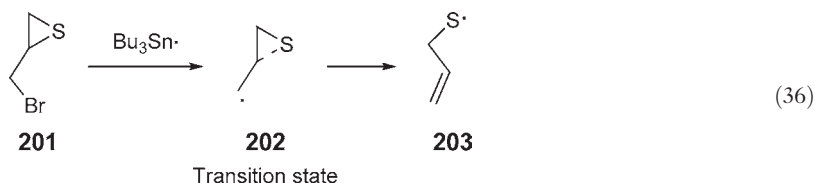
**Scheme 50**

2-Mono- and 2,2-disubstituted thiiranes reacted with alkylthiols, in the presence of zeolites or triethylamine in methanol (lower yields of product were obtained when other solvents were used) at room temperature, to give alkylthioethanethiols as major products (**Scheme 51**) <1998JP22441>.

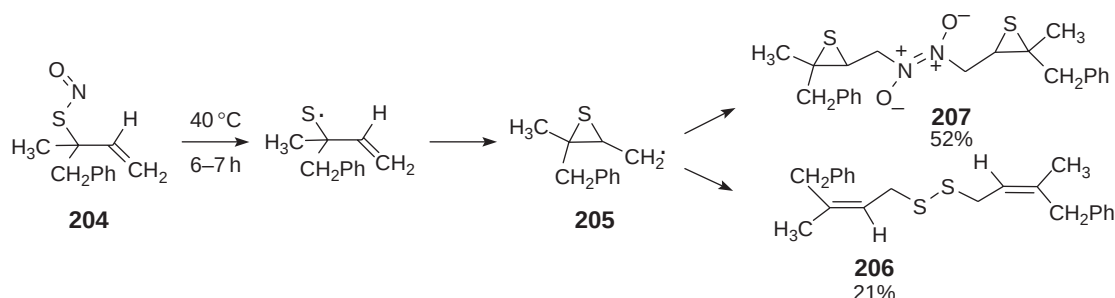
**Scheme 51**

1.05.6.6 Radical Reactions

Franz *et al.* determined absolute rate expressions for reactions of tributylstannyl radicals with 2-methylthiirane to generate propene and for abstraction of the bromine atom from bromomethylthiirane **201** <2004JOC1020>. Those expressions are: $\log(k_S/\text{M}^{-1} \text{s}^{-1}) = (8.75 \pm 0.91) - (2.35 \pm 1.33)/\theta$ and $\log(k_{\text{Br}}/\text{M}^{-1} \text{s}^{-1}) = (9.21 \pm 0.20) - (2.23 \pm 0.28)/\theta$, where $\theta = 2.3RT/\text{kcal mol}^{-1}$. The value of k_{Br} was $4.21 \times 10^8 \text{ M}^{-1} \text{s}^{-1}$ at 353 K. Abstraction of Br from bromomethylthiirane is about 7 times faster than abstraction of sulfur and was taken to mean that abstraction of Br is concerted with ring opening to generate the allylthiyl radical. That conclusion was confirmed with computation at the B3LYP/6-31G(d) and B3LYP/6-311+G(2d,2p)/B3LYP/6-31G(d) levels of theory. Pasto had concluded earlier, on the basis of calculations at the UHF 6-31G* level, that the thiiranylmethyl radical **202** is not at an energy minimum but opens spontaneously to the allylthiyl radical **203** (Equation 36) <1996JOC252>.

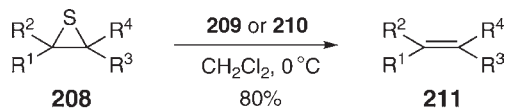


Motherwell and co-workers generated thiiranylmethyl radicals **204** by heating allylic thionitrites **205** at 40 °C <2002CC2394>. Four systems other than the one shown in Scheme 52 were reported and both benzene and dichloromethane solutions were used. Yields were structure and solvent dependent, and in some cases the yield of disulfide **206** was zero. The nitroso dimer **207** was a mixture of diastereomers in the case illustrated but a single diastereomer in some other cases.



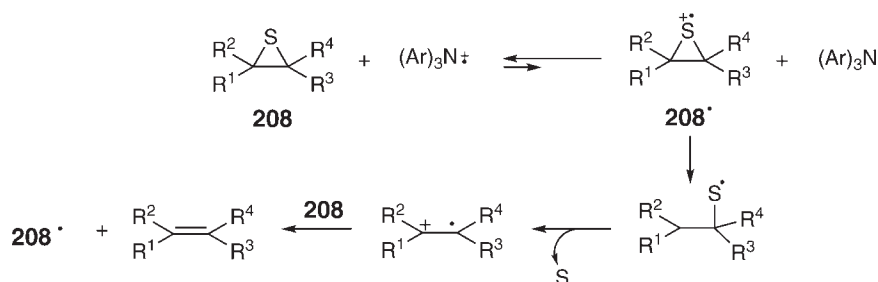
Scheme 52

Reaction of various thiiranes **208**, catalyzed by aminium salts (tris-(4-bromophenyl)aminium hexachloroantimonate **209** or tris-(2,4-dibromophenyl)aminium hexachloroantimonate **210**) in freshly distilled dichloromethane, led to desulfurization of starting thiiranes to alkenes **211** in good yield (typically 80%) (Scheme 53) <1995T8935>. The mechanism of desulfurization of thiiranes catalyzed by aminium salts is presented in Scheme 54.



- a:** $\text{R}^1 = \text{H}; \text{R}^2 = \text{Ph}; \text{R}^3 = \text{R}^4 = \text{CH}_2 = \text{CH} - \text{CH}_2$
b: $\text{R}^1 = \text{R}^4 = \text{H}; \text{R}^2 = \text{Ph}; \text{R}^3 = \text{CH}_2(\text{CH}_3)\text{CH} = \text{CH}_2$
c: $\text{R}^1 = \text{H}; \text{R}^2 = \text{Ph}; \text{R}^3 = \text{R}^4 = \text{CH}_2\text{CH} = \text{CHCH}_2\text{CH}_3$
d: $\text{R}^1 = \text{R}^4 = \text{H}; \text{R}^2 = \text{Ph}; \text{R}^3 = \text{PhCH} = \text{CHCH}_2$
e: $\text{R}^1 = \text{R}^3 = \text{H}; \text{R}^2 = \text{Ph}; \text{R}^4 = \text{CH}_2 = \text{CH} - \text{CH}_2$

Scheme 53



Scheme 54

The reactions of thiiranes with alcohols, water, or acetic acid, in the presence of equimolar amounts of cerium(IV) trifluoromethanesulfonate, led to corresponding disulfides in 75–90% yield. When the reaction was carried out without nucleophiles in carbon tetrachloride, only the cyclic disulfide was formed (Equation (37); Table 7) <1998SC347>. A radical cation from thiirane and Ce(IV) is formed first. It attacks a molecule of solvent and the resultant radical dimerizes to form the disulfide.

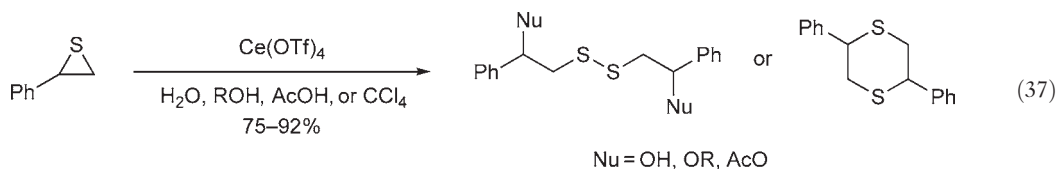
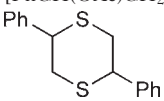


Table 7 Reaction of thiiranes with NuH cerium(IV) triflate

Solvent	Mole ratio of Ce(OTf) ₄ :thiirane	Time (h) (Temp. (°C))	Product	Yield (%)
MeOH	1.5	1 (25)	[PhCH(OMe)CH ₂ S] ₂	87
EtOH	1	1 (80)	[PhCH(OEt)CH ₂ S] ₂	90
Me ₂ CHOH	1	4 (80)	[PhCH(OCHMe ₂)CH ₂ S] ₂	90
H ₂ O/MeCN	1	2 (80)	[PhCH(OH)CH ₂ S] ₂	89
HOAc	1	2 (80)	[PhCH(OAc)CH ₂ S] ₂	80
CCl ₄	1	2 (80)		80

1.05.7 Reactivity of Substituents at Ring Carbon Atoms – Allene Episulfides, Thiiranones, and Thiiranimines

1.05.7.1 Introduction

Allene episulfides, thiiranones, and thiiranimines have a common feature – the double bond exocyclic to a three-membered ring. That feature is expected to result in significant strain, in general, above that of thiirane and to increased reactivity.

1.05.7.1.1 Allene episulfide (methylene thiirane)

Allene episulfide itself is known but papers concerned with derivatives were the only ones located for the period 1996–2006. Geng *et al.* studied the system theoretically <2005HX1402>. This subject is also discussed in Section 1.05.9.1.2.

1.05.7.1.2 Thiiranones (α -thiolactones)

α -Thiolactones are expected to be very reactive with regard to nucleophilic addition to the carbonyl group. Examples of such a reaction were not found, but α -thiolactones or sulfur-alkylated cations of such lactones have been postulated as reactive intermediates in various processes <2002JMP709, 2001RJO326, 2005HX1402, 1998JOC7421>. Some of those references are mentioned briefly under Section 1.05.2.

1.05.7.1.3 Thiiranimine

Thiiranamine itself is known and various derivatives have been isolated, but recent papers were not found. A Canadian group studied conjugate acids of various thiiranimines in 1995 <1995CJC1468>.

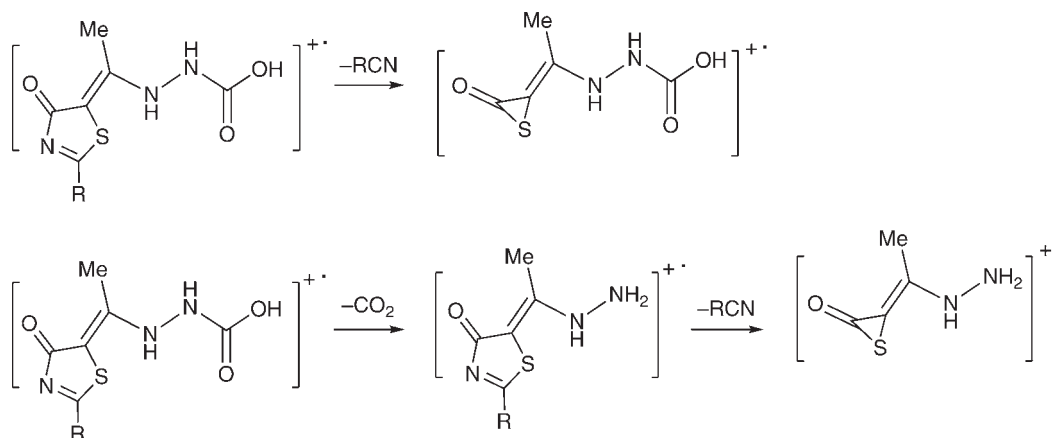
1.05.7.2 Thermal and Photochemical Reactions

1.05.7.2.1 Allene episulfide

Thermal or photochemical reactions of allene episulfide do not appear to have been reported in the period 1996–2006.

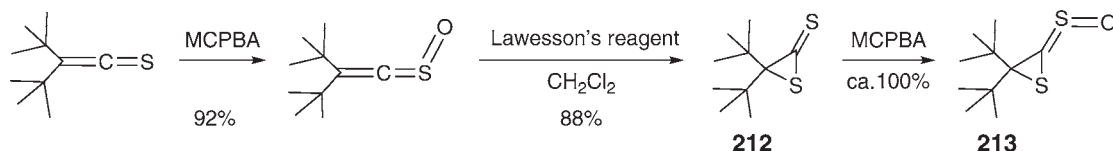
1.05.7.2.2 Thiiranone

Thiiranone fragments were proposed to explain the fragmentations observed in the electron ionization of substituted 2-thiazolin-4-ones (Scheme 55) <2002JMP709>.



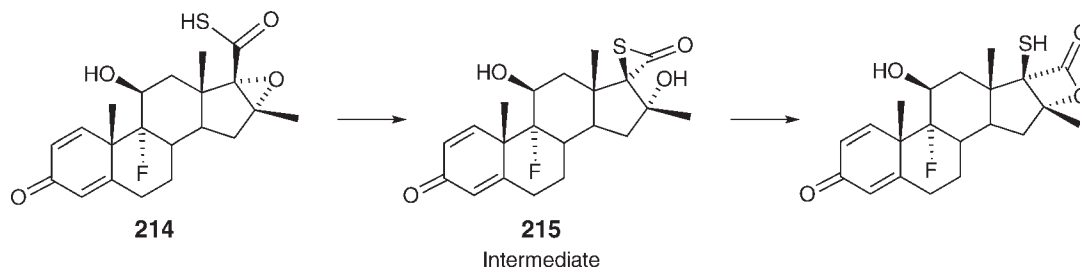
Scheme 55

There is also a report concerning two sulfur derivatives, namely 3,3-di-*t*-butylthiirane-2-thione **212** and the corresponding 1-oxide **213** <2004JA9508>. Those compounds were prepared from reaction of di-*t*-butylthioketene *S*-oxide with Lawesson's reagent (Scheme 56). An X-ray structure of **213** gave the following bond lengths (Å): S(1)–C(1) = 1.923, S(1)–C(2) = 1.697, C(1)–C(2) = 1.464, C(2)–S(2) = 1.608, S(2)–O(1) = 1.485. Other parameters are listed in the original paper.



Scheme 56

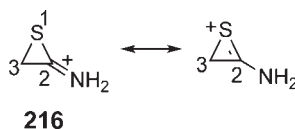
A spirocyclic α -thiolactone **215** was considered as a potential intermediate in the rearrangement of a $16\alpha,17\alpha$ -epoxy- 16β -methylandrostande- 17β -carbothioic acid **214** (Scheme 57) <1998JOC7421>.



Scheme 57

1.05.7.2.3 Thiiranimine

Ab initio calculations were used to explore the $C_2H_4NS^+$ surface and to compare it with the $C_2H_4NO^+$ surface <1997JST117>. The former includes the thiiraniminium ion **216** which was found to have the lowest energy and the following bond lengths (Å) at the MP2(full)/6-311G(dp) level: C(2)–N = 1.295, C(2)–S(1) = 1.651, C(3)–S(1) = 1.884, and C(2)–C(3) = 1.450. The contributing structure **216** describes the species best.



1.05.8 Reactivity of Substituents at Sulfur – Thiiranium Ions, Thiirenium Ions, and Episulfuranes

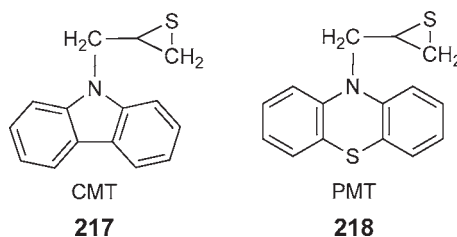
1.05.8.1 Introduction

Substitution at sulfur of thiirane without ring opening necessarily places a positive charge on that atom, with resultant high reactivity toward anions and neutral species with lone pairs.

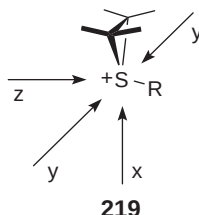
1.05.8.2 Thermal and Photochemical Reactions

These reactions are discussed in the following sections.

Cationic polymerization of thiiranes CMT (9-(thiiran-2-ylmethyl)-9*H*-carbazole) **217** and PMT (10-(thiiran-2-ylmethyl)-10*H*-phenothiazine) **218** was studied by a Lithuanian group <2002JPH63>. Initiators were di-(*n*-butylphenyl)iodonium tetrafluoroborate (BPIT), diphenyliodonium tetrafluoroborate, cyclopropyldiphenylsulfonium tetrafluoroborate, and (η^5 -2,4-cyclopentadien-1-yl)[1,2,3,4,5,6- η](1-methylethyl)benzene]-iron(+)-hexafluorophosphate(–1). The influences of temperature and initiator concentration on the polymerization rate and the conversion limit were determined. The values of initiator exponent and activation energy for the photopolymerization of CMT and PMT initiated with BPIT in 1,2-dichloroethane was established.



Modena and *et al.* concluded, on the basis of experimental evidence, that nucleophilic substitution at thiiranium and thiirenium sulfur is sensitive to substituents, and that dialkyl disulfides approach the sulfur in a perpendicular sense, not in the collinear sense shown as the *x*-direction in **219**; see also Section 1.05.8.3 <1999JA3944, 2000CEJ589>. Their rationale for the apparent difference between experimental and theoretical substitution mechanisms focused on bicentric versus monocentric nucleophiles. The former attack thiiranium ions in the *x*-direction and the latter in the *y*-direction. Radom's group disagrees on the basis of theory <1998JA7063, 2000CEJ590>.

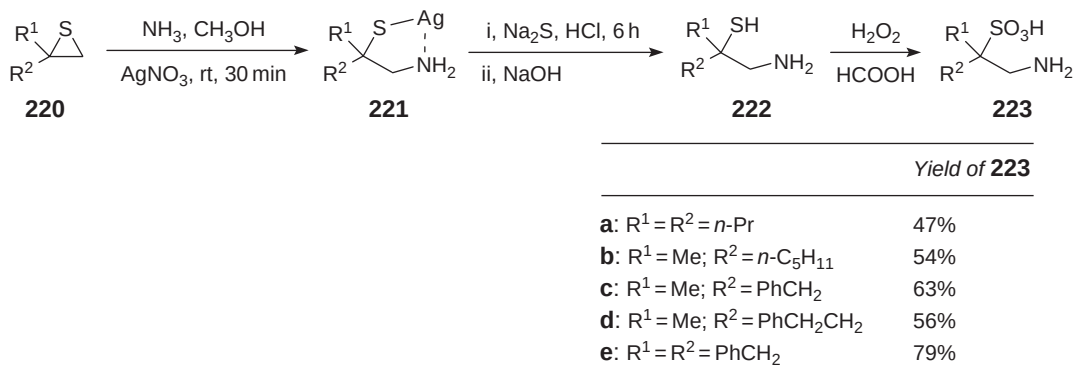


Transition states for analogous reactions with π -nucleophiles, such as alkenes, were calculated by Radom and co-workers to have a co-linear structure <1998JA7063>. Radom and co-workers <2000CEJ590> disagree with Modena *et al.* <1999JA3944, 2000CEJ589> about the structures of transition states for attack by monocentric and bicentric nucleophiles, arguing, on the basis of theory, that both are probably collinear or nearly collinear. Apparently the matter is not settled, possibly because the theoretical calculations are for the gas phase whereas the experiments were done in solution. Moreover, the substrates were different in the two cases.

1.05.8.3 Electrophilic Attack at Sulfur or at Carbon

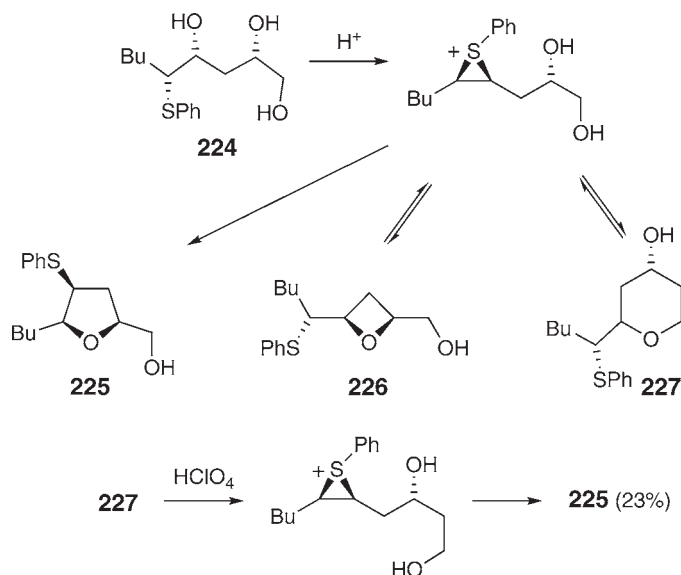
1.05.8.3.1 Episulfonium ions

Thiiranes are very useful starting materials for synthesis of 1-mono- and 1,1-disubstituted taurines <2005S2122, 2006S315>. Reaction of thiiranes **220** with silver nitrate and ammonia in methanol at room temperature for 30 min gave **221**. After reaction of **221** with hydrogen sulfide for 6 h to form **222**, oxidation of the latter with performic acid gave the corresponding mono- or disubstituted taurines **223** (Scheme 58).



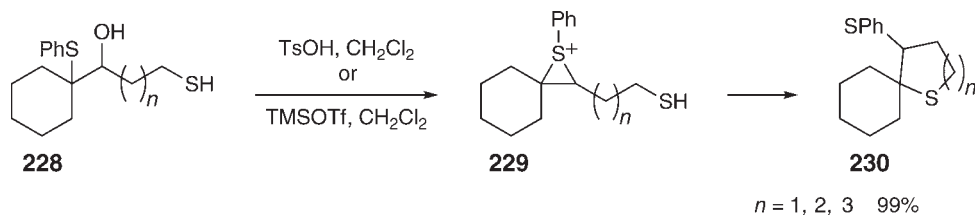
Scheme 58

THFs and tetrahydropyrans are formed stereoselectively, via intermediate thiiranium ions formed from hydroxy sulfides **224**, upon treatment with acid <2001JHC765>. 5-*endo*-Cyclizations produced the kinetic product **225** (THF) whereas 6-*exo*-cyclization produced the thermodynamically more stable tetrahydropyran **227**. The four-membered ring **226**, which would be formed by 4-*exo*-cyclization, was not observed but it could be an intermediate rapidly equilibrated with the thiiranium ion, as shown in Scheme 47. More concentrated perchloric acid converted **227** slowly to THF **225** in low yield (Scheme 59).



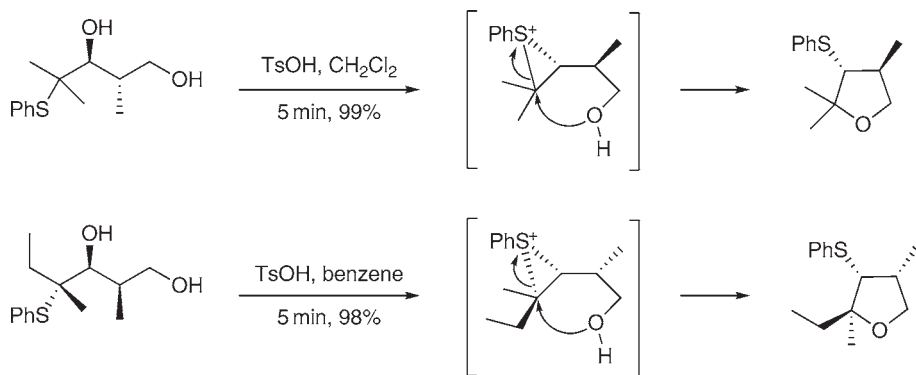
Scheme 59

Reaction of **228** with $TsOH$ or $TMSOTf$ in dichloromethane gave a thiiranium ion **229**, which was captured by a thiol sulfur atom to give cyclic sulfide **230** in quantitative yield (Scheme 60) <1996TL707>.



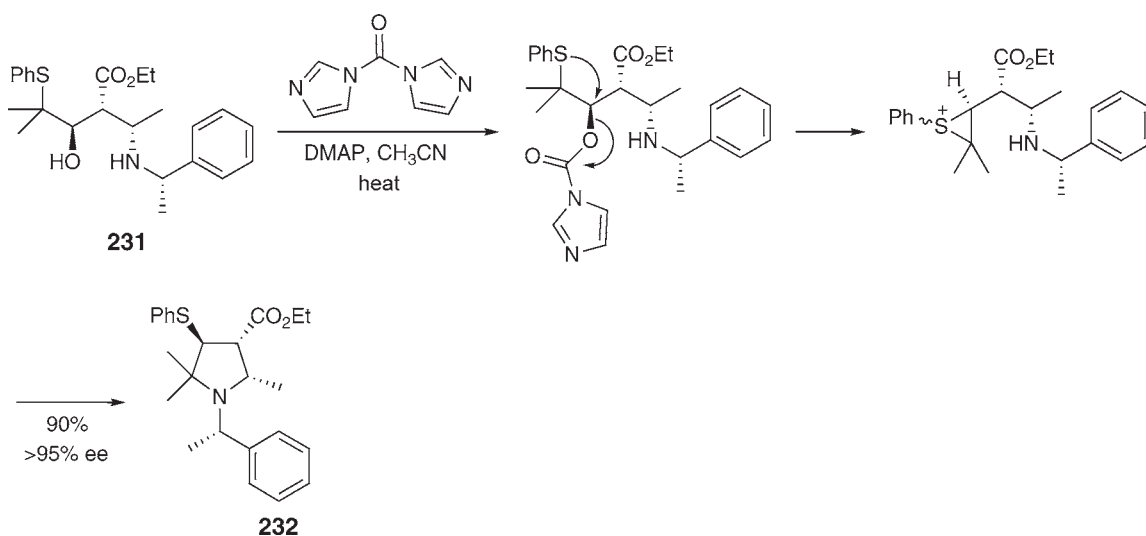
Scheme 60

anti-4-Phenylsulfanyl-1,3-diols reacted with toluene-*p*-sulfonic acid in benzene to give stereospecifically substituted tetrahydrofurans in good yield, via a [1,2]-SPh shift (Scheme 61) <2000JP1533>.



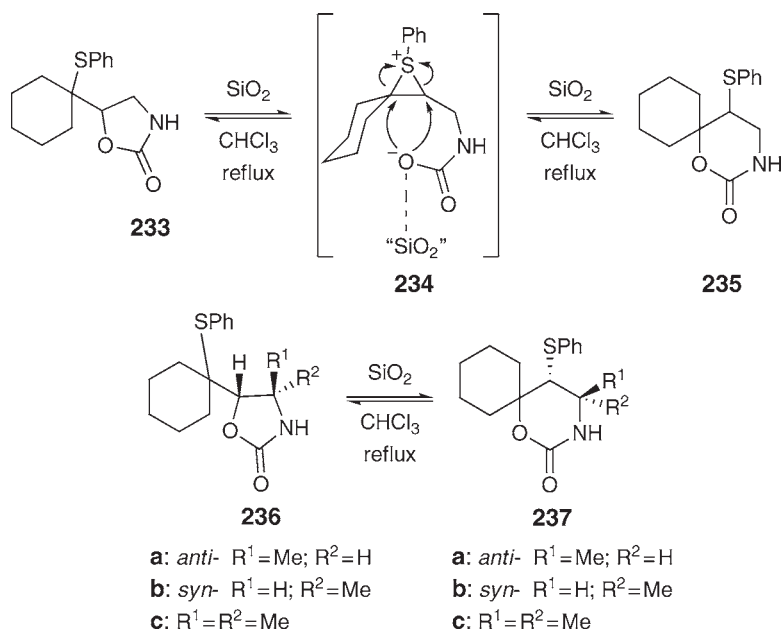
Scheme 61

Similar methodology was applied for synthesis of enantiomerically pure 2,2,3,4,5-pentasubstituted pyrrolidines **231**. In this method, the thiiranium ions, generated by reaction of corresponding aminoalcohols **232** with carbonyl-diimidazole, were captured by the internal nitrogen nucleophile (**Scheme 62**) <2002OL4381>.



Scheme 62

Treatment of oxazolidinone **233** and **236** with silica gel in refluxing chloroform gave a 17:83 mixture of starting material and six-membered-ring carbamate **235** and **237**, which are formed by reopening of episulfonium ion **234** (**Scheme 63**; **Table 8**) <2003CC1650>.

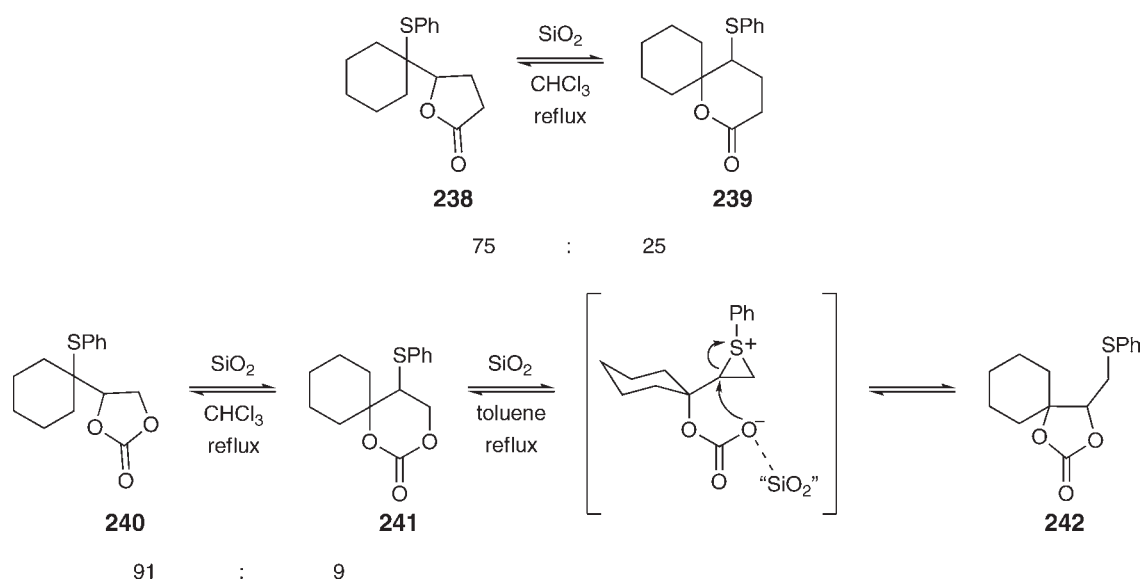


Scheme 63

Table 8 Rearrangement of 4-substituted oxazolidinones **236** to oxazinones **237**

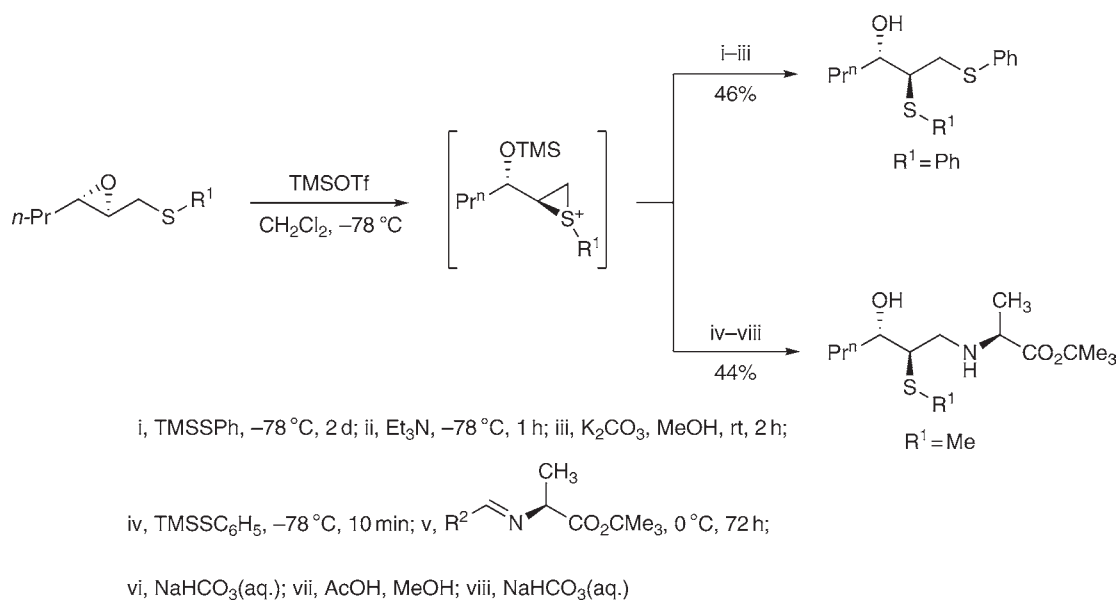
R^1	R^2	Oxazinone	Rearrangement equilibrium ratio
H	H	235	(233 : 235) 13:87
Me	H	237a	(236a : 237a) 64:36
H	Me	237b	(236b : 237b) 2:98
Me	Me	237c	(236c : 237c) 2:98

When pure **235** was used as starting material in this reaction, under the same conditions for 32 h, **233** was re-formed and a similar mixture of **233** and **235** (12:88) was observed. Silica gel also catalyzes the generation of episulfonium ions from carbonates and other esters <2002CC2528>. Cyclic carbonates and lactones can be used for generation of episulfonium ions as well <2003CC1650>. Refluxing of lactone **238** with silica gel in chloroform gave a mixture of **238** and corresponding carbonate **239** in the molar ratio 75:25. When the cyclic carbonate **240** was refluxed with silica gel in chloroform, a mixture of starting material and bicyclic carbonate **241** was obtained in molar ratio 91:9. When the mixture of **240** and **241** was refluxed in toluene in the presence of silica gel, a second bicyclic carbonate **242** was formed. It is worthwhile to note that this reaction is the first example of a C₆H₅S double migration in this type of rearrangement process, (Scheme 64).

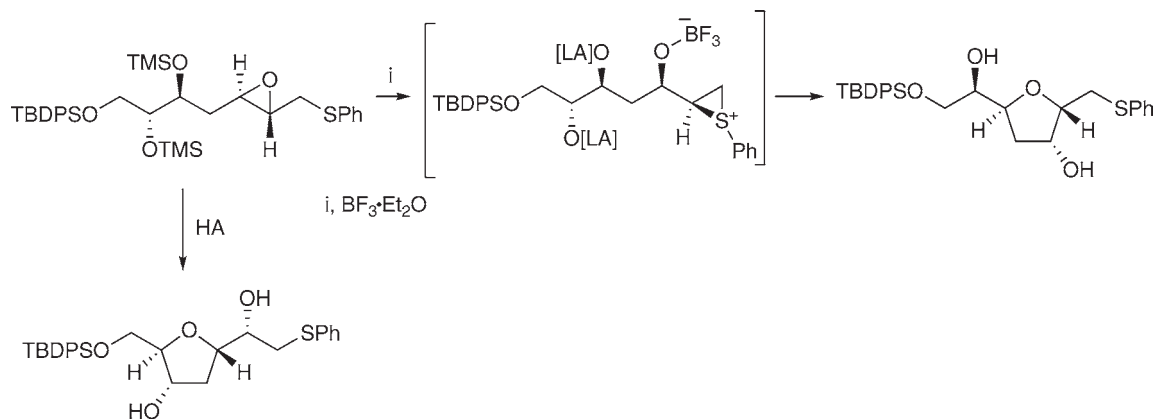
**Scheme 64**

Reaction of 2,3-epoxy sulfides with a Lewis acid (e.g., TMSOTf at -78°C in dichloromethane) gave thiiranium ions, which underwent regiospecific ring opening at C-1 with nucleophiles such as TMSSPh, imines, α -amino ester imines, nitrogen heterocycles, amides, amino acid esters, or alcohols (Schemes 65 and 66) <1997SL11, 1999TL7015, 1997T3383, 1996T3609, 1995SL1275, 1995TL8327, 2003TL5547>.

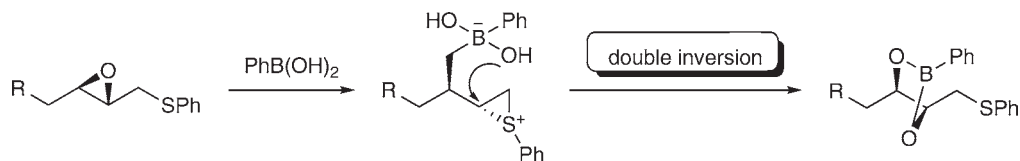
The ring-opening reaction of epoxy sulfides with phenylboronic acid in boiling benzene presumably occurs stereoselectively (de > 99%) via episulfonium ions, as shown in Scheme 67 and Table 9 <1999TL3191>.



Scheme 65



Scheme 66



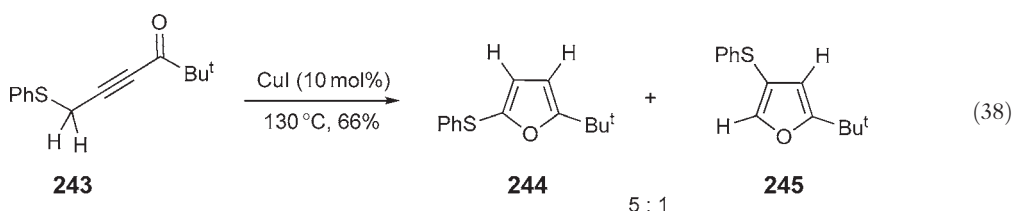
Scheme 67

Table 9 Reaction of epoxy sulfides with phenylboronic acid

Substrate	Temp. (°C)	Time (h)	Product	Yield (%)	de (%)
	70	3		99	>99
	70	20		100	>99
	70	13.5		97	>97
	60 ^a	48		30	
				70	

^a1 equiv of BF₃·Et₂O was added.

1,2-Migration of the phenylsulfanyl group was suggested as a key step in formation of 2,5-disubstituted furans **243** and **244** from ketopropargyl sulfides **245**, by heating them at 130 °C in the presence of catalytic amounts of CuI (Equation 38) <2003AGE98>.

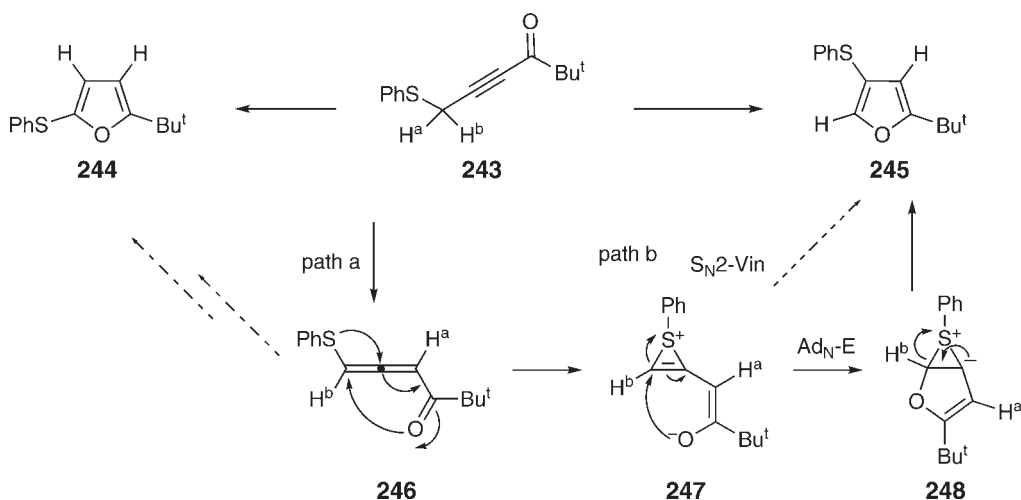


It was hypothesized that propargyl allenyl isomerization produces an allenic intermediate **246** first which cycloisomerized to the major product **246** (path a, Scheme 68). Alternatively, an intermolecular nucleophilic attack of the sulfur atom at the central carbon atom of the allene can transform it into the thiirenium ion **247**, which then is transformed into the minor product **245** via Ad_N-E **247** → **248** or through a direct S_N2-Vin-type of process (path b, Scheme 68). This reaction was successfully applied for synthesis of furans and pyrroles (from thiopropargylimines) (Scheme 69; Table 10).

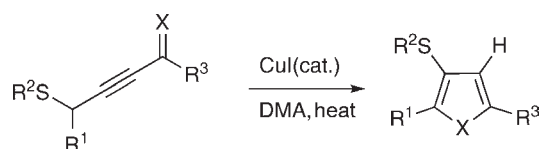
It was found that phenylthioallenyl ketones **249** were transformed into **250** in quantitative yield even in the absence of CuI (Scheme 70).

Episulfonium ions were also proposed as intermediates in the geminal alkylation of β-arylthio-α-chloroalkyl ethers <2006EJO1317>.

Reaction of disubstituted thiirene-1-oxides **251** with Lawesson's reagent, in dichloromethane at room temperature for 15 or 30 min, gave the corresponding α-dithiones **252** in 20% yield. Only when R = 1-adamantyl was the α-dithione isolated in pure form (Scheme 71) <2003JA12114>.



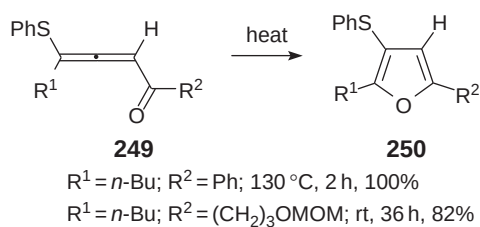
Scheme 68



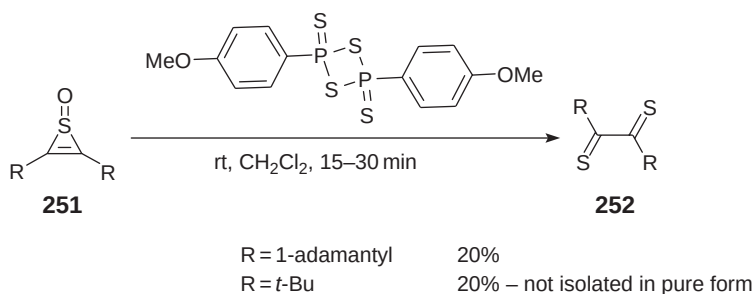
Scheme 69

Table 10 Cu-catalyzed synthesis of 3-substituted furans and pyrroles

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>X</i>	Yield (%)
<i>n</i> -Bu	Ph	H	O	71
<i>n</i> -Bu	Ph	Me	O	76
<i>n</i> -Bu	Ph	Me ₃ C	O	89
<i>n</i> -Bu	Ph	Ph	O	91
<i>n</i> -Bu	Ph		O	95
Me	Ph	(CH ₂) ₂ COOCH ₃	O	71
<i>n</i> -Bu	Ph	H	N- <i>t</i> -Bu	78
<i>n</i> -Bu	Ph	H	NTr	85
<i>n</i> -Bu	Ph	H		74

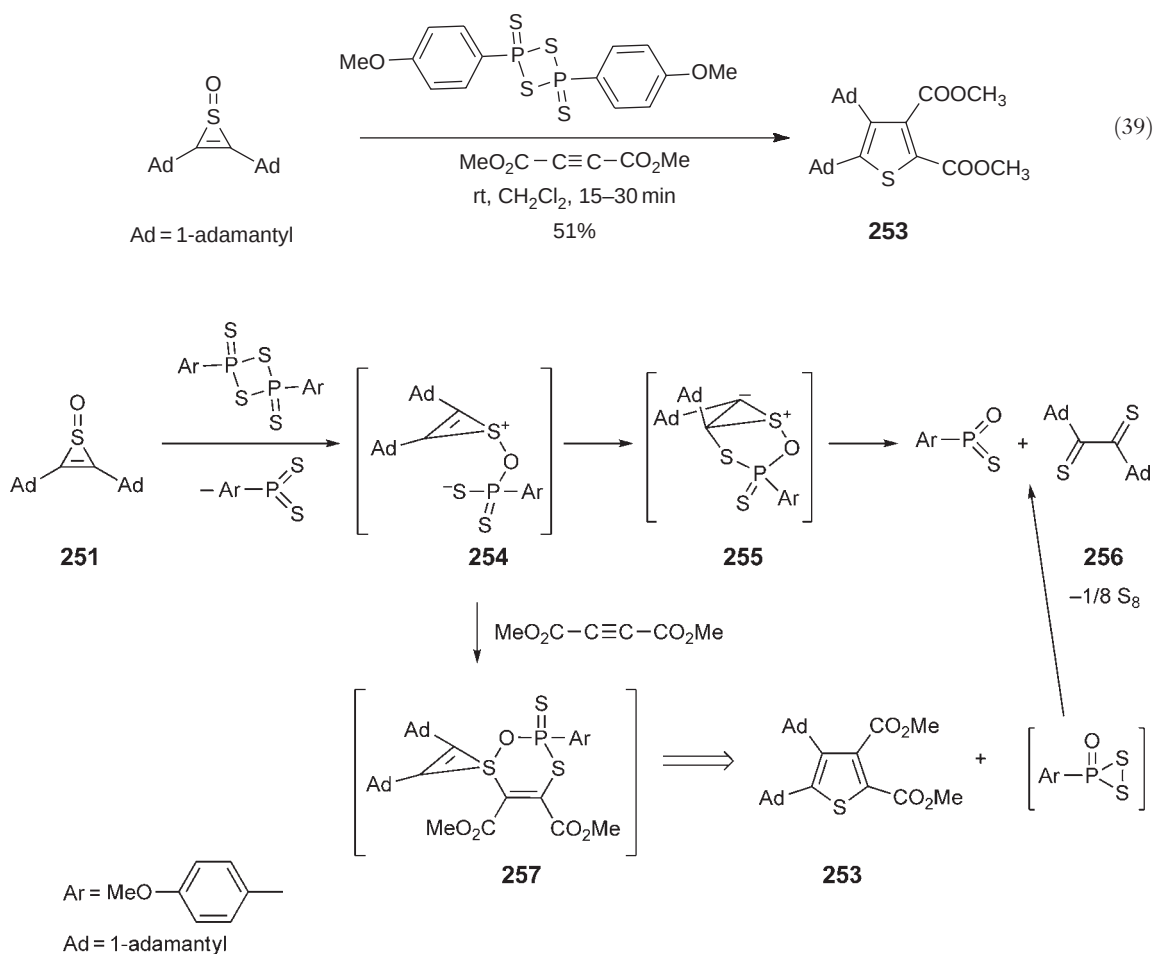


Scheme 70



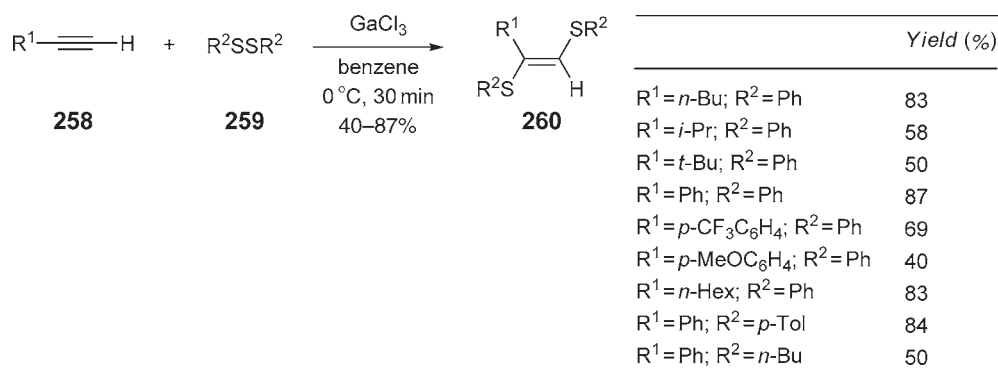
Scheme 71

When this reaction was carried out in the presence of DMAD in carbon disulfide, thiophene **253** was obtained in 51% yield (Equation 39). A tentative mechanism of formation of α -dithiones is shown in Scheme 72. First, episulfonium ions **254** are formed and then sulfur ylides **255** are obtained. From the ylides the α -dithiones **256** are formed, while the episulfonium ions **254**, by reaction with DMAD to produce **257**, finally lead to the formation of **253**.

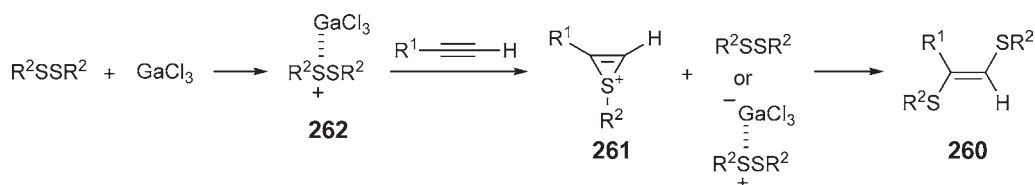


Scheme 72

Alkynes **258** reacted with disulfides **259** in the presence of gallium chloride, in benzene at 0°C for 30 min, to give disulfides **260** in good yield (Scheme 73). The mechanism of formation of **260** is shown in Scheme 74. Thiirenium ions **261**, generated from **262** and alkynes, undergo nucleophilic substitution to give **260** <2004OL601>.

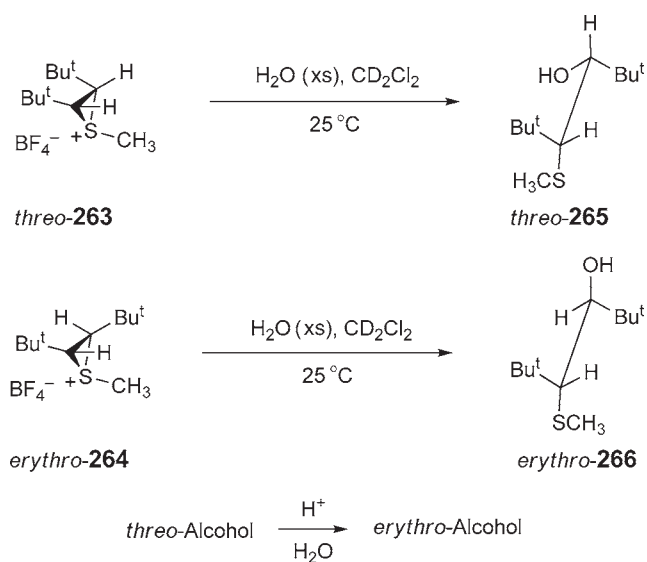


Scheme 73



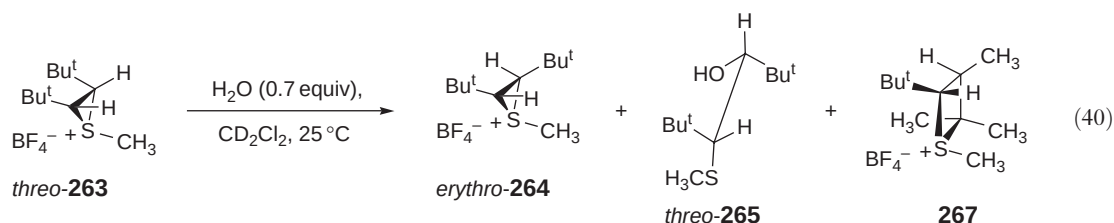
Scheme 74

Pasquato and co-workers isolated *cis*- and *trans*-di-*t*-butylthiiranium tetrafluoroborates and examined their reactions with water in dichloromethane (Scheme 75) <1997JOC7018>. *erythro*- and *threo*-2,3-di-*t*-butylthiiranium tetrafluoroborate **263** and **264**, in reaction with excess water in CD₂Cl₂ at 25 °C, led to *erythro*- and *threo*-2,2,5,5-tetramethyl-4-(methylthio)-3-hexanol **265** and **266**, respectively.



Scheme 75

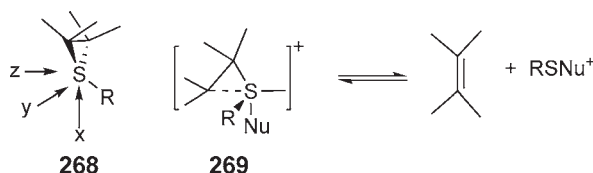
Under the same conditions, but using only 0.7 equiv of water, the reaction of *threo*-**263** afforded a mixture of *erythro*-**264**, *threo*-**265**, and thietanium ion **267**, (Equation 40).



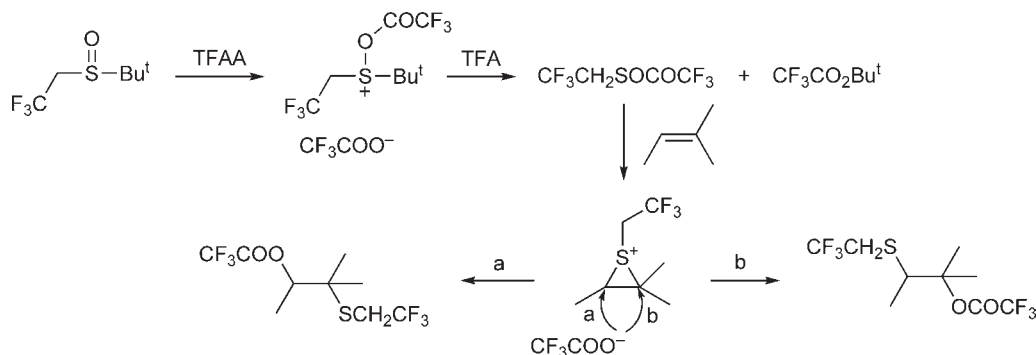
The *trans*-thiiranium ion, in separate experiments, reacted with water to afford *trans*-di-*t*-butylethene, in amounts depending on the concentration of water and the thietanium ion. The authors estimated rate constants for the reactions of both the *cis*- and the *trans*-thiiranium ions with water at 25°C and pointed out that the thiiranium salts are models for transition states for addition of electrophilic sulfur compounds to alkenes. A summary of the findings and their interpretation was published in 1997 <1997G177>.

Pasquato and co-workers also studied reactions of *S*-methyl, *S*-ethyl, and *S*-isopropyl thiiranium hexachloroantimonates with dialkyl disulfides <1999JA3944>. Reactions that occur at thiiranium sulfur are subject to steric hindrance at thiiranium sulfur and at ring carbons. Analysis of the kinetic data suggested that disulfides attack the ring sulfur from a direction that is parallel to the ring C–C bond. That direction is a subject of disagreement with Radom's group, as discussed in Section 1.05.2.2. The *trans*-thiiranium ion and the thiirenium ion rearrange by methyl migration, concerted with ring opening. The product of rearrangement of the thiirenium ion closes to a thietanium ion. Rearrangement of the *cis*-thiiranium ion presumably occurs also but it is obscured by faster reactions <1997JOC7018>.

Nucleophilic attack on thiiranium and thiirenium ions was investigated by means of kinetics, molecular geometries, and the shapes and energies of frontier molecular orbitals <1999PS235>. Substituents at carbon were *t*-butyl groups while those at sulfur were Me and Et for thiiranium ions and Me, Et, or isopropyl for thiirenium ions. The anion was F_4B^- in each case. X-Ray bond lengths and angles were also calculated by means of *ab initio* optimization at the RHF/3-21G*/RHF/3-21G* level and agreement with experimental numbers was reasonably close. The X-ray results serve as a check on the validity of the computational method. Substitution at thiiranium and thiirenium sulfur by dimethyl or diethyl disulfide generates thiirane or thiirene. The kinetic dependence on the exocyclic substituent at sulfur suggested that the nucleophile approaches the sulfur of **268** along the *y*-direction shown (left) to generate a sulfuran type of intermediate **269** which undergoes a pseudorotation to afford the products.

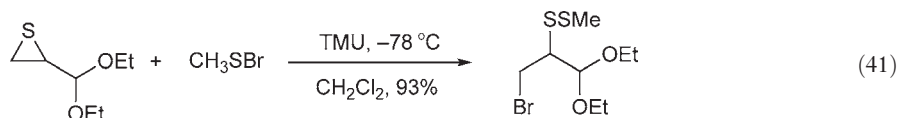


Thiiranium and thiirenium ions undergo a nucleophilic ring-opening reaction by trifluoroacetic acid anion (Scheme 76) <1997T15717>.



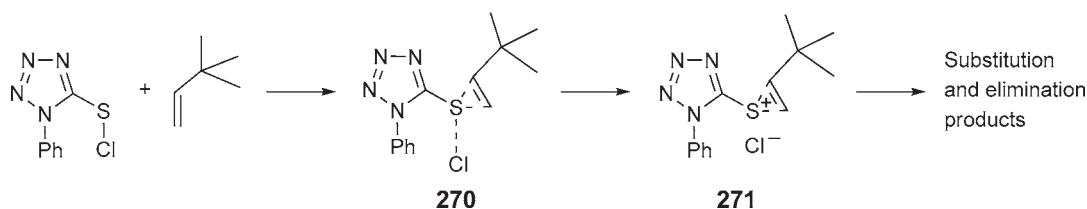
Scheme 76

Reaction of 2-(diethoxymethyl)thiirane with methylsulfenyl bromide at low temperature in dichloromethane effectively opens the thiirane, producing brominated disulfide via episulfonium ions (Equation 41) <2001JO910>.



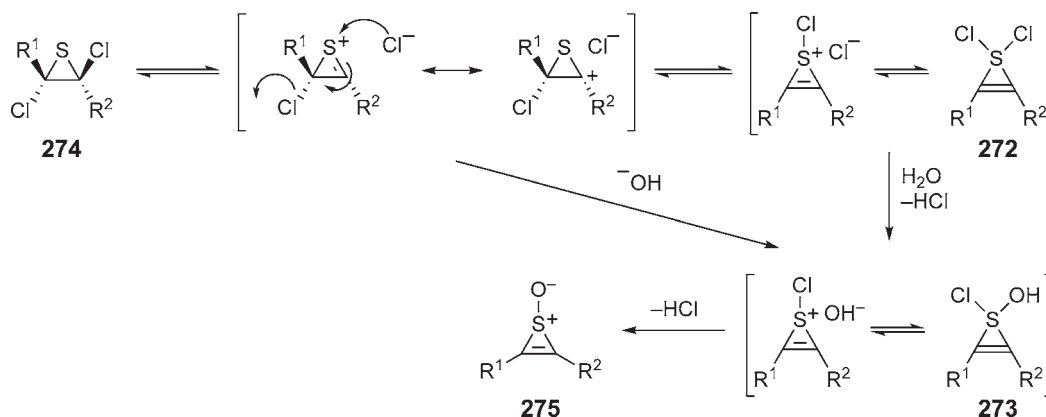
1.05.8.3.2 Episulfuranes

Reaction between 3,3-dimethyl-1-butene and 1-phenyltetrazolylsulfenyl chloride was examined by means of quantum chemistry <2002RJO765>. A thiirene-like species **270**, which is formed first, goes on to afford a tight ion pair **271** from which the products are derived (Scheme 77).



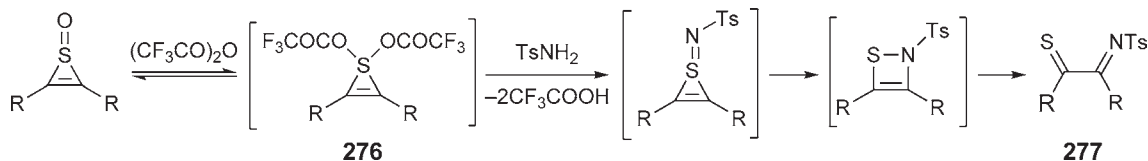
Scheme 77

Episulfuranes **272** and **273** were proposed as intermediates for explanation of the mechanism of alkaline hydrolysis of 2,2'-dialkyl-2,2'-dichlorothiirane **274** to form 2,2'-dialkylthiirene-1-oxide **275** (Scheme 78) <2002HAC424>.



Scheme 78

Episulfuranes **276** were proposed as intermediates in the mechanism of reaction of thiirene 1-oxides with TFAA followed by TsNH₂, which gave α-iminothioketones **277** (for more details, see Section 1.05.6.3; Scheme 79) <2002CL314; 2002HAC424>.



Scheme 79

1.05.9 Ring Syntheses Classified by Number of Ring Atoms in Each Component

1.05.9.1 From Nonheterocyclic Sulfur Compounds

1.05.9.1.1 General survey of syntheses

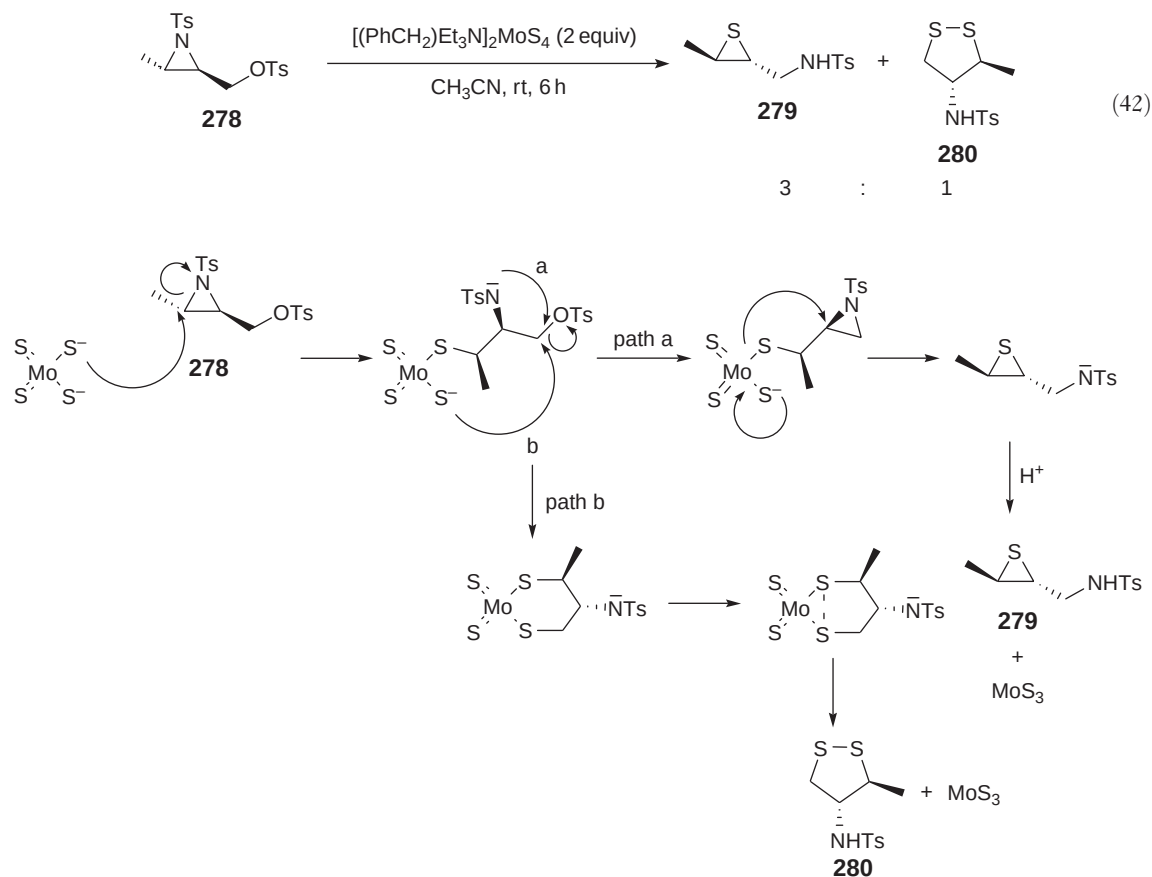
There are three main synthetic methods for synthesis of thiiranes: C–S bond-forming reactions, C–C bond-forming reactions, and two bond-forming reactions. These methods are described in detail in CHEC(1984) and CHEC-II(1996), and the references until 1995 are cited therein <1984CHEC(7)131, 1996CHEC-II(1)174>. Described here are methods published after 1996 for synthesis of thiirane, thiirane-1-oxide, thirane-1,1-dioxide, and thiirene-1-oxide.

A distinction between the approaches is based on the overall result and not on the mechanism. A simple approach to the thiirane ring is the addition of a carbene or a carbenoid to a thiocarbonyl compound. That addition is generally stepwise to generate a thiocarbonyl ylide in the first step. In the overall process though, two bonds are formed sequentially. Mechanistically, the thiirane-1,1-dioxide is formed by formation of one C–C bond when the ylide cyclizes but two bonds are made in the overall process. Addition of a diazo compound to a thiocarbonyl compound generally affords a 2,5-dihydro-1,3,4-thiadiazole that then can be made to lose N₂ to afford a thiocarbonyl ylide also. Again, the method could be described in a number of ways, including synthesis of the thiirane ring system from a heterocyclic, five-membered ring.

1.05.9.1.2 Synthesis by formation of a C–S bond

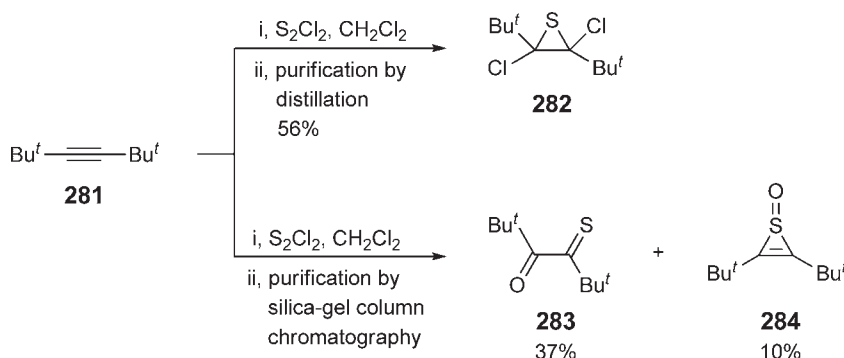
Some methods described below afford both monocyclic and bicyclic thiiranes. Examples of both are included if they have a preparative method in common. Duplication of some material in another chapter will undoubtedly occur.

Reaction of *trans*-(3-methyl-1-toluenesulfonylaziridin-2-yl)methyl toluenesulfonate **278** with benzyltriethylammonium tetrathiomolybdate gave *trans*-2-(*N*-toluenesulfonylaminomethyl)-3-methylthiirane **279** as a major product and 3-methyl-4-(toluenesulfonylamino)-1,2-dithiolane **280** as a minor product, with excellent regio- and stereocontrol (Equation 42) <2005JA12760>. A tentative mechanism for the formation of thiirane **279** and 1,2-dithiolane **280** is shown in Scheme 80.



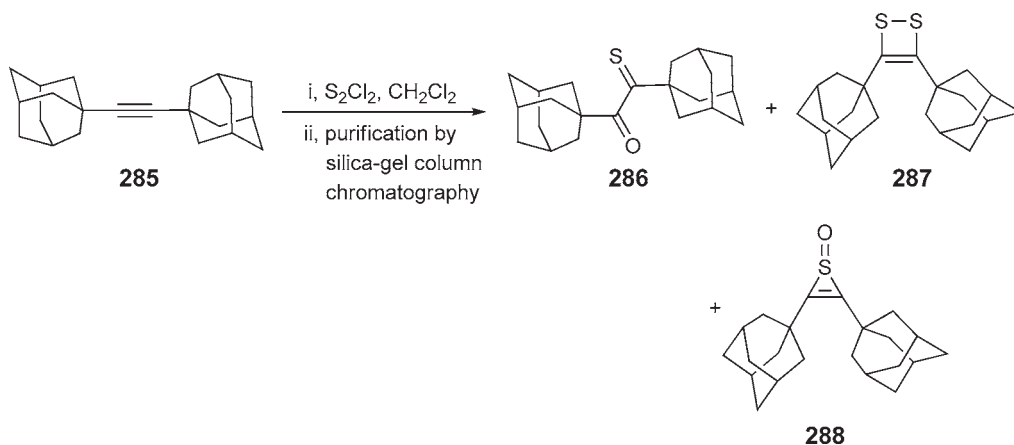
Scheme 80

Di-*t*-butylacetylene **281** reacted with an equimolar amount of disulfur dichloride in dichloromethane at room temperature to give 2,3-di-*t*-butyl-2,3-dichlorothiirane **282**, which was isolated in 56% yield by distillation from the crude reaction mixture <2000TL8349, 2002HAC424>. When the reaction mixture was purified by silica-gel column chromatography, 2,2,5,5-tetramethyl-4-oxo-3-hexanethione **283** and 2,3-di-*t*-butylthiirene 1-oxide **284** were obtained in 37% and 10% yields, respectively (Scheme 81).



Scheme 81

When di(1-adamantyl)acetylene **285** was used in this reaction, a mixture of 1,2-di(1-adamantyl)-2-thioxoethanone **286**, 3,4-di(1-adamantyl)-1,2-dithietene **287**, and 2,3-di(1-adamantyl)thiirene 1-oxide **288** was obtained in 4–33%, 8–27%, and 3–35% yields, respectively. Small amounts of starting **285** were recovered (3–35%) (Scheme 82).

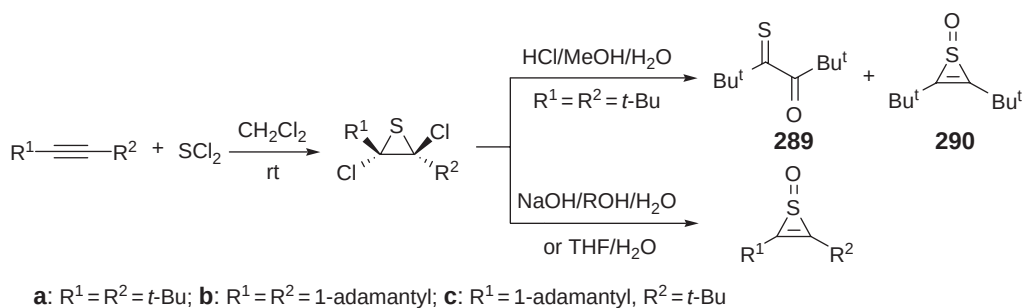


Scheme 82

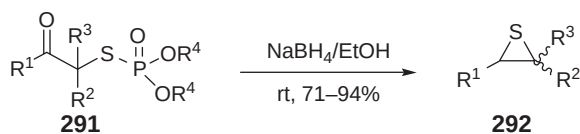
Replacement of disulfur dichloride by sulfur dichloride in reaction with acetylenes in dichloromethane led to formation of 2,3-dichlorothiiranes in quantitative yield <2001TL4017>. Acid hydrolysis of 2,3-dichlorothiirane ($\text{R}^1 = \text{R}^2 = t\text{-Bu}$) gave a mixture of 2,2,5,5-tetramethyl-4-oxo-3-hexanethione **289** and 2,3-di-*t*-butylthiirene-1-oxide **290** (Scheme 83). Exclusive formation of thiirene-*S*-oxides was observed during alkaline hydrolysis of 2,3-dichlorothiiranes.

Reaction of *S*-(β -oxoalkyl) thiophosphonates **291** with sodium borohydride gave the corresponding thiirane **292** in good yield (Scheme 84; Table 11) <1997S1134, 2003T6057>.

Reaction of **293** with sodium borohydride involves formation of the corresponding oxyanions **295**, which undergo rearrangement with migration of the phosphoryl group from the sulfur atom to oxygen affording anion **296**. Cyclization of the anion **296** and elimination of the phosphonate anion **297** gives a mixture of (*Z*)- and (*E*)-thiirane **294** (Scheme 85).



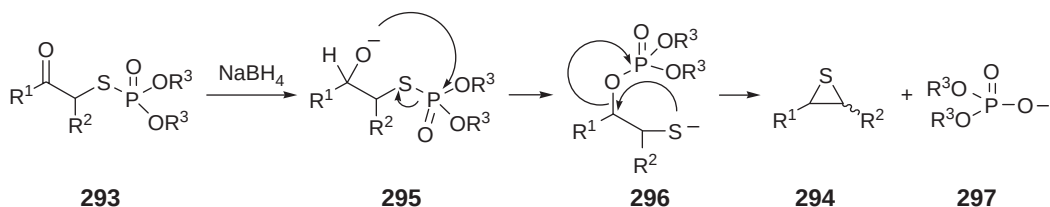
Scheme 83



Scheme 84

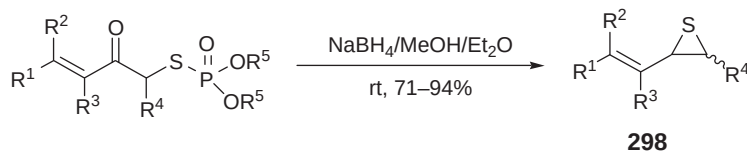
Table 11 Reaction of *S*-(β -oxoalkyl) thiophosphonates with sodium borohydride

R^1	R^2	R^3	R^4	<i>trans/cis</i> of 292	Yield of 292 (%)	Reference
Et	Me	H	Et		82	1997S1134
<i>n</i> -Pr	Et	H	Et		78	1997S1134
<i>i</i> -Bu	<i>i</i> -Pr	H	Et		85	1997S1134
4-FC ₆ H ₄	Me	H	Et		86	1997S1134
Ph	Ph	H	Et		71	1997S1134
Ph	Ph	Me	Et	28/72	78	2003T6057
Ph	Me	H	<i>i</i> -Pr		84	1997S1134
Ph	Me	Me	Et		93	2003T6057
Ph	<i>i</i> -Pr	Me	Et	66/34	67	2003T6057
Ph	<i>n</i> -Bu	Me	Et	50/50	92	2003T6057
Ph	<i>n</i> -Hex	Me	Et	65/35	90	2003T6057
Ph	PhCH ₂	Me	Et	56/44	83	2003T6057
Ph	-CH ₂ -CH ₂ -		Et		50	2003T6057
<i>i</i> -Pr	Me	Me	Et		64	2003T6057
4-PhCH ₂ OC ₆ H ₄	Me	H	Et		94	1997S1134



Scheme 85

This method was applied successfully in synthesis of vinyl thiiranes **298** (Scheme 86; Table 12) <1999TL3791, 2005PJC515>.

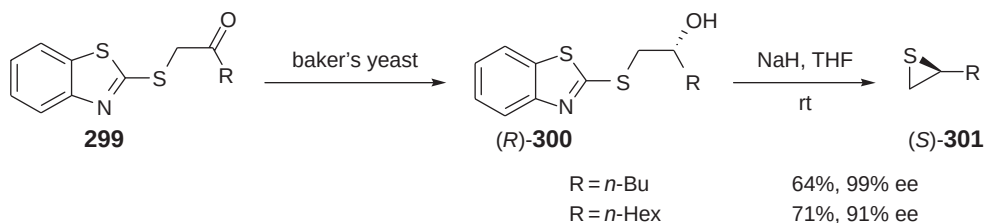


Scheme 86

Table 12 Synthesis of vinyl thiiranes **298** from *S*-(β -oxoalkyl) thiophosphonates

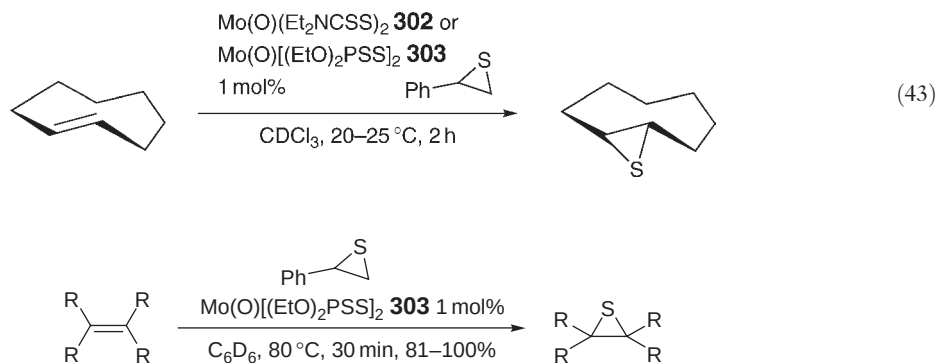
R^1	R^2	R^3	R^4	R^5	<i>cis/trans</i> of 298	Yield of 298 (%)	Reference
Me	H	H	H	Et		63	2005PJC515
<i>i</i> -Pr	H	H	H	Et		71	1999TL3791
Me	H	Me	H	Et		64	2005PJC515
Ph	H	H	H	Et		76	2005PJC515
Ph	H	H	Me	C(Me) ₂ (CH ₂) ₂	60/40	63	1999TL3791
Ph	H	H	<i>i</i> -Pr	<i>i</i> -Pr	60/40	70	2005PJC515
Ph	H	H	<i>i</i> -Pr	C(Me) ₂ (CH ₂) ₂	70/30	91	2005PJC515
H	H	H	Me	Et	57/43	62	1999TL3791

Asymmetric reduction of 1-(benzothiazol-2-sulfanyl)-2-alkanones **299** by baker's yeast gave the corresponding optically active chiral 1-(benzothiazol-2-sulfanyl)-2-alkanols (*R*)-**300** which are readily converted into optically active thiiranes (*S*)-**301** by reaction with sodium hydride in THF at room temperature (Scheme 87) <1999TA1913>.



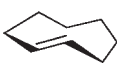
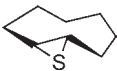
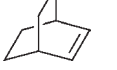
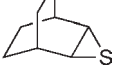
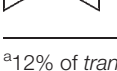
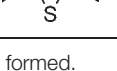
Scheme 87

Efficient catalysts for direct episulfidation of alkenes by sulfur-atom donors are also diethyldithiocarbamate and dithiophosphonate molybdenum oxo complexes **302** and **303**, respectively (Equation 43; Scheme 88; Table 13) <2003JA3871>. The most efficient sulfur-atom donor in this reaction is 2-phenylthiirane. The best results were obtained, in most cases, when 1 equiv of 2-phenylthiirane was used as sulfur-atom donor in deuterated benzene at 80 °C for 30 min. Reaction of *trans*-cyclooctene catalyzed by either of the oxomolybdenum complexes gave *trans*-epithiocyclooctane. When this reaction was carried out in the presence of **302**, the yield of the corresponding thiirane was only 20%, whereas catalyst **303** converted the olefin in almost quantitative yield (Table 14).



Scheme 88

Table 13 Episulfidation of alkenes by 2-phenylthiirane in the presence of molybdenum oxo complexes

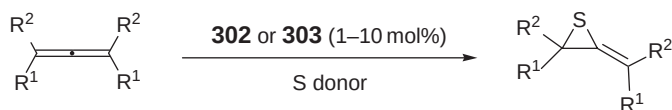
Alkene	Thiirane	Yield of thiirane (%)
		95
		85
		100
		90
		88 ^a

^a12% of *trans*-thiirane was formed.**Table 14** Episulfidation of *trans*-cyclooctene with 2-phenylthiirane catalyzed by the molybdenum oxo complexes **302** and **303**

Catalyst	Conversion of <i>trans</i> -cyclooctene (%)	Yield of thiirane (%)
302	22	>95
303	>95	>95

Reaction of allenes with a sulfur-atom donor (e.g., 2-phenylthiirane, 2-methylthiirane, sodium tetrasulfide, or elemental sulfur) in the presence of molybdenum oxo complexes gave the appropriate vinylthiirane in moderate to quantitative yield (Scheme 89; Table 15) <2003JA3871>.

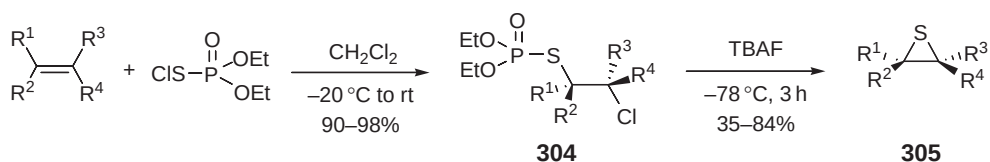
Readily available 2-chloroalkyl-*O,O*-diethylthiophosphates **304**, prepared from alkenes and diethoxyphosphoranesulfenyl chloride, reacted, during 3 h at -78°C , with tetrabutylammonium fluoride trihydrate in THF to give thiiranes **305** in moderate or good yield <1997HAC429>. A one-pot version of this reaction is known (Scheme 90; Table 16).



Scheme 89

Table 15 Episulfidation of allenes with various sulfur donors, catalyzed by molybdenum oxo complex **302** or **303**

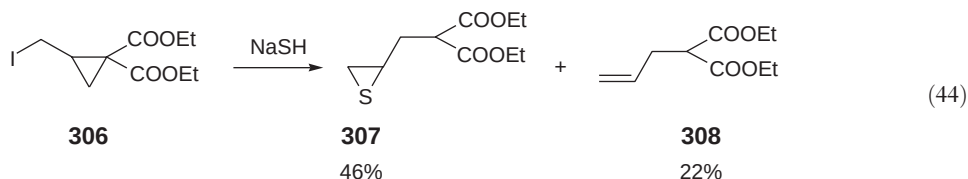
Allene	Thiirane	Catalyst [mol%]	S donor [equiv]	Solvent	Temp. (°C)	Time (h)	Yield of vinylthiirane (%)
			Na ₂ S ₄ [1.5]	CD ₃ COCD ₃	20	96	56
			S ₈	CD ₃ COCD ₃	60	12	36
		302 [10]	[0.25]				
		303 [1]	[2.0]	CDCl ₃	65	4	83
		302 [10]	[1.0]	C ₆ D ₆	80	0.5	70
		303 [1]	[2.0]	CDCl ₃	65	4	95
		303 [1]	[1.0]	C ₆ D ₆	80	0.5	>95
		302 [10]	[2.0]	CDCl ₃	65	4	67
		303 [1]	[1.0]	C ₆ D ₆	80	0.5	65



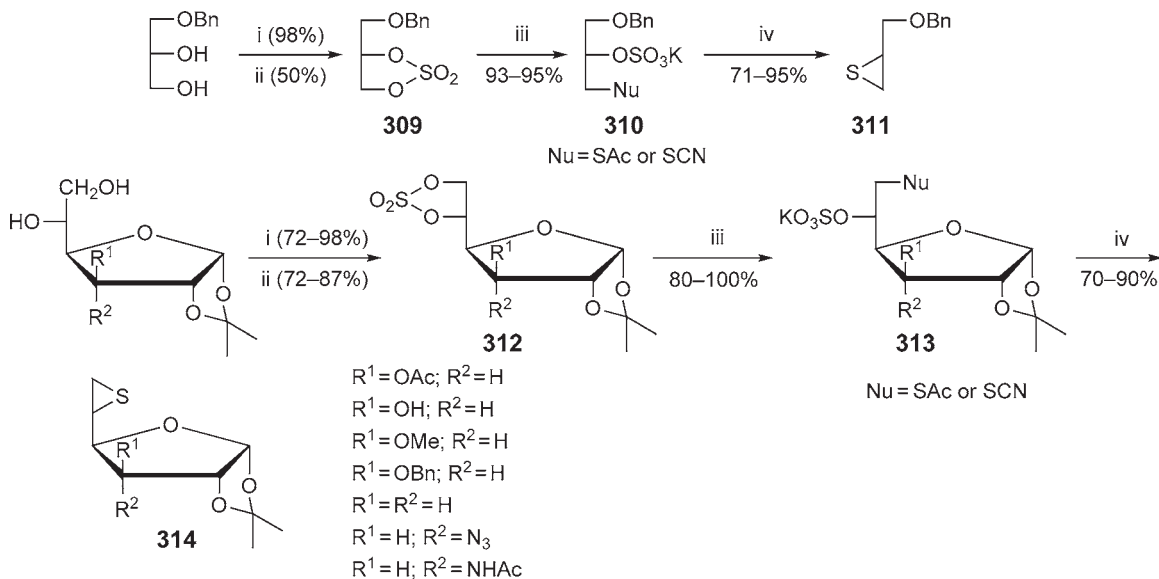
Scheme 90

1,1-Bis(ethoxycarbonyl)-2-iodomethylcyclopropane **306** reacted with sodium hydrogen sulfide to give diethyl 2-thiiranylmethylmalonate **307** in 46% yield and diethyl allylmalonate **308** in 22% yield (Equation 44) <2005TL469>. Mechanistic proposals are in Section 1.05.3.

Table 16 Reaction of alkenes with ClSP(O)(OEt)₂ and then with TBAF

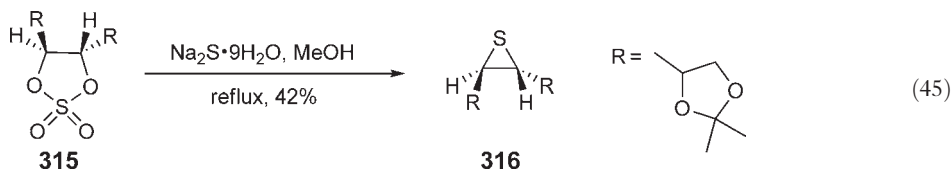


Treatment of cyclic sulfates **309** or **312**, derived from acyclic polyols (e.g., glycerol, D-mannitol) and sugars (e.g., 1,2-*O*-isopropylidenehexofuranoses), with potassium thioacetates and thiocyanates in dry acetone at room temperature, gave the corresponding salts **310** or **313** in high yields (72–100%). Reaction of these salts in methanol with sodium methoxide produced the corresponding thiiranes **311** or **314** in high yield (63–95%; **Scheme 91**) [\[1997JOC3944\]](#).

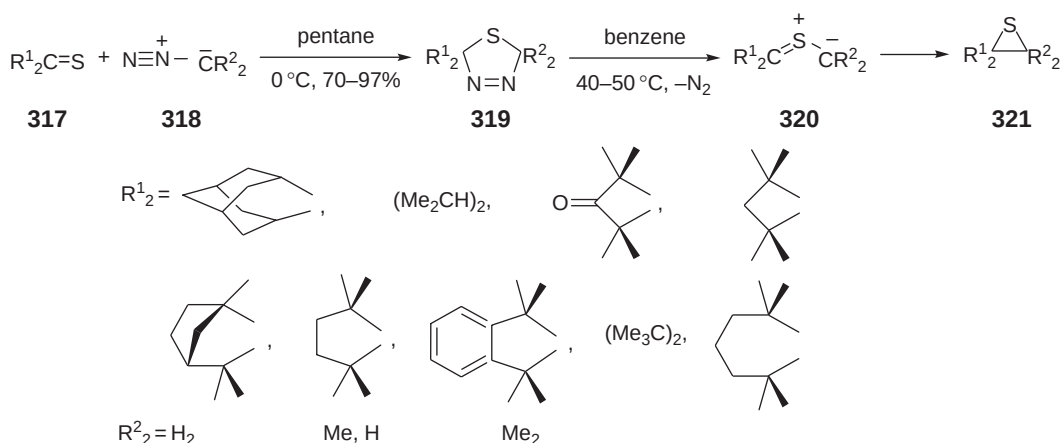


Scheme 91

The opening of nonterminal cyclic sulfates **315** could not be accomplished with potassium triacetate and thiocyanate. However, when sodium sulfide was used as nucleophile in boiling methanol, the thiiranes **316** were formed in 42% yield (Equation 45) <1997JOC3944>.

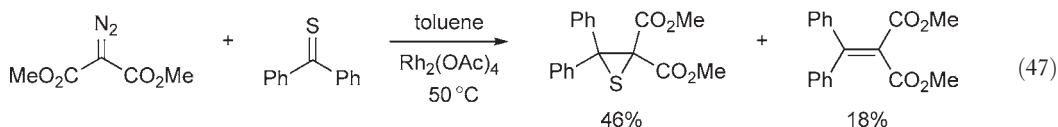
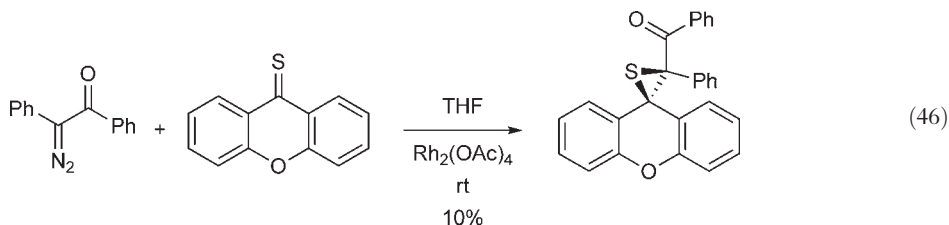


Reaction of thioketones **317** with an excess of diazomethane **318** gave 2,5-dihydro-1,3,4-thiadiazoles **319**. Thermolysis of **319** in refluxing benzene for 2 h gave thiocarbonyl *S*-methylides **320**, which underwent electrocyclicization to give corresponding thiiranes **321** (Scheme 92) <2005EJO1519>.

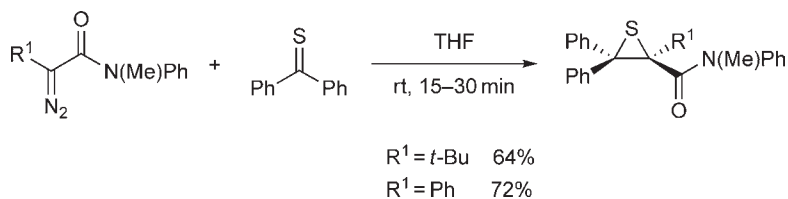


Scheme 92

Other diazocompounds, such as diazoesters <1996HCA1785, 1998PJC678> or diazoalkanes <1999PJC635, 2000EJO1685>, were used in reaction with various thioketones to afford corresponding thiiranes in good yield. Diazomethylphosphonates were also used in reaction with thiobenzophenone to give unstable thiiranes which lost the sulfur atom to give vinylphosphonates in good yield <2006T7776>. Reactions of thioketones with diazo compounds (e.g., dimethyl diazomalonate and azibenzil) were carried out in the presence of $\text{Rh}_2(\text{OAc})_4$ as catalyst at room temperature; however, the thiiranes were formed in low yield (Equations 46 and 47) <1998HCA285, 1996HCA1785>.

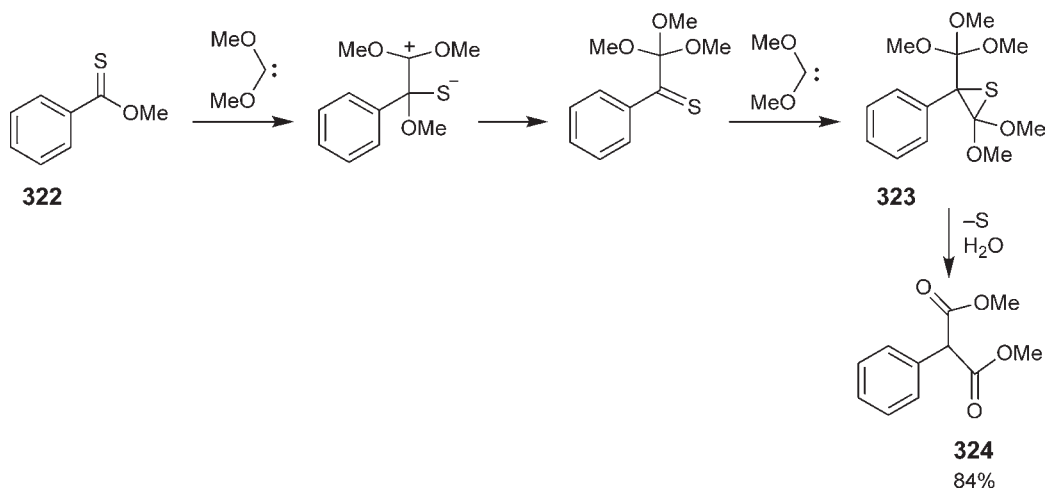


Reactions of thioketones with diazoamides at room temperature in THF for 15–30 min gave corresponding thiiranes in 64–72% yield (Scheme 93) <1998HCA285>.

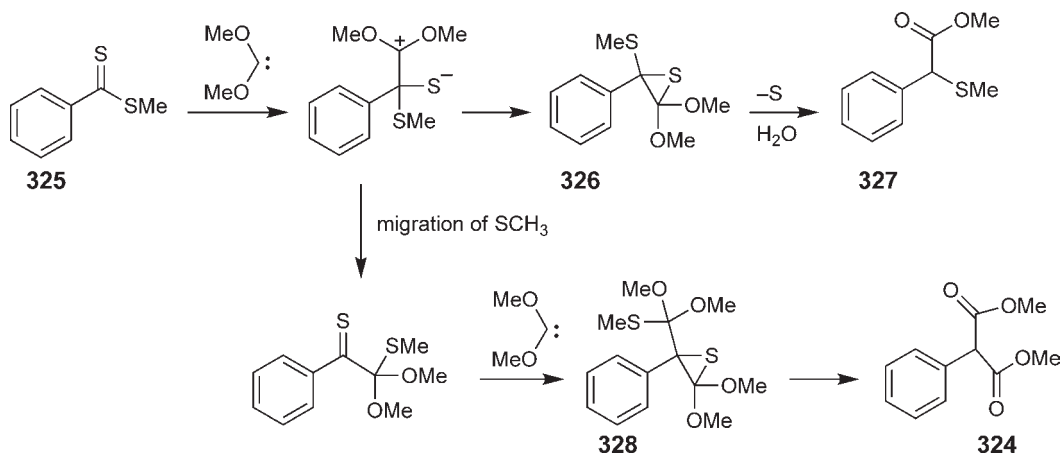


Scheme 93

Dimethoxycarbene reacted with *O*-methyl thiobenzoate **322** to give thiirane **323**, which lost the sulfur atom. Following hydrolysis, **323** gave dimethyl phenylmalonate **324** in 84% yield (Scheme 94). Similar reaction of dimethoxycarbene with methyl dithiobenzoate **325** gave a mixture of methyl methylthiophenylacetate **327** in 22% yield via thiirane **326**, and **326**, via thiirane **328**, in 28% yield (Scheme 95) <2005JPO86>. Other thio and dithioesters were used successfully as dipolarophiles in reaction with thiocarbonyl ylides <2005EJO1604>.

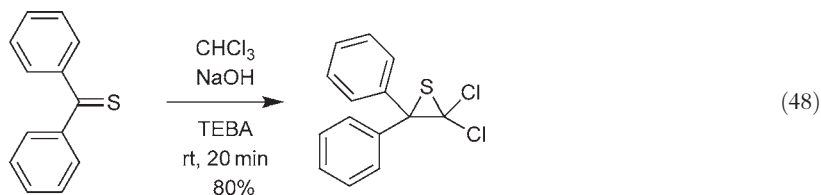


Scheme 94

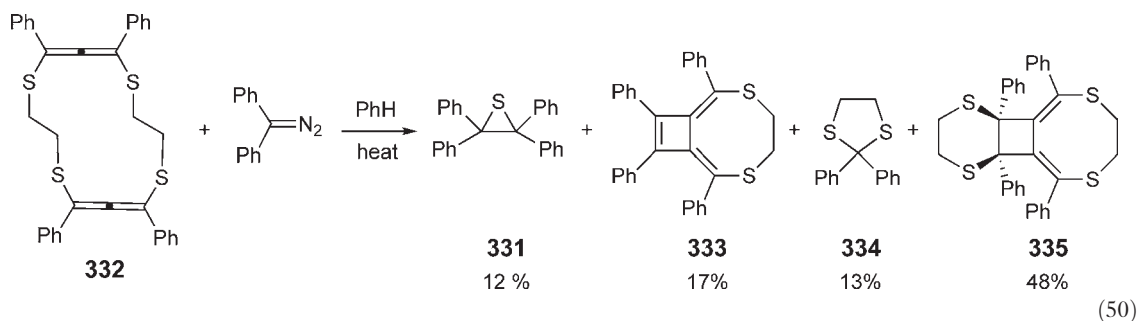
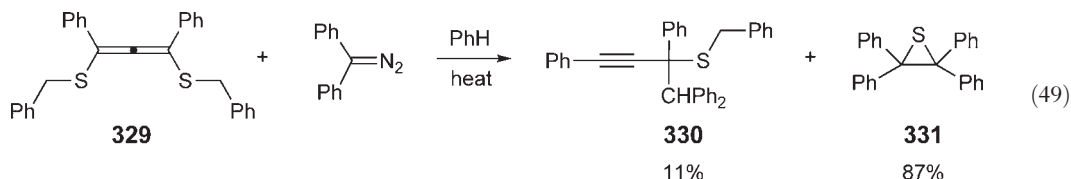


Scheme 95

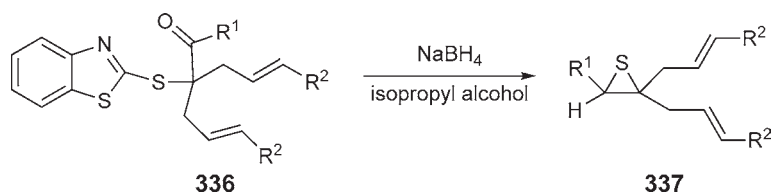
Thiobenzophenone reacted in 20 min with dichlorocarbene, generated from chloroform and NaOH in the presence of benzyl(triethyl)ammonium chloride, in a two-phase system, to give 2,2-dichloro-3,3-diphenylthiirane in 80% yield (Equation 48) <1999HCA946>.



Thermolysis of allene **329** with diphenyldiazomethane in benzene afforded 3-benzylthio-1,3,4,4-tetraphenyl-1-butyne **330** and 2,2,3,3-tetraphenylthiirane **331** in 11% and 87% yields, respectively. Thermolysis of bicyclic allene **332** with diphenyldiazomethane under the same conditions as above gave a mixture of thiirane **331**, compound **332**, 1,3-dithiolane **334**, and tricyclic **335** in 12%, 17%, 13%, and 48% yields, respectively (Equations 49 and 50). It was found that heating of a benzene solution of **335** with diphenyldiazomethane gave a mixture of **333** and **334** together with thiirane **331** in 41%, 29%, and 20% yields, respectively <2000JOC1721>.



Allylthiiranes **337** can be prepared easily, in 78–90% yield, from **336** (prepared from 2-(β-ketoalkylthio)benzothiazole and allylic carbonates in a Pd-catalyzed reaction) in a reaction with sodium borohydride in isopropyl alcohol at room temperature for 6–48 h (Scheme 96; Table 17) <1996T2155>.

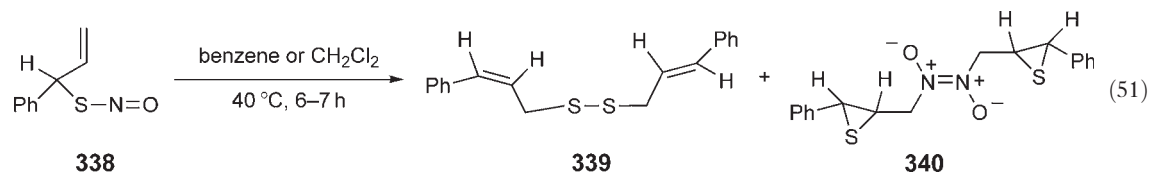


Scheme 96

Table 17 Synthesis of allylthiiranes **337**

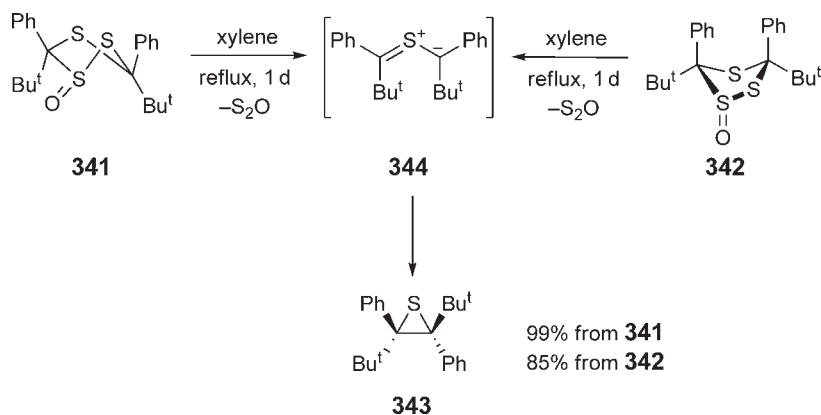
R^1	R^2	Yield of 337 (%)
Me		85
Me	Et	78
	Et	90
	H	85

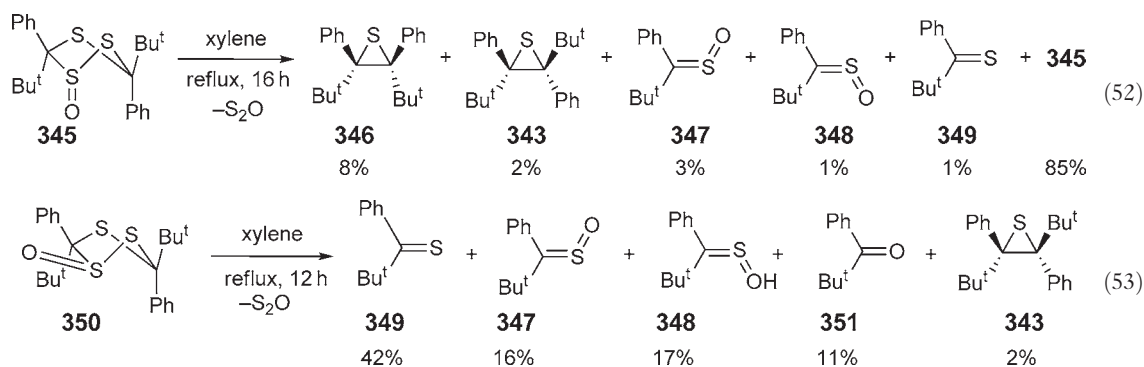
Tertiary *S*-nitroso allylthiols **338**, heated at 40 °C in benzene or dichloromethane for 6–7 h gave a mixture of disulfides **339** and nitroso dimers **340** (Equation 51) <2002CC2394>. First formed from **338** is the allyl thiyl radical which isomerizes reversible into the thiiranylcarbinyl radical. Dimerization, after the latter had added to NO, gave **340** and dimerization of the allylthiyl radical gave **339**. This topic is also discussed in Section 1.05.6.6.



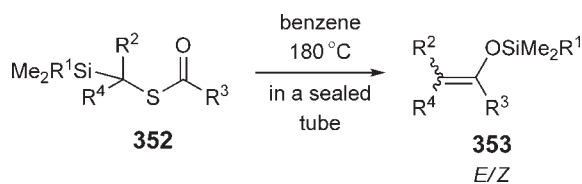
1.05.9.1.3 Synthesis by formation of a C–C bond

cis-1,2,4-Trithiolane-1-oxides, **341** and **342**, heated in xylene, lost S₂O and formed corresponding *trans*-thiirane **343** (from both 1-oxides) in good or quantitative yield via a thiocarbonyl ylide intermediate **344** Scheme 97 <2004JOC1695>. Thermolysis of *trans*-1,2,4-trithiolane-*S*-oxide **345** in xylene for 16 h gave the expected *cis*-thiirane **346** and *trans*-thiirane **343**, with 85% of recovery of **345**, as major products. Thermal decomposition of **350** in refluxing xylene for 12 h gave a mixture of thioketone **349**, sulfines **347** and **348**, as well as ketone **351**. In addition, there were small amounts of *trans*-**343** (Equations 52 and 53).

**Scheme 97**



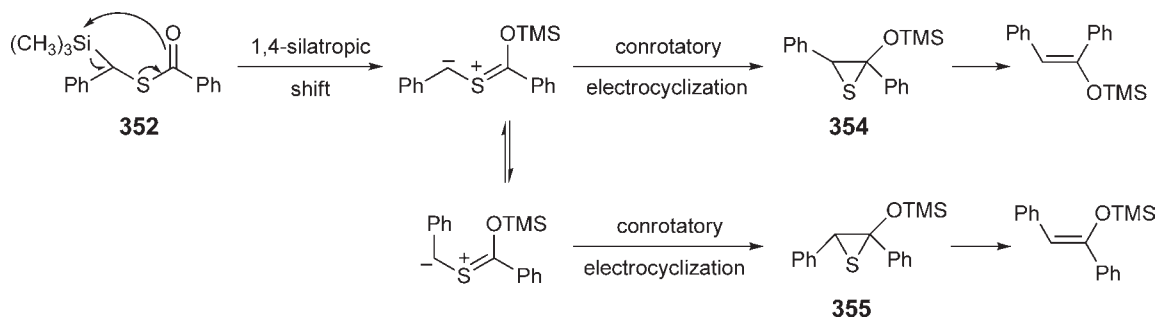
Thermolysis of *S*- α -silylbenzyl thioesters **352** in benzene at 180 °C, in a sealed tube for 1–126 h, gave vinyl silyl ether **353** (Scheme 98; Table 18) via thiiranes **354** and **355** (Scheme 99) <2003JOC6164>.



Scheme 98

Table 18 Synthesis of vinyl silyl ether **353**

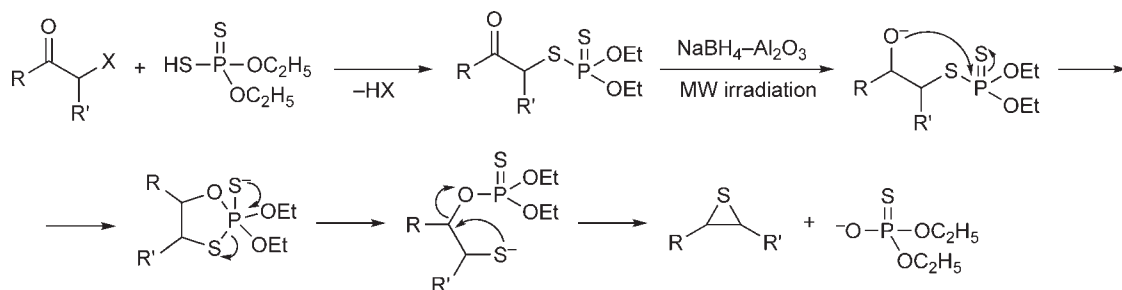
R^1	R^2	R^3	R^4	Time (h)	Yield	Ratio of Z:E
Me	H			24	93	91:9
Me	H			8	92	91:9
Me	Me ₃ Si			1	96	11:89
	H			5	87	88:12



Scheme 99

1.05.9.2 Synthesis by Formation of Two Bonds

Reaction of α -haloketones with *O,O*-diethyl hydrogen phosphorodithiate and sodium borohydride, supported on alumina, under microwave irradiation for a few minutes, gave thiiranes in good or excellent yield (Scheme 100; Table 19) <2002S2344>. (See also Scheme 11 and Equation 15).

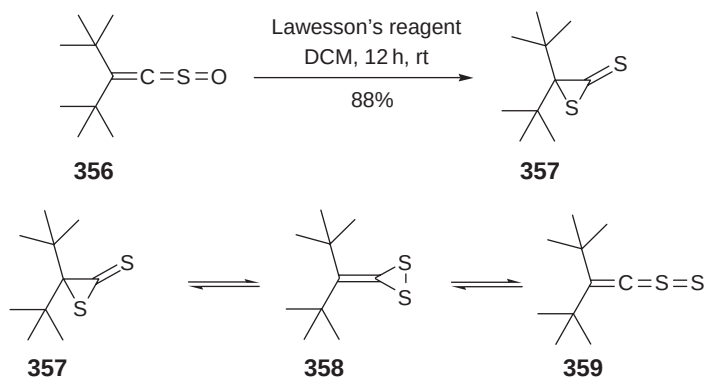


Scheme 100

Table 19 Synthesis of thiiranes from α -haloketones and $HSP(S)(OEt)_2$ and $NaBH_4-Al_2O_3$ under microwave irradiation

Ketone	Product	Reaction time (min)	<i>trans:cis</i> ratio	Yield (%)
		2.0		88
		3.0	91:9	85
		3.0	91:9	88
		3.5	93:7	86
		4.0	89:11	81
		2.5		94
		2.5		92

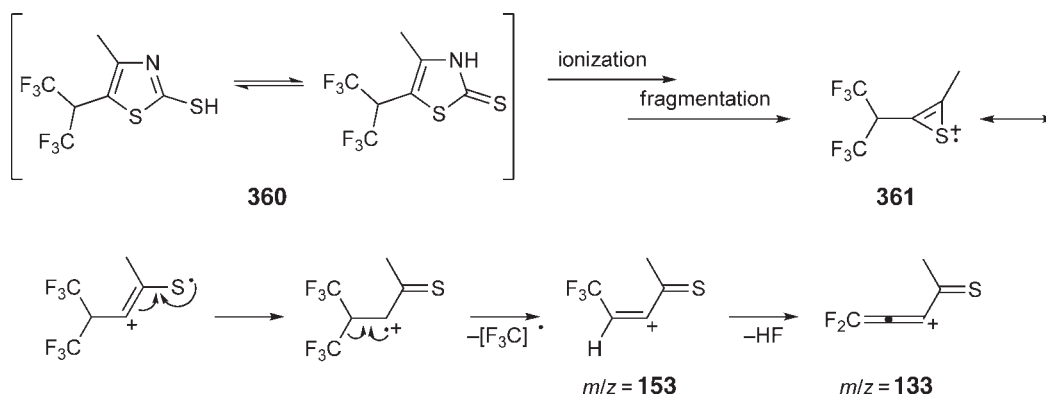
Reaction of di-*t*-butylketene **356** with Lawesson's reagent at room temperature in dichloromethane for 12 h give 3,3-di-*t*-butylthiirane-2-thione **357** in 88% yield <2004JA9508>. Compound **357** is an isomer of 3-(2,2,4,4-tetramethylpentan-3-ylidene)dithiirane **358** and of di-*t*-butyl thioketene *S*-sulfide **359** (Scheme 101).



Scheme 101

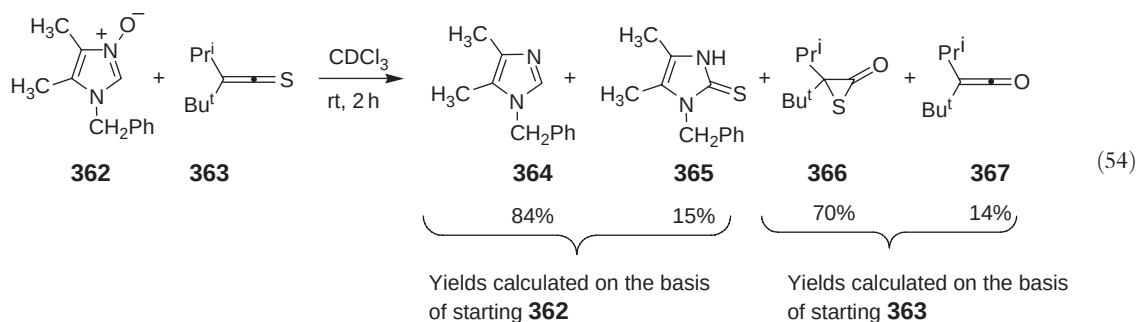
1.05.9.3 Miscellaneous Methods

In the mass spectrum of thiazoline **360**, the molecular ion M^+ is observed as well as a signal corresponding to $[M-CF_3]^+$. Moreover, fragmentation of **360** by cleavage of the 1,2- and 3,4-bonds results in a thiirenium ion radical **361**, with charge retention by the sulfur-containing portion (Scheme 102) <2002JFC185>. Loss of CF_3 from **361** could give rise to the signals at $m/z = 153$ and loss of HF from the latter ion could account for $m/z = 133$.



Scheme 102

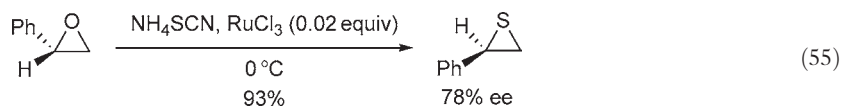
Reaction of 1-benzyl-4,5-dimethylimidazole 3-oxide **362** with thioketene **363** in $CDCl_3$ at room temperature for 2 h gave a mixture of deoxygenated imidazole **364** as well as imidazole-2(3*H*)-thione **365** in 84% and 15% yields, respectively. Thiiranone **366** and ketene **367** were also obtained in 70% and 14% yield, respectively (Equation 54) <1998HCA1585>.



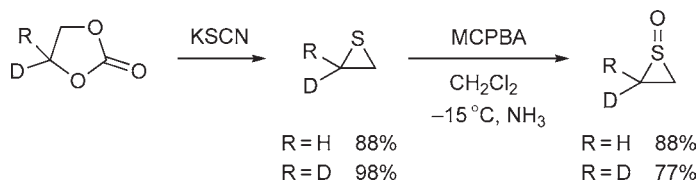
1.05.10 Ring Syntheses by Transformation of Another Ring

1.05.10.1 From Oxiranes

Reactions of oxiranes with thiocyanates or thiourea are well-known methods of synthesis of thiiranes. Since 1996, many new and efficient catalytic systems for conversion of oxiranes into thiiranes were described. Transformations of oxiranes into thiiranes by reaction with thiocyanates or thiourea were successfully catalyzed by: ruthenium(III) chloride (0.02 equiv) (Equation 55) <1997T11377>; iron(III) 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (Fe(TF₅PP)Cl) <1999JCM370>; tin(IV) porphyrin <2004T6105, 1999SC2079>; sulfuric acid <2002RJO1676; 2003HC174; 2003RJAC1280>; bismuth(III) fluoroacetate or trifluoromethanesulfonate <2001MOL996>; bismuth(III) chloride <1998SC3943>; magnesium hydrogen sulfate <2003SC3041>; cerium(IV) ammonium nitrate (CAN) <1996S821>; titanium(IV) oxobis(trifluoroacetate) and titanium(IV) trichloride trifluoromethanesulfonate <1998SC3913>; cerium polyoxometallate <2002SC621>; lithium tetrafluoroborate <2003SC595>; titanium dioxide <2004SC2823>; aluminium chloride supported on silica gel <2005SC2575> or on cross-linked polystyrene <2004SC65>; poly(vinylamine) or poly(allylamine) <2004TL1535>; β -cyclodextrin <2004ASC395, 2004TL6523>; Amberlite IRA-400 <1996SC3953>; and cyanuric chloride <2006TL4775>. Reaction of oxirane with thiourea in methanol was successfully applied in synthesis of bistiiranes from bisoxiranes <1999RJO1802>.



2-Deuteriothiirane and 2,2-dideuteriothiirane were prepared by reaction of 1-deutero- or 1,1-dideuteroethylene carbonate with potassium thiocyanate. The thiiranes were oxidized to corresponding 2-deutero- and 2,2-dideuterothiirane 1-oxides in reaction with MCPBA (Scheme 103) <1998CEJ441>.

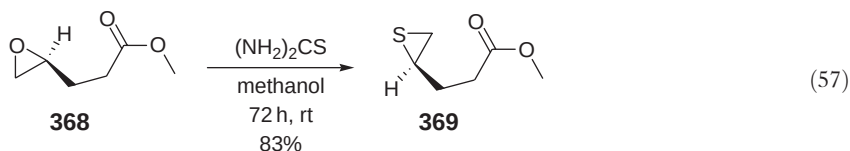


Scheme 103

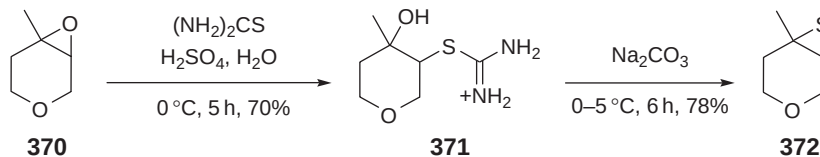
Transformations of oxiranes into thiiranes by reaction with potassium thiocyanates, carried out in mixtures of ionic liquids (1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) or tetrafluoroborate ([bmim]BF₄) and water (2:1), gave the corresponding thiiranes in very good yield (up to 96%; Equation 56) <2003JOC2525>. The ionic liquid may be reused after extraction of products with ether; for example, treatment of 2-phenyloxirane with potassium thiocyanate in [bmim]PF₆ ionic liquid afforded 2-phenylthiirane in 93%, 89%, 85%, 81%, and 78% yields over five cycles.



Reaction of methyl (4S)-4,5-epoxypentanoate **368** with thiourea in methanol at room temperature led to the replacement of the oxygen atom by sulfur, to give methyl (4R)-4,5-epithiopentanoate **369** in 83% yield with inversion of configuration at C-4 (Equation 57) <2000TA765>.

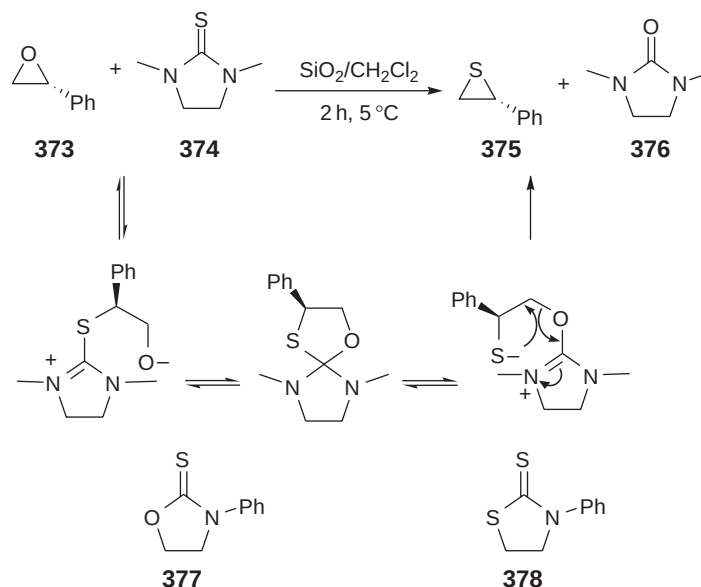


In the reaction of 4-methyl-3,4-epoxytetrahydropyran **370** with thiourea in water at 0 °C for 5 h, in the presence of an equimolar amount of sulfuric acid, *S*-(4-hydroxy-4-methyl-3-tetrahydropyranyl)isothiuronium sulfate **371** was formed in 70% yield. Addition of an equimolar amount of sodium carbonate in water to **371** at 0–5 °C for 6 h give 4-methyl-3,4-epithiotetrahydropyran **372** in 78% yield (Scheme 104) <2003HC174>.



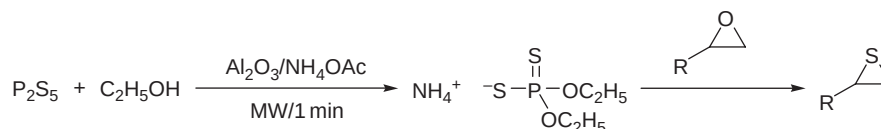
Scheme 104

Reaction of (*R*)-2-phenyloxirane **373** with 1,3-dimethylimidazolidine-2-thione **374**, in the presence of silica gel in anhydrous dichloromethane at 5 °C, for 2 h under a nitrogen atmosphere, afforded (*S*)-2-phenylthiirane **375** in 83% yield (ee 97%) and 1,3-dimethylimidazolidine-2-one **376** (Scheme 105) <2005HCA3253>. The proposed mechanism for the stereoselective transfer of sulfur is presented in Scheme 104. Use of 3-phenyloxazolidine-2-thione **377** or 3-phenylthiazolidine-2-thione **378** as sulfur donor in place of 1,3-dimethylimidazolidine-2-thione, in a reaction with (*R,S*)-2-phenyloxirane under the same conditions for 10 h, afforded racemic 2-phenylthiirane in 66% and 58% yield, respectively. It is worthwhile to note that 1,3-dimethylimidazolidine-2-thione can easily be regenerated by thionation of **376** with Lawesson's reagent.



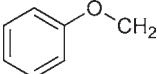
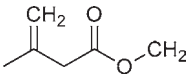
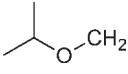
Scheme 105

Phosphorus pentasulfide reacted with ethanol and ammonium acetate in the presence of alumina under microwave irradiation to give *O,O'*-diethyl ammonium phosphorodithiophosphate, which is a convenient sulfur donor for conversion of oxiranes into thiiranes (Scheme 106; Table 20) <2004S2035>.



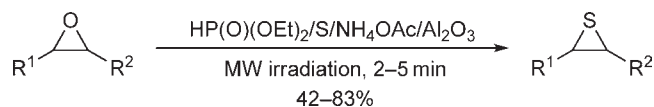
Scheme 106

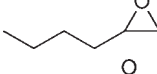
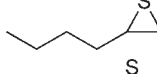
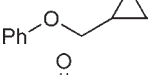
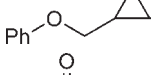
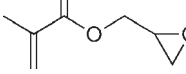
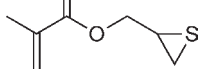
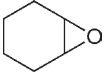
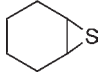
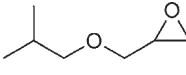
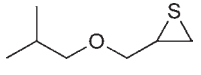
Table 20 Conversion of epoxides into thiiranes using P_2S_5 in EtOH in the presence of ammonium acetate with or without MW irradiation

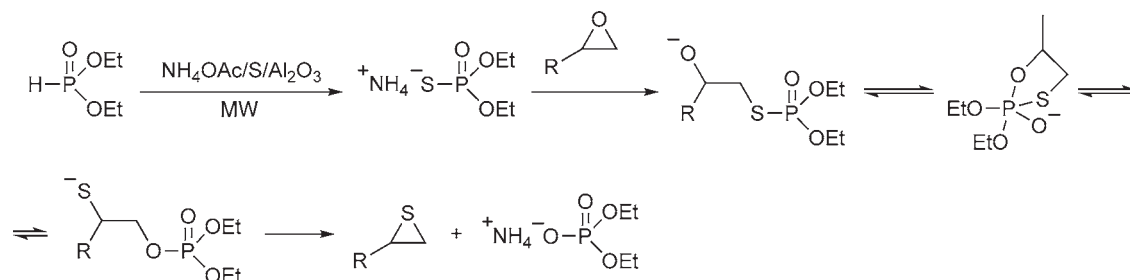
<i>R</i>	<i>Time</i> ^a (min)	<i>Yield</i> ^a (%)	<i>Time</i> ^b (min)	<i>Yield</i> ^b (%)
	2	83	0.5	91
	180 ^c	30		
	2	82	2	90
	4	76	1	83
	3	55	3	50
$CH_3(CH_2)_{11}$	4	10	2	76

^aReaction carried out under MW irradiation.^bReaction carried out at reflux.^cShaking without MW irradiation.

Epoxides are readily converted to thiiranes by a mixture of diethyl phosphate, ammonium acetate, sulfur, and aluminium oxide under microwave irradiation <2004TL1283> (**Scheme 107**; **Table 21**). The mechanism of formation of thiiranes under those conditions is presented in **Scheme 108**.

**Scheme 107****Table 21** Reaction of oxiranes with a mixture of sulfur, ammonium acetate, diethyl phosphate, and aluminium oxide with microwave irradiation

<i>Oxirane</i>	<i>Thiirane</i>	<i>Time</i> (min)	<i>Yield of thiirane</i> (%)
		0.5	82
		6	80
		2	78
		4	62
		3	69
		3	42



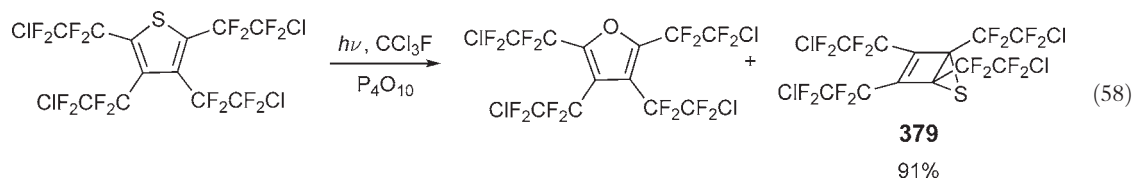
Scheme 108

1.05.10.2 From Four-Membered Heterocycles

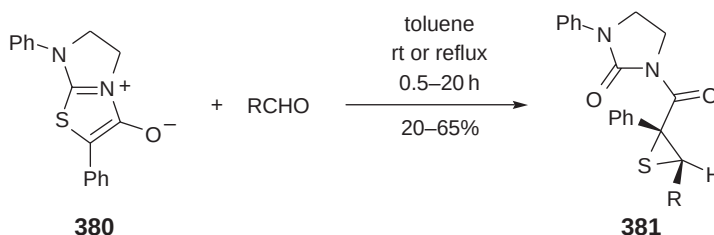
In the period 1996–2006, there did not seem to be any papers concerned with formation of thiiranes from four-membered heterocycles.

1.05.10.3 From Five-Membered Heterocycles

Irradiation of 1,2,3,4-tetrakis(2-chloro-1,1,2,2-tetrafluoroethyl)thiophene, with a Vycor-filtered medium pressure mercury arc in a quartz vessel in dry and degassed trichlorofluoromethane with added P_4O_{10} , gave 1,2,3,4-tetrakis(2-chlorotetrafluoroethyl)-5-thiabicyclo[2.1.0]pent-2-ene **379** in 91% yield (Equation 58) <2000JFC323>.



Reaction of 2,7-diphenyl-5*H*,6*H*,7*H*-imidazole[2,1-*b*]-1,4-thiazolium-3-thiolate **380** with aromatic aldehydes in toluene give thiiranes **381** (Scheme 109) <2001CEJ3033>. The yields of thiiranes are collected in Table 22.

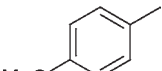
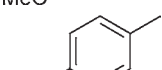
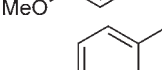
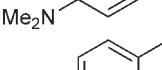


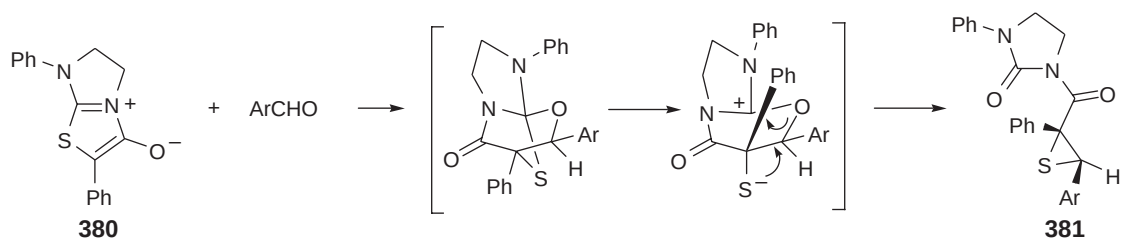
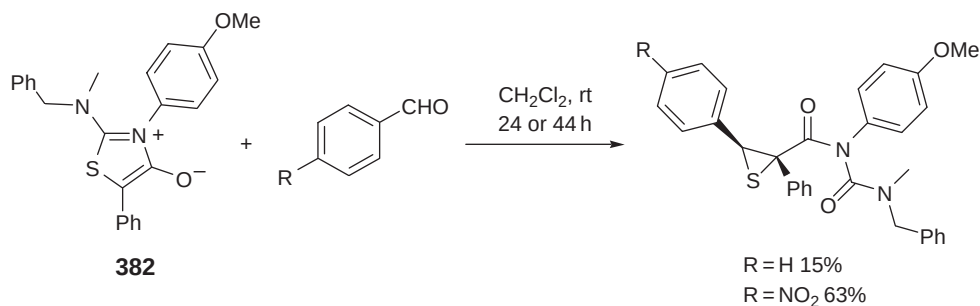
Scheme 109

The formation of thiiranes **381** by reaction of **380** with aryl aldehydes can be explained by assuming a preferential *endo* [3+2] cycloaddition of the aldehydes to **380** followed by ring opening of the cycloadduct (Scheme 110).

Reaction of 3-(4-methoxyphenyl)-2-(*N*-methyl)benzylamino-5-phenyl-1,3-thiazolium-4-olate **382** with benzaldehyde or 4-nitrobenzaldehyde in dichloromethane at room temperature gave corresponding thiiranes in 63% and 15% yields (Scheme 111). Reaction of **383** with tetra-*O*-acetyl-D-arabinose in refluxing benzene for 1 h gave a mixture of thiiranes **384** in 45–50% yield (Scheme 112) <2001TA2265, 2003JOC6338>.

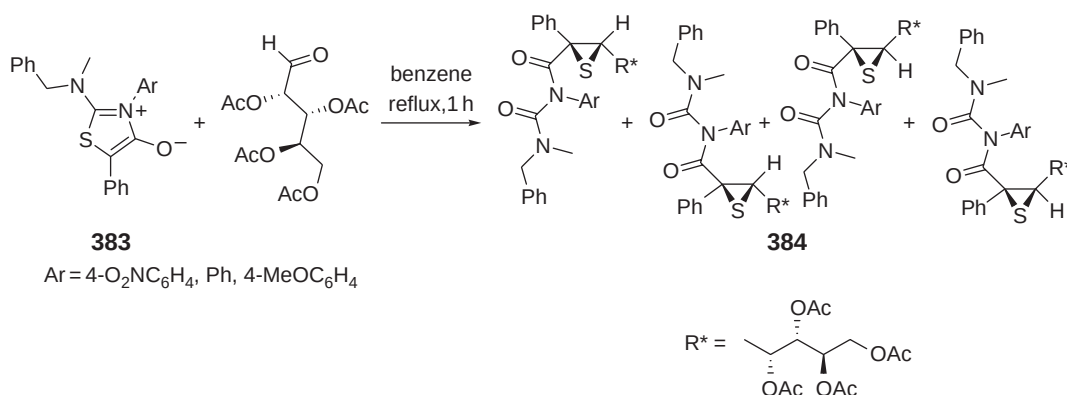
Table 22 Synthesis of thiiranes **381**

<i>R</i>	Temperature (°C)	Time (h)	Yield of 381 (%)
	25	1.5	65
	110	0.5	20
	110	1	50
	110	20	35
	110	1.5	17
	110	20	

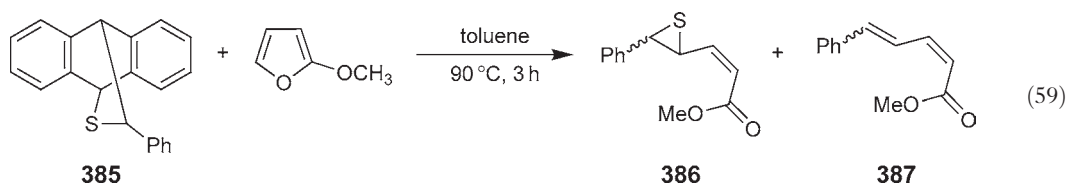
**Scheme 110****Scheme 111**

1.05.10.4 From Six-Membered Heterocycles

Reaction of thiobenzaldehyde–anthracene cycloadduct **385** with 2-methoxyfuran in toluene at 90 °C for 3 h gave thiirane **386** (mixture of (*E*)- and (*Z*)- isomers) and methyl 2-(*Z*)-penta-2,4-dienoate **387** (Equation 59) <2003TL1179>.



Scheme 112



1.05.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Since the publication of CHEC(1984) <1984CHEC(7)131>, and CHEC-II(1996) <1996CHEC-II(1)174>, a variety of remarkable new syntheses of thiiranes have appeared. However, many of these reactions are of limited general utility. There are a variety of syntheses of thiiranes from various precursors, most of which are quite specific, as well as numerous syntheses from oxiranes, which are more general in their utility and scope.

1.05.12 Important Compounds and Applications

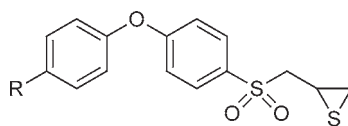
1.05.12.1 Naturally Occurring Thiiranes and Thiirenes

Thiirane was determined in volatile materials formed from onion inoculated by the pathogen *Botrytis allii* <2004MI371>. A variety of biologically active glucosinolate breakdown products, including allyl isothiocyanate and 1-cyano-2,3-epithiopropene, are released by mechanical disruption of raw Brussels sprout tissue <2005MI3895>. In an earlier study by another group, allyl isothiocyanate was highlighted as a potential food preservative <1998MI621>. It was also held to be more responsible for the flavor of fresh cabbage than 1-cyano-2,3-epithiopropene <1996JMI101>.

1.05.12.2 Drugs

'Drugs' in this section is interpreted very broadly (see also Section 1.05.3). Included also are discoveries that may lead to drugs in the future.

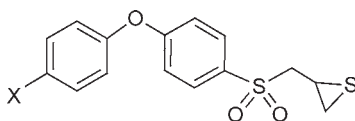
Many thiiranes have been tested as potential therapeutic agents. For example, a thiirane unit has been introduced into the 17- β -position of a steroid to act as a potential inhibitor of P450 17 <2000JME4437>. The antitumor agent leinamycin reacts with thiols to form episulfonium ions that alkylate the N-7 position of guanine residues in DNA <2002JOC9054, 2004CRT942>. Thiiranes **388** and **389** are potent and selective inhibitors for human gelatinases <2000JA6799, 2004JOC3572, 2005JOC5709, 2005OL4463>.



388: R = H

389: R = MeOCOCH₂

Analogous mechanism-based inhibitors (including **390–392**) for matrix metalloproteinases (MMPs) were reported by Ikejiri *et al.* <2005JBC33992>. Matrix metalloproteinases are zinc-dependent endopeptidases that play important roles in physiological and pathological conditions. Gelatinases (MMP-2 and -9) and membrane-type-1 MMP have been shown to play important roles in various diseases, including cancer. Full kinetic analysis for the inhibitors is included. The first thiirane derivative **390** targets MMP-2, -9, and -14, whereas **391** and **392** were inhibitory toward MMP-2 only.

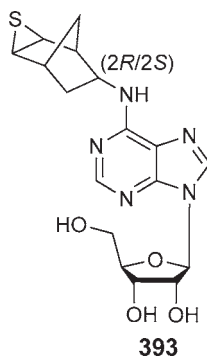


390: X = NHSO₂Me

391: X = NO₂

392: X = NHC(OMe)

Thiirane **393** has been reported to be an extremely potent and selective A₁ adenosine receptor agonist <2004BMC4877>.



393

Thiirancarboxamides (prepared from methyl or ethyl esters of glycine, alanine, valine, and isoleucine, and thiirancarboxylic acid) were reported as inhibitors of papain <2004AP90>. Thiiranes were used as key substrates in the synthesis of nucleosides as potential inhibitors of HIV <1996JOC3604, 1996JOC3611>.

The effects of Brussel sprout juice on the cell cycle and adhesion of human colorectal carcinoma cells (HT29) *in vitro* was studied to explore the effect of naturally occurring glucosinolate breakdown products on cell cycle progression and apoptosis <2005MI3895>. A variety of biologically active glucosinolate breakdown products, including 1-cyano-2,3-epithiopropene, are released by mechanical disruption of raw Brussel sprout tissue. Contrary to previous assumptions, allyl isothiocyanate is not the main compound responsible for the inhibition of cell proliferation.

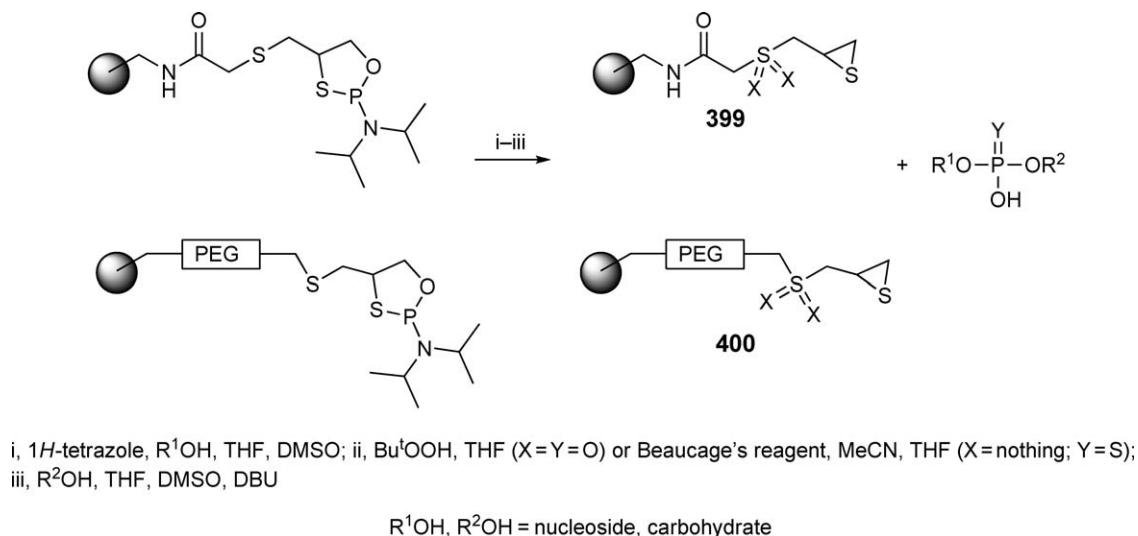
The structures of hepatitis A viral 3C proteinases complexed with tetrapeptidyl-based methyl ketone inhibitors were shown to have an episulfide cation embedded in them. The authors concluded that the mechanism of inactivation of 3C peptidases by methyl ketone inhibitors is different than those operating in serine proteinases or in papain-like cysteine peptidases <2006MI673>.

1.05.12.3 Insecticides and Herbicides

Methyl esters prepared from undecylenic acid and containing an episulfide group were tested as inhibitors of JH III epoxide hydrolase activity to evaluate its biological role in insects <2005MI140>.

During polymerization of (*RS*)-2-(phenoxyethyl)thiirane by diethylzinc/L-amino acid, the S-enantiomer of the thiirane was consumed preferentially <2002PSA3443>. Synthesis of optically active polymers prepared from thiiranes was described <2005TA2149>.

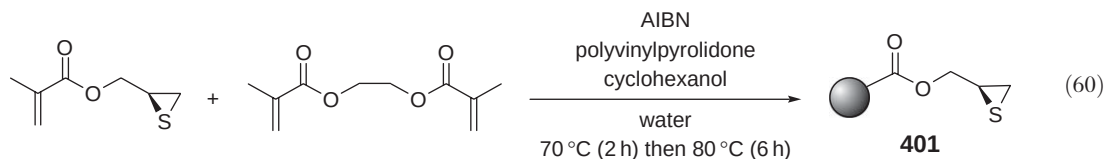
Polymer-supported thiiranes **399** and **400** were formed in the solid-phase synthesis of dinucleoside and nucleoside-carbohydrate phosphorodiester and thiophosphodiester (Scheme 115) <2006JOC6693>.



Scheme 115

Thiirane resin was synthesized from epoxy resin by reaction with potassium thiocyanate <2006MI4023, 2006MI379>.

Chiral polymer-supported thiiranes **401** were prepared by free radical copolymerization of TMA ((*S*)-thiiranylmethyl-methacrylate) and ethylene glycol dimethacrylate (EDMA) (Equation 60) <2006TA1944>. These chiral thiiranes were transformed into polymer-supported aminothiols by the facile ring opening of the thiirane group with benzylamine and methylamine. These derivatives, complexed with [RuCl₂(*p*-cymene)]₂, were used in asymmetric reduction of acetophenone to gave (*S*)-1-phenylethanol (39% ee from methylamine and 50% ee from benzylamine derivatives).



Thiirane-containing mesogenic stilbene units were polymerized to give liquid crystals <1998MI525>.

1.05.12.5 Toxicity

An episulfonium ion derived from *S*-(2-chloroethyl)glutathione reacted at the catalytic sites of protein disulfide isomerase. The adducts may have important toxicological significance for the toxicity of 1,2-dichloroethane <2004MI136>.

1.05.13 Further Developments

Since this review was submitted in October, 2006, there has been further activity in the area of thiiranes and thiirenes. Some papers published since then, including early pages from 2007, are listed below together with a few that were missed earlier <2002TL351, 2005STC28, 2006JHC1, 2006PCA13183, 2006EJO4528, 2006EJO4473, 2006MI1365, 2006MI295, 2006TL8471, 2006MI251, 2006MI289, 2006M235, 2006RJA331, 2006HCA1910, 2006HCA2815, 2006HCA3014, 2007HAC28, 2007JMT79, 2007MI63, 2007HCA86, 2007MI289, 2007MI335, 2007HCA337, 2007H(72)541, 2007JA2768, 2007MI>.

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Biographical Sketch



John Warkentin was born near Grunthal, Manitoba, on a farm. Following high school, he attended United College in Winnipeg and the University of Manitoba for his B.Sc. and M.Sc. degrees. After that he attained a Ph.D. degree from Iowa State College (G. S. Hammond) and undertook postdoctoral studies at Caltech and Harvard (P. D. Bartlett). He joined the Chemistry Department at McMaster University in 1960. Teaching included 2nd-, 3rd-, and 4th-year courses, as well as graduate courses in organic chemistry and a stint as instructor in 1st-year general chemistry. During sabbatical leaves, he was a guest at the University of California (San Diego), the National Research Council (Ottawa), the Australian National University, the Georg August University (Göttingen), the Ohio State University, and the Central Queensland University (Australia). His research was concentrated initially on the organic chemistry of free radicals and later on the chemistry of carbenes. He is now officially retired but still active in research.



Damian Plazuk was born in Radom, Poland. He received his M.S. (2001) and Ph.D. (2005) from the University of Łódź, in the area of electrophilic reactions of ferrocene while working with Professor J. Zakrzewski. During his Ph.D. study, he spent seven months in France (2003) at l'École Nationale Supérieure de Chimie de Paris (ENSCP), with Professor G. Jaouen on a Marie-Curie Fellowship, and four months (2004) in Canada at McMaster University, with Professor J. Warkentin. Now he is a lecturer in the Department of Organic Chemistry, University of Łódź. Teaching included 1st-, 2nd-, 3rd-, and 4th-year courses in organic and organometallic chemistry. His research is concerned with the synthesis of non-centrosymmetric, ferrocene-based molecular materials for second-order, nonlinear optics as well as synthesis of new ferrocenyl compounds that may be applied in medicinal chemistry. Currently, he is on a one-year fellowship (ENSCP, with Professor G. Jaouen) granted in the framework of Foreign Fellowships for young Ph.D.'s launched by the Foundation for Polish Science.

1.06

Thiiranes and Thiirenes: Fused-ring Derivatives

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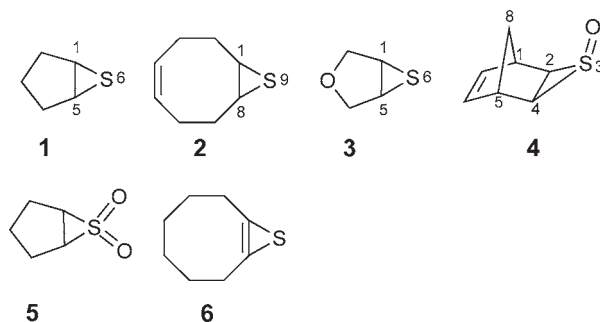
1.06.1 Introduction

1.06.1.1 Historical Perspective

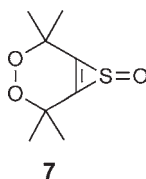
Despite the fact that there are a large number of structurally and chemically interesting fused-ring thiiranes and thiirenes, their chemistry has not been widely explored. One of the very first general reviews for this class of compounds along with their oxygen analogues emerged in CHEC(1984) <1984CHEC(7)185>. In CHEC-II(1996) <1996CHEC-II(1)241>, there was a chapter devoted solely to fused-ring thiiranes and thiirenes, which represented the literature between 1983 and 1995. This chapter focuses mainly on contributions published between late 1995 and the middle of 2006. However, some related works reported prior to or after that period may also be included when appropriate.

1.06.1.2 Nomenclature

The systematic nomenclature of fused-ring thiiranes and thiirenes is based on their parent hydrocarbons, for example, 6-thiabicyclo[3.1.0]hexane **1**, 9-thiabicyclo[6.1.0]non-4-ene **2**, 3-oxa-6-thiabicyclo[3.1.0]hexane **3**, and 9-thiabicyclo[6.1.0]non-1(8)-ene **6**. A different nomenclature, which is frequently used, especially for more complex structures, is based on the name of the parent cyclic olefins and the addition of 'sulfide' or 'episulfide' as a suffix. In this manner, **2** is named cycloocta-1,5-diene monoepisulfide. Alternatively, 'epithio' can be used as a prefix, leading to the name epithio-2,5-dihydrofuran for **3** <1996CHEC-II(1)241>.



The sulfoxides and sulfones analogues can be named as oxides or dioxides, for example, 3-thiabicyclo[3.2.1.0^{2,4}]oct-6-ene 3-oxide **4**, 6-thiabicyclo[3.1.0]hexane 6,6-dioxide **5**, and 2,2,4,4-tetramethyl-3,4-dioxa-7-thiabicyclo[4.1.0]hept-1(6)-ene 7-oxide **7**. These oxidized analogues are sometime named with the suffix episulfoxide or episulfone.



1.06.2 Theoretical Methods

The orbital hybridization and ^{13}C , ^{13}C spin–spin coupling constants of the bridging bond in 5-thiabicyclo[2.1.0]pentane and some heteroatom analogues including 2,3-unsaturated derivatives were calculated by using the self-consistent finite perturbation theory (SCPT INDO) <2002RJO394>. In all examples, the bridging C–C bond has a remarkable low *s*-character, for example, 14.39% ($\text{sp}^{5.95}$) for the parent compound **8**, which is considerably low compared to regular thiirane ($\text{sp}^{3.06}$). On the other hand, the length of the bridging C–C bond (1.50–1.53 Å) is very similar to that of thiirane as well as the bond angle C–S–C (50–51°). The fused-ring system, however, is essentially nonplanar.



The comparative study on the molecular structure and relative stability of sulfur-containing heteropropellane compounds **9** with other heteroatoms such as NH and O were investigated by *ab initio* method <2000JCM93>.



In 2001, *ab initio*, density-functional and semiempirical calculations on the reactivity of polycyclic aromatic hydrocarbon episulfides **10–22** were reported. Episulfides are predicted to open more easily than the corresponding *O*-protonated derivatives, epoxides and diol epoxides <2001HCA3588>. Calculation results for the episulfide ring opening of the *S*-protonated compounds are shown in Table 1.

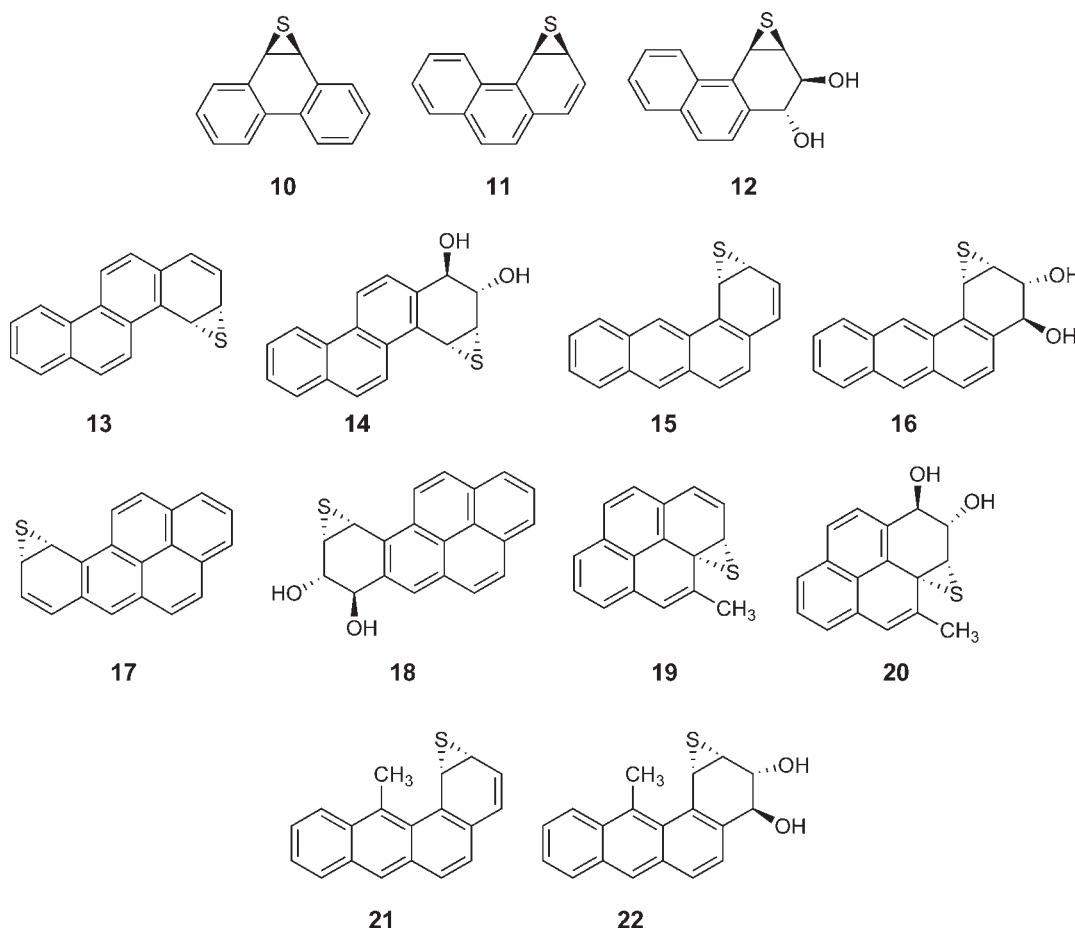


Table 1 Calculated enthalpy change involved in the the ring-opening reaction of the S-protonated thiiranes

Compounds	ΔH_r (kcal mol ⁻¹)		AM1 Charge at the carbocationic center
	AM1 ^a	PM3	
10	-1.27	4.88	0.130
11	-6.12	-2.23	0.060
12	-4.23	b	0.114
13	-5.37	-1.62	0.077
14	-5.16	-0.24	0.114
15	-9.33	-5.46	0.018
16	-7.72	-1.29	0.072
17	-8.43	-5.19	0.056
18	-13.59	-9.14 ^a	0.046
19	-6.64	-2.25	0.068
20	-6.00	-0.22	0.101
21	-10.80	-6.84 ^a	0.008
22	-14.42	-9.71 ^a	0.018

^aValue estimated by keeping fixed the S-C-C bond angle of the episulfide ring as the fully optimized protonated species into the open carbocation.

^bThe open structure collapses into the closed one.

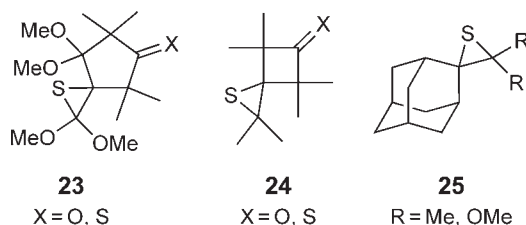
Theoretical study using semiempirical Austin Model 1 (AM1) and modified neglect of diatomic overlap (MNDO) methods on the interconversion of the closed [6,6] and the open [5,6] isomers of C₆₀S revealed a stepwise pathway via a local energy minimum corresponding to the closed [5,6] isomer. The results are in good agreement with those derived from the experiments <2002JPC9284>.

1.06.3 Experimental Structural Methods

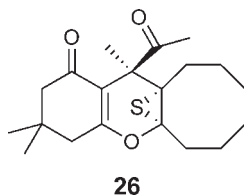
¹H, ¹³C NMR (NMR – nuclear magnetic resonance), and infrared (IR) spectra of many fused thiiranes, thiirenes, and their oxides have been reported as parts of standard characterization. Papers specifically devoted to this particular subject, for the period 1996–2006, were not found.

1.06.3.1 NMR Spectroscopy

Several fused-ring thiiranes have been synthesized and characterized by ¹H, ¹³C NMR, and MS. For instances, thiiranes **23–25** are products from the reaction of dimethoxycarbene with 2,2,4,4-tetramethyl-3-thioxocyclobutanone <2002CEJ2184>. Compound **24** was also identified as a product from the cycloaddition of a thiocarbonyl ylide <2001HCA1805>.



Episulfide **26** was obtained from the reaction of endoepoxide with cyclooctyne. Its structure was fully characterized by spectroscopic means including various NMR spectral methods (H,H-COSY, C,H-COSY, INADEQUATE; COSY – correlation spectroscopy), MS, and X-ray analysis <2002JA8316>.

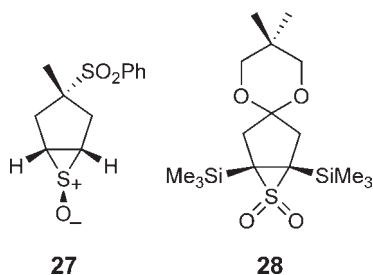


1.06.3.2 Infrared, Raman, Ultraviolet, and Microwave Spectra

Papers on this subject, for the period 1996–2006, were not found.

1.06.3.3 X-Ray Crystallography

Crystal structures of new fused thiirane such as **26** <2002JA8316>, *S*-oxides **27** <2000J(P1)153>, and *S,S*-dioxides **28** <1996J(P1)661> have been reported as parts of standard characterization. Papers specifically devoted to this particular subject, for the period 1996–2006, were not found.



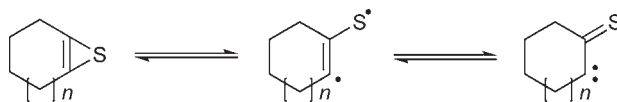
1.06.4 Thermodynamic Aspects

Papers on this subject, for the period 1996–2006, were not found.

1.06.5 Reactivity of Fully Conjugated Rings – Fused Thiirene, Fused Thiirene 1-Oxide, and Fused Thiirene 1,1-Dioxide

1.06.5.1 Introduction

Similar to their open chain counterparts, fused thiirenes are highly reactive substances due to their antiaromatic character <1996CHEC-II(1)174>. They are thought to be in equilibrium with diradicals and carbenes (**Scheme 1**). In addition to behaving as dienophiles, they can therefore undergo typical carbene and radical reactions <1987TL2867>.

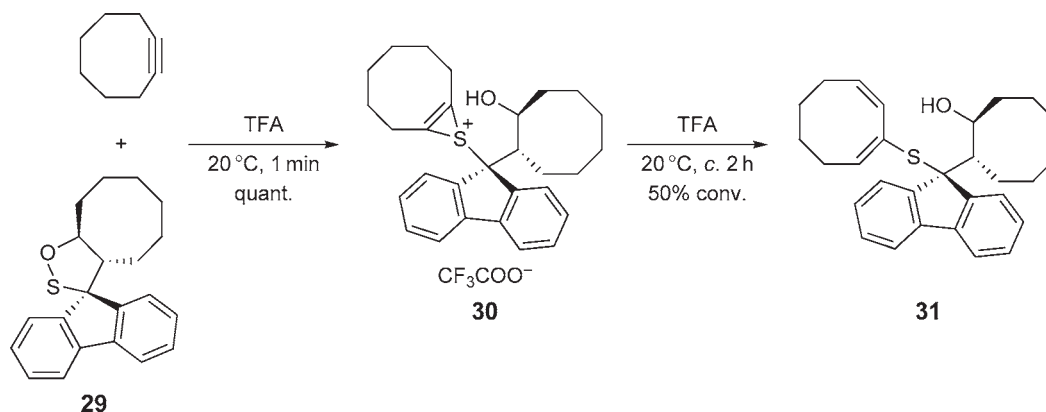


Scheme 1

Thiirene oxides are more stable as the electrons on the sulfur are less available to make the ring antiaromatic. Stable fused thiirene oxides have been isolated and shown to be powerful dienophiles and dipolarophiles <1996CHEC-II(1)241, 1982JA4981, 1984JA2216>. Other reactions of fused thiirenes and their oxides remain relatively unexplored.

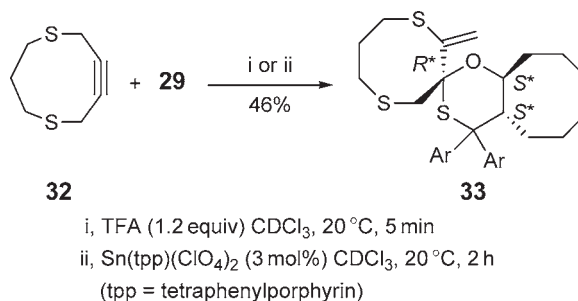
1.06.5.2 Unimolecular Thermal and Photochemical Reactions

A persistent fused thiirenium ion **30** was prepared in quantitative yield by the action of sultene **29** on cyclooctyne in the presence of trifluoroacetic acid (TFA) or the Lewis acidic $\text{Sn}(\text{tpp})(\text{ClO}_4)_2$ (tpp = tetraphenylporphyrin) [<2002JA8316>](#). Nucleophilic ring opening and rearrangement of **30** is expected to be difficult therefore contributing to its high stability. The compound is stable enough for characterization by ^{13}C NMR spectroscopy but it decomposes to a diene **31** in a matter of hours (**Scheme 2**). Addition of a base to **30** caused complete reversion to starting materials.



Scheme 2

The analogous thiirenium ion derived from 1,5-dithia-cyclonon-7-yne **32** could not be isolated but instead the spirocyclic compound **33** was obtained (**Scheme 3**). The reactions were proposed to proceed through an intermediate α -thiocarbonyl-stabilized carbene analogous to the ring opening of oxirenes (**Scheme 4**) [<2002JA8316>](#).



Scheme 3

1.06.5.3 Electrophilic Attack at Carbon

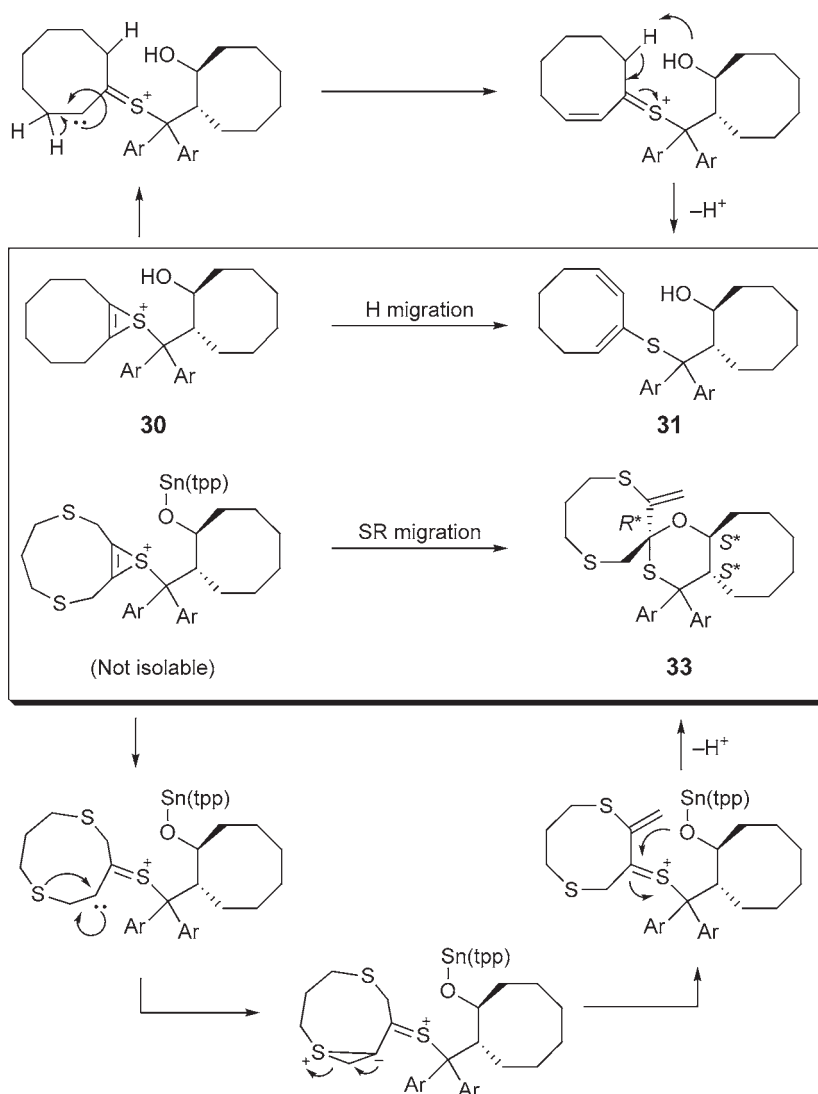
Papers on this subject, for the period 1996–2006, were not found.

1.06.5.4 Electrophilic Attack at Sulfur

Papers on this subject, for the period 1996–2006, were not found.

1.06.5.5 Nucleophilic Attack at Carbon

While open-chain thiirenium ions can undergo a ring substitution by $\text{S}_{\text{N}}2$ -Vin mechanism [<1993JA4527, 1997T15717, 2000JOC3367>](#), no analogous reaction for fused-ring analogues were reported for the period of 1996–2006.



Scheme 4

1.06.5.6 Nucleophilic Attack at Sulfur

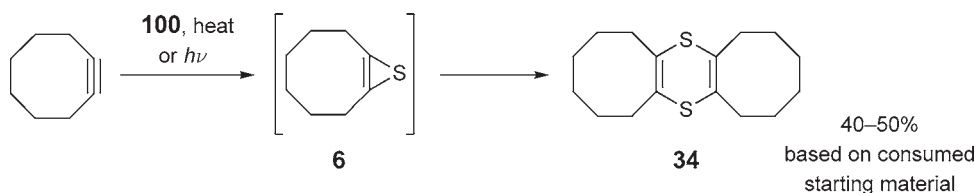
The thiirenium salt **30** reverted to starting materials **29** and cyclooctyne by addition of K_2CO_3 as a base. This probably results from nucleophilic attack on the thiirenium sulfur atom by the side chain hydroxyl group [\[2002JA8316\]](#).

1.06.5.7 Nucleophilic Attack at Hydrogen Attached to Carbon (Deprotonation)

Papers on this subject, for the period 1996–2006, were not found.

1.06.5.8 Reactions with Radicals and Electron-Deficient Species

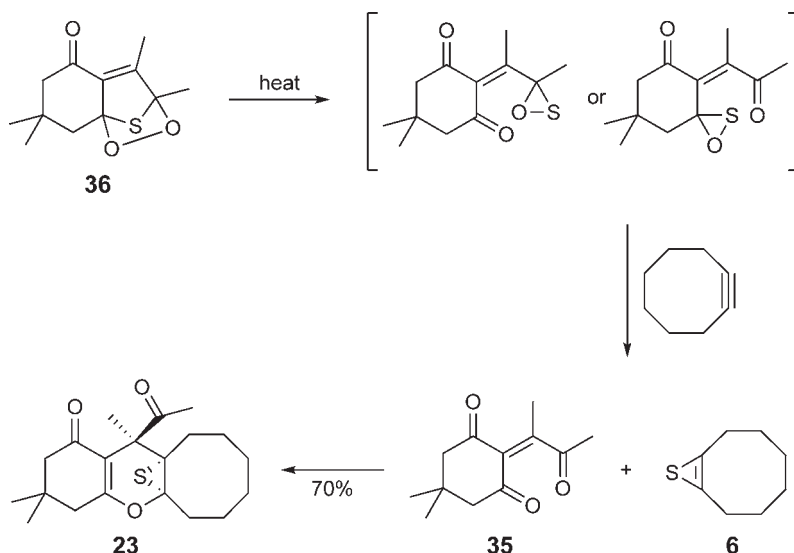
Simple thiirene **6** was shown to dimerize to dithiin **34** upon its formation by episulfidation of cyclooctyne [\[1998JOC9154\]](#), probably via diradical and/or carbene intermediates ([Scheme 5](#)).



Scheme 5

1.06.5.9 Reactions Involving Cyclic Transition States

The thiirene **6** was proposed as an intermediate in the formation of a cycloadduct **23** obtained from the reaction of a thiophene endoperoxide **36** <1996CC177> and cyclooctyne under thermal conditions (Scheme 6). The structure of **23** has been verified by X-ray crystallography <2002JA8316>.



Scheme 6

1.06.6 Reactivity of Nonconjugated Rings – Fused Thiirane, Fused Thiirane 1-Oxide, and Fused Thiirane 1,1-Dioxide

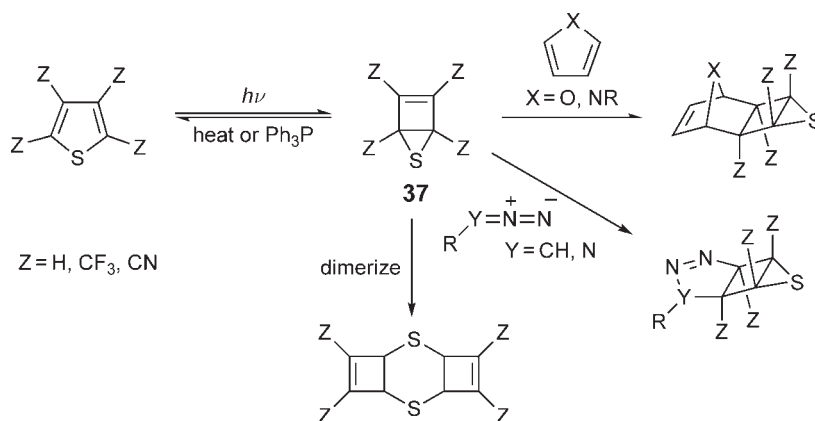
1.06.6.1 Introduction

Reactivities of fused thiiranes and their *S*-oxides are generally similar to their monocyclic analogues <1996CHEC-II(1)174, 1996CHEC-II(1)241>. Chemistry of Dewar's thiophenes is perhaps an exception that is unique to fused thiiranes.

1.06.6.2 Unimolecular Thermal and Photochemical Reactions

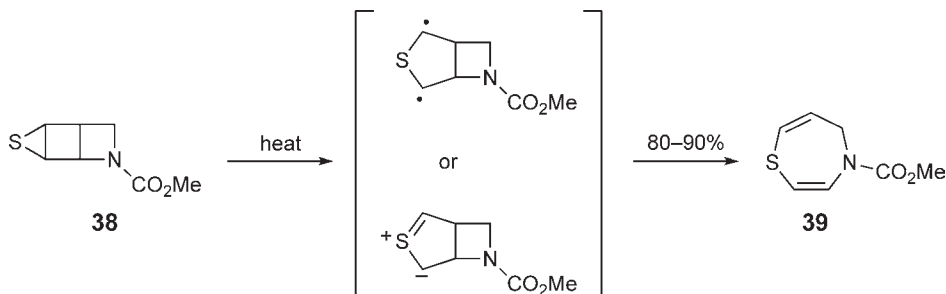
1.06.6.2.1 Reactions involving Dewar's thiophenes

Photoisomerization of thiophenes to Dewar's thiophenes **37** is a well-known reaction. Most of the chemistry of Dewar's thiophene was studied during the 1970s and 1980s, and are summarized in Scheme 7. Reversion of Dewar's thiophene to thiophene is symmetry forbidden and therefore they are relatively thermally stable <1995TL3177>. In polar aprotic solvents, they dimerize readily to form dithiins <1977H(9)1587>. Phosphines catalyze isomerization to thiophenes <1977H(9)1587>. They behave as dienophiles, and dipolarophiles and form cycloadducts with furans, pyrroles, dienes, diazoalkanes, and azides. The topic is well covered in previous reviews <1996CHEC-II(1)174, 1996CHEC-II(1)241> and only examples that have not been covered will be presented here.



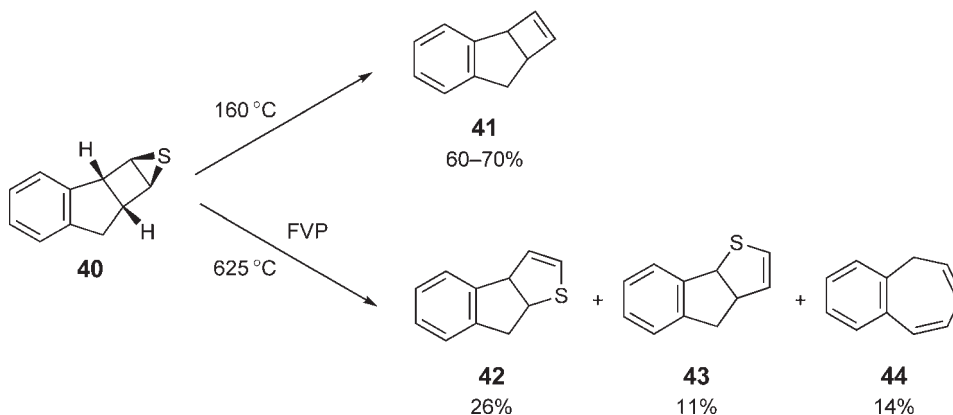
Scheme 7

In refluxing xylene, the fused Dewar's thiophene **38** including its oxygen and nitrogen analogues underwent a formal electrocyclic ring opening to afford the 1,4-thiazepine ring system **39** in 80–90% yield [<1985CPB4572, 1983CC941>](#). The reaction is likely to proceed through a biradical or ion-pair intermediates (**Scheme 8**).



Scheme 8

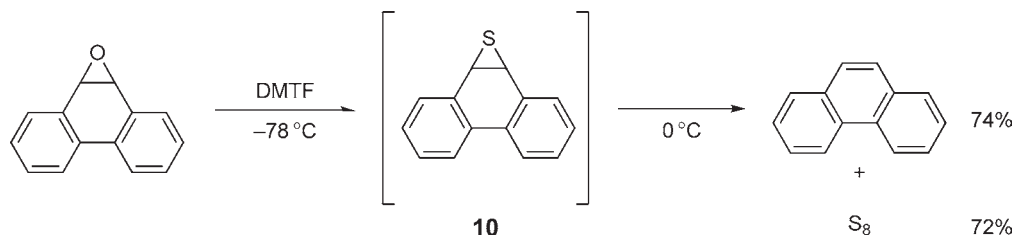
In refluxing xylene (160°C), fused Dewar's thiophene **40** mainly desulfurized to give cyclobutene **41** but under flash vacuum pyrolysis conditions, a mixture of isomeric dihydrothiophenes **42**, **43**, and 5H-benzocycloheptatriene **44** was formed (**Scheme 9**). Evidently the latter product derived from a formal electrocyclic ring opening of the cyclobutene intermediate **41** [<1990H\(31\)1769>](#).



Scheme 9

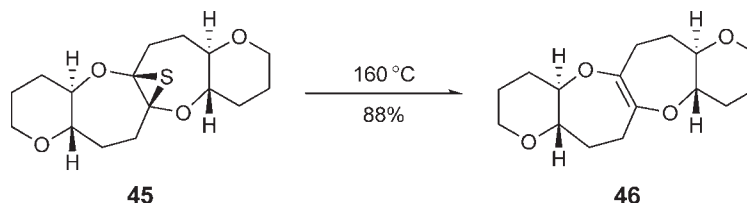
1.06.6.2.2 Desulfurization

Thiiranes derived from aromatic hydrocarbons are thermally labile. For example, phenanthrene episulfide **10** was detected spectrometrically at -55°C but was too unstable to isolate <2000JOC8083>. It decomposed spontaneously to elemental sulfur even at 0°C , thus restoring the parent aromatic compound (Scheme 10). The relative stability of various arene episulfides has been calculated and in general they are much less thermodynamically stable than the corresponding epoxide <1998T14283>.



Scheme 10

Other fused thiiranes are more thermally stable. For example, the compound **45** desulfurizes at 160°C (Scheme 11) <1987JA3801, 1990JA3029>. The reaction provided alkenes with retention of stereochemistry. In the presence of a desulfurizing agent such as phosphines or phosphites, the desulfurization temperature may be decreased to room temperature (Section 1.06.6.6) <1984CHEC(7)131>. The desulfurization of thiiranes is also subjected to transition metal catalysis. Since the initial step involves coordination of the metal to thiirane sulfur atom, the topic is discussed further in Section 1.06.6.4.



Scheme 11

Thiirane *S*-oxides are effective precursors for sulfur monoxide (SO) under thermal conditions <1997JOC8366>. The sulfur monoxide has been trapped by a variety of dienes to form cyclic sulfoxides. Extrusion of SO_2 from thiirane *S,S*-dioxides to form alkenes under thermal conditions is well known. The reaction takes place readily at room temperature in the presence of KO^tBu in tetrahydrofuran (THF). It constitutes the final step of the Ramberg–Bäcklund rearrangement <2003OR357, 1999CC217>.

1.06.6.3 Electrophilic Attack at Carbon

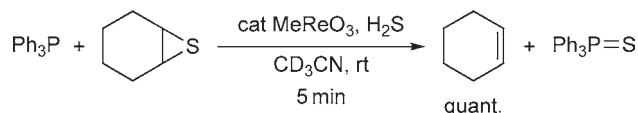
Papers on this subject, for the period 1996–2006, were not found.

1.06.6.4 Electrophilic Attack at Sulfur

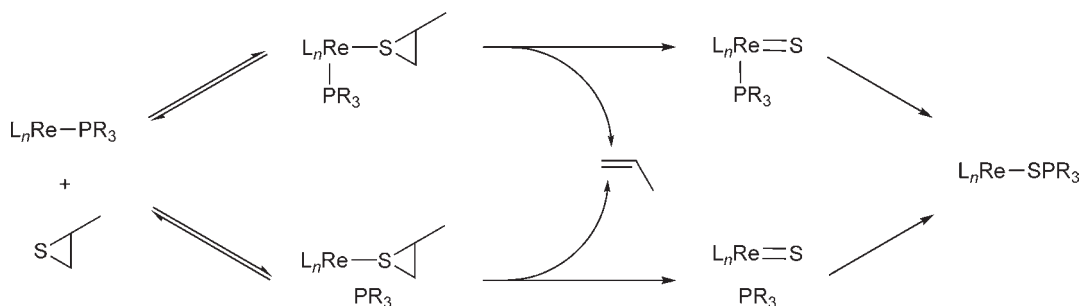
1.06.6.4.1 Metal ions

Transition metal complexes catalyze desulfurization of thiiranes. Complexes of Rh <1986TL3573>, Re <1997TL7701, 1999CC1003>, and Mo <2003JA3871> have been successfully employed in catalytic quantities. The presence of a stoichiometric sulfur acceptor such as carbon monoxide or an alkene, phosphine, or arsine is required. In Re-catalyzed desulfurization, the formation of an intermediate $\text{Re}^{(\text{VII})}=\text{S}$ species via initial coordination of the thiirane ligand has been suggested (Schemes 12 and 13) <1997TL7701>. Kinetics and mechanism of sulfur

transfer from thiiranes to phosphines and arsines catalyzed by an oxorhenium(v) complex have been investigated <2006IC5351>. Thiiranes, especially propylene sulfide or phenylthiirane have, in fact, been employed as effective sulfur transfer agent to another alkene in the presence of such metal catalysts <1997CRV7701>.



Scheme 12



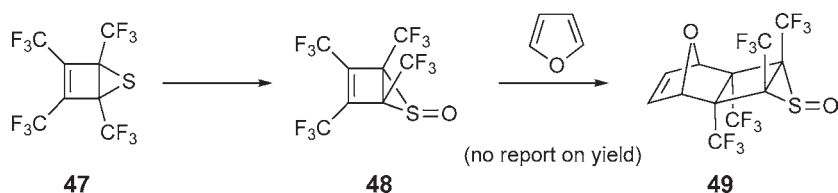
Scheme 13

In the presence of $\text{Rh}_2(\text{OAc})_4$ catalyst, the S atom as well as SO transfer to another alkene at room temperature are possible <1998SL391, 2000J(P1)153>.

1.06.6.4.2 Oxidation of sulfur

Oxidation of fused thiiranes to the corresponding thiirane *S*-oxides was discussed in CHEC-II(1996) <1996CHEC-II(1)241>. Typical oxidants include *m*-chloroperbenzoic acid (MCPBA), NaIO_4 , and singlet oxygen. Propylene sulfide, cyclohexene sulfide, as well as other cyclic sulfides have been enzymatically oxidized to sulfoxides with varying degree of diastereo- and enantioselectivities by a chloroperoxidase from *Caldariomyces fumage* <1998CH246>. No other new oxidants have been investigated during the period 1996–2006. New applications of known oxidants were found, for example, MCPBA <1997JOC8366, 2000JOC8083>.

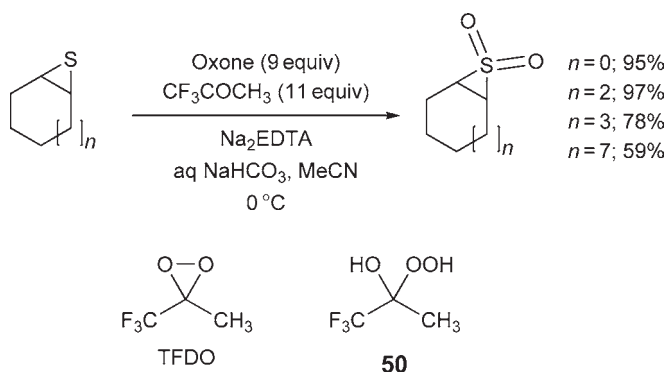
Tetrakis(trifluoromethyl)-5-thiabicyclo[2.1.0]pent-2-ene *S*-oxide **48**, a cyclobutadiene episulfoxide, has been prepared by selective oxidation of the corresponding episulfone **47** with peroxytrifluoroacetic acid (Scheme 14) <1976JA4325, 1977JA629>. In an analogous manner, the episulfoxide of type **48** bearing four 2-chloro-1,1,2,2-tetra-fluoroethyl groups was obtained by oxidation in dichloromethane <2000JFC(102)323>.



Scheme 14

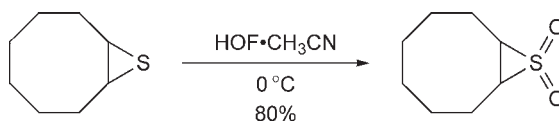
Direct oxidation of thiiranes to thiirane *S,S*-dioxides employing typical oxidants listed above had not been successful due to a number of competing side reactions including ring open and loss of SO_2 . Although there is one earlier report on oxidation of a fused thiirane to the corresponding *S,S*-dioxide using H_2O_2 /glacial acetic acid mixture <1992PS183>, the first direct and fairly general oxidation of thiiranes, including fused thiiranes, to thiirane

S,S-dioxides using oxone and trifluoroacetone system was reported in 1997 <1997TL5873>. Fused thiiranes gave good to excellent yield of the dioxides (**Scheme 15**). Cyclohexene sulfide failed to give the corresponding dioxide presumably due to the high reactivity of the dioxide <1993SL660>. In some cases, thiirans *S*-oxides were also isolated as side products, especially for monocyclic thiiranes containing large ring substituents. Surprisingly, only sulfoxides were obtained when methyl (trifluoromethyl)dioxirane (TFDO) was used as the oxidant. Apparently, the active oxidant in this reaction was not TFDO, but perhaps some other hydroperoxy species such as **50** <2001CR3499>.



Scheme 15

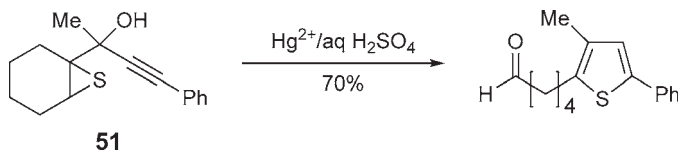
More recently, $\text{HOF} \cdot \text{CH}_3\text{CN}$ was described as another powerful oxidizing agent, providing thiirane *S,S*-dioxides directly from thiiranes, including cyclooctene sulfide, in >80% yield in a matter of seconds (**Scheme 16**) <2006OL1213>. The oxidation of thiiranes was faster than that of thiirane *S*-oxides and therefore it was possible to stop the reaction at the *S*-oxide stage by conducting the oxidation at -78°C . Using *O*-labeled water as a precursor of hypofluorous acid (HOF), it was possible to prepare sulfones with any variation of oxygen isotopes. These compounds are valuable precursors of oxygen-labeled SO_2 with any label combinations.



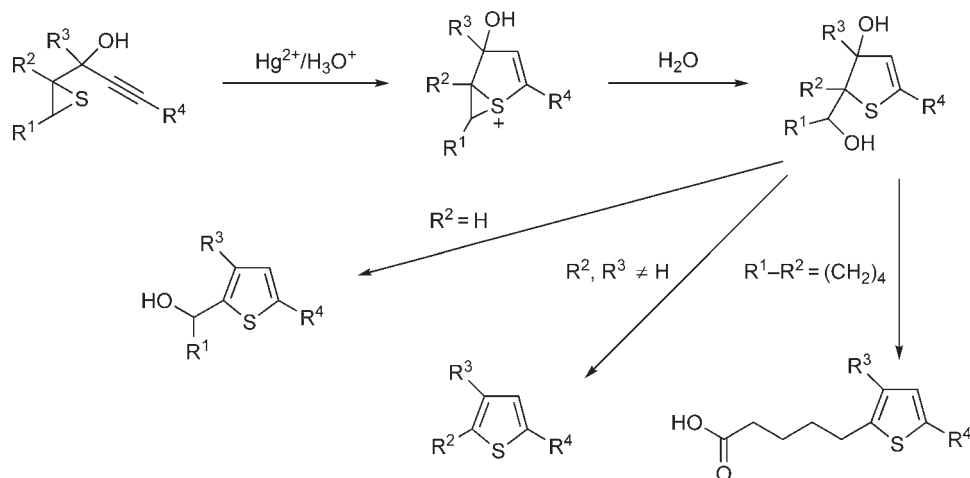
Scheme 16

1.06.6.4.3 Other electrophiles

An interesting conversion of 1-alkynyl-2,3-epithioalcohols **51** to substituted thiophenes under Hg(II) catalysis was reported (**Scheme 17**) <1997TL7785>. The reaction proceeded through hydrolytic ring opening of episulfonium intermediates. Disubstituted thiiranes including fused thiiranes such as cyclohexene sulfide provide abnormal products in which cleavage of the C–C bond, which used to be part of the episulfide ring six-membered ring, took place in order to form the fully aromatic thiophene ring (**Scheme 18**).

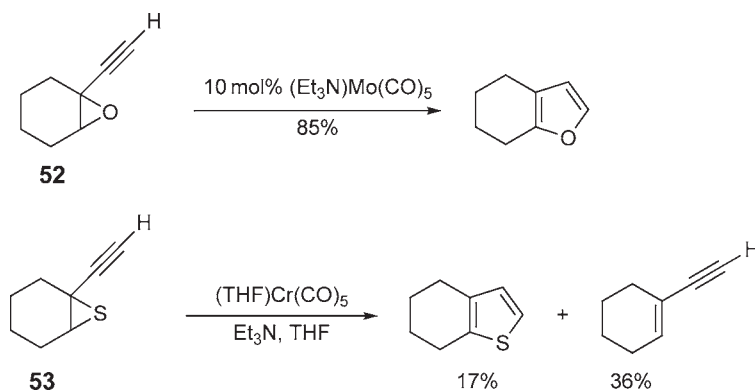


Scheme 17



Scheme 18

The alkynyl epoxide **52** cycloisomerized to a furan in the presence of a group VI transition metal catalyst <1994JA9363>. The analogous reaction with alkynyl thiirane **53** was also observed although thermal extrusion of sulfur was the major competing side reaction (Scheme 19) <2000S970>.



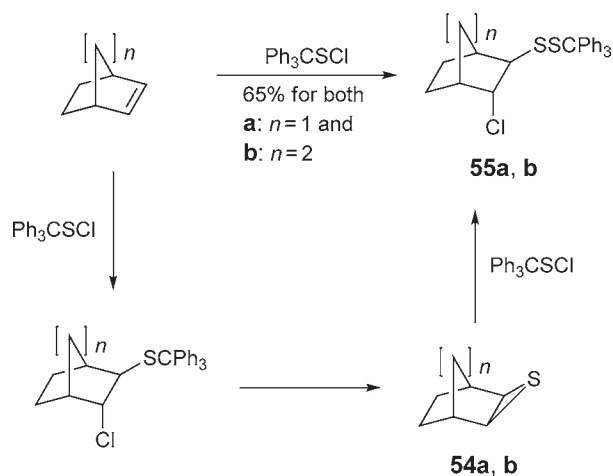
Scheme 19

An unusual β -chlorodisulfide product **55a** was formed in the reaction between norbornene and triphenylmethylsulfenyl chloride (Scheme 20) <1993TL4289>. The structure was verified by X-ray crystallography. A similar result was obtained with bicyclo[2.2.2]octene. These products were probably formed by electrophilic attack of sulfur atom on the thiirane intermediate **54a** and **54b**.

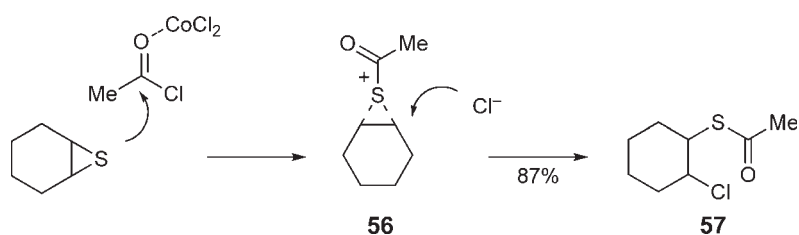
In the presence of metal salts, thiiranes including cyclohexene sulfide react with acetyl chloride to afford β -chlorothioacetate **57** in good yield <2003SC2321>. Cobalt(II) chloride (0.05 equiv) was found to be the best catalyst. Under these conditions, cyclohexene sulfide provided the ring-open product in 87% yield (Scheme 21). Similar reactions in the absence of the metal salts provided only low yield of the ring-open product <1978CJC2677>.

1.06.6.5 Nucleophilic Attack at Carbon

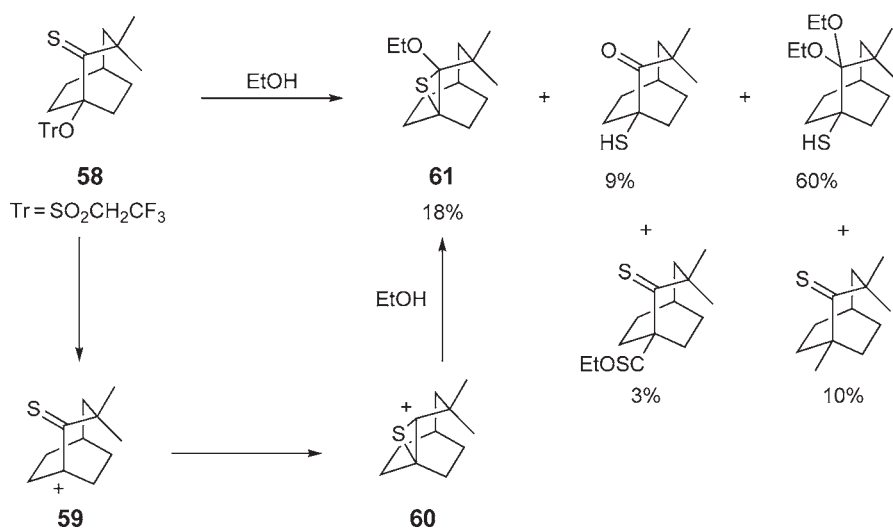
Most nucleophilic attacks at the ring carbons of thiiranes result in ring opening except for one particular example. Solvolysis of thio ketone **58** in ethanol in the presence of lutidine afforded a mixture of products including **61** (18%) <1996TL2241, 1998JOC2209>. The formation of **61** has been explained as a result of nucleophilic attack of the solvent on the episulfide cation intermediate **60** (Scheme 22).



Scheme 20



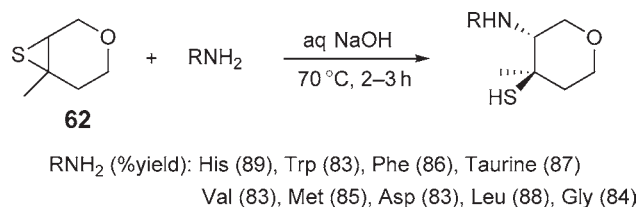
Scheme 21



Scheme 22

There are numerous examples of ring opening of fused thiiranes by amine nucleophiles in the literature. The yields are usually only moderate, but at a synthetically useful level. No other catalysts are required. Ring opening of cyclohexene sulfide with dibenzylamine in ethanol was reported to give only poor yield (18%). Oxidation and debenzylation of the product afforded a cyclic analogue of taurine [2005S2122](#). Similarly a ring opening of cyclohexene sulfide with other amines afforded only a low yield (piperidine: 30%, *n*-hexylamine: 40%,

cyclohexylamine: 29%, benzylamine: 35%, *tert*-butylamine: 15%) <1947JA2672, 1982J(P1)2777>. On the other hand, under aqueous basic conditions, the fused thiirane **62** reacted with a variety of amino acids to give the ring-open products resulting from nucleophilic attack at the less hindered carbon in surprisingly good yields (Scheme 23) <2003CHE174>.



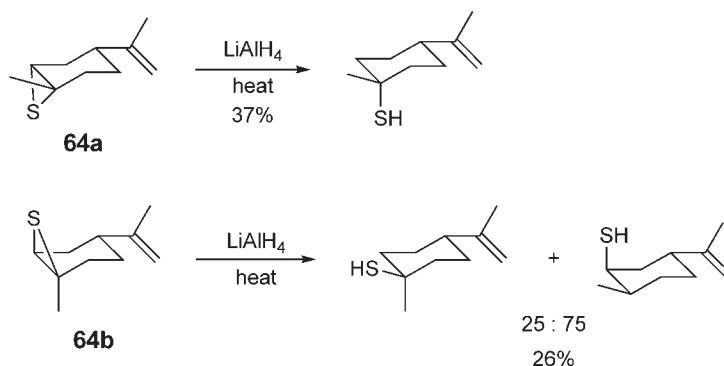
Scheme 23

Ring opening of fused thiirane **63** by tetrabutylammonium azide required activation of the thiirane ring by a thiophilic promoter (Hg²⁺) to give 68% yield of the diaxial isomer accompanied by 17% of the diequatorial diastereomer (Scheme 24) <2001JA1587>. These ring-opened products were used as intermediates for a synthesis of glycopeptide mimetics. Similar activation by Hg²⁺ has been previously observed <1978CJC2677>.



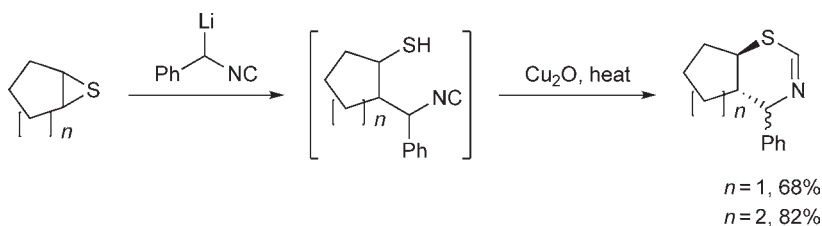
Scheme 24

Treatment of thiiranes **64a** and **64b** by LiAlH₄ resulted in reductive ring opening. The yields were only moderate (Scheme 25) <2003FFJ52>.

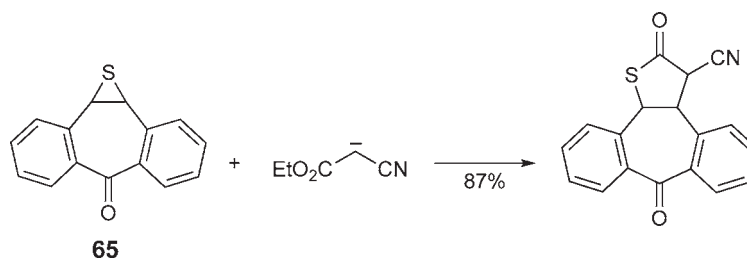


Scheme 25

Ring opening of thiiranes by both stabilized and unstabilized carbon nucleophiles are known <1996CHEC-II(1)241>. A reaction of cyclohexene sulfide with allylmagnesium bromide gave the normal ring-opened product <1983CCCC1749> while the more basic phenyllithium and *n*-butyllithium gave cyclohexene and the corresponding thiols as major products <1954JA1082>. Lithiated isonitriles reacted with cyclopentene sulfide and cyclohexene sulfide to afford ring-opened products which cyclized by heating with Cu₂O (Scheme 26) <1979LA451>. An additional example with cyanoacetate ester followed by cyclization is shown in Scheme 27 <1992PS183>.

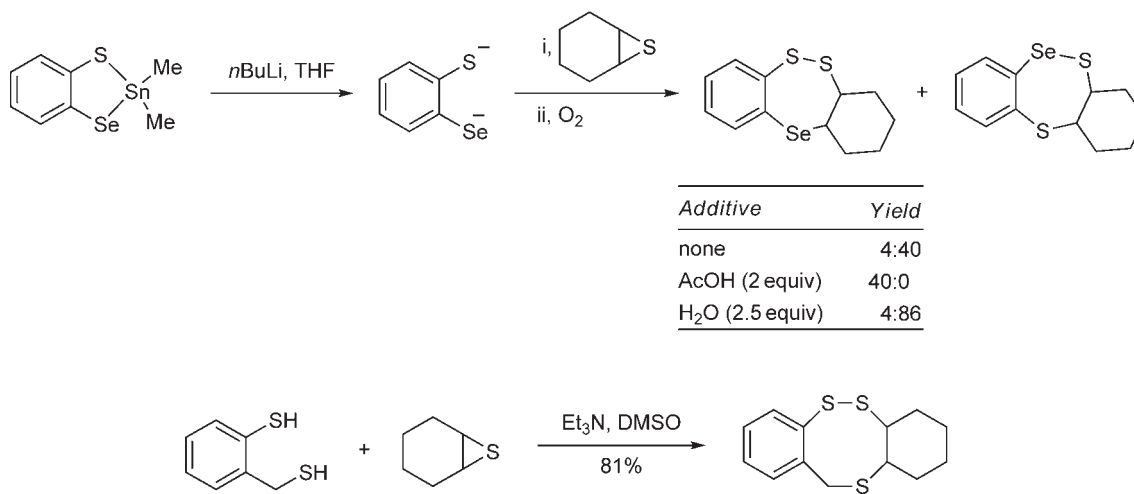


Scheme 26



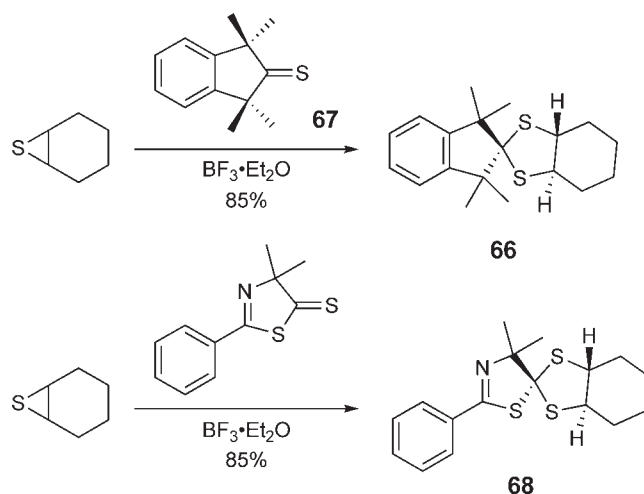
Scheme 27

Ring opening of cyclohexene sulfide by thiophenoxide ions has been conducted under basic conditions [<1999TL7745>](#). Ring opening of the thiirane ring with sulfur or selenium bis-nucleophiles to give benzotrithiepins or benzotrithiocins after air oxidation has also been reported ([Scheme 28](#)) [<1997TL5821, 1994TL891>](#).



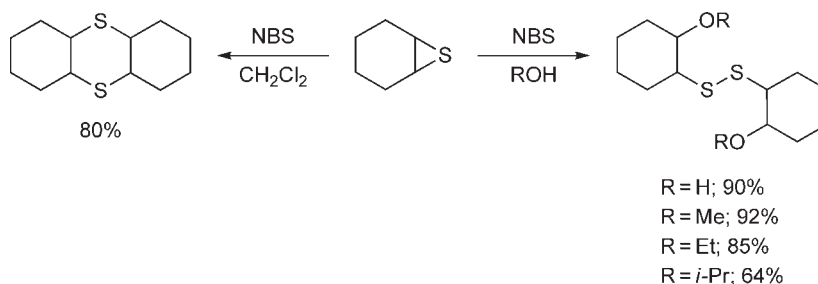
Scheme 28

A spirocyclic dithiolane **68** was reported to be the product from the reaction of cyclohexene sulfide and 4,4-dimethyl-2-phenyl-1,3-thiazole-5(4*H*)-thione in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ [<1999HCA1458>](#). The cyclic thioketone **67** reacted with cyclohexene sulfide similarly to form the dithiolane **66** ([Scheme 29](#)) [<1999HCA2316>](#). Extensive polymerization of the thiirane induced by the Lewis acid catalyst was also observed under these conditions.



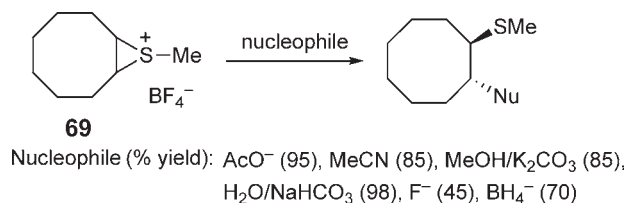
Scheme 29

Solvolysis of fused thiiranes by lower alcohols or water takes place readily in the presence of an activator. For activators which are also oxidizing agents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) <1990SC1047>, Ce(IV) salts <1991T149>, I₂ on silica gel <1997CJC1913, 2002SC1251>, *N*-halosuccinimides <2002T7037, 1990SC1047>, or 2,4,4,6-tetrabromo-2,5-cyclohexadiene-1-one (TABCO) <2002T7037>, disulfides were obtained due to further oxidation of the ring-opened product initially formed. In the absence of nucleophiles, dimerization occurred to afford dithiins (Scheme 30).



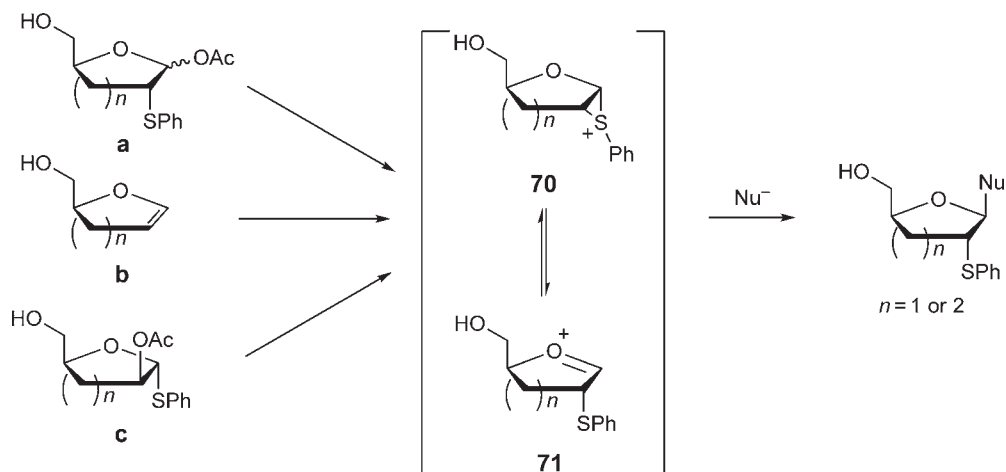
Scheme 30

The fused thiiranium salt **69** was isolated as a stable solid <1980T1361>. This, as well as other similar thiiranium salts, reacts readily with a variety of nucleophiles including amines, H₂O, alcohols, acetonitrile, halides, and borohydride giving products resulting from nucleophilic attack at carbon (Scheme 31) <1980TL383, 1980T1361, 1975TL2451>. Products resulting from 1,5-hydride shift were observed in some cases.



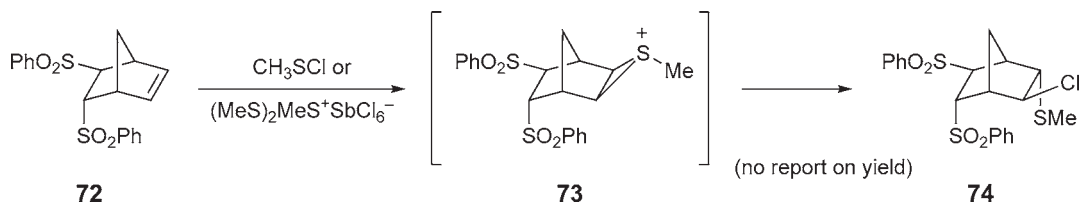
Scheme 31

Episulfonium chemistry has been used extensively in the synthesis of glycosides <2000TL407>. The sulfide groups can be removed selectively using Raney nickel <1986JA2466>. Although the episulfonium ion **70** has long been proposed as an intermediate in the glycosylation involving acceptors of types **a**, **b**, or **c** (Scheme 32), the nature of the intermediate has been questioned <1993TL7209, 1999JOC1247>. A recent density functional theory (DFT) calculation suggested that the geometry of the actual intermediates is closer to the oxonium ions **71** for both pyranose and furanose series <2003JOC686>. The exact nature of the intermediate, however, depends on the type of substituent on the heteroatom.



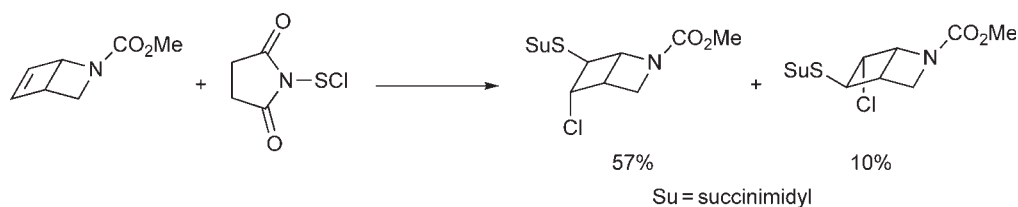
Scheme 32

Treatment of alkene **72** with methanesulfonyl chloride afforded the adduct **74** via the intermediacy of a thiiranium ion **73** (Scheme 33). This intermediate **73** has been independently synthesized and was shown to react with *N*-methylpyridinium chloride to provide **74** <1992CC293>.



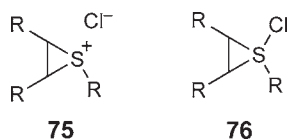
Scheme 33

Addition of succinimidyl sulfonyl chloride to a bicyclic alkene afforded a ring-opened product derived from thiiranium ion (Scheme 34) <2003JOC5292>.



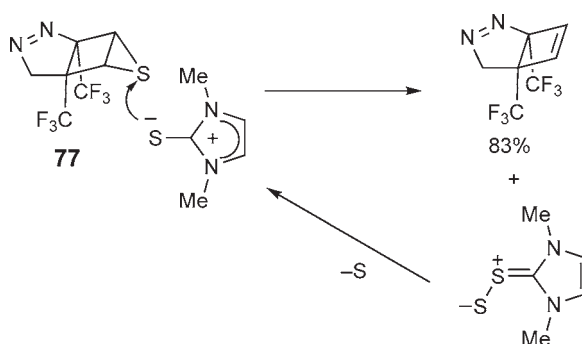
Scheme 34

The absence of rearrangement or solvolysis by-products from reactions of alkenes with sulfenyl chlorides suggested that very tight ion pairs **75** or episulfuranes **76** might be the intermediates <1980T1361>.



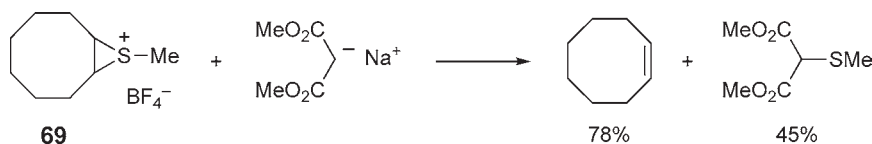
1.06.6.6 Nucleophilic Attack at Sulfur

Desulfurization of thiiranes by trialkylphosphines or phosphites takes place via nucleophilic attack on sulfur atom <1984CHEC(7)131>. These desulfurizing agents need to be present in stoichiometric quantity. However, some desulfurizing agents operate in catalytic fashion. These include Me₃SiX (X=I or Br) <1988TL4177> and *N,N*-dimethylimidazole-2-thione <1983JA3563>. In these cases, the catalysts were regenerated by decomposition of the catalyst-sulfur adducts containing relatively weak Si-S or S-S bonds (Scheme 35).



Scheme 35

While most nucleophiles react with the fused thiiranium salt at carbon (Section 1.06.6.5), certain soft nucleophiles including anion of malonate ester, iodide, thiourea, phosphines, and tertiary amines promote elimination of the sulfur atom by nucleophilic attack on sulfur (Scheme 36) <1980T1361>.



Scheme 36

1.06.6.7 Nucleophilic Attack at Hydrogen Attached to Carbon (Deprotonation)

The ring protons of thiirane *S*-oxide and thiirane *S,S*-dioxides are quite acidic. Furthermore, the resulting lithiated thiirane oxides are stabilized by chelation with the *syn*-oxygen atom. Thiirane *S,S*-dioxides can therefore be readily deprotonated with strong bases such as KO^{*t*}-Bu, lithium diisopropylamide (LDA), or Schwesinger's *t*-Bu-P₄ phosphazene base and subsequently trapped by an electrophile <1994TL7281, 1994JOC5141, 1996J(P1)661, 1997J(P1)323>. A high dilution and slow addition of the base to a mixture of the electrophile and the episulfone are necessary (*in situ* quenching protocol) to ensure good yield of the alkylated products <1994TL7281, 1996J(P1)661>. Bis-alkylations are relatively difficult; therefore, it is possible to stop at the monoalkylation stage (Table 2). Apart from trialkylsilyl and trialkyltin halides, electrophiles studied included benzoyl chloride and benzaldehyde but the yields were rather low.

Better results (up to 76% yield with PhCHO) were obtained when the anion was generated indirectly via the reaction of the α -silylated episulfone in the presence of CsF [<1996J\(P1\)661, 1997J\(P1\)323>](#) (see also [Section 1.06.8](#)).

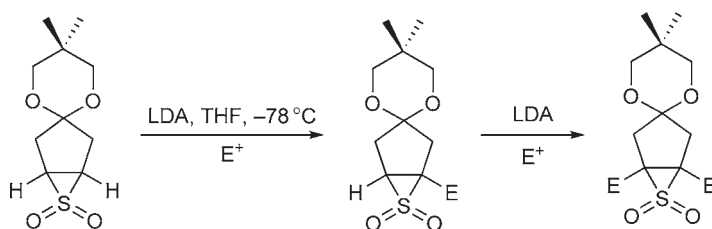


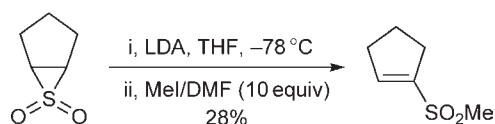
Table 2 Examples of deprotonation of a fused thiirane *S,S*-dioxide followed by alkylation

E^+	E	Yield ^a
Me_3SiCl	Me_3Si	54 (69) ^b
Et_3SiCl	Et_3Si	70
Bu_3SnCl	Bu_3Sn	52
PhCOIm	PhCO	27

^aYield of monosubstituted products.

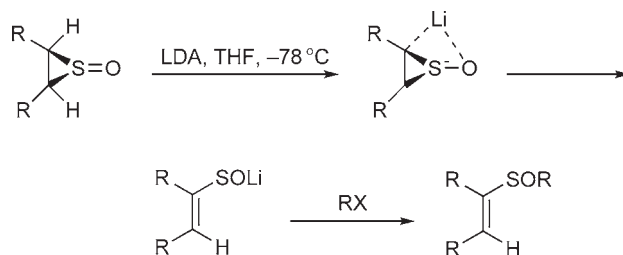
^bYield in parentheses refers to bis-substituted product when 5 equiv of the electrophile were employed.

In the absence of the electrophile, or when the electrophile was added after the base treatment, rearrangement to a vinylic sulfoxide was observed ([Scheme 37](#) [<1997J\(P1\)323>](#)). At high temperature or in the presence of $\text{KO}^t\text{-Bu}$, elimination of SO_2 (the Ramberg–Bäcklund reaction) took place [<1989TL3267, 1993SL660>](#).



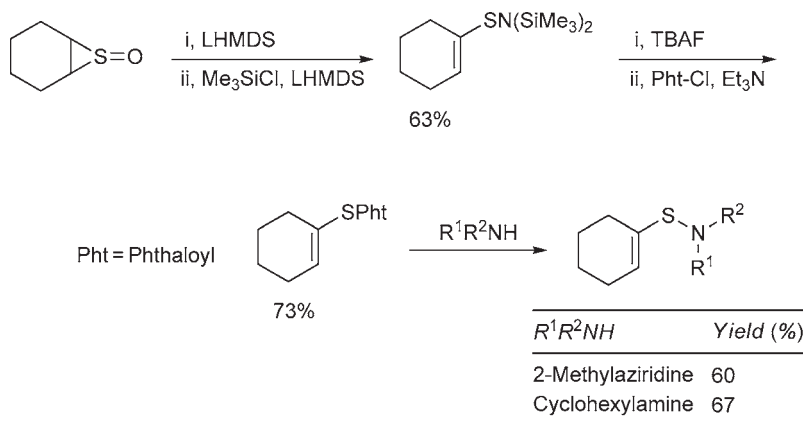
Scheme 37

Thiirane *S*-oxides underwent regioselective deprotonation to form lithiated species with the lithium chelated by the *syn*-SO group ([Scheme 38](#)). The lithiated thiirane *S*-oxides stereospecifically ring-opened to a lithium sulfenate, which may be trapped by an alkylating agent [<1995JA184, 1993CC1312>](#). The only example of fused thiirane involves deprotonation of cyclohexene episulfide followed by treatment with benzyl bromide to give the vinyl sulfoxide in 75% yield. When R can form stabilized carbocation (such as *p*-methoxybenzyl or diphenylmethyl), treatment of the resulting sulfone with SO_2Cl_2 at -78°C afforded the corresponding 1-alkenesulfinyl chloride [<1998JOC7825>](#).

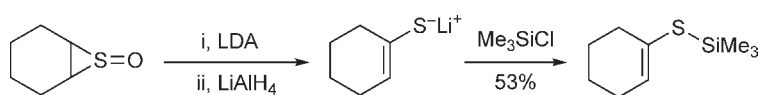


Scheme 38

The lithium sulfenates can be silylated and reacted with LDA to give *N,N*-bis(trimethylsilyl)-alkenesulfenamides in 40–60% yield, which were further transformed to a number of sulfenamides via the corresponding *S*-phthalimido derivatives (Scheme 39) <1995CC1949>. Desilylation of the silylated sulfenamide in the presence of a carbonyl compound lacking α -hydrogens afforded sulfenimines <1996T8387>. Reduction of the lithium sulfenates using LiAlH_4 at -40°C provided an efficient way of generating synthetically useful lithium thioenolates, which could be trapped by alkylating agents or silylating agents (Scheme 40) <1998SL96>.

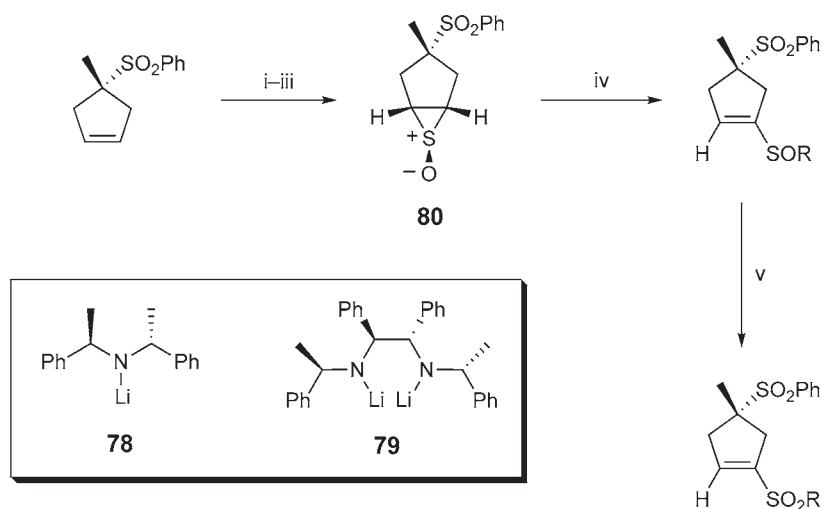


Scheme 39



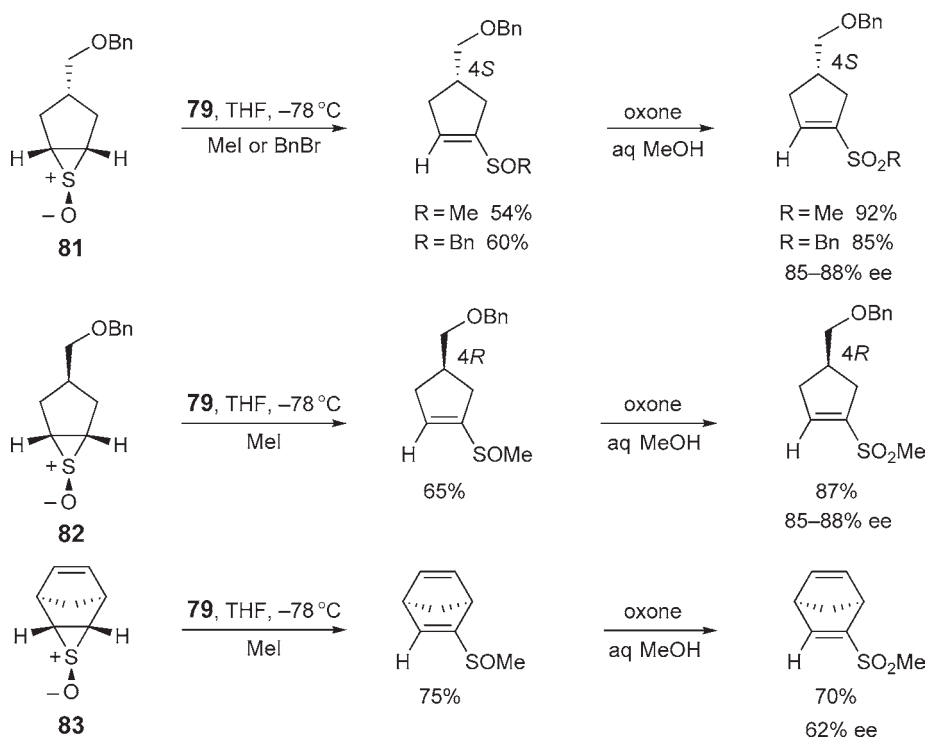
Scheme 40

Fused-ring thiirane *S*-oxides have been enantioselectively deprotonated by chiral lithium amides **78** or **79**. The desymmetrized products were obtained after oxidation of the sulfoxide to remove the additional stereogenic center in good yield and up to 88% ee (Schemes 41 and 42) <1997SL919, 2000J(P1)153>.



Reagents: i, MCPBA (86%); ii, Ph_3PS , TFA, PhH (49–60%); iii, Oxone, aq. MeOH (81%)
iv, **78** or **79**, MeI or BnBr, THF, -78°C ; v, Oxone, aq MeOH (58%)

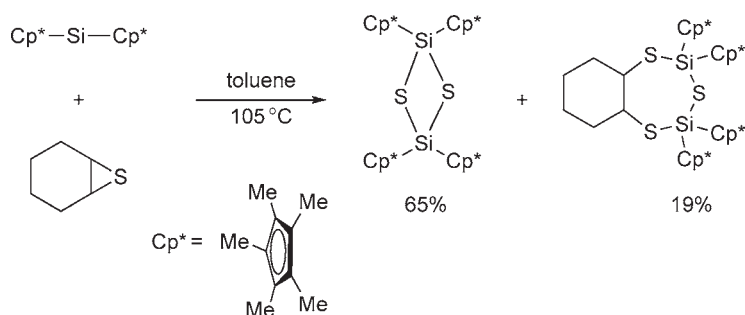
Scheme 41



Scheme 42

1.06.6.8 Reactions with Radicals and Electron-Deficient Species

Tetramesityldisilene quantitatively desulfurizes cyclohexene sulfide at room temperature [<1993CC1348>](#). Products with Si-S bonds were obtained from a reaction between cyclohexene sulfide and decamethylsilicocene (**Scheme 43**) [<1989AGE1518>](#).



Scheme 43

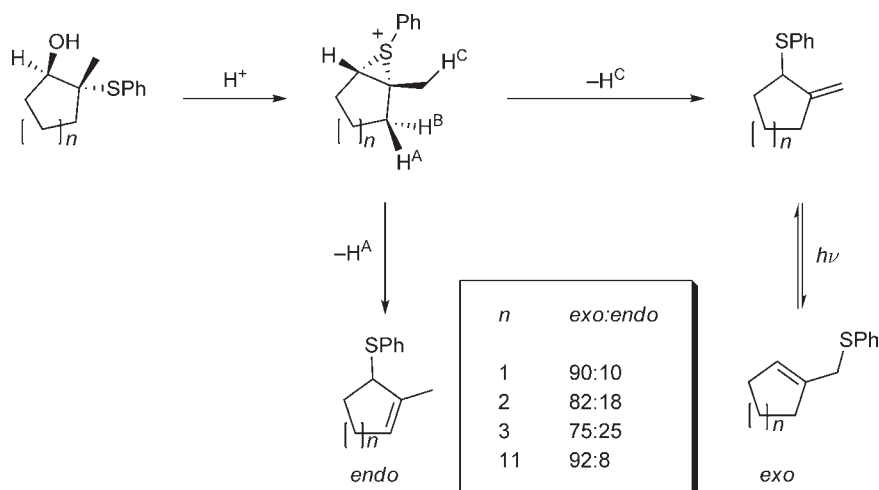
Desulfuration of thiiranes by metallic lithium [<1984IJB879>](#) or sodium [<1998TL2671>](#) in refluxing hydrocarbon solvents probably proceeds via a radical mechanism. The method is also effective for desulfurization of other organic sulfides but both monocyclic and fused thiiranes are particularly reactive.

1.06.6.9 Reactions Involving Cyclic Transition States

Papers on this subject, for the period 1996–2006, were not found.

1.06.7 Reactivity of Substituents at Ring Carbon Atoms

In the absence of other nucleophiles, cyclic episulfonium ions generated *in situ* from the corresponding β -hydroxy-sulfides rearranged into a mixture of allylic sulfides <1992J(P1)2609>. Rearrangements were observed only when an antiperiplanar arrangement of the sulfide and the OH group could be satisfied. Therefore, only the *syn*-isomers of small ring compounds ($n=5-7$) rearrange while larger ring ($n=15$) both *syn*- and *anti*-isomers can rearrange (Scheme 44).



Scheme 44

α -Silylated-fused thiirene *S,S*-dioxides when treated with fluoride ion generated carbanions, which may be protonated with the net result of desilylation, or trapped with an electrophile to result in ring-substituted products (Table 3) <1996J(P1)661>. Similar reactions on monocyclic silylated analogues provided somewhat better yields but in these cases products were isolated as the corresponding alkenes <1997J(P1)323>.

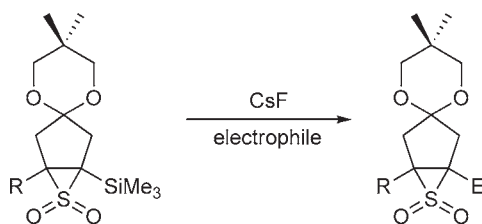


Table 3 Examples of fluoride-mediated desilylation of ring-silylated fused thiirane *S,S*-dioxides followed by electrophilic substitutions

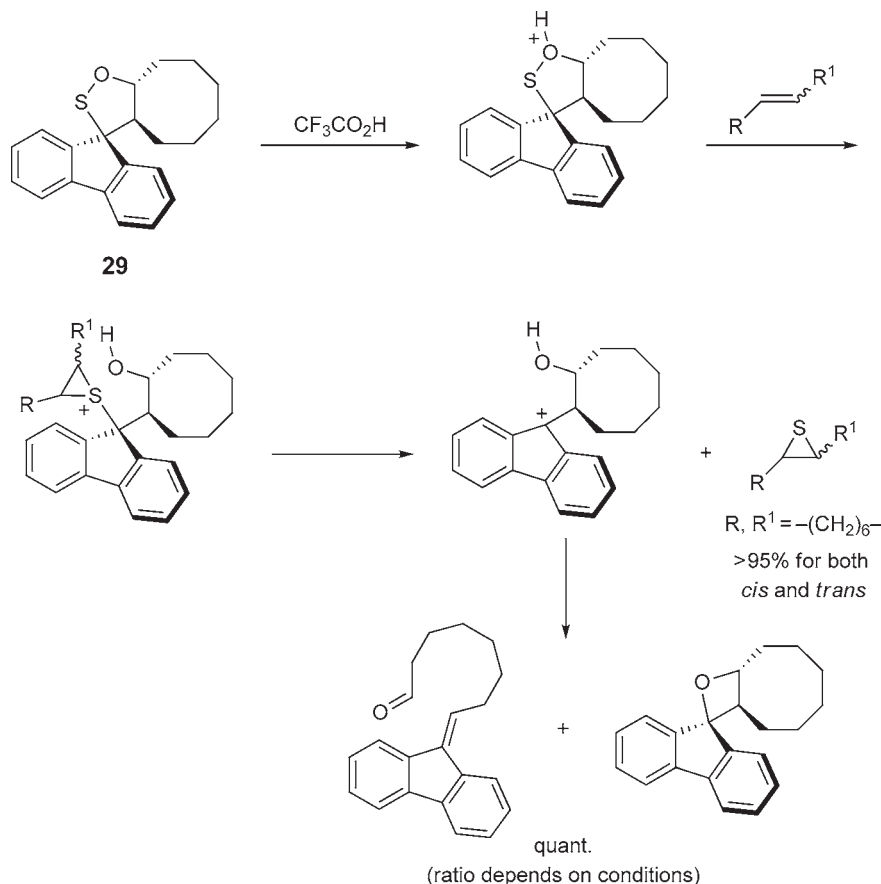
<i>R</i>	<i>Electrophile</i>	<i>E</i>	<i>Yield (%)</i>
SiEt ₃	H ₂ O	H	52
SiMe ₃	H ₂ O	H	26 ^a
SiMe ₃	PhCHO	Ph(OH)CH-	15

^a26% of bisdesilylated product was also isolated.

1.06.8 Reactivity of Substituents at Sulfur

Although formation of episulfuranes from monocyclic thiirane *S*-oxides is known, no analogous chemistry of fused-ring thiiranes have been reported. (see Chapter 1.05).

Thiiranium ions were proposed as intermediates in acid-catalyzed sulfur-atom transfer from sultene **29** to cyclic olefins under thermal conditions (Scheme 45). A high degree of diastereospecificity was observed during the sulfur atom transfer reaction to *trans*-cyclooctene. *S*-Dealkylation is facilitated by the formation of a stabilized carbocation, which may further cyclize or rearrange <1998JA4861>. Similar sulfur-atom transfer to cyclooctyne afforded a relatively stable thiirenium salt that did not undergo *S*-dealkylation (Section 1.06.5.2) <2002JA8316>.



Scheme 45

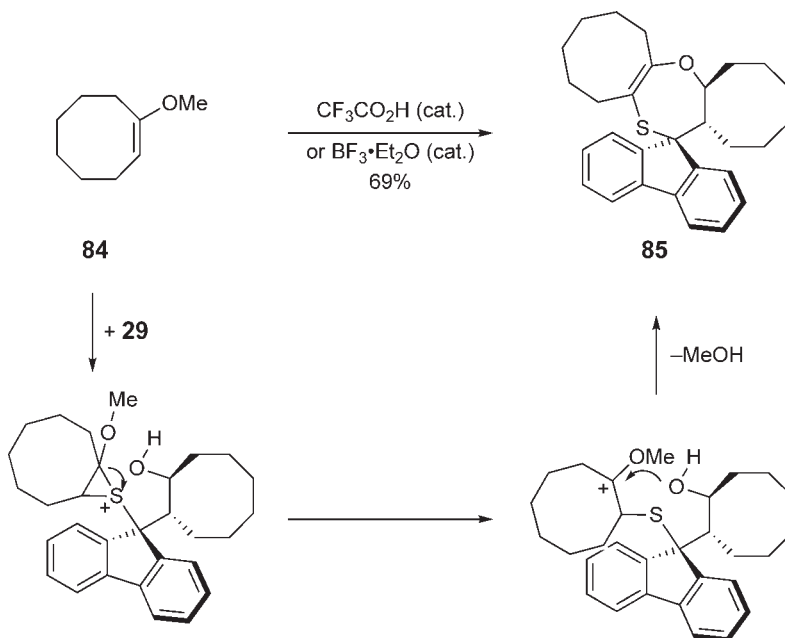
Acid-catalyzed sulfur atom transfer from the sultene **29** to methoxycyclooctene **84** provided, instead of the expected thiirane, 1,4-oxathiepin **85** in 69% yield <2002OL599>. Formation of this unusual product may be rationalized by the nucleophilic attack of the initially formed thiirenium ion by the sulfur substituent as shown in Scheme 46.

1.06.9 Synthesis of Fused-Ring Thiiranes and Thiirenes

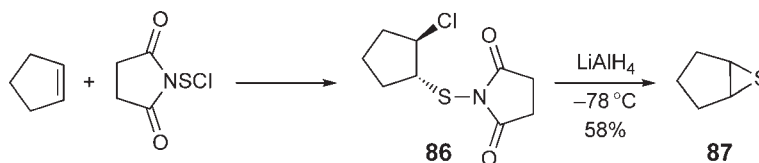
1.06.9.1 Episulfidation of Olefins

This method can be considered as a sulfur analogue of alkene epoxidation. The general principle is that a cycloalkane thiolate is generated, which bears a leaving group at the adjacent position. These precursors can conveniently formed via addition reactions of cycloalkenes. For example, cyclopentene sulfide **87** had been prepared in 58%

yield by the reaction of succinimidyl sulfonyl chloride with cyclopentene to give the protected thiol **86**. Reductive cleavage of the S–N bond led to the thiolate, which cyclized via an intramolecular S_N2 -reaction (Scheme 47) <1979J(P1)3013>.

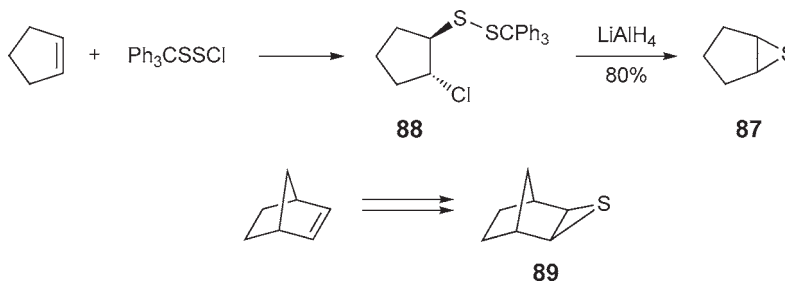


Scheme 46



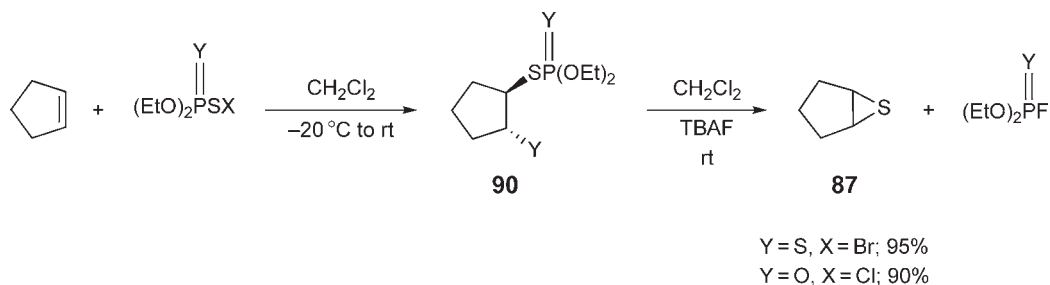
Scheme 47

New and efficient procedures for the direct episulfidation of alkenes have been developed. Addition of triphenylmethylthiosulfonyl chloride to cyclopentene leads to the adduct **88**, which by reduction of the disulfide with LiAlH_4 give episulfide **87** in high yield (Scheme 48) <2000SUL131, 1998JOC8654>. The analogous reaction with norbornene yields the *exo*-episulfide **89** in a diastereoselective fashion.



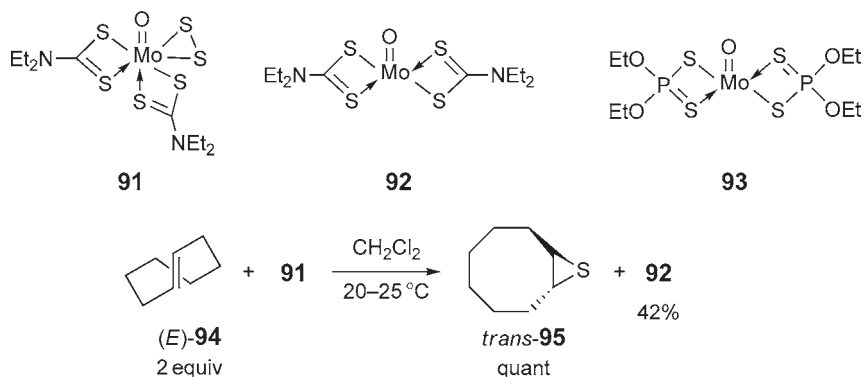
Scheme 48

A similar reaction via addition–elimination occurs with diethoxythioxaphosphorane sulfonyl bromide <1994SL267> or diethoxyoxophosphoranesulfonyl chloride <1997HAC429> and subsequent treatment of the 1,2-adduct with tetrabutylammonium fluoride (TBAF). The advantage of this protocol is the smooth formation of adducts of type **90** and their transformation into the corresponding thiiranes under neutral reaction conditions (Scheme 49). The entire sequence can be carried out as a one-pot reaction.

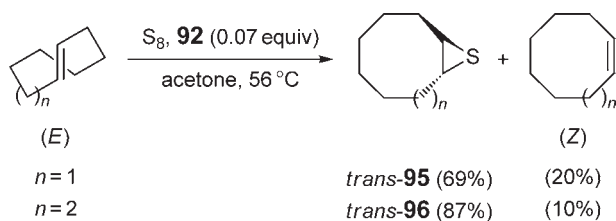


Scheme 49

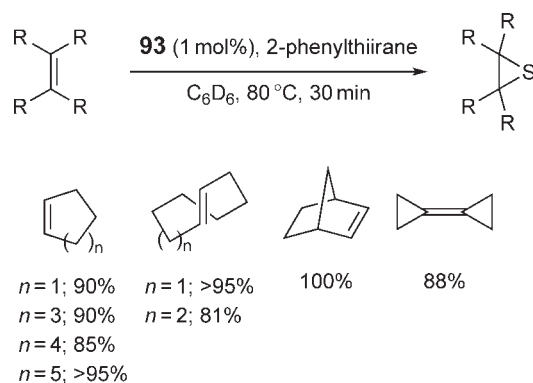
Another highly attractive approach to thiiranes is the transition metal-catalyzed episulfidation of strained cycloalkenes <2004CRV251>. For example, treatment of (*E*)-cyclooctene **94** with elemental sulfur in the presence of the molybdenum disulfide complex **91** in CH_2Cl_2 at 56°C gives *trans*-**95** along with the molybdenum complex **92** (Schemes 50 and 51) <2001CC1910>. The complex **91** can be prepared in a three-step procedure from Na_2MoO_4 via the air-sensitive complex **92**. The latter is also an efficient catalyst for the direct episulfidation of the highly strained (*E*)-cyclooctene and (*E*)-cyclononenes. An even more efficient catalyst is the molybdenum oxo-complex **93**, which allows the sulfur transfer to a series of cycloalkenes and cycloallenes in high yield in benzene at 80°C with 2-phenylthiirane as sulfur source <2003JA3871>. The two protocols mentioned above are also efficient in the catalytic episulfidation of norbornene and several other olefins including cyclic allenes (Schemes 52 and 53).



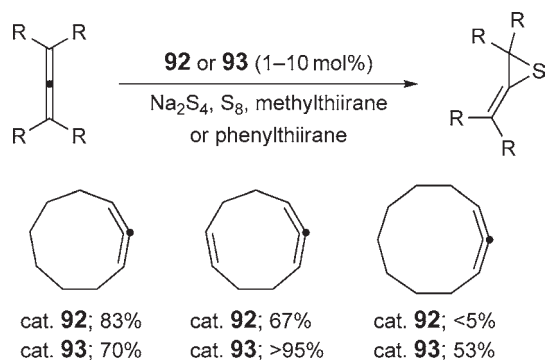
Scheme 50



Scheme 51

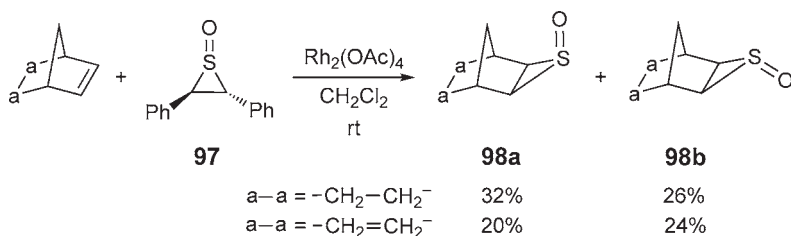


Scheme 52



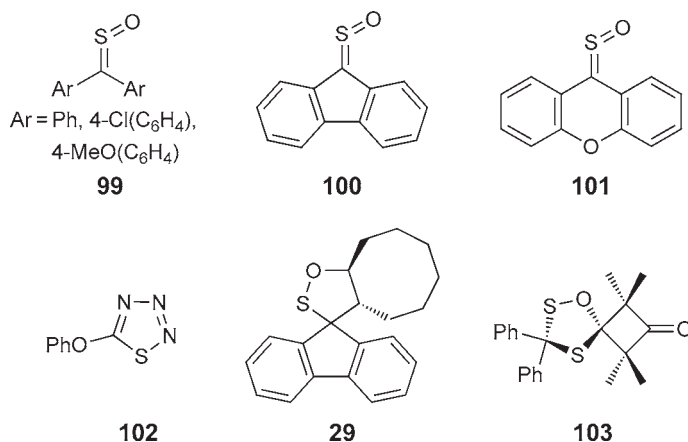
Scheme 53

An analogous sulfur transfer with methylthiirane as sulfur source and $Rh_2(OAc)_4$ as catalyst converts norbornene and norbornadiene to their episulfides in a so-called thiirane metathesis [\[1998SL391\]](#). In the same paper, examples of the SO transfer from thiirane *S*-oxide (**97**, an episulfoxide) to norbornene and norbornadiene have been described. In both cases, two diastereomers of type **98a** and **98b** are obtained, both with an *exo*-oriented episulfoxide structure ([Scheme 54](#)).

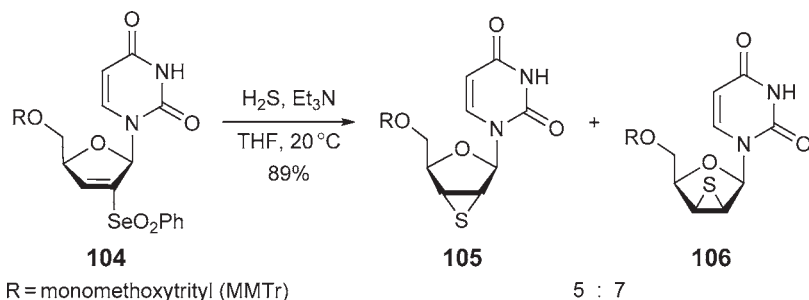


Scheme 54

In addition, a series of episulfidations of cycloalkenes has been reported using diaryl sulfoxes **99–101** under photolytic conditions [\[1997JOC7084\]](#), 5-aryloxy-1,2,3,4-thiatriazoles **102** at room temperature [\[2001EJO1959\]](#), and a spirocyclic sultene **29** in the presence of TFA or Lewis acids [\[2002OL599\]](#), respectively, as the sulfur donors. The 1,2,4-oxadithiolane **103** was proposed as the episulfidating agent in a stereospecific episulfidation of *trans*-cyclooctene in the presence of thiobenzophenone *S*-oxide and 2,2,4,4-tetramethyl-3-thioxocyclobutanone under thermal conditions [\[2003EJOC4012\]](#).

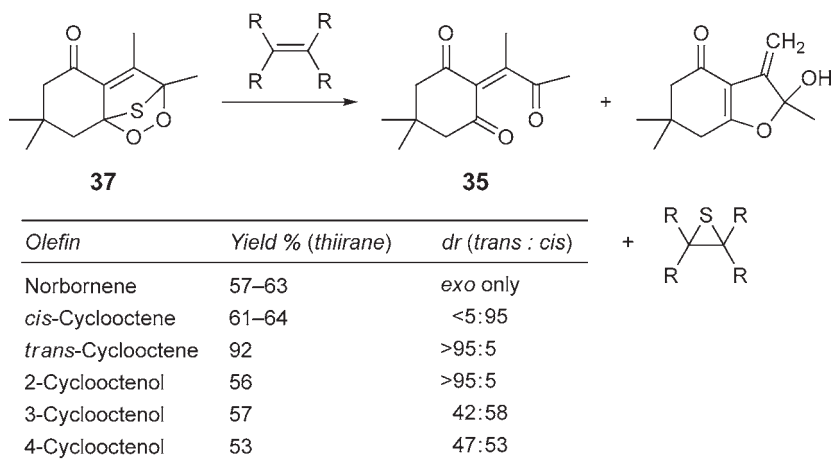


Nucleosides **105** and **106** with $\text{R} = \text{H}$, acetyl, or benzoyl are previously known [\[1976JCY365\]](#). A recent paper describes the synthesis of a mixture of these derivatives in good yield by treatment of the phenylselenone **104** with hydrogen sulfide in the presence of triethylamine ([Scheme 55](#)) [\[1991T3431\]](#). The double nucleophilic attack at C-2 and C-3 of the five-membered ring is rationalized by a Michael addition at C-3, followed by the nucleophilic substitution of phenylselenenic acid via neighboring group participation of the urea CO group of the uracil residue.



Scheme 55

Another interesting synthesis of fused-ring thiiranes was reported by Weinkötz and co-workers in a sulfur-transfer reaction from 3,3,7,8-tetramethyl-9,10-dioxo-11-thiatricyclo[6.2.1.0^{1,6}]undec-6-en-5-one (a derivative of thiophene endoperoxide) **37** to cyclic olefins under thermolysis conditions, or at low temperature using tetraphenylporphine cobalt(II) complex as a catalyst ([Scheme 56](#)) [\[1996CC177\]](#). The endoperoxide was prepared by photo-oxygenation

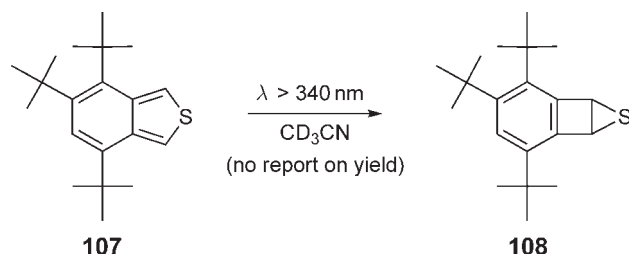


Scheme 56

of the parent thiophene. The reaction produced thiirane along with the other two products resulting from extrusion of elemental sulfur. A detailed mechanistic investigation, process improvement, as well as diastereoselective studies were also reported by the same group <1998JA8914>.

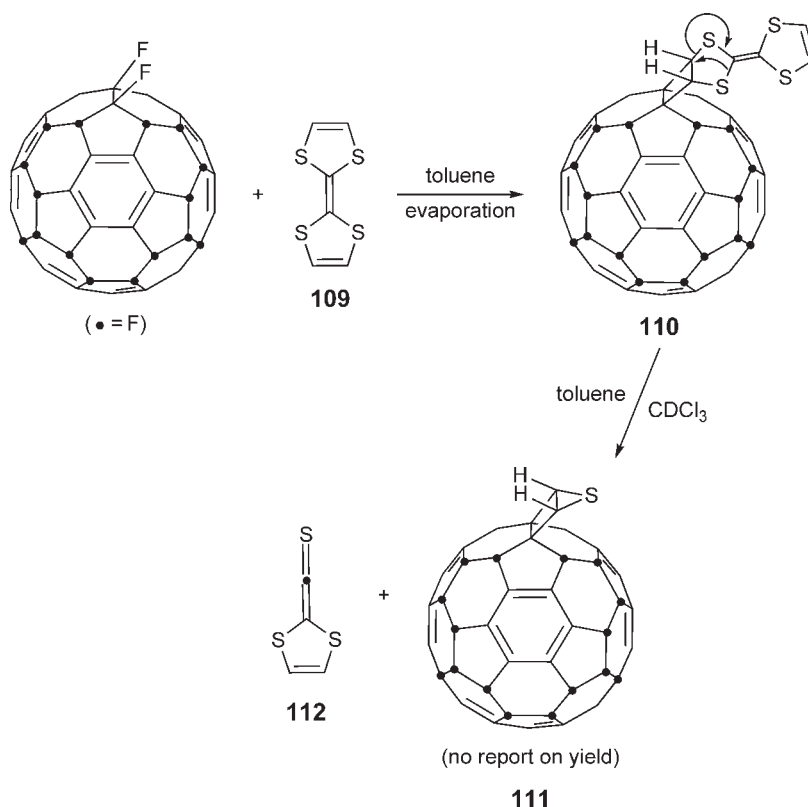
1.06.9.2 From Other Heterocycles

The first Dewar benzo[*c*]thiophene **108** was obtained by irradiation of 4,5,7-tris(*tert*-butyl)benzo[*c*]thiophene **107** with ultraviolet (UV) light ($\lambda > 340$ nm) in trideuteroacetonitrile (Scheme 57) <1995TL3177>. This product is thermally surprisingly stable (Section 1.06.5.2) and no change was observed after heating a solution in acetonitrile at 100 °C for 40 h.



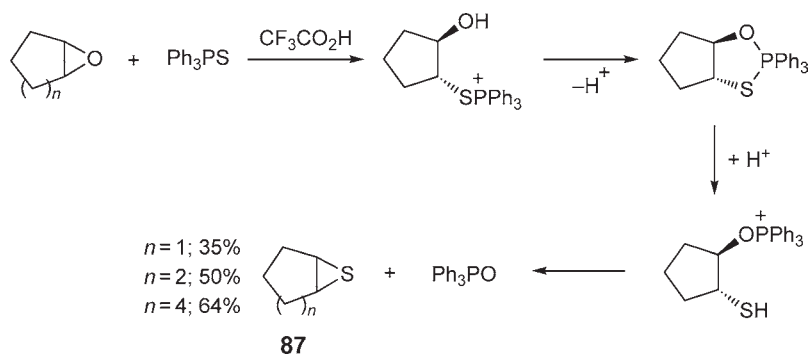
Scheme 57

Very recently, a stable 5-thiabicyclo[2.1.0]pentane derivative has been prepared by a thermal reaction. Co-evaporation of solutions of the partially fluorinated fullerene $\text{C}_{60}\text{F}_{18}$ and tetrathiafulvalene **109** in toluene led to **110** as the major product, which, on standing in toluene in the presence of CDCl_3 , reacted further to give the episulfide **111** (Scheme 58) <2003CEJ2008>. The formation of the initial product **110** was formulated via a unique six-electron process involving elimination of fluorine. The second reaction proceeds by elimination of the thioketene derivative **112**.



Scheme 58

Direct transformation of fused-ring epoxides such as cyclopentene oxide into thiiranes by treatment with potassium thiocyanate in water was reported almost 50 years ago <1954JCS1528, 1958JA1680, 1959JA4924>. Similar to this approach is the base-catalyzed reaction of *trans*-2-chlorocycloalkanol, which has been prepared from fused-ring epoxide by successive treatment with sodium hydrosulfide and HCl <1951JA3444>. Another related approach is the transformation of cyclopentene oxide into **87** by treatment with triphenylphosphine sulfide and TFA in benzene (Scheme 59) <1972JA2880>.



Scheme 59

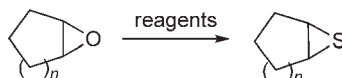
Since 1995, an enormous number of modifications and significant improvements of the earlier described methods have appeared in the literature (Table 4). For example, the transformation of cyclopentene oxide into the corresponding thiirane by treatment with NH_4SCN in the presence of ceric ammonium nitrate (CAN) as a catalyst in *tert*-butanol at room temperature gives the product in 90% yield <1996S821>. Other efficient Lewis acid catalysts in the reaction with potassium or ammonium thiocyanate are RuCl_3 <1997T11377>, $\text{TiO}(\text{TFA})_2$ and $\text{TiCl}_3(\text{OTf})$ <1998SC3913>, BiCl_3 <1998SC3943>, $\text{Bi}(\text{TFA})_3$ and $\text{Bi}(\text{OTf})_3$ <2001MOL996>, SbCl_3 <1999IJB605>, $\text{Fe}(\text{TFA})_3$ <2000BJC675>, LiBF_4 <2002JCM176>, InBr_3 <2003SL396>, $(\text{NH}_4)_8[\text{CeW}_{10}\text{O}_{36}] \cdot 20 \text{ H}_2\text{O}$ <2002SC621>, $\text{Ce}(\text{OTf})_4$ <2003OBC724> and poly(4-vinylpyridine)- $\text{Ce}(\text{OTf})_4$ <1999SC3313>, $\text{Mg}(\text{HSO}_4)_2$ <2003SC3041>, $\text{Sn}(\text{tpp})(\text{OTf})_2$ <2004T6105>, 2,6-bis[2-(*o*-aminophenoxy)methyl]-4-bromo-1-methoxybenzene <2004PS499>, and a Fe(III) porphyrin complex <1999JCM370>. Furthermore, the reaction can be catalyzed with oxalic acid under nonaqueous conditions and heating or microwave irradiation <2003PS1333>, 1-butyl-3-methylimidazolium hexafluorophosphate ($[\text{bmim}]\text{PF}_6$, an ionic

Table 4 Representative examples of the conversion of fused-ring epoxides into their thiirane derivatives

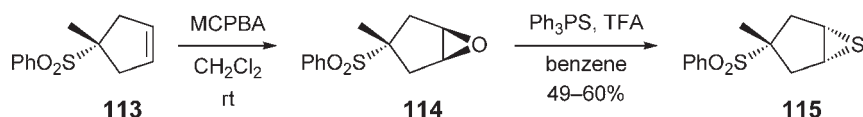
Reagents	<i>n</i>	Yield (%)	Reference
NH_4SCN , CAN, <i>t</i> -BuOH	1	90	1996S821
	2	92	
	4	95	
Thiourea, CAN, MeCN	2	86–89	2003JCM290
NH_4SCN , RuCl_3 , MeCN	1	95	1997T11377
	2	93	
NH_4SCN , LiBF_4 , <i>t</i> -BuOH	2	92–94	2002JCM176
	4	90	
Thiourea, LiBF_4 , MeCN	2	92	2003SC595
	4	80	
KSCN, InBr_3 , MeCN	2	85–87	2003SL396
NH_4SCN , $(\text{NH}_4)_8[\text{CeW}_{10}\text{O}_{36}] \cdot 20 \text{ H}_2\text{O}$	2	96	2002SC621
NaSCN , $\text{Ce}(\text{OTf})_4$	2	89	2003OBC724
NH_4SCN , $\text{Mg}(\text{HSO}_4)_2$, MeCN	2	95	2003SC3041
Thiourea, $\text{Sn}(\text{tpp})(\text{OTf})_2$, MeCN	2	99	2004T6105
Thiourea, PS-AlCl_3 , MeCN	1	92	2004SC65
	2	85	
Thiourea, K-10 clay, MeCN	2	98	2000JCM122
P_2S_5 , acidic Al_2O_3 , NH_4OAc , EtOH	2	72–75	2004S2035
$\text{HP}(\text{O})(\text{OEt})_2$, S, acidic Al_2O_3	2	61–69	2004TL1283

liquid) <2003JOC2525>, and with β -cyclodextrin in water/acetone <2004ASC395>. Additional protocols describe the use of NaOH in water and polymeric cosolvents such as poly(vinylamine) or poly(allylamine) <2004TL1535> and amberlite IRA-400-supported thiocyanate in cyclohexane <1996SC3953>.

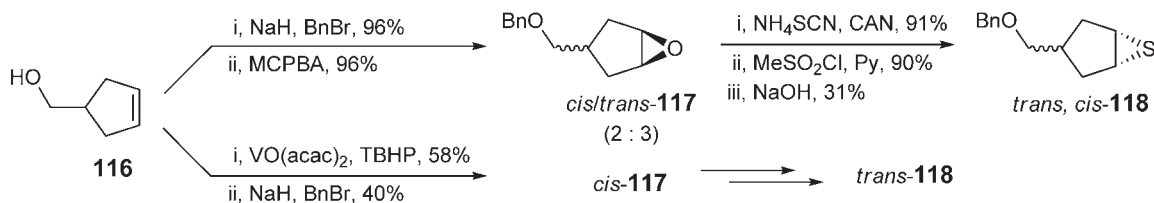
Similarly, the reactions of epoxides with thiourea as the sulfur source have been catalyzed by different Lewis acids, for example, CAN <2003JCM290>, RuCl_3 and alumina <2001PS135>, LiBF_4 <2003SC595>, $\text{Sn}(\text{tpp})(\text{OTf})_2$ <2004T6105>, $\text{Sn}(\text{tpp})(\text{ClO}_4)_2$ <1999SC2079>, and polystyrene-supported AlCl_3 <2004SC65>. This transformation has also been carried out using β -cyclodextrin <2004TL6523> and heterogeneous catalysts such as the acidic clay montmorillonite K-10 <2000JCM122>. In addition, reactions of epoxides with P_2S_5 , acidic alumina, and ammonium acetate in boiling ethanol or under solvent-free conditions and microwave irradiation are reported to give thiiranes in good yield <2004S2035>. The advantages of using these methods are the less polluted character and inexpensive cost of catalysts, as well as the uncomplicated workup procedures. Analogously, a mixture of diethyl phosphite, acidic alumina, ammonium acetate, and elemental sulfur can serve the same purpose <2004TL1283>.



Substituted derivatives of cyclopentene sulfide have been prepared by using some of the methods presented in the preceding section. As a recent example, the sulfonylated cyclopentene **113** is transformed stereoselectively to the epoxide **114**, which on treatment with Ph_3PS and TFA gives the episulfide **115** in good yield (Scheme 60) <1997SL919>. Similarly, the mixture of the diastereomeric oxiranes *cis/trans*-**117**, which is prepared from 4-(hydroxymethyl)-cyclopentene **116**, is transformed to the corresponding thiiranes *trans/cis*-**118**. The stereoselective course of the episulfide formation is shown by using *cis*-**117** to give *trans*-**118** (Scheme 61) <2000J(P1)153>.

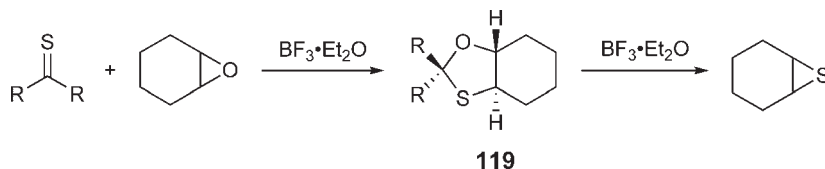


Scheme 60



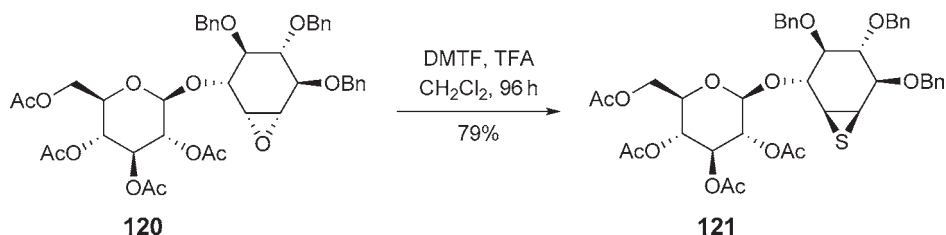
Scheme 61

The formation of thiiranes can also be achieved by treatment of epoxides with 1,3-dithiolan-2-thione and a catalytic amount of $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ in anhydrous CH_2Cl_2 or chlorobenzene <1996J(P1)289>. The reaction mechanism involved 1-oxa-4,6,9-trithiaspiro[4.4]nonane intermediate as it could be isolated in good yield when the reaction was carried out in chlorobenzene at low temperature. Related to this approach is the conversion of epoxides to thiiranes using nonenolizable thioketones and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ <1999HCA2316>. In this stepwise procedure, the stable 1,3-oxathiolane intermediates **119** could be isolated and characterized (Scheme 62).



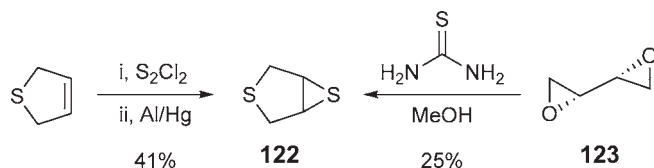
Scheme 62

Another way of converting epoxides to thiiranes is the use of *N,N*-dimethylthioformamide (DMTF) and TFA, which was demonstrated by Uzan and co-workers in the synthesis of new cyclitol thiirane analogues as glycosidase inhibitors <1996SI435>. As shown in **Scheme 63**, the reaction of **120** with DMTF and TFA in refluxing CH_2Cl_2 for 4 days provided the thiirane **121** in 79% yield. It is worth noting that the same transformation was unsuccessful when **120** was treated with potassium thiocyanate or thiourea.



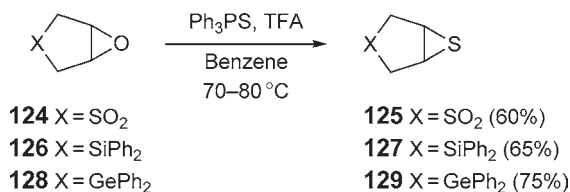
Scheme 63

Syntheses of several fused-ring thiiranes containing another heteroatom have also been reported. The most simple example is 3,6-dithiabicyclo[3.1.0]hexane **122**, which can be obtained in 41% yield by addition of sulfur monochloride (S_2Cl_2) to 2,5-dihydrothiophene and subsequent treatment with aluminium amalgam (**Scheme 64**) <1969JOC3991>. The same product is formed when a solution of (2*S*,3*S*)-1,2,3,4-diepoxybutane **123** in methanol is reacted with thiourea <1996JOC3611>. Surprisingly, no thiirane **122** is formed when **123** is treated with KSCN; the only product under these conditions is (2*R*,3*R*)-1,2,3,4-diepithiobutane (see also <1969JMC556>).



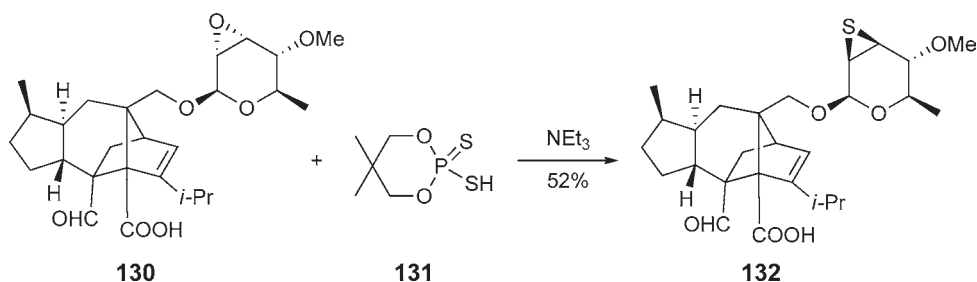
Scheme 64

The formation of **122** from 2,5-dihydrothiophene via the corresponding epoxide is not possible because of the easy oxidation of the sulfur atom. However, the analogous transformation of the sulfone has been reported to occur without difficulties. The reaction of oxirane **124** with thiirane **125** by treatment with Ph_3PS and TFA at 70–80 °C was achieved (**Scheme 65**) <1983CHE1287>. With the same method, 3,3-diphenyl-3-sila-6-thiabicyclo[3.1.0]hexane **127** and the corresponding 3-germa derivative **129** are also accessible <1987JOM(327)C25>.



Scheme 65

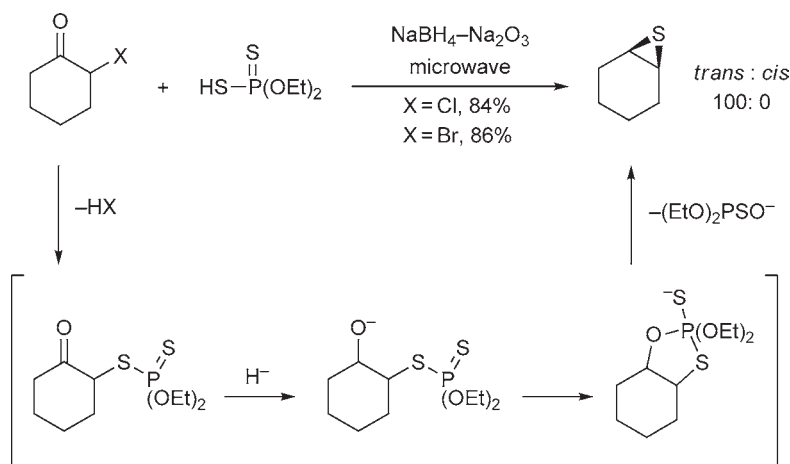
Treatment of epoxide **130** with 2-mercapto-5,5-dimethyl-2-thioxo-1,3-dioxaphosphorinane **131** under reflux in triethylamine resulted in the corresponding thiirane **132** (**Scheme 66**) <2002BML1371>.



Scheme 66

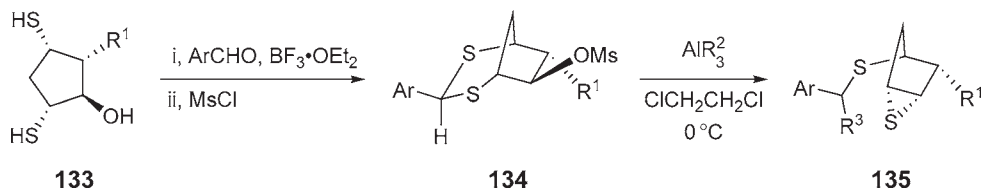
1.06.9.3 Miscellaneous

A very attractive synthesis of fused-ring thiiranes based on nucleophilic substitution–elimination was demonstrated by Yadav and Kapoor [\[2002S2344\]](#). The procedure involves treatment of 2-chloro- or 2-bromocyclohexanone with $(\text{EtO})_2\text{P}(\text{S})\text{SH}$ and NaBH_4 -alumina (Scheme 67). Upon microwave irradiation of this solvent-free mixture, the nucleophilic replacement and subsequent reductive cyclization gave rise to thiiranes in good yield.



Scheme 67

In connection with the synthesis of disulfide analogues of prostaglandin derivatives, the stereoselective preparation of fused-ring thiiranes has been described (Scheme 68) [\[1987JOC862\]](#). Starting with **133**, protection of the thiol groups occurs by treatment with an aromatic aldehyde and $\text{BF}_3 \cdot \text{OEt}_2$, and the hydroxy group is transformed into the mesylate. Reaction of **134** with alanes yields the episulfide **135** via nucleophilic attack of the C-nucleophile at the dithioacetal C-atom leading to a thiolate, which in turn forms the thiirane by intramolecular nucleophilic substitution of the mesylate. As an alternative, the formation of an episulfonium ion intermediate from **134** is discussed, which is then attacked by the C-nucleophile at the dithioacetal C-atom.

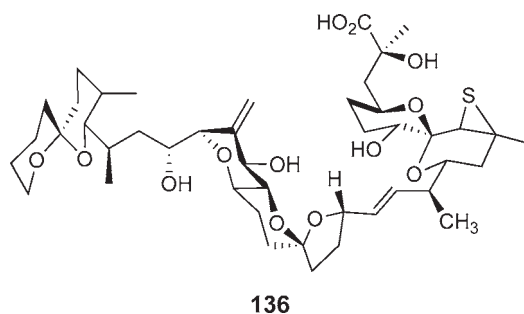


Scheme 68

1.06.10 Important Compounds and Applications

1.06.10.1 Naturally Occurring Thiiranes

Acanthifolic acid **136** is a naturally occurring polyether containing fused thiirane isolated from marine sponge (*Pandaros acanthifolium*), the structure of which was determined by X-ray crystallography. It shows potent cytotoxicity against cancer cell lines (ED₅₀ values for lymphocytic leukemia P388 in mice: 0.28 ng ml⁻¹, nasopharynx human carcinoma KB: 2.1 ng ml⁻¹, and lymphocytic leukemia L1210: 3.9 ng ml⁻¹) <1981US4302470>. The compound also displays antibiotic activities. A closely related compound named melanodocin was also isolated from a different species of sponge (*Halichondria melanodocia*) <1982US4314057>. No full structural details and biological activities have been disclosed.



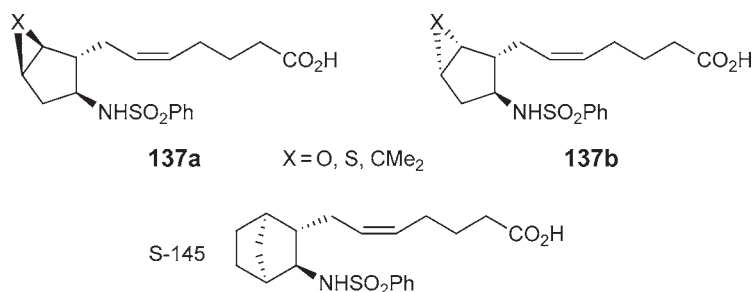
1.06.10.2 Polymers

A majority of patents involving thiiranes describe polymers derived from polymerization of thiirane or fused thiirane monomers <1984CHEC(7)131, 1996CHEC-II(1)174>. These polymers possess certain desirable properties such as high modulus of elasticity, solvent resistance and high refractive indices, which make them useful in the manufacturing of optical lenses <2003US6631021, 2007US7169845> or coating materials <2006US2006/0167217A1>.

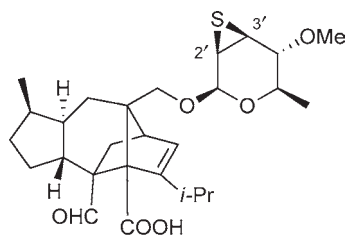
1.06.10.3 Drugs

Biological activities of steroidal thiiranes are well documented <1984CHEC(7)131, 1966JMC693, 1965T329>. No new steroid thiirane derivatives have been reported during the period 1996–2006. The anticancer activities of acanthifolic acid **136**, a naturally occurring fused thiirane, have already been discussed (Section 1.06.10.1).

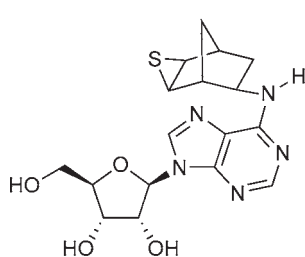
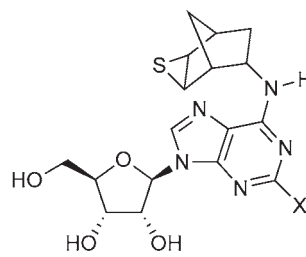
Compounds **137a** and **137b** containing 6-thiabicyclo[3.1.0]hexane and their analogues have been synthesized as thromboxane receptor antagonists <1990JMC229>. They possess lower inhibition activities against aggregation of rat washed platelets than the reference compound S-145.



Derivatives of Sordarin antifungal agents **132** with 2' and 3' fused oxirane and thiirane moieties were synthesized for a structure–activity relationship (SAR) study <2002BML1371>. This compound possesses the opposite stereochemistry at the 2' and 3' positions of the pyranose portion and displayed a slight improvement in activity against *Candida* spp.

**132**

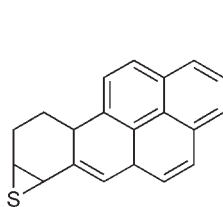
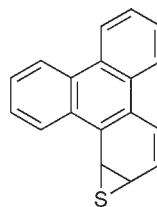
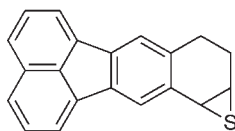
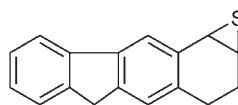
Adenosine derivatives **138** and **139** containing a fused thiirane moiety were synthesized and reported to be a highly potent and selective A1 adenosine receptor (A₁AR) agonists. Differences in affinities toward human A₁AR and other subtypes of adenosine receptors are more than three orders of magnitude [<2004BMC4877>](#).

**138****139**

X = H, F

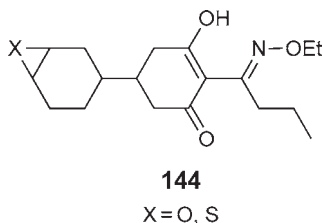
1.06.10.4 Toxicity

Thiiranes derived from polycyclic aromatic hydrocarbons have been of considerable interest due to their similarity to the carcinogenic polycyclic aromatic epoxides. The high polarizability, the relative weakness of the C–S bond compared to C–O bond, and the better leaving ability of the sulfide ion should make these compounds even more highly electrophilic toward DNA compared to the corresponding epoxides. This has been supported by *ab initio*, DFT, and semi-empirical calculations [<2001HCA3588>](#) (see also Section 1.06.2.1). Some of these episulfides such as **140–143** and their *S*-oxides have been prepared, mostly with the ring fused to the thiirane being saturated or partially saturated [<2000JOC8083, 1996JHC53, 1994PS453, 1999PS307>](#). Weak to moderate mutagenic activities (*in vitro* reversion of histidine-dependent *Salmonella typhimurium* tests) were reported for these compounds [<1996JHC53, 2000JHC1109>](#).

**140****141****142****143**

1.06.10.5 Insecticides and Herbicides

Compounds **144** containing a 2,3-epoxy and 2,3-epithiocyclohexyl substituents were synthesized and claimed as herbicidal compounds <1992US5169426, 1985EP0172502>. Although they potentially possess multiple stereoisomers, which presumably display different potency, the stereochemical details were not provided.



1.06.11 Conclusion

Fused-ring thiiranes and thiirenes represent rare but interesting classes of sulfur-containing heterocyclic compounds. They have unique physical characteristics which can be predicted by computational calculations and some structures have been characterized by X-ray crystallography and spectroscopy. These small ring thio-systems are quite versatile in their chemistry, as both the sulfur and carbon atoms can react with either nucleophiles or electrophiles. This class of compounds can be prepared by the episulfidation of olefins or from related heterocycles such as oxiranes. These sulfur-containing rings are of great significance in both theoretical and application senses.

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Biographical Sketch



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1.07

Three-membered Rings with One Selenium or Tellurium Atom

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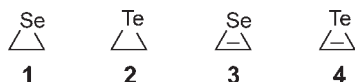
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1.07.1 Introduction

It is a challenge to treat three-membered rings with one selenium or tellurium ring member in the context of traditional heterocyclic chemistry because they are generally unstable and rarely isolated. Nevertheless, their intermediacy or presumed intermediacy plays an important role in organic chemistry. Seleniranes **1**, telluriranes **2**, selenirenes **3**, and tellurirenes **4** and their derivatives have been comprehensively reviewed previously <1996CHEC-II(1)259, 2001SOS61>.



This chapter updates the prior reviews as well as considers some additional reactions in which these heterocycles, their derivatives, or related species are presumptive intermediates that have been advantageously exploited in synthesis. They are reviewed in depth. (Recent theoretical calculations on heterocyclic systems in these classes of compounds have provided surprising results which may stimulate renewed interest in these systems.)

1.07.2 Theoretical Methods

1.07.2.1 Introduction

Three-membered rings with one selenium or tellurium atom have attracted some theoretical attention since the last review <1996CHEC-II(1)259>. Of particular interest are the comparison of theoretical methods, computations on a reaction course (that of selenirane with silylene), and the valence tautomerization of [3]chalcogena[3]pericyclynones.

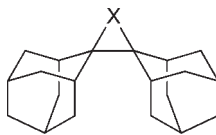
1.07.2.2 Selenirane and Tellurirane

Different computational methods were used to calculate the geometries and ring strain energy in selenirane, **1** <1998MI1>. There was good agreement among the different methods, particularly between MP2 and density functional theory (DFT) results. The ring strain energy for selenirane was calculated to be approximately 16 kcal mol⁻¹ which is substantially below that in cyclopropane (27 kcal mol⁻¹).

In the above cited work, the 6-31G* basis set was used for C and H and a contracted 641(d) basis set for Se. In a more recent work, *ab initio* calculations at the MP2 level of theory using the 6-31G** basis set on selenirane with geometry optimization were carried out <2000CJC1496>. The calculated C–Se and C–C bond lengths are 197.0 and 147.2 pm, respectively, and the calculated SeCC bond angle is 68.0°. The reaction of silylene, SiH₂, with selenirane forming H₂Si=Se and ethene was studied theoretically using MP2/6-31G** <2000CJC1496>. The highly exothermic reaction ($\Delta G^\circ_{298} = -52.9$ kcal mol⁻¹) occurs in a single step and is predicted to occur spontaneously in the gas phase.

Semi-empirical molecular orbital methods (AM1, PM3, and PM5) were used to optimize the structures of **5**, X = Se and X = Te <2004JMT179>. The calculated C–C distance in the three-membered heterocyclic ring for **5**, (X = Se)

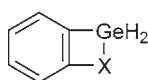
and **5** (X = Te) is 148.6 and 139.3 pm, respectively. In addition, the computed lowest ionization potential and HOMO–LUMO gap in these compounds are 8.874 and 8.141 eV, 8.829 and 8.115 eV, respectively (HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital).



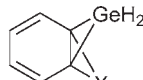
5: X = Se, Te

Semi-empirical molecular orbital calculations on C_{60} Se isomers including that in which there is a selenirane ring have been reported <1994PES267, 1995MI55>.

To determine the relative energies of **6** and **7**, DFT calculations at the B3LYP level were done using the 6-311 (2d) basis set for C and H and TZ (2d) basis set for Ge. Using the LanL2DZdp basis set for Se and Te, **6** (X = Se) and **6** (X = Te) were more stable than **7** (X = Se) and **7** (X = Te) by 75.0 and 69.8 kcal mol^{−1}, respectively. Using the 6-311G (2d, p) basis set for Se, **6** (X = Se) is more stable than **7** (X = Se) by 75.7 kcal mol^{−1} <2005OM612>.

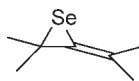


6: X = Se, Te



7

Ab initio calculations on compound **8** were undertaken to validate its formation. The observed infrared (IR) frequencies and intensities of the synthesized compound were in good agreement with those calculated <1996T1965>.



8

1.07.2.3 Selenirene

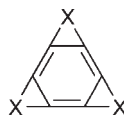
Optimized geometry for selenirene **3**, using *ab initio* calculations at the MP2 (FU) 6-31 G(d) level, were reported <2000EJO1411> as well as the G2(MP2) E_0 electronic energy of selenirene. In addition, the harmonic vibrational frequencies and IR intensities for selenirene were calculated at the QCISD/6-31G(d) level.

1.07.2.4 Valence Tautomerization of [3]Chalcogena[3]Pericyclynines

DFT studies [B3LYP/6-311G(d)] on [3]chalcogena[3]pericyclynines **9** and their valence tautomeric benzotrischalco-genirenes **10** led to a remarkable result <2004OL589>. The benzene derivative **10** (X = Se or Te) is more stable than the corresponding pericyclyne. This contrasts with the results obtained for X = O or S in which the corresponding pericyclyne is calculated to be more stable.



9: X = Se, Te (O,S)



10

1.07.3 Experimental Structural Methods

Owing to the reactivity of these ring systems, no new structural results have been reported.

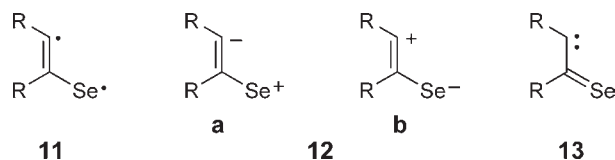
1.07.4 Thermodynamic Aspects

Some calculated thermodynamic aspects have been summarized in Section 1.07.2.

1.07.5 Reactivity of Fully Conjugated Rings

1.07.5.1 Introduction

In this section, reactions that may involve selenirenene are presented. However, this need not be the case because species best described as diradicals **11**, zwitterions **12**, or carbenes **13** may be involved without the intermediacy of selenirenene. This ambiguity results from the difficulty in isolating selenirenene and then studying the reactions of these isolated and characterized heterocycles.

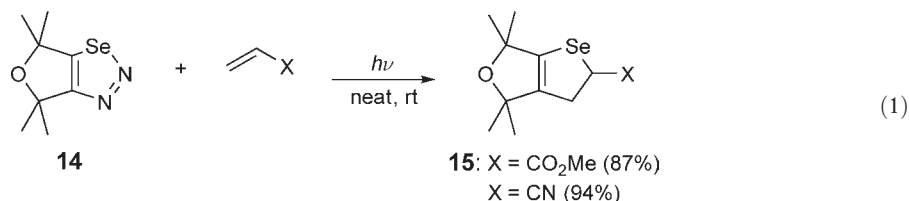


1.07.5.2 Thermal and Photochemical Reactions

Recent studies on the thermolysis of 1,2,3-selenadiazoles have provided evidence for diradical and zwitterionic species after loss of nitrogen. These species may be in equilibrium with selenirenene and, if so, then these reactions formally constitute reaction pathways for thermolysis of these heterocycles. However, there is no direct evidence for this in the reactions outlined in the following sections in which these proposed intermediates are trapped. In addition, in the formation of alkynes from 1,2,3-selenadiazoles discussed in Section 1.07.12.6, pathways not involving the intermediacy of selenirenene have been proposed <2000JOM4887>.

1.07.5.3 Cycloaddition Reactions

Cycloaddition of the species provided by irradiation or thermolysis of 1,2,3-selenadiazole **14** to alkenes was reported <1986TL6107, 1987TL2867, 1988JPO317> as shown in Equation (1). For example, irradiation of **14** with 365 nm light (or thermolysis) with excess methyl acrylate or acrylonitrile gave **15** ($\text{X} = \text{CO}_2\text{Me}$) and **15** ($\text{X} = \text{CN}$) in 87% and 94% yield, respectively. Owing to the observed regiochemistry of the cycloadducts, zwitterion **12a**, $\text{R,R} = \text{CMe}_2\text{OCMe}_2$ was suggested as the species undergoing cycloaddition.

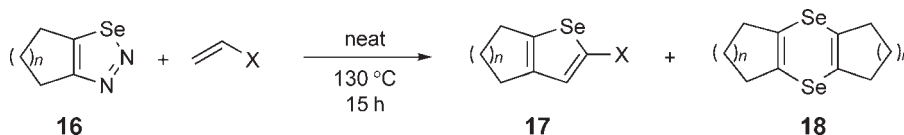


Subsequent studies on the thermolysis of 1,2,3-selenadiazole **16** ($n=2$) in the presence of a variety of alkenes (methyl acrylate, acrylonitrile, methyl vinyl ketone, methyl methacrylate, methyl 2-butenic acid, butyl vinyl ether, and 1-octene) also afforded cycloadducts **17**, in 12–76% yield with the same regiochemistry as observed for cycloadditions with **14** <2000JOM488>. Analogous cycloadditions with methyl derivatives of **16** ($n=2$) as well as **16** ($n=1, 3$, and 4) and ethyl acrylate was also observed in yields of 35–76% (Table 1). In addition to the cycloadduct,

Table 1 Thermal reaction of 1,2,3-selenadiazoles **16** with alkenes (Scheme 1) <2000JOM488>

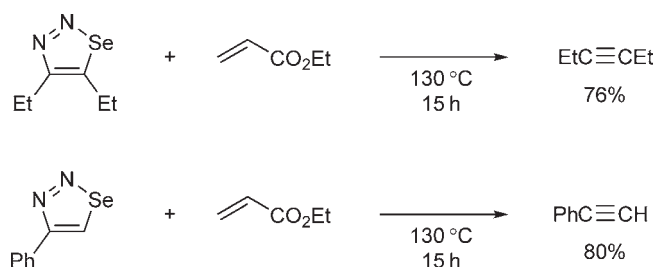
Entry	<i>n</i>	X	Yield of 17 (%)	Yield of 18 (%)
i	2	CO ₂ Me	76	
ii	2	CN	74	
iii	2	COMe	25	
iv	2	OBu	12	74
v	2	C ₆ H ₁₃	16	71
vi	1	CO ₂ Et	75	21
vii	3	CO ₂ Et	47	32
viii	4	CO ₂ Et	35	27

the corresponding 1,4-diselenin **18** is formed (Scheme 1). Indeed thermolysis (130 °C, 15 h) of **16** ($n=2$) in the absence of alkene produces 1,4-diselenin **18** ($n=2$) in 80% yield.



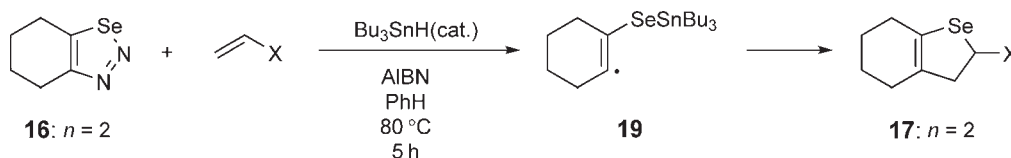
Scheme 1

Cycloadducts with ethyl acrylate were not obtained from 1,2,3-selenadiazoles that were not annulated with rings of eight or fewer carbons but rather fragmentation to the corresponding alkynes was observed as shown in Scheme 2.



Scheme 2

In analogy with the cycloaddition reactions of **14**, a zwitterion **12** intermediate would account for the regiochemistry of the products with the alkenes bearing an electron-withdrawing group. However, the regiochemistry reported for the cycloadduct with alkenes bearing electron-donating groups (butyl vinyl ether and 1-octene) is the opposite of that expected from zwitterion **12**. Consequently, a diradical **11** may better represent the intermediate because it would give rise to the observed regiochemistry. In support of this suggestion, it was reported ^{<1999TL6293, 2002JOC1520>} that tributylstannyl radical catalyzed cycloaddition of alkenes with 1,2,3-selenadiazole **16** ($n=2$) to afford cycloadducts **17** ($n=2$) as shown in Scheme 3 and Table 2. The likely intermediate in this catalyzed reaction is vinyl radical **19** which preferentially adds to the less-substituted carbon of the alkene to ultimately produce **17**. Thus, assuming the cycloaddition of diradical **11** is initiated by the vinyl radical moiety, the regiochemistry in these cycloadditions is accounted for by radical **11**.



Scheme 3

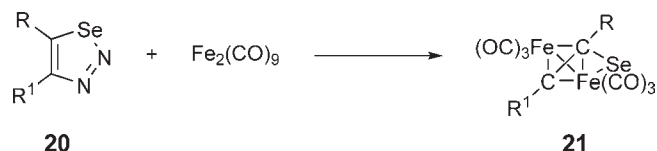
Table 2 Tin-catalyzed reaction of 1,2,3-selenadiazole **16** ($n=2$) with alkenes (Scheme 3) ^{<2002JOC1520>}

Entry	X	Yield of 17 (%)
i	CO ₂ Me	79
ii	CN	67
iii	COMe	74
iv	Ph	76
v	OBu	11
vi	OMe	5
vii	C ₆ H ₁₃	7

1.07.5.4 Reactions with Transition Metals

Reaction of selenirenes with transition metals has not been reported. However, reaction of 1,2,3-selenadiazoles with transition metals, which may involve selenirenes or their equivalents as intermediates, has been studied. These studies are reviewed here.

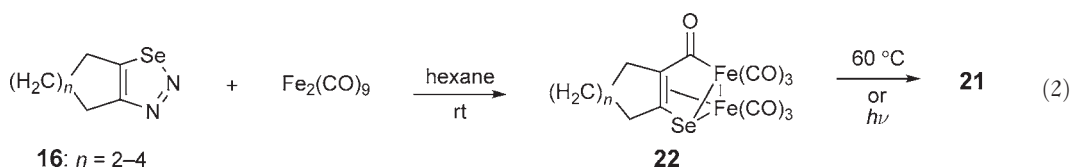
Reaction of 4,5-diphenyl-1,2,3-selenadiazole, **20** ($R = R^1 = \text{Ph}$) with $\text{Fe}_2(\text{CO})_9$ results in N_2 loss with the formation of **21** ($R = R^1 = \text{Ph}$) <1972J(P1)2165, 1973JA2501> as shown in Scheme 4 and Table 3. Use of the isomeric 1,2,3-selenadiazoles **20** ($R = p\text{-}(t\text{-Bu})\text{C}_6\text{H}_4$, $R^1 = \text{Ph}$) and **20** ($R = \text{Ph}$, $R^1 = p\text{-}(t\text{-Bu})\text{C}_6\text{H}_4$) give rise to a mixture of isomeric products **21** that are not fully equilibrated. Since the isolated products do not equilibrate, isomerization occurs before product formation, possibly via the diarylselenirene. Similar reaction occurs with cycloalkeno-1,2,3-selenadiazoles **16**, with $\text{Fe}_2(\text{CO})_9$ but a precursor **22** has been isolated in this case <1980AGE632>, as shown in Equation (2). Thermolysis or photolysis of **22** results in decarbonylation providing complexes analogous to **21**.



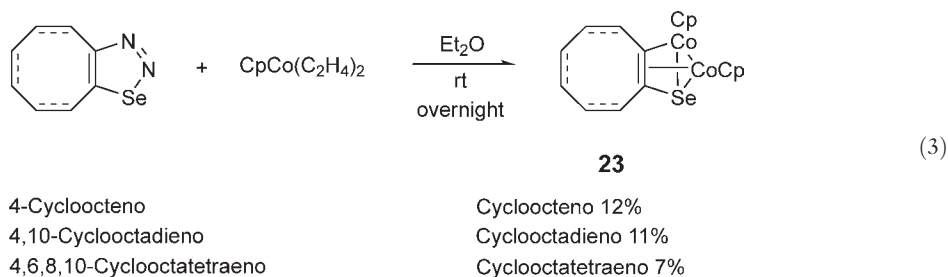
Scheme 4

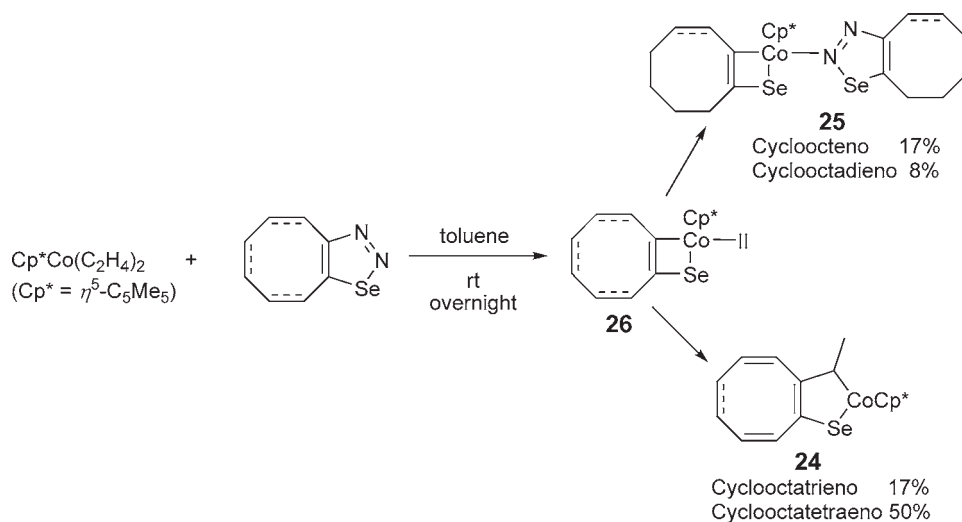
Table 3 Reaction of 1,2,3-selenadiazoles **20** with diiron nonacarbonyl (Scheme 4)

Entry	R	R ¹	Conditions	Yield (%)	Reference
i	Ph	Ph	reflux, PhH 12 h	21	1973JA2501
ii	Ph	Ph	reflux, DME 0.5 h	6	1972J P12165
iii	Ph	<i>p</i> - <i>t</i> -BuPh	reflux, DME 0.5 h	26	1972J P12165

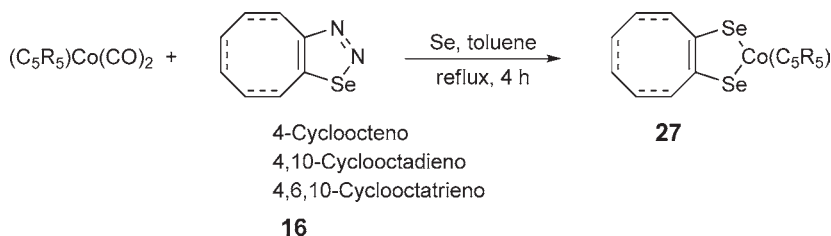


η^5 -Cyclopentadienylcobalt(i) complexes react with 1,2,3-selenadiazoles **16** annulated with unsaturated cyclooctane rings to afford fluxional complexes **23** <1987JOMC39, 1989OM800>, as illustrated in Equation (3). Reaction of these 1,2,3-selenadiazoles with η^5 -pentamethylcyclopentadienylcobalt di(ethene), $\text{Cp}^*\text{Co}(\text{C}_2\text{H}_4)_2$, affords further insightful results. Ethene insertion complexes **24** or complex **25** are formed, as shown in Scheme 5. This suggests that initial complex **26** is formed. This can either undergo insertion or ligand substitution to yield **25**.

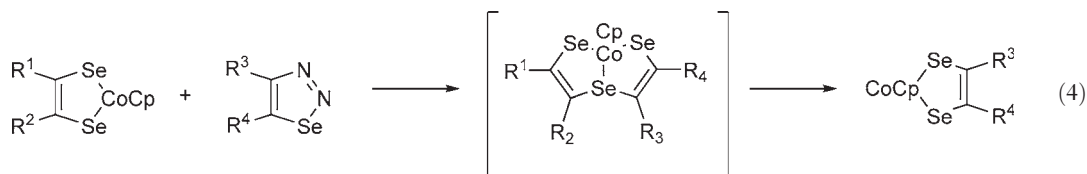


**Scheme 5**

In the presence of selenium, these and other 1,2,3-selenadiazoles yield the corresponding diselenolenes **27** likely via **26** (without ethene coordinated to Co) on treatment with $\text{Cp}^*\text{Co}(\text{CO})_2$ or $\text{Cp}^*\text{Co}(\text{CO})_2$ (**Table 4**) <1993JCD703>. Diselenolene cobalt complexes undergo ligand exchange as shown in **Equation (4)** and **Table 5** purportedly through the Se_3 chelate shown <1993JOM219>.

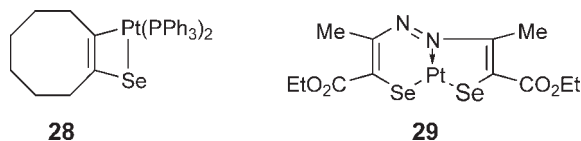
**Table 4** Reactions of cycloocteno-1,2,3-selenadiazoles **16** with $(\text{C}_5\text{R}_5)\text{Co}(\text{CO})_2$ and selenium to give **27** <1993JOM219>

Entry	R	16	Yield (%)
i	H	4-Cycloocteno	25
ii	Me	4-Cycloocteno	28
iii	H	4,10-Cyclooctadieno	32
iv	Me	4,10-Cyclooctadieno	44
v	H	4,6,10-Cyclooctatrieno	34
vi	Me	4,6,10-Cyclooctatrieno	59

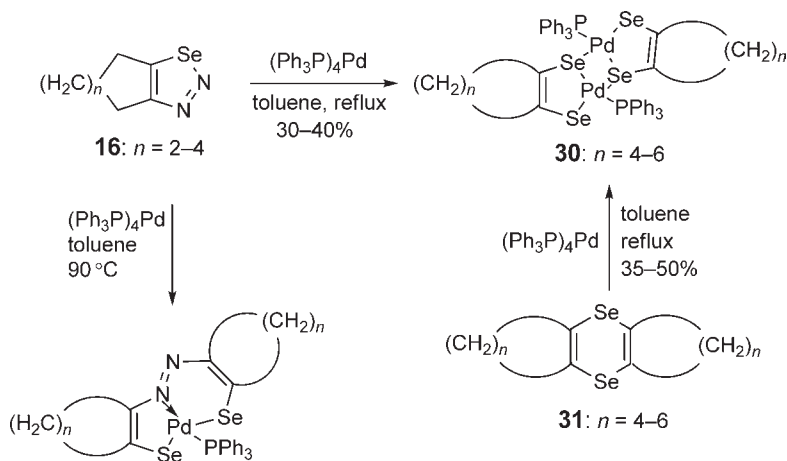
**Table 5** Reaction of cyclopentadienylcobalt diselenolenes with cycloocteno-1,2,3-selenadiazoles <1993JOM219>

Entry	R^1	R^2	R^3	R^4	Yield (%)
i	Ph	H	$-(\text{CH}_2)_6-$		100
ii	Ph	Ph	$-(\text{CH}_2)_6-$		100
iii	$-\text{CH}=\text{CH}(\text{CH}_2)_2\text{C}=\text{CH}-$		$-(\text{CH}_2)_6-$		100

Treatment of 1,2,3-selenadiazole **16** ($n=4$) with $(\text{Ph}_3\text{P})_4\text{Pt}$ in toluene at reflux provides **28** in addition to polymer [<1995JCM64>](#). With ethyl 4-methyl-1,2,3-selenadiazole-5-carboxylate and $(\text{Ph}_3\text{P})_4\text{Pt}$ oxidative addition of $\text{Pt}(0)$ to the Se–N bond apparently occurs followed by reaction with the corresponding selenirene or zwitterion to give **29** [<2005TL1001>](#).



With $(\text{Ph}_3\text{P})_4\text{Pd}$, **16** affords **30** on heating in toluene at reflux [<1999JCD791>](#). At lower temperatures, the Pd species analogous to **29** forms as shown in [Scheme 6](#). Since **30** is formed from **31** and $(\text{Ph}_3\text{P})_4\text{Pd}$, it is presumed that **31** is an intermediate in the formation of **30**. In the presence of trialkylphosphines, $\text{Pd}_2(\text{dba})_3$ reacts with **16** in toluene at reflux to provide **32** as shown in [Equation \(5\)](#) and [Table 6](#) (dba = dibenzylideneacetone) [<1998CC1305, 2004POL2967>](#).



Scheme 6

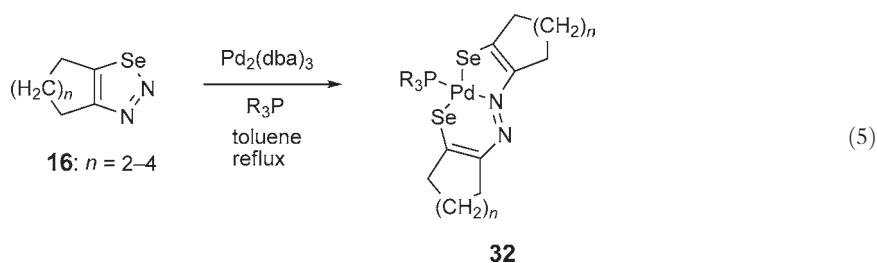
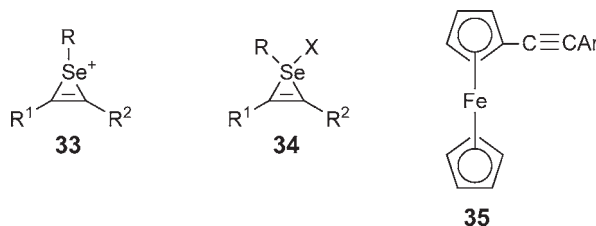


Table 6 Reaction of 1,2,3-selenadiazoles **16** with $\text{Pd}_2(\text{dba})_3$ and trialkylphosphines [<1998CC1305, 2004POL2967>](#)

Entry	n	R	Yield (%)
i	2	Et	48
ii	3	Et	36
iii	4	Et	55
iv	3	Bu	53
v	3	Bu	46
vi	4	Bu	51

1.07.5.5 Nucleophilic Ring Opening

Addition of electrophilic $RSeX$, especially areneselenenyl halides to alkynes, has been studied mechanistically <B-1978MI275, B-1994MI873>. Based on these studies, it has been suggested that a selenirenium ion **33** and/or selenurene **34** are intermediates, although alternative mechanistic possibilities exist <2002CEJ2799>.



Formation of **33** ($R = Ph$, $R^1 = R^2 = Me$) in solution has been claimed <1975TL3991>. Assuming the intermediacy of **33**, nucleophilic ring openings by Cl^- , Br^- , <1978MI275> or F^- <1990TL2127, 1992CL1507, 1994SI043> preferentially affords the *anti*-product with unsymmetrically substituted **33**, and mixtures of regioisomers are often, but not always, obtained. Recently, the addition of $PhSeCl$ to arylferrocenylethyne **35** has been reported <2004EJO521>. Mechanistic studies on this reaction support the intermediacy of the corresponding selenirenium ion. The structure of the presumed intermediary selenirenium ion **33** ($R = R^1 = Ph$, $R^2 = ferrocenyl$) was calculated using semi-empirical methods. Nucleophilic ring opening by chloride ion on the presumed intermediary selenirenium ion produces the *anti*-addition product whose regiochemistry depends on the substituent in the aryl ring of the starting alkyne.

1.07.5.6 Free Radical Reactions

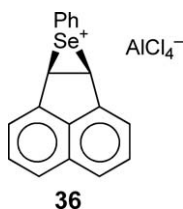
A major reaction pathway for selenirenes is ring opening to diradical **11** or direct formation of this diradical by thermolysis or photolysis of 1,2,3-selenadiazoles as discussed in Sections 1.07.5.2 and 1.07.5.3.

1.07.6 Reactivity of Nonconjugated Rings

1.07.6.1 Introduction

Reactions in which seleniranes, or their derivatives, are presumed to be intermediates are reviewed in this section. As is the case with selenirenes, seleniranes have proven difficult to isolate <1996CHEC-II(1)259>. Studies on reactions of isolated seleniranes support the reactivity patterns proposed for the presumed selenirane intermediates.

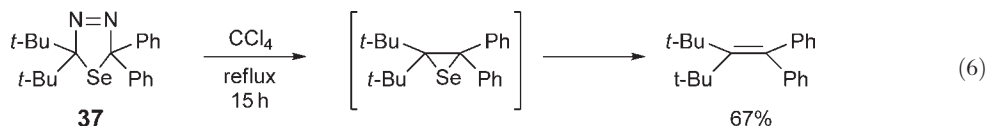
Addition of electrophilic selenium reagents to alkenes in which seleniranium ions are presumed to be intermediates have been extensively studied and reviewed <B-1984MI208, B-1986MI185, B-1987MI56, B-1987MI127, B-1999MI35, 2000TCC7>. The X-ray crystal structure of seleniranium salt **36** has also been reported <1986IZV2832>.



1.07.6.2 Thermal Reactions

As pointed out previously, seleniranes thermally extrude selenium to yield the corresponding alkenes <1996CHEC-II(1)259>. Thus, thermolysis of the 1,3,4-selenadiazoline **37**, as shown in Equation (6), results in the loss of N_2 to form the presumed selenirane intermediate. This intermediate loses selenium to form an alkene <B-1999MI193>. The 1,3,4-selenadiazoline is prepared but usually not isolated by the 1,3-dipolar cycloaddition of a diazo compound

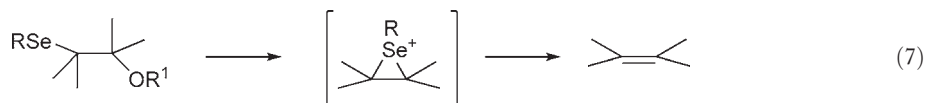
and selenoketone or by the reaction of ketohydrazones with diselenium dihalides and trialkylamines <2000JOC1799, 2002HAC351, 2003H(60)299, 2004EJO820, 2005BCJ1121>.



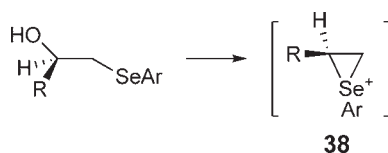
Similarly, telluriranes lose tellurium on thermolysis to give alkenes <1996CHEC-II(1)259>. Thermolysis of 1,3,4-telluradiazolines, affords alkenes presumably via the tellurirane intermediate. However, the yield of alkene is low apparently because 1,3,4-telluradiazolines undergo retro-1,3-cycloaddition to diazo compound and telluroketone in preference to loss of N₂ <1993JA7019, 1997TL2501, 1997T8137>.

1.07.6.3 Reactions on Ring Chalcogen Atoms

β -Hydroxyselenides can be stereospecifically converted to alkenes as shown in Equation (7), on treatment with acid <1976TL1385>, thionyl chloride/triethylamine <1976TL3743>, or trimethylsilyl chloride/sodium iodide <1981JOC231>. This last reagent will also generate alkenes from other β -oxygenated selenides, for example, β -alkoxyselenides. These reactions are presumed to occur via the corresponding seleniranium ions followed by the loss of formally RSe⁺ <1995COFGT716>. It is likely that some nucleophile in solution attacks the selenium of the seleniranium ion resulting in the loss of RSeNu rather than RSe⁺. As such, this would constitute the reverse of the addition of electrophilic RSeX to an alkene, a reaction discussed in the next section.



Reaction of seleniranium salts formed from β -chlorophenylselenides and ZnBr₂ undergo attack on Se by allyltrimethylsilane and *O*-silylated enolates <1983TL5911>. Selenophilic versus carbophilic attack has been studied in the reactions of chiral seleniranium salts **38** obtained by treatment of chiral β -hydroxyselenides with acid <1998PS649, 2005PS935>.



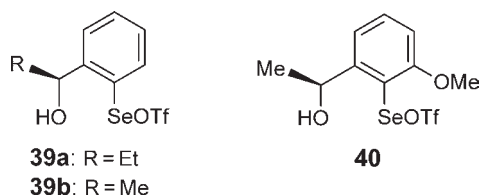
Racemization of **38** is suggested to occur by nucleophilic attack of the hydroxyl group of the β -hydroxyselenide on the selenium atom of **38**. This results in a postulated selenurane which undergoes reversible fragmentation into ArSeOH and alkene. Reaction of achiral ArSeOH and alkene results in racemic seleniranium salt.

1.07.6.4 Nucleophilic Ring Opening

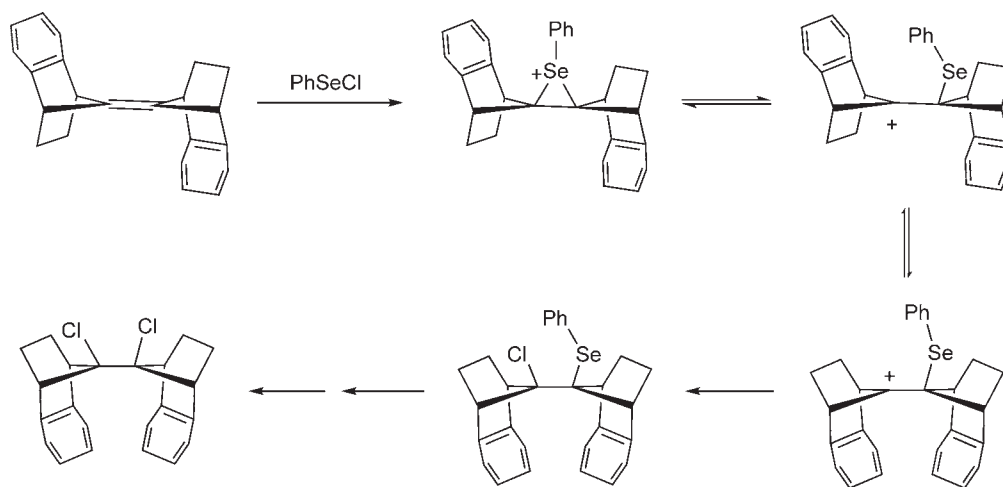
The addition of electrophilic selenium reagents to alkenes has been extensively studied and reviewed <B-1984MI208, B-1986MI185, B-1987MI56, B-1987MI27, B-1999MI35, 2000TCC7>. Since seleniranium ions are presumed intermediates in these reactions which then undergo nucleophilic ring opening, it is appropriate to provide a brief overview of the reviewed work. In addition, more recent studies, that have not as yet been reviewed, will be considered. The range of nucleophiles used in these ring openings is large including O, S, N, and carbon nucleophilic centers both in intermolecular and intramolecular (cyclofunctionalization providing cyclic ethers, lactones, S- or N-heterocycles or carbocycles) examples. As pointed out in the preceding section, nucleophiles, in particular allyl trimethylsilane and *O*-silylated enolates, can attack at selenium rather than at carbon of the intermediary seleniranium ions. Consequently, efforts have been made to promote carbophilic attack. It has been found that steric protection of the selenium, by use of a 2,4,6-tri-*tert*-butylphenyl group attached to selenium, prevents nucleophilic attack at selenium <1996JA2756, 2005PS935>. In addition, both this group and 2,6-bis(trifluoromethyl)phenyl attached to Se prevents racemization of **38** <1996JA2756, 1998PS649>.

There have been many studies on the use of chiral electrophilic selenium reagents for stereoselective additions to alkenes <1998JA3376, B-1999MI35, 1999T1, 2000AGE3740> with notable diastereoselectivity in some cases.

Ab initio calculations on the reaction of **39** and **40** with alkenes account for the diastereomeric product ratios and stabilities of the intermediary seleniranium ions <1998JA3376, 2000JA10914>.



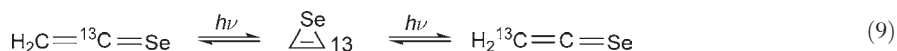
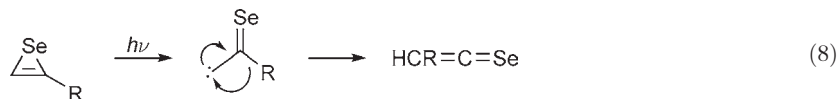
Equilibration of diastereomeric seleniranium salts derived from styrene and **39b** has been demonstrated and occurs via cleavage to styrene and electrophilic selenium reagent followed by readdition <1998JA3376>. Cleavage of one C–Se bond, not both, in a purported seleniranium ion has also been suggested <2001H625>. Reaction of either *syn*- or *anti*-9,9-bibenzonorbornylidenes with benzeneselenenyl chloride provide the same *vic*-dichloride with *syn*-stereochemistry. That is, the *anti*-isomer isomerizes during the course of this reaction. The suggested pathway for this reaction starting with *anti*-isomer is shown in Scheme 7.



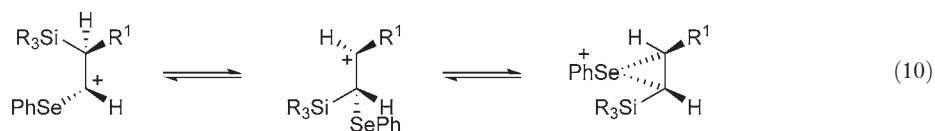
Scheme 7

1.07.7 Reactivity of Substituents Attached to Ring Carbon Atoms

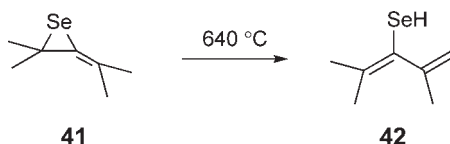
An important reaction pathway for selenirenes is rearrangement to selenoketenes <1996CHEC-II(1)259>. Presumably the group attached to the ring carbon is induced to migrate subsequent to ring opening to the selenoketocarbene as shown in Equation (8). Such a process may also be involved in the randomization of the C-13 label in selenoketene on irradiation as shown in Equation (9) <1985J(P1)907>.



A novel 1,2-shift of silicon ascribed to seleniranium ion formation has been reported <1994JA2356>. The key rearrangement is shown in Equation (10).



Thermal rearrangement of **41** to **42** involves migration of a substituent hydrogen <1996T1965>.



1.07.8 Reactivity of Substituents Attached to Ring Heteroatoms

No relevant reactions have been noted.

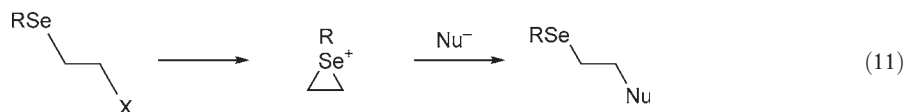
1.07.9 Ring Synthesis from Acyclic Compounds

1.07.9.1 Introduction

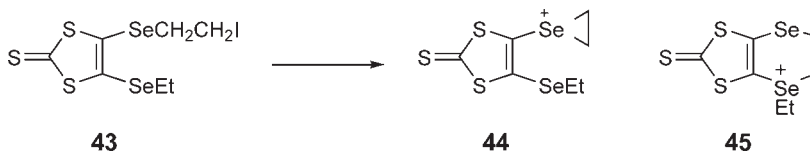
The methods relevant to this section have been extensively reviewed previously <1996CHEC-II(1)259>. The more recently reported methods are extensions of the previously reported work and, therefore, will be only briefly described.

1.07.9.2 Neighboring Group Participation in β -Substituted Chalcogenides

The rate of nucleophilic substitution at positions β to selenium is greatly enhanced. This anchimeric assistance has been ascribed to neighboring group participation with formation of the corresponding seleniranium ion in the rate-determining step as shown in Equation (11).



Furthermore, this participation by Se has stereochemical consequences. The neighboring group participation occurs with inversion at the center undergoing substitution. Nucleophilic attack on the seleniranium ion also occurs with inversion. Consequently, overall retention of configuration is observed at the center undergoing substitution. Examples of such neighboring group participation have been presented in Section 1.07.6.4. Another recent example involves **43**, which allegedly preferentially forms three-membered seleniranium ring **44** as opposed to the six-membered ring **45** <2002JOC4218>. Additional examples which are synthetically advantageous are presented in Sections 1.07.12.3 to 1.07.12.5. Arguments accounting for the stabilization of carbocations generated β to Se by vertical (hyperconjugative) effects rather than by bridging to form seleniranium ions (neighboring group participation) have been presented <2002CEJ2799>.



1.07.9.3 Addition to Alkenes

As discussed in Section 1.07.6.4, addition of electrophilic selenium reagents to alkenes, which is suggested to lead to seleniranium ion intermediates, has been extensively studied. Some recent examples are also illustrated in that section.

1.07.9.4 Addition to Alkynes

Addition of electrophilic selenium reagents to alkynes presumed to generate intermediary selenirenium ions has been presented in Section 1.07.5.5.

1.07.10 Ring Synthesis by Transformation of Another Ring

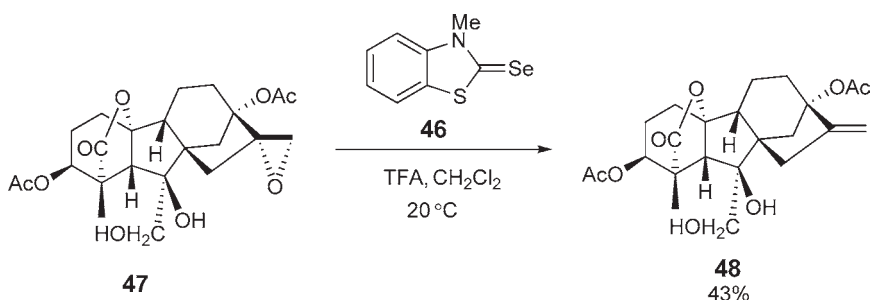
Most of the methods covered in this section have been reviewed and, therefore, will not be discussed in depth. However, the new section on aziridines and on selenepines and tellurepines warrants a more extensive treatment.

1.07.10.1 Introduction

In the reactions reviewed below, the selenium and tellurium three-membered ring compounds are not isolated but presumed intermediates.

1.07.10.2 From Oxiranes

The reactions of 3-methyl-2-selenoxobenzothiazole **46** with oxiranes and thiiranes to give alkenes via seleniranes was reviewed <1996CHEC-II(1)259>. This reaction has been applied to natural product synthesis for the conversion of **47** to **48** shown in Scheme 8 <1996TL8937>.



Scheme 8

Nucleophilic reduction by telluride ion of oxirane tosylates provides allylic alcohols, presumably via telluriranes as shown in Equation (12) and Table 7 <1997T12131>. When used in conjunction with the Sharpless–Katsuki asymmetric epoxidation, optically active transposed allylic alcohols can be made in high enantiomeric excess <1993JOC718, 1994JOC4311, 1994JOC4760>.

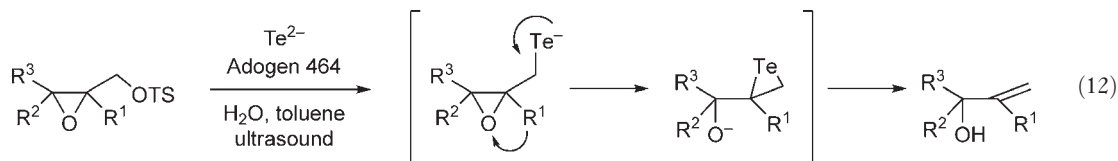
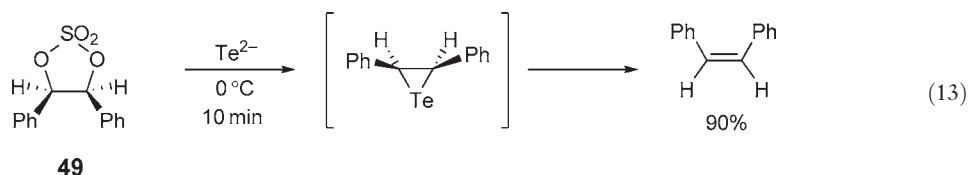


Table 7 Reduction of oxirane tosylates by Te^{2-} under phase-transfer conditions <1997T12131>

Entry	R^1	R^2	R^3	Yield (%)
i	H	Ph	H	97
ii	Me	Ph	H	99
iii	H	$n\text{-C}_5\text{H}_{11}$	H	93
iv	H	$n\text{-C}_6\text{H}_{13}$	H	98
v	H	$\text{Me}_2\text{C}=\text{CH}(\text{CH}_2)_2$	Me	90

1.07.10.3 From Cyclic Sulfates and Thionocarbonates

Reaction of cyclic sulfates or thionocarbonates, derived from 1,2-diols, with telluride results in stereospecific alkene formation [<1995TL7209>](#). This is illustrated by the conversion of the cyclic sulfate *meso*-1,2-diphenyl-1,2-ethanediol **49** into *cis*-stilbene exclusively by Te^{2-} , as shown in [Equation \(13\)](#). Treatment of the cyclic sulfate of *dl*-1,2-diphenyl-1,2-ethanediol with Te^{2-} produces *trans*-stilbene exclusively. These results are accounted for by intermolecular Te^{2-} $\text{S}_{\text{N}}2$ displacement followed by intramolecular $\text{S}_{\text{N}}2$ displacement to form the corresponding tellurirane. The tellurirane then thermally loses tellurium stereoselectively forming alkene. Cyclic sulfates need not be used; dimethanesulfonates or di-*p*-toluenesulfonates prepared from 1,2-diols also, stereospecifically, provide alkenes via telluriranes [<1993CC923, 1996SL655>](#).



1.07.10.4 From Aziridines and 2-Oxazolidinones

In an analogous fashion to the reaction of telluride ion with oxirane tosylates (Section 1.07.10.2), aziridinemethanol-sulfonates form allylic amines as shown in [Equation \(14\)](#). It is suggested that telluriranes are intermediates as shown [<1997JOC7920, 1997T12131>](#). The related reaction using sulfonates of 5-hydroxymethyl-2-oxazolidinones, shown in [Equation \(15\)](#), has also been reported (see [Table 8](#)) [<1999TL2255>](#).

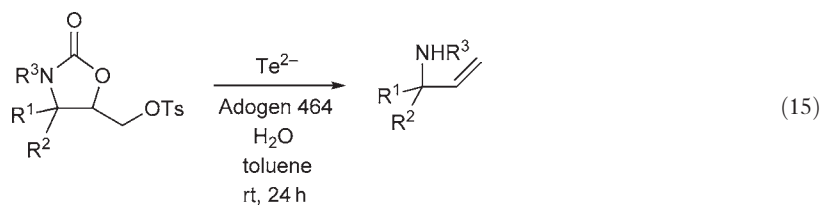
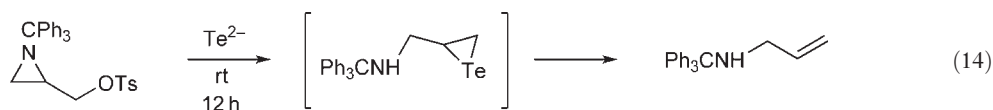


Table 8 Reaction of 5-hydroxymethyloxazolidinone tosylates with telluride [<1999TL2255>](#)

Entry	R^1	R^2	R^3	Yield (%)
i	H	Ph	<i>n</i> -C ₆ H ₁₃	95
ii	H	Ph	PhCH ₂	93
iii	H	<i>n</i> -C ₃ H ₇	4-MeOC ₆ H ₄ CH ₂	66
iv	Me	Me ₂ C=CH(CH ₂) ₂	<i>n</i> -C ₆ H ₁₃	79

1.07.10.5 From 1,2,3-Selenadiazoles

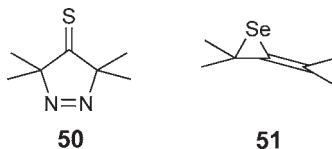
Use of 1,2,3-selenadiazoles as precursors of intermediary selenirenes has been discussed extensively in the preceding sections. Furthermore, their use in alkyne and metal selenide synthesis is treated in Section 1.07.12. Consequently, there is no need for further discussion here.

1.07.10.6 1,3,4-Selenadiazolines

This method for forming intermediary seleniranes has been discussed in Section 1.07.6.2 and synthetic applications are presented in Section 1.07.12.2. The corresponding but less favorable reaction with 1,3,4-telluradiazolines has also been discussed (Section 1.07.6.2).

1.07.10.7 From 4-Selena-3,5-dihydropyrazoles

Low-temperature photolysis or gas-phase thermolysis followed by low-temperature quenching of **50** provided **51**, as shown by low-temperature IR spectroscopy <1996T1965>.



1.07.10.8 From Selenepines and Tellurepines

Selenepines **52a** and tellurepines **52b** extrude selenium and tellurium, respectively. It is likely that this occurs via formation of the corresponding chalcogenanorcaradiene **53**, containing a three-membered ring heterocycle, which rapidly loses chalcogen thermally (Section 1.07.6.2), as shown in Equation (16). Thus **54** cleanly extrudes selenium to form diethyl 4,5-di-*tert*-butyl-phthalate quantitatively, as shown in Equation (17) <1990AGE424>. 3-Benzochalcogenepines **55** extrude chalcogen to form naphthalene, as shown in Equation (18) <1991CC802, 1996CC2183>. The rate of extrusion depends on the chalcogen and follows the order **55** (X=Te) < **55** (X=Se) < **55** (X=S), as shown in Table 9. That is, the relative stabilities are **55** (X=Te) > **55** (X=Se) > **55** (X=S) <1996CC2183>. 1-Benzochalcogenepines **56** (R=H) are more stable not only than their 3-benzoanalogues **55** but also decompose to naphthalene (Equation 19). The stability dependence based on the heteroatom follows the same order as for **55**, as shown in Table 10 <1996CC2183>. Similarly 1-benzoselenepine **56** (X=Se; R=*t*-Bu, Me) and 1-benzotellurepines **56** (X=Te; R=*t*-Bu, Me) decompose within 2–3 days at room temperature to the corresponding 1-substituted naphthalene <1993CC1493, 1995CPB19>. Dithienochalcogenepines **57** are more stable than the corresponding 1-benzochalcogenepines **56** but less stable than the corresponding dibenzochalcogenepines. They decompose, as shown in Equation (20) and Table 11, presumably via valence tautomerization, to **58** <1997H1899>. In support of the requirement for valence tautomerization, the isomeric dithienochalcogenepines **59**, which cannot valence-tautomerize to chalcogenanorcaradienes, are thermally stable <1997H1899>.

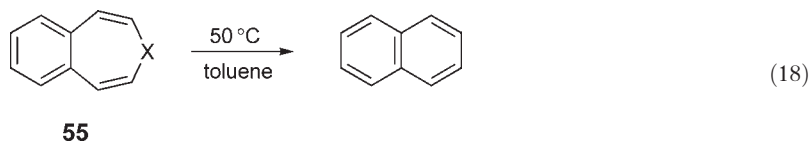
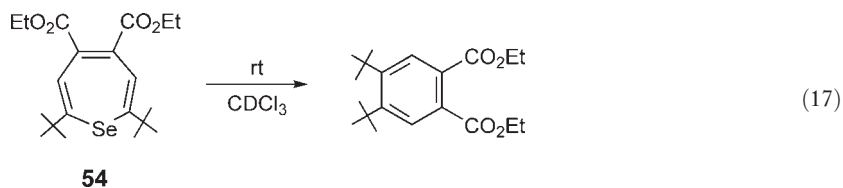
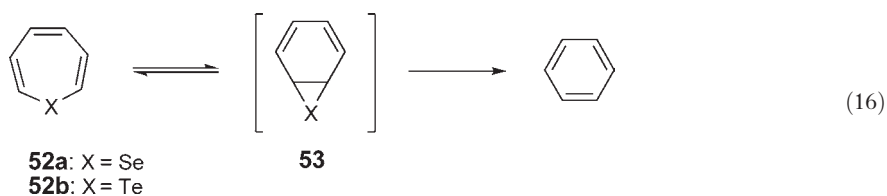
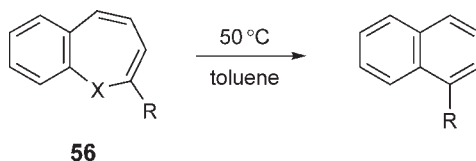


Table 9 Half-lives for thermal decomposition at 50 °C of 3-benzochalcogenepines **55** <1996CC2183>

Entry	X	Half-life (min)
i	S	1
ii	Se	4
iii	Te	48



(19)

Table 10 Half-lives for thermal decomposition at 50 °C of 1-benzochalcogenepines **56** <1996CC2183>

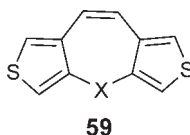
Entry	X	R	Half-life (min)
i	S	H	44
ii	Se	H	110
iii	Te	H	133



(20)

Table 11 Thermal Decomposition of **57** to **58** <1997H1899>

Entry	X	Temp. (°C)	Time (h)
i	Se	110	5
ii	Te	180	1



1.07.11 Synthesis of Particular Classes of Compounds and Critical Comparison of Various Routes Available

Owing to the instability of these heterocycles and limited methods by which they have been made as unstable intermediates, there is not much to discuss in this section. However, in the next section, there are limited discussions on the various methods for synthesizing precursors to these heterocycles.

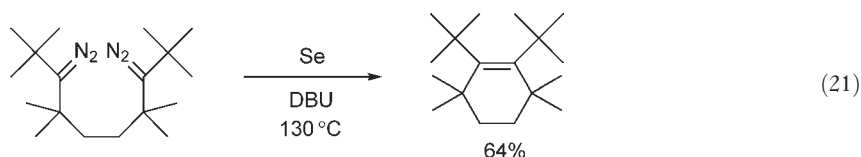
1.07.12 Important Compounds and Applications

1.07.12.1 Introduction

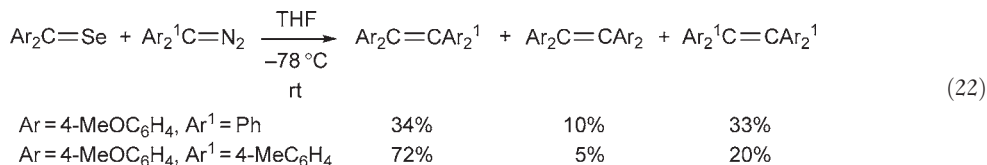
There are a number of synthetically important applications, involving these heterocycles, as unstable intermediates, which are reviewed here. These applications feature the ability of selenium to be readily extruded from seleniranes and selenirenes, neighboring group participation by β -Se to control the stereochemistry of nucleophilic substitution reactions, and facile, chemoselective replacement of Se by H in radical-induced reactions.

1.07.12.2 Synthesis of Sterically Hindered Alkenes

Thermolysis of 1,3,4-selenadiazolines, discussed in Section 1.07.6.2, is the method of choice for synthesizing sterically hindered alkenes [<B-1999MI193>](#). The 1,3,4-selenadiazolines are made by 1,3-dipolar cycloaddition of diazo compounds and selenoketones. This requires the availability of both components which presents a limitation to the method. Efforts to overcome this limitation have been successful. Treatment of ketohydrazone with Se_2Br_2 or Se_2Cl_2 and trialkylamines provide 1,3,4-selenadiazolines probably via *in situ* generalization of diazo compound and selenoketone [<2000JOC1799, 2003H\(60\)299, 2004EJO820, 2005BCJ1121>](#). In addition, treatment of bis(diazo) compounds with selenium and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) can generate the corresponding selenoketone-diazo compound which forms the alkene as illustrated in [Equation \(21\) <2002HAC351>](#). Unfortunately, the bis(selenoketone) may also form resulting in the formation of di- or triselenides.



Another limitation of the 1,3-dipolar cycloaddition of diazo compounds and selenoketones is that it is reversible. Consequently, mixtures of alkenes may be obtained as illustrated in [Equation \(22\) <2004EJO820>](#).



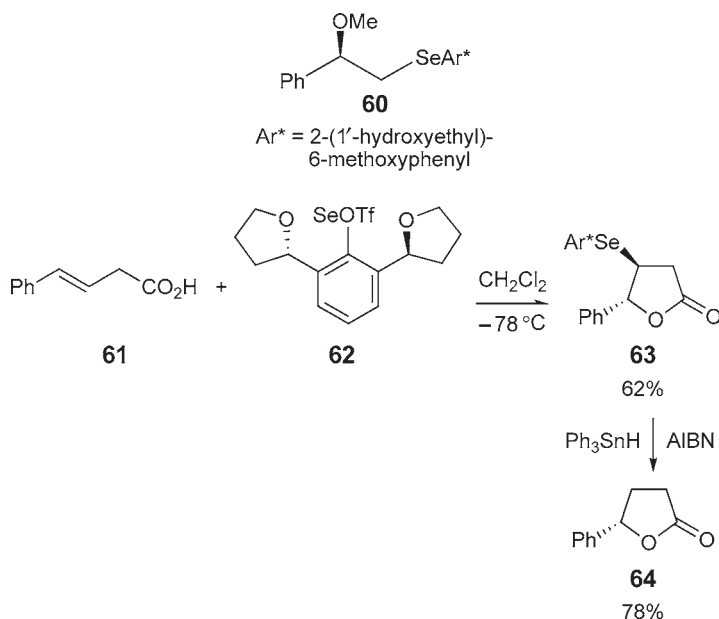
1.07.12.3 Stereoselective Synthesis of β -Substituted Chalcogenides

In Section 1.07.6.4, ring opening of presumed seleniranium salts, obtained by addition of electrophilic selenium reagents to alkenes, was discussed. This provides access to cyclic ethers, lactones, S- or N-heterocycles or carbocycles and has been widely used. Recently, use of chiral electrophilic selenium reagents has been studied in an effort to develop effective asymmetric syntheses. As already mentioned, notable progress has been made. Two particularly successful examples are illustrated here. Treatment of styrene with **40** in methanol afforded **60** in 55% yield with a 50:1 ratio of diastereomers [<1998CC1867>](#). Reaction of **61** with **62** at -78°C in dichloromethane containing methanol (2.5% v/v) gave **63** in 62% yield with a $>100:1$ ratio of diastereomers [<1997TL4753>](#). Reduction of **63** with Ph_3SnH and AIBN provided the *S*-enantiomer of **64** in 78% yield, thereby providing a highly enantioselective synthesis of **64** ([Scheme 9](#)).

1.07.12.4 Stereoselective Glycosylation: 2',3'-Dideoxy and 2',3'-Didehydro-2',3'-dideoxynucleoside Synthesis

2',3'-Dideoxy- and 2',3'-didehydro-2',3'-dideoxynucleosides are potent antiviral drugs that are effective against human immunodeficiency virus (HIV), especially in combination therapies. In synthesizing such compounds, stereochemical control of the glycosylation reaction is key (see [Table 12](#)). Selenium moieties provide such control presumably owing to their formation of seleniranium salts **68**, as shown in [Scheme 10](#).

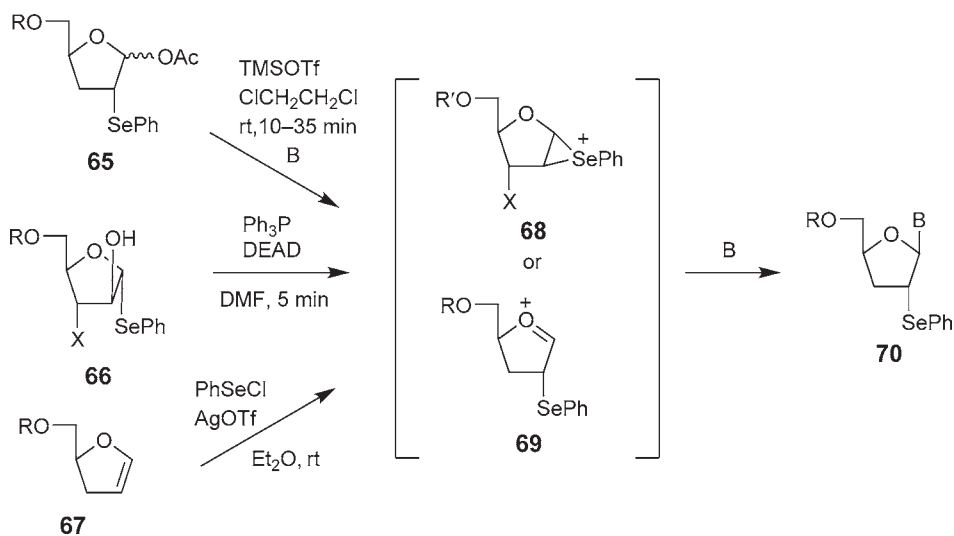
The seleniranium salts can be formed by neighboring group participation by selenium in the 2'-position [<1990JOC1418, 1992JOC3887>](#) or 1'-position [<1999JOC1375>](#) or addition of electrophilic selenium reagents to glycals [<1997JOC1501>](#). Reduction of selenonucleoside **70** provides 2',3'-dideoxynucleosides. Alternatively,



Scheme 9

Table 12 Stereoselective glycosylation

Entry	Compound	R	X	B	Yield (%)	α/β ratio	Reference
i	65	<i>t</i> -BuPh ₂ Si		Silylated thymine	78	1/99	1992JOC3887
ii	65	<i>t</i> -BuPh ₂ Si		Silylated uracil	67		1992JOC3887
iii	65	<i>t</i> -BuPh ₂ Si		Silylated <i>N</i> ⁴ -acetyl cytosine	72		1992JOC3887
iv	66	Bn	F	(6- <i>C</i>) Purine	81	N ⁹ 1/1.7	1999JOC1375
					N ⁹ /N ⁷ = 4.5/1	N ⁷ 1/1.8	
v	67	<i>t</i> -BuPh ₂ Si		Bis(TMS) uracil	60	1/99	1997JOC1501
vi	67	<i>t</i> -BuPh ₂ Si		Bis(TMS) thymine	95	9/99	1997JOC1501
vii	67	<i>t</i> -BuPh ₂ Si		Silylated (6- <i>C</i>)purine	78	11/89	1997JOC1501

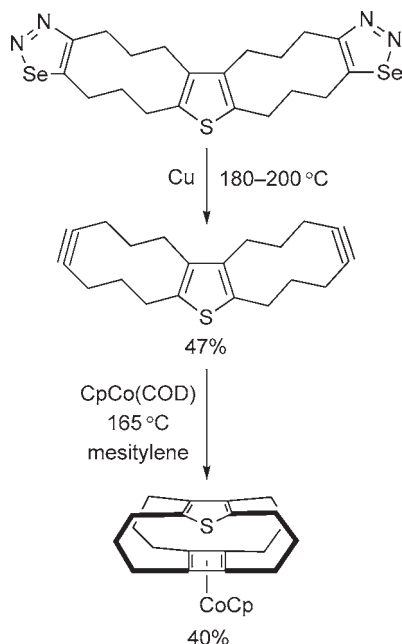


Scheme 10

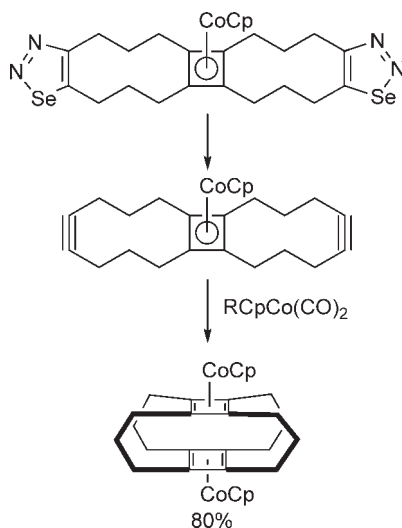
oxidation to selenoxide followed by elimination converts **70** into 2',3'-didehydro-2',3'-dideoxynucleosides. Although seleniranium ion **68** is a reasonable intermediate in these reactions, oxonium ion **69** has been suggested instead. Indeed, DFT calculations have shown that the relative stability of **68** and **69** depends on the nature of the R substituent attached to selenium <2003JOC686>. When R is electron donating, especially *tert*-butyl, 2,4,6-trimethyl, and 2,4,6-trimethoxyphenyl and trimethylsilyl, **68** is favored.

1.07.12.5 Alkyne Synthesis

An attractive method for synthesizing alkynes from ketones involves the intermediacy of a selenirene or its equivalent. Conversion of α -methylene ketones to the corresponding semicarbazones followed by reaction with selenium dioxide affords 1,2,3-selenadiazoles. Thermolysis of 1,2,3-selenadiazoles affords the alkyne <B-1998MI172, 1996CHEC-II(1)259>. Recent examples of this methodology involve the superphane syntheses shown in **Schemes 11** <2004OM1116> and **12** <2000OM147> and formation of 1,6-cyclodecadiyne units for stepwise oligomerization <2002AGE1181>.



Scheme 11



Scheme 12

1.07.12.6 Metal Selenide Synthesis

Thermal decomposition of 1,2,3-selenadiazoles generally provides alkynes, even strained alkynes. However, as the ring size decreases, the yield of alkyne decreases and 1,4-diselenins are produced. In these cases, the lifetime of the selenirene or its equivalent presumably increases and provides an advantageous source of selenium for metal selenide synthesis <2005PS951>. Thus, thermal decomposition of cyclohepteno-1,2,3-selenadiazole in the presence of silver metal provides β -Ag₂Se, a narrow-band-gap semiconductor <2004ML1030>. Thermal decomposition of cycloocteno-1,2,3-selenadiazole in the presence of Cd²⁺, which is presumably reduced to cadmium metal by the solvent 1,2-ethanediol or dimethylformamide (DMF), affords semiconductor CdSe <2003ML1464, 2004ML966>. Although thermal decomposition of 1,2,3-selenadiazoles provides alkynes releasing selenium which could then react with the metal, this is unlikely to be the case here because thermolysis of cycloocteno-1,2,3-selenadiazole in the absence of metals provides the corresponding 1,4-diselenin <2004MCP323>. Consequently, selenirenes or their equivalents formed in these thermolyses are presumably the sources of selenium in these reactions.

1.07.13 Further Developments

A review including seleniranes and seleniranium cations has recently appeared <2007ARK14>.

A recent study on the mechanism of selenocyclization of beta, gamma-unsaturated acids and their derivatives has revealed evidence for the intermediacy of seleniranium ions <2006JOC7293>.

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Biographical Sketch



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1.08

Phosphiranes, Phosphirenes, and Heavier Analogues

H. Heydt

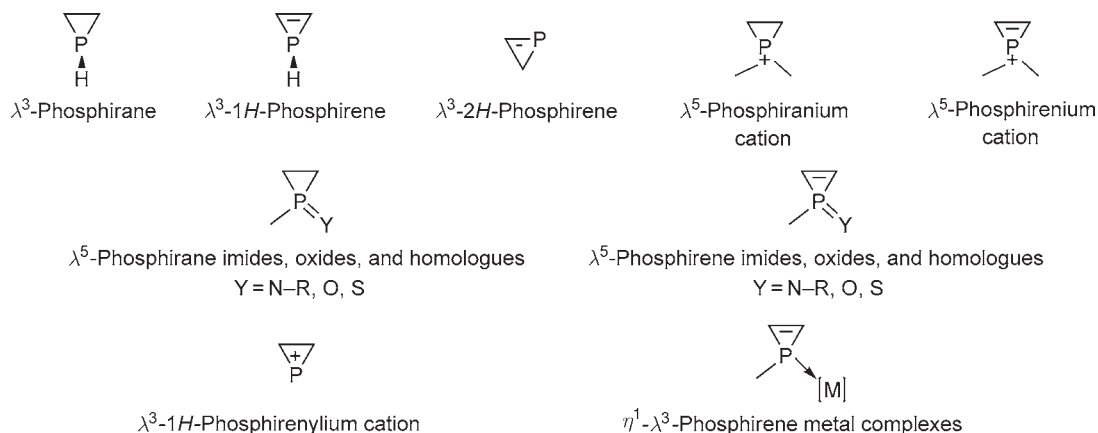
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1.08.1 Introduction

The first publication of a phosphirane in a US patent by Wagner (1963) was fully confirmed in 1967 [<1967JA1102>](#). In 1982, Mathey and co-workers prepared and described the first stable 1*H*-phosphirene [<1982JA4484>](#), while Regitz and co-workers obtained the first 2*H*-phosphirene in 1987 [<1987AGE1257>](#). Whereas the 2*H*-isomers are unstable and can only be prepared with difficulty, the chemistry of the 1*H*-phosphirenes is well explored. Phosphirenium and phosphirenylium cations, phosphirane and phosphirane oxides, imides and homologues, and phosphirane and phosphirene metal complexes are also topics of investigations and their chemistry is partially included herein ([Scheme 1](#)). The advances in this field since 1995 have been discussed in several review articles [<1996CHEC-II\(1A\)277, B-1998MI181, 2001SOS\(9\)85, B-2001MI17>](#).



Scheme 1

1.08.2 Structure of Phosphiranes and Phosphirenes

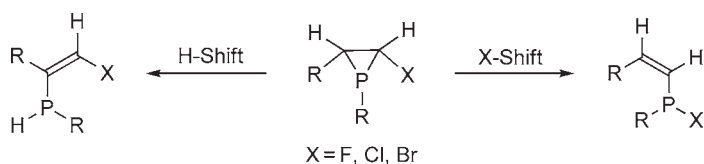
1.08.2.1 Theoretical Data

Only the most recent theoretical data with few exceptions are treated here.

1.08.2.1.1 Phosphiranes

Some new efforts have been attempted to explore the ring-strain energy for phosphirane and to compare these values with the ring strain of cyclopropane and other three-membered heterocycles. The ring-strain energies on the basis of high-level *ab initio* calculations (G2 theory) decrease in the order of cyclopropane ($114.6 \text{ kJ mol}^{-1}$) > 1*H*-aziridine ($113.0 \text{ kJ mol}^{-1}$) > oxirane ($110.5 \text{ kJ mol}^{-1}$) > phosphirane (82.4 kJ mol^{-1}) > thiirane (74.5 kJ mol^{-1}) <2005JOC6018>. Bachrach calculates the ring strain of phosphirane at the HF/6-31G* level of theory as 84.1 kJ mol^{-1} <1993JPC4996>, which differs from the value calculated by Lammertsma *et al.* of 89.1 kJ mol^{-1} (G2(MP2) level of theory) <1999JA11650> and 89.5 kJ mol^{-1} (G3(M3) level of theory) <2003EJO2941>. The strain energy of phosphirane was also calculated at the RHF/6-31G* level from a homodesmotic reaction and amounts to 84.5 kJ mol^{-1} and the authors point out that the decrease of ring strain for phosphirane is correlated with the σ - and π -relaxation by delocalization between geminal ring bonds which is found to be significant because of the acute bond angles <2003PCA2860>.

The transition state for the ring opening of phosphiranes into bis(methylene)phosphoranes was calculated on the generalized valence bond (GVB)/6-31G** level of theory and shows a disrotatory behavior in contradiction to the Woodward–Hoffmann rules <1995JOC3723>. Another study deals with the ring opening of 2-halo-phosphiranes into vinylphosphines (Scheme 2) and emerges with the findings that the rearrangement remains a concerted process in which ring opening and migration of a substituent at C-2 occurs simultaneously <2001JOC5671>; see also <2005OM5172> regarding this rearrangement in the case of complexed 2-chlorophosphiranes.



Scheme 2

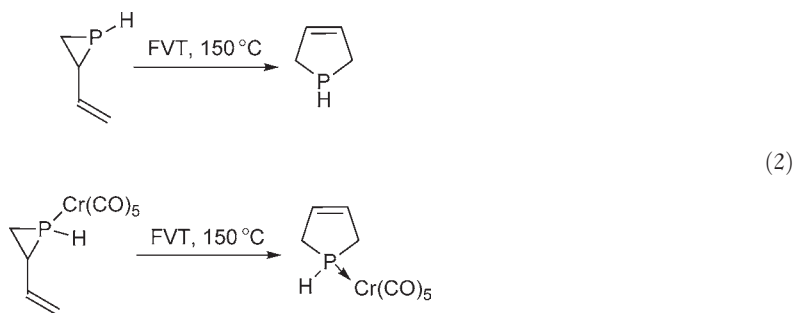
In the unsubstituted parent system (R=X=H), the energy barrier for the whole process amounts to about $188 \pm 21 \text{ kJ mol}^{-1}$. The reaction involving a hydrogen migration is consistently favored over that of halogen migration. These findings differ from experimental studies with metal-complexed phosphiranes where the halogen migration

dominates <1995SL353, 2000JOC652>. The transition state is highly pyramidal and has diradical character. In this context, the Cope rearrangement of *cis*-2,3-divinylphosphirane to 4,5-dihydro-1*H*-phosphepine was investigated via a density functional theory (DFT) study. The minimum-energy path proceeds through an *endo*-boat-like, aromatic transition structure. Compared to the Cope rearrangement of *cis*-divinylcyclopropane, the activation barrier increases, which agrees qualitatively with the decreasing ring strain of cyclopropane to phosphirane <2005JOC6018>.

The flash thermolysis of 1-vinylphosphirane which yields ethyldynephosphine via the rearrangement of a vinylphosphinidene has been studied in some depth from a theoretical standpoint (Equation 1) <1996OM4904>.



The conversion of free and Cr(CO)₅-complexed 2-vinylphosphirane into 2,5-dihydro-1*H*-phosphole via 1,3-sigmatropic shifts was studied with DFT and compared with the corresponding vinylcyclopropane–cyclopentene rearrangement (Equation 2) <2002JA13903>. 2-Vinylphosphirane has smaller barriers as in the case of vinylcyclopropane and the complexed species has still smaller one. The rearrangement of *syn*- and *anti*-2-vinylphosphirane is a concerted process under inversion of phosphorus with activation barriers of 153.6 and 122.6 kJ mol^{−1}, respectively. The complexed *anti*-isomer has the lowest barrier for the 1,3-shift (85.8 kJ mol^{−1}).



The study of the thermal and photochemical decomposition of 1-aryl-1*H*-phosphiranes to ethene and arylphosphinidenes is further under investigation. A detailed theoretical study (CASSCF, CASPT2, CCSD(T), (U)B3LYP) of the thermal fragmentation of 1-phenyl-1*H*-phosphirane reveals that the stepwise pathway for the generation of triplet phenylphosphinidene is 88 kJ mol^{−1} less endothermic and has a 50 kJ mol^{−1} lower barrier height than concerted fragmentation to give singlet phenylphosphinidene <2005JA9886>.

The mechanism and kinetics of the propagation step in the radical ring-opening polymerization of methylphosphirane were studied via high-level *ab initio* calculations (B3LYP/6-31G(d)). It was found that the polymerization occurs via attack of the propagating carbon radical at the ring phosphorus. The rate constant of order of 10⁴–10⁶ l mol^{−1} s^{−1} at 298.15 K reflects a facile process with a relatively stable phosphoranyl radical <2005MM8902>.

Various studies have dealt with the valence bond description <1995JST(341)13> and the molecular polarizability of phosphiranes <1997MI255>. Also, the capture of electrons by phosphiranes has been an object of investigation <1996JST(371)69, 1998JST(424)67>. An electron localization function (ELF, <1991AGE409, 1992AGE185, 1997AGE1808>) study <2000PCA11644> is used to characterize the lone pair of 1*H*-phosphirane. The lone-pair basin attractor reveals the lone pair distance from phosphorus of 1.092 Å and the angular disposition of the lone pair with regard to neighboring atoms and bond centers of 82.0°. The last value clearly reveals bent single bonds to be in place. The stereoelectronic profile of phosphirane as ligand in catalysis with complexes of transition metals in regard to the Tolman map expand the envelope of the phosphine family and have very interesting properties <2003JA4318>.

1.08.2.1.2 Phosphirenes

An extremely high value of 278.2 kJ mol^{−1} for the inversion at phosphorus was calculated for 1-fluoro, 1-chloro, and 1-bromo-phosphirenes <1997CC1033>. The inversion is described as a turnstile rotation whereby the P–X fragment rotates around the symmetry axis of the three-membered ring. The calculated inversion barriers range between 190.2 and 212.0 kJ mol^{−1} and are lower in energy by 42–84 kJ mol^{−1} as calculated for the pyramidal inversion. The pyramidal inversion at phosphorus is even more difficult for 1*H*-phosphirenes as in the phosphirane case due to the antiaromatic character of the planar 1*H*-phosphirene structure; see also the calculations (SINDO1) of Malar,

which deal with the antiaromaticity of three-membered ring systems including 1*H*-phosphirene <1996T4709>. Again, the preferred inversion mechanism is best described as a turnstile rotation having a barrier of 218.4 kJ mol⁻¹ at the [CCSD(T)/6-31G^{*}/(MP2/6-31+G^{*})] level of theory <1997CC1033>. The vertical electron affinity <1997BSF1033> as well as the electronic structure of the lowest excited states of substituted 1*H*-phosphirenes at position 1 (R = H, F, CN) were objects of further studies <1996T4709>. The isomeric system of 2-phosphino-2*H*-phosphirene and 1-phosphino-1*H*-phosphirene and the thermal rearrangement of the former to 1,2-dihydro-1,2-diphosphete has been investigated by *ab initio* methods (self-consistent field/double zeta plus polarization, SCF/DZP). The calculations emphasize the effect of amino substituents at the phosphine phosphorus which stabilize the 2*H*-phosphirene structure and that the intrinsic stability between 1*H*- and 2*H*-phosphirenes is rather small (68 kJ mol⁻¹) <1999CEJ274>.

1.08.2.1.3 Phosphiranium and phosphirenium cations

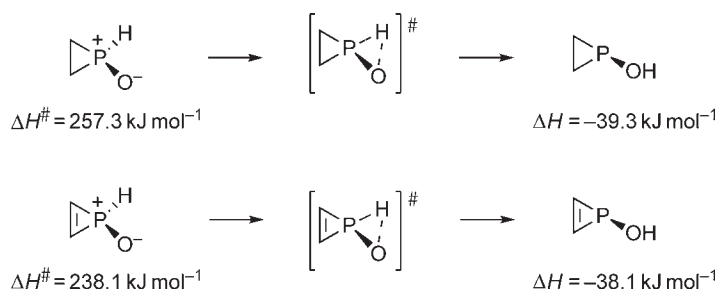
The chemistry of phosphiranium salts has been further investigated from a theoretical point of view <1995CC257, 1997JOM(529)189, 1998JA7063, 1999JOM(580)320>. The formal transfer of a phosphonium ion from one unsaturated hydrocarbon to another resembles the π -ligand exchange in transition metal complexes. Therefore the phosphiranium and the phosphirenium cations can be treated as π -alkene or π -alkyne complexes of the six-electron phosphonium ion. π -Ethylene and π -acetylene exchange on PH₂⁺ can occur by an associative pathway through a spirocyclic transition state with C_{2v} symmetry whose barriers were calculated to be 3.8 and 39.3 kJ mol⁻¹, respectively, at the G2 level of theory <1998JA7063>. Kinetic investigations also reveal that a reversible π -ligand exchange on phosphonium ions takes place between free and coordinated phosphirenium salts which is independent from alkyne concentration <2004OM299>. 1*H*-Phosphirenium salts are of theoretical interest with regard to the aromatic or antiaromatic character of this cationic species. *Ab initio* calculations reveal that a low-lying σ^* -orbital at phosphorus interacts with the carbon/carbon double bond in terms of a third p orbital in an aromatic 2 π -Hückel system. Because this orbital is antibonding for phosphorus ligands, the former described interaction is designated as σ^* -aromaticity <1996JOC5840>.

1.08.2.1.4 Phosphirenylium cations

Ab initio treatment of the phosphirenylium cation at the MP4SDTQ(fc)/6-31+g^{*}//RHF/6-31g^{*} level reveals a precise description of its electron structure <1995JST(343)49>. The P–X bond of halophosphirenes has a strong ionic character, especially when X = F. Introduction of amino substituents at carbon atoms and interaction with SO₂ molecules stabilizes the cation by 167.4–175.7 kJ mol⁻¹ and lowers the heterolysis energy of the phosphorus–halogen bond by ca. 75.3 kJ mol⁻¹. Due to a homodesmotic reaction, the resonance energy of the unsubstituted parent phosphirenylium cation was predicted to be ca. 159 kJ mol⁻¹ <1998JOC2814>. The same method yielded an estimate for the resonance energy of the cyclopropenylium ion of 406 kJ mol⁻¹ <1996JCP17801>. In comparison with the cyclopropenylium ion, the stabilization energy of the phosphirenylium ion is much smaller because the overlap of the p orbitals between phosphorus and the carbon atoms is less than between two C_{2p} atomic orbitals, but nevertheless significant indicating the aromatic character of this ion. DFT calculations at the B3LYP/6-31G^{*} and G3//B3LYP/6-31G^{*} levels of 10 isomers of C₂H₂P⁺ reveal that the phosphirenylium cation in its singlet state is a global minimum with a ΔH_f of 1041 kJ mol⁻¹ predicted at the G3//B3LYP/6-31G^{*} level <2005OM3125>. These results are fairly agreeable with calculations of Lopez and co-workers (MP2/6-31G^{*}) <1995JPC6432> and Maclagan (HF/6-31G^{*}) <1989CPL(163)349>, whereas the DFT and MP2 calculations are more comparable because both take in account the electron correlation. Recently, the gas-phase chemistry of the 2-*tert*-butyl-3-phenylphosphirenylium ion, the sole phosphirenylium ion prepared in solution <1994JA9407>, was reported. The cation detected at *m/z* 189 in a pentaquadrupole mass spectrometer was assigned to a fairly stable phosphirenylium ion structure and reversible reactions of this ion with nucleophilic heteroatoms were further basis for this assignment <2003OBC395>.

1.08.2.1.5 Miscellaneous three-membered phosphorus heterocycles

A theoretical investigation (atoms-in-molecules (AIM), <1991CRV893> and electron localization function (ELF) analysis together with nuclear magnetic resonance (NMR) chemical shifts) has been performed for phosphirane and 1*H*-phosphirene oxides, which demonstrates an aromatic stabilization for the unsaturated P-ring of 74.9 kJ mol⁻¹ (G2 level) <2000JOC8574>. Furthermore, the Meisenheimer rearrangement of these phosphorus heterocycles yielding *P*-hydroxy phosphiranes or phosphirenes, respectively, has been conducted at the B3LYP/6-311G^{*} level of theory by the corresponding AIM and ELF analysis (Scheme 3). The rearrangements proceed exothermically with high $\Delta H^\ddagger$ values. The presence of the C=C bond does not appreciably change the reaction profile.



Scheme 3

The photochemistry of transition carbonyl complexes of chromium or iron with phosphirane or 1*H*-phosphirene ligands is studied with time-dependent DFT theory to explore the propensity of the excited metal–phosphine–carbonyl complexes to expel their ligands [<2003JA3558>](#). The complexes of these phosphorus heterocycles show similar behavior as carbonyl complexes with the PH_3 ligand and they differ mainly in their enhanced σ -donating ability. The calculations point that the excited complexes prefer the expulsion of the phosphorus substituents, which can be an alternative method to demetallate transition metal complexes of organophosphorus compounds.

1.08.2.2 Structural Data

A listing of most structural data of phosphorus three-membered ring systems has been published [<1990CRV997, 1996CHEC-II\(1A\)277, B-2001MI17>](#). In addition, some representative, selected structural data are now collected in [Tables 1\(a\) and 1\(b\)](#). These new data are mostly calculated by *ab initio* methods for the body structures.

Table 1(a) Selected structural parameters of representative three-membered phosphorus heterocycles; bond angles ($^\circ$)

<i>P-Heterocycles</i>	<i>Bond angles</i> ($^\circ$)		<i>Method</i>	<i>Reference</i>
 lp = lone pair	46.7 (C–P–C)	126.5 (H–P–lp)	DFT	2000PCA11644
	46.6 (C–P–C)	66.7 (P–C–C)	DFT MP2/6-31G* DFT	1999JA11650 2002JOC2485 2000JOC8574
	46.3 (C–P–C)	68.9/64.9 (P–C–C)	DFT MP2/6-31G*	1999JA11650 2002JOC2485
	46.1 (C–P–C)	66.9 (P–C–C)	DFT MP2/6-31G*	1999JA11650 2002JOC2485

(Continued)

Table 1(a) (Continued)

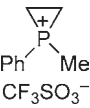
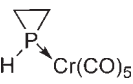
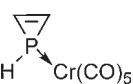
<i>P-Heterocycles</i>	<i>Bond angles (°)</i>		<i>Method</i>	<i>Reference</i>
	117.4 (H–P–O)		DFT	2000JOC8574
	113.7 (H–P–O)		DFT	2000JOC8574
	51.7	117.6–118.8 (C–P–Me) 119.1 (C–P–Ph) 64.0–64.3 (P–C–C)	X-Ray	1995CC257

Table 1(b) Selected structural parameters of representative three-membered phosphorus heterocycles; bond lengths (Å)

<i>P-Heterocycles</i>	<i>Bond lengths (Å)</i>			<i>Method</i>	<i>Reference</i>
 lp = lone pair	1.472 (P–H) 1.092 (P–lp)			DFT	2000PCA11644
	1.886 (C–P) 1.886 (C–P) 1.880 (C–P)	1.493 (C–C) 1.488 (C–C) 1.490 (C–C)	1.420 (P–H)	DFT MP2/6-31G* DFT	1999JA11650 2002JOC2485 2000JOC8574
	1.849/1.905 (C–P) 1.830/1.889 (C–P)	1.475 (C–C) 1.469 (C–C)		DFT MP2/6-31G*	1999JA11650 2002JOC2485
	1.886 (C–P) 1.850 (C–P)	1.461 (C–C) 1.452 (C–C)		DFT MP2/6-31G*	1999JA11650 2002JOC2485
	1.863 (C–P)	1.518 (C–C)	2.357 (P–[Cr])	DFT	2003JA3558
	1.796 (C–P)	1.570 (C–C)	1.411 (P–H) 1.491 (P–O)	DFT	2000JOC8574
	1.854 (C–P)	1.292 (C–C)	1.444 (P–H)	DFT	2000JOC8574
	1.832 (C–P)	1.314 (C–C)	2.341 (P–[Cr])	DFT	2003JA3558

(Continued)

Table 1(b) (Continued)

<i>P-Heterocycles</i>	<i>Bond lengths (Å)</i>			<i>Method</i>	<i>Reference</i>
	1.761 (C–P)	1.336 (C–C)	1.409 (P–H) 1.486 (P–O)	DFT	2000JOC8574
	1.756/1.761 (C–P)	1.533 (C–C)	1.779 (C–Me) 1.763 (C–Ph)	X-Ray	1995CC257

Typically the C–P–C intracyclic angle of phosphirane and its uncomplexed derivatives amounts mostly in the range of 46–47°. The C–P bond lengths range from 1.830 to 1.886 Å whereas the C–C bonds vary from 1.488 to 1.466 Å, reflecting the influence of the substitution pattern. Worthy of mention is that the complexed phosphirane has an explicitly lengthened C–C bond length in comparison to the uncomplexed phosphirane, which is also true in the case of the phosphirane oxide. The same tendency is determined in the phosphirene case.

1.08.2.3 Spectroscopic Data

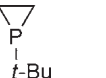
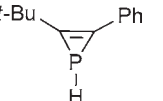
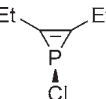
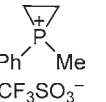
Some recent, selected ^1H , ^{13}C , and ^{31}P NMR data on three-membered phosphorus heterocycles are collected in **Tables 2(a)** and **2(b)**.

Computed (GIAO/B3LYP/6-311+GDP) $\delta^{31}\text{P}$ shifts of phosphiranes **1**, substituted at position 2, display a remarkable dependency on the conformation of the C–R group (GIAO = gauge-independent atomic orbital). For the parent compound (R = H), the calculated value of –307 is upfield compared with the experimental one of –341 ppm. With respect to the unsubstituted phosphirane, all other derivatives have $\delta^{31}\text{P}$ ppm shifts at lower fields <2001JOC5671>. Worthy of mention is that the $\delta^{31}\text{P}$ ppm shifts of –167 and –110 which were reported for the $[\text{W}(\text{CO})_5]$ -complexed phosphiranes (R = Cl, Br; Ph instead of H) <1995SL353, 2000JOC652> differ by 100–150 ppm from the calculated values by the GIAO method.

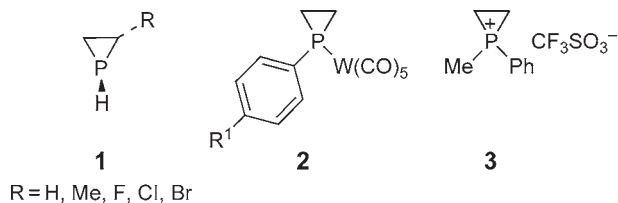
Table 2(a) Selected NMR spectroscopic data of representative three-membered phosphorus heterocycles; ^1H NMR and ^{31}P NMR

<i>P-Heterocycles</i>	^1H NMR ^a	^{31}P NMR ^a	<i>Reference</i>
	0.45, 0.6 (–CH ₂) 0.72 (H- <i>t</i> -Bu)	–206	1997OM1526
	1.38 (H- <i>t</i> -Bu) 1.54 ($^1J_{\text{P,C}} = 107.0$ Hz) (PH)	–247.1 ($^1J_{\text{P,C}} = 107.0$ Hz)	1997MI711
	1.32, 2.79 (H–Et)	–60.7	1995S941
	2.45 (Me) 2.36–2.57 (–CH ₂)	–96.8	1997JOM(529)189

^a δ (ppm) from TMS or 85% H_3PO_4 . Values in parentheses are couplings to ^{31}P or ^{13}C in Hz.

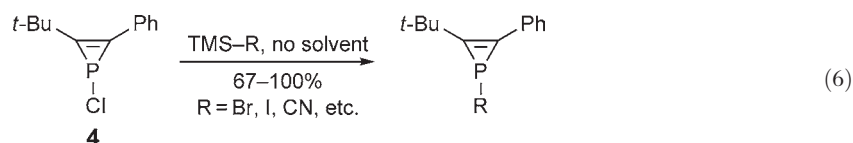
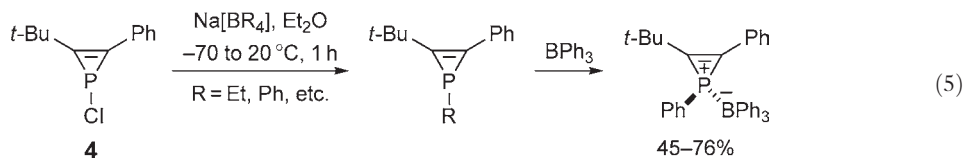
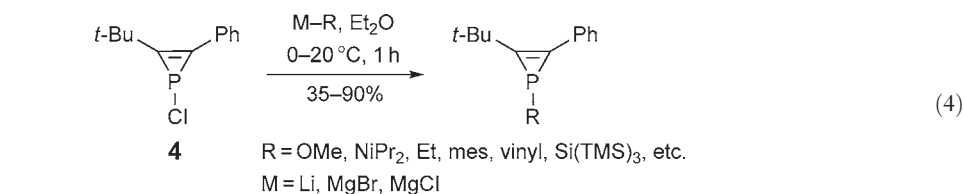
<i>P-Heterocycles</i>	^{13}C NMR ^a	<i>Reference</i>
	2.7 (–CH ₂)	1997OM1526
	108.1, 126.8 ($^1J_{\text{P,C}} = 68.0, 39.2, 45.6$ Hz) (=C)	1997MI711
	12.15, 20.49 (C–Et) 141.00 ($^1J_{\text{P,C}} = 68.0$ Hz) (=C)	1995S941
	3.10 (C–Me) 2.36–2.57 (–CH ₂)	1997JOM(529)189

Study of the correlation between and the Hammett σ -constant of the *para*-substituents ($R^1 = \text{OMe, Me, H, F, Cl, Br}$) of the 1-aryl-phosphirane complexes **2** has also been done and shows a significant positive slope, suggesting a strong electronic effect of the remote Ar group on the positive phosphorus [<1995JOM\(489\)1>](#). Phosphiranium cations experience a downfield shift in comparison to the phosphirane ring system because of the intrinsic positive charge; so for instance 1-methyl-1-phenylphosphiranium trifluoromethylsulfonate **3** shows a $\delta^{31}\text{P}$ ppm shift of -97 which is shifted to 137 ppm downfield compared to 1-phenylphosphirane (**1**: $R = \text{H}$) [<1995CC257>](#).

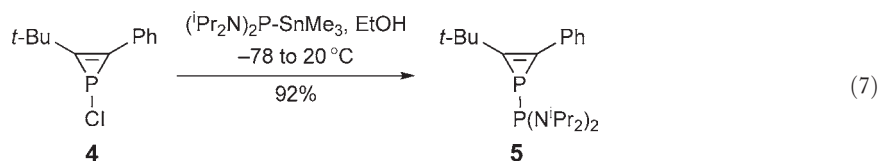


1.08.3.1 Reactions at Phosphorus Atom with Retention of the Three-Membered Ring

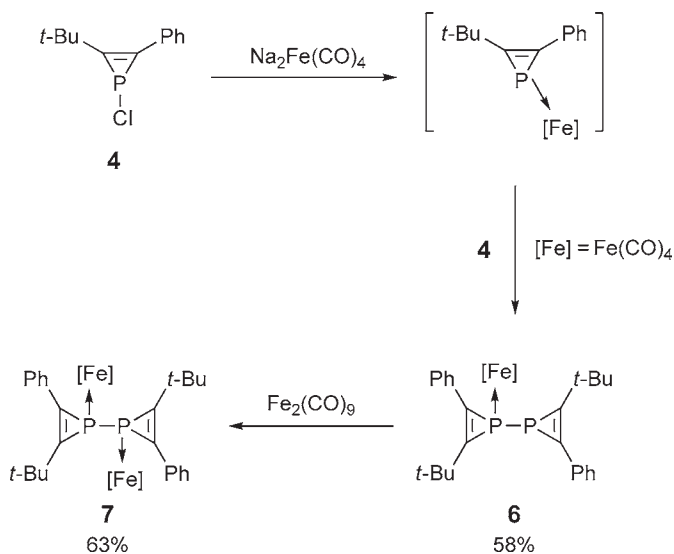




The reaction of **4** with a stannylphosphine affords the phosphirene **5** with a phosphorus substituent at the ring phosphorus atom (Equation 7) <1999CEJ274>.



The reaction of 1-chloro-1*H*-phosphirane **4** with disodium tetracarbonylferrate leads to selective formation of monocomplexed bi-1*H*-phosphirene **6**, which is converted into the doubly complexed species **7** upon treatment with diiron nonacarbonyl (Scheme 4) <2001EJI2067>.

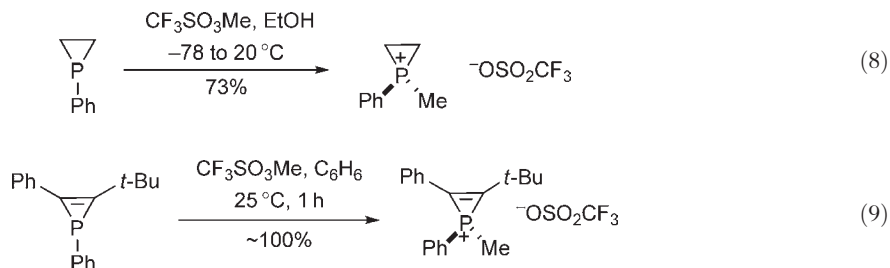


Scheme 4

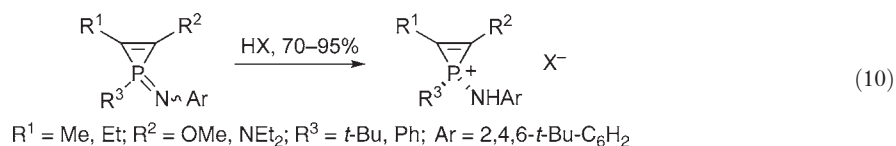
Stable η^1 -1*H*-phosphirane and η^1 -1*H*-phosphirene metal complexes are known, especially carbonyl complexes of Cr, W, and Fe. Most of them are obtained by reaction of phosphinidenes stabilized by the corresponding metal fragment with alkenes ($\rightarrow$ phosphirane complexes) or alkynes ($\rightarrow$ phosphirene complexes); see discussion in Section 1.08.4.1. In general,

η^1 -1*H*-phosphirane and η^1 -1*H*-phosphirene metal complexes serve as precursors for the preparation of phosphiranes and phosphirenes by decomplexation methods, for example, with 1,2-bis(diphenylphosphino)-ethane <1995S941>. However, the reverse route, namely the complexation of phosphiranes or phosphirenes with metal fragments, is also possible. Thus η^1 -coordination is achieved without problems when group 6 metals are used; for new examples, see <1996OM1301> and <1997OM1526>. In contrast, electron rich metals tend to insert into the C–P bond with incorporation of the transition metal. The new polycyclic phosphirane BABAR-Phos <1999AGE1623> on the other hand allows the synthesis of fairly stable Rh(I) and Pt(0) complexes <2003OM2202>, which are active hydrosilylation <2000T143> and hydroboration catalysts <2000AGE2479>.

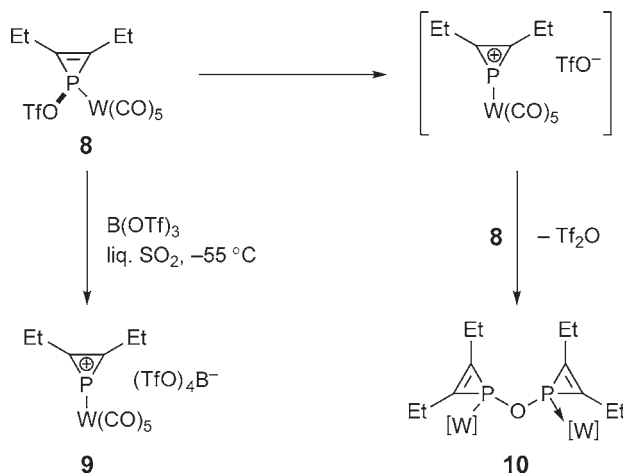
Alkyl triflates are strong alkylation reagents and are able to alkylate phosphiranes and phosphirenes, respectively, to form phosphiranium or phosphirenium triflates; examples are shown in Equation (8) <1997JOM(529)189> and Equation (9) <1998S175>.



λ^5 -1*H*-Phosphirene imides prepared by [2+1] cycloaddition of iminophosphines with alkynes can be protonated with hydrohalic acids to afford phosphirenium halides bearing an amino substituent on the phosphirene phosphorus (Equation 10) <1995ZOR400>.



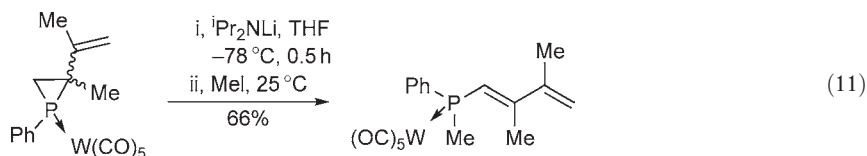
Phosphirenium cations have been postulated as intermediates in numerous reactions of 1-chlorophosphirenes including phosphirene complexes. Recently, the uncomplexed cation has been generated in the gas phase from **4** upon 70 eV electron ionization and its reactivity toward representative nucleophiles and dienes has been studied by pentaquadrupole mass spectrometry <2003OBC395>. The first complex of a phosphirenium cation **9** was prepared from **8** according to Scheme 5. The phosphirene complex **8** is rather unstable in neat or in solution and decomposes with the formation of the bisphosphirenyl ether **10** <1999OM817>.



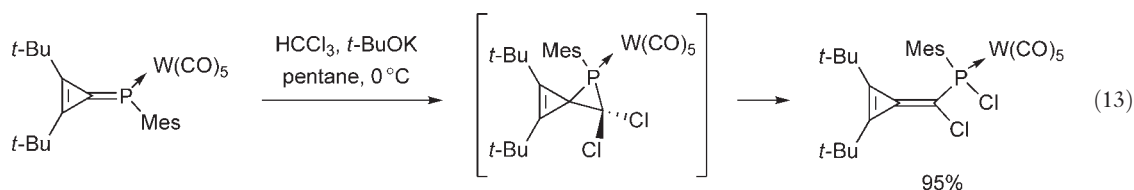
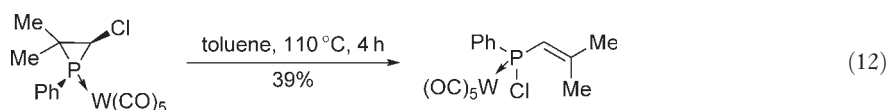
Scheme 5

1.08.3.2 Reactions with Cleavage of One Carbon–Phosphorus Bond

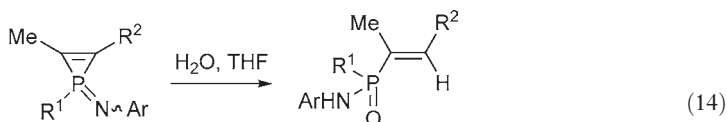
The P–C bonds of the phosphirane ring are high in energy and polarized in the sense of positive partial charge at phosphorus and negative partial charge at carbon according to theoretical calculations leading to ring-opened products by nucleophilic (basic) or electrophilic attack either at carbon or phosphorus [<1996CHEC-II\(1A\)277>](#). Some new results in this field are depicted in this context. The metalation of a complexed 2-vinylphosphirane yields a 1-phosphapentadienyl complex via ring opening of the P–C(2) bond (Equation 11) [<1995OM4048>](#).



Complexed 2-halophosphiranes cleanly rearrange thermally ($\sim 110^\circ\text{C}$) to complexed halo(vinyl)phosphines in, presumably, a concerted ring opening and migration of the halo substituent from carbon to phosphorus (Equation 12) [<1995SL353, 2000JOC652>](#); see also [<2001JOC5671>](#) for a theoretical background. This rearrangement proceeds much easier in the case of a phosphaspiropentene which cannot be isolated by the addition of dichlorocarbene to a phosphatetrafulvene (Equation 13) [<2005OM5172>](#). The calculated barrier of 77.4 kJ mol^{-1} is consistent with a reaction temperature of -40°C .



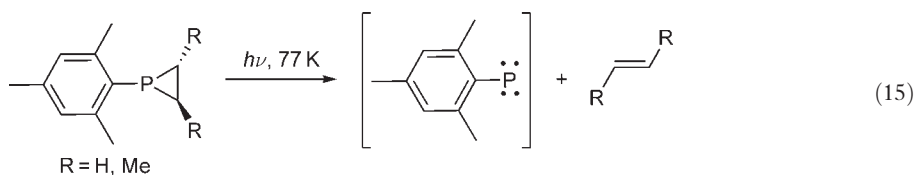
Ring opening is also dominant in the chemistry of the phosphiranium [<1995CC257, 1997JOM\(529\)189>](#) and phosphirenium cations [<1998S175>](#) which yield open-chained phosphine oxide derivatives. In fact, this reaction is so easy that the salts must be handled and kept under argon and in extremely dry solvents to prevent hydrolysis. The same type of reaction has been observed for the hydrolysis of phosphirene imines (Equation 14) [<1995ZOR400, 1995ZOR404>](#).



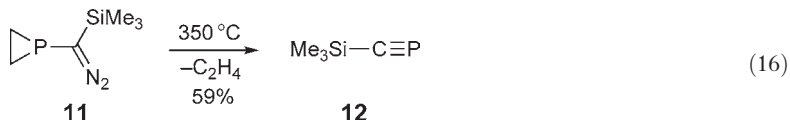
$\text{R}^1 = t\text{-Bu, Ph}$; $\text{R}^2 = \text{OMe, NEt}_2$; $\text{Ar} = 2,4,6\text{-}t\text{-Bu-C}_6\text{H}_2$;
yields are mostly quantitative

1.08.3.3 Reactions with Cleavage of Two Carbon–Phosphorus Bonds

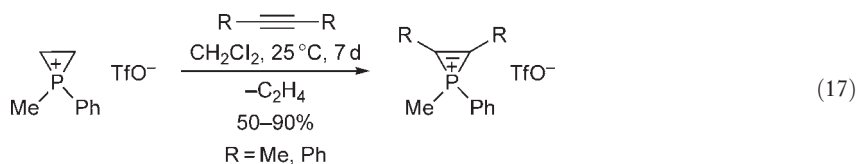
The pioneering work of Gaspar on the thermal and photolytic decomposition of 1-mesitylphosphirane yielded arguments for the formation of mesitylphosphinidene with cleavage of two C–P bonds (Equation 15) [<1994JA7899>](#). The existence of triplet phosphinidene was demonstrated by means of photolysis in a cyclohexane matrix at 77 K and electron spin resonance (ESR) monitoring. Recently, triplet phosphinidene was unequivocally identified by using a variety of low-temperature spectroscopic techniques such as infrared (IR), ultraviolet/visible (UV/Vis), and W-band electron paramagnetic resonance (EPR) spectroscopy [<2005AGE3289>](#). Additional data on the photolysis of bulky 1-arylphosphiranes yielding phosphinidenes are available [<1998HAC607>](#).



The flash thermolysis of 1-[diazotrimethylsilyl]methyl]phosphirane **11** at 350 °C led to [(trimethylsilyl)methylidyne]phosphine **12** in 59% yield (Equation 16) <1996OM4904>; see also Equation (1).

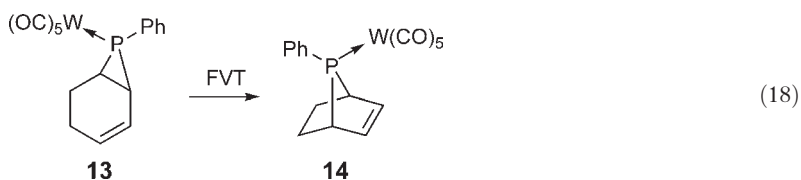


An exchange process has been observed between phosphiranium salts and alkynes. The reaction proceeds by a formal transfer of the methylphenylphosphonium cation from ethane to the alkyne (Equation 17) <1997JOM(529)189>. A theoretical discussion on this transfer reaction is given in Section 1.08.2.1.3.

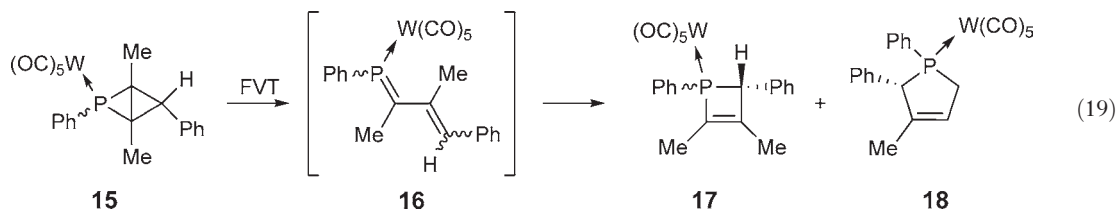


1.08.3.4 Reactions under Enlargement of the Three-Membered Ring

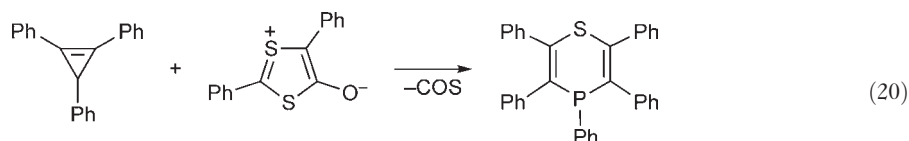
The ring expansion of phosphiranes and phosphirenes can occur via internal reorganization or insertion reactions. Often, the synthesis of these compounds is followed by a rearrangement of the first formed products. Two new findings concerning the phosphirane series are depicted in Equations (18) <1996JA1690> and (19) <2005AGE6579>. The cycloadducts of a tungsten phosphinidene complex (see Section 1.08.4.1) with 1,3-cyclohexadiene, 1,3-cycloheptadiene, and 1,3-cyclooctadiene are formed as isomeric mixtures of *syn*- and *anti*-vinylphosphiranes. Only the *syn*-vinylphosphirane complex of cyclohexa-1,3-diene **13** rearranges under [1,3]-migration to yield a phosphabicyclo[2.2.1]hept-2-ene system **14**, whereas in other cases an *anti*-*syn*-isomerization occurs. The mechanism of this rearrangement – biradical or concerted – is discussed (Equation 18).



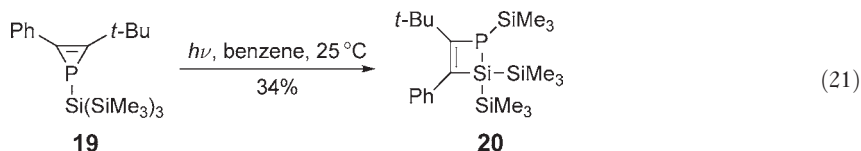
exo-2-Phosphabicyclo[1.1.0]butane complex **15** undergoes a valence isomerization to give the *cis*- and *trans*-1,2-dihydrophosphete complex **17** besides the 2,5-dihydro-1*H*-phosphole complex **18** (Equation 19) <2005AGE6579>. Accompanying calculations imply that the 1-phosphabuta-1,3-diene complex **16** is the reaction intermediate and that a 2-vinyl-phosphirane complex is involved. The formation of phospholene complexes from appropriate substituted 2-vinyl-phosphirane complexes is established <2002JA13903>.



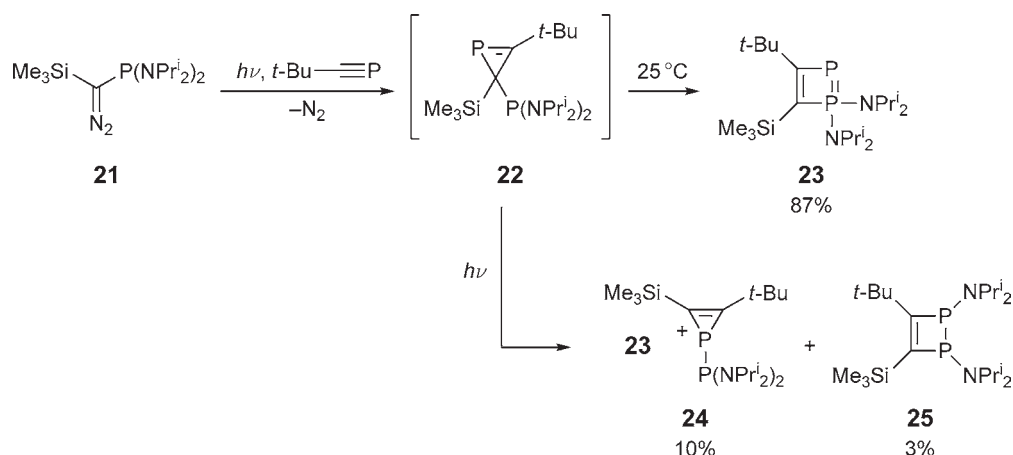
Interestingly, phosphirenes can act as dipolarophiles in 1,3-dipolar cycloaddition reactions. The mesoionic dithioliumolate yields a 4*H*-1,4-thiaphosphinine with 1,2,3-triphenylphosphirene via the primary cycloadduct (Equation 20) <1995H(40)311>.



Photolysis of the silyl-substituted phosphirene **19** proceeds selectively with cleavage of silicon–silicon bond and ring expansion to furnish the 1,2-dihydro-1,2-phosphasilete **20** (Equation 21) <1999CEJ1581>. The corresponding 1,2-dihydro1,2-phosphagermete is prepared analogously.

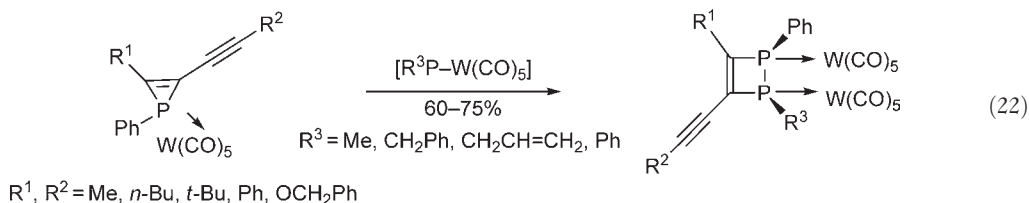


Finally, a rearrangement in the chemistry of 2*H*-phosphirenes is worth mentioning. Photolysis of the diazo compound **21** in the presence of (2,2-dimethylpropylidene)phosphine affords the diphosphete **23** as the major product via 2*H*-phosphirene **22** which is thermally unstable and quantitatively rearrange to **23**. Photolysis of **22** produces, besides **23**, the 1*H*-phosphirene **24** and the 1,2-dihydrodiphosphete **25** (Scheme 6) <1995JA10785, 1999CEJ274>.

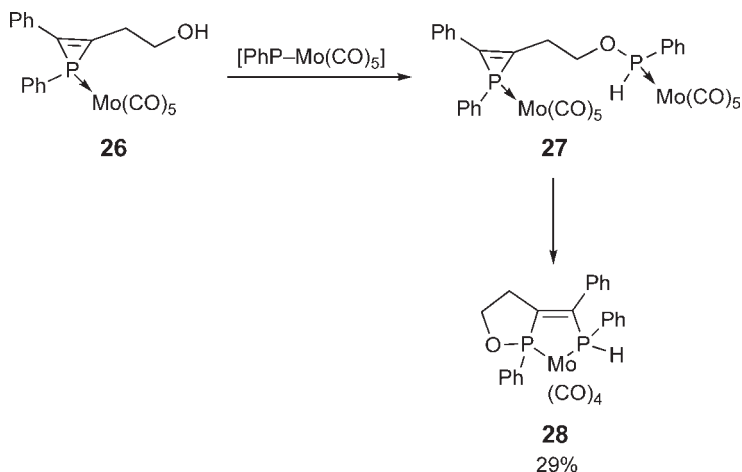


Scheme 6

An example for the above-mentioned insertion reactions for enlargement of three-membered phosphorus heterocycles is the intercalation of terminal phosphinidene complexes in the conjunctively destabilized P–C(2) bond of 2-alkynylphosphirene complexes (Equation 22) <1997OM4501, 1999OM796>. An intramolecular version of the same reaction which does not required the destabilizing alkynyl substituent has also been described <1999JOM(582)53>.



The phosphirene complex **26**, as generated from a terminal phosphinidene complex and 4-phenylbut-3-yn-1-ol, reacts with a second molecule of the phosphinidene complex giving an intermediate phosphirene **27** with additional secondary alkoxyphosphine functionality. An intramolecular hydrophosphination yields then the complex **28** as a mixture of two diastereomers (Scheme 7) <2005OM696>.

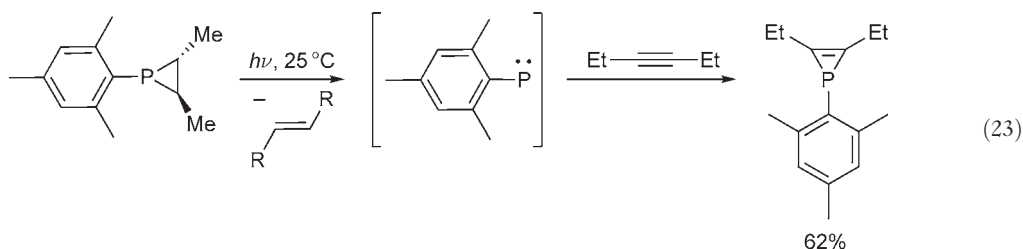


Scheme 7

1.08.4 Synthesis of Phosphiranes and Phosphirenes

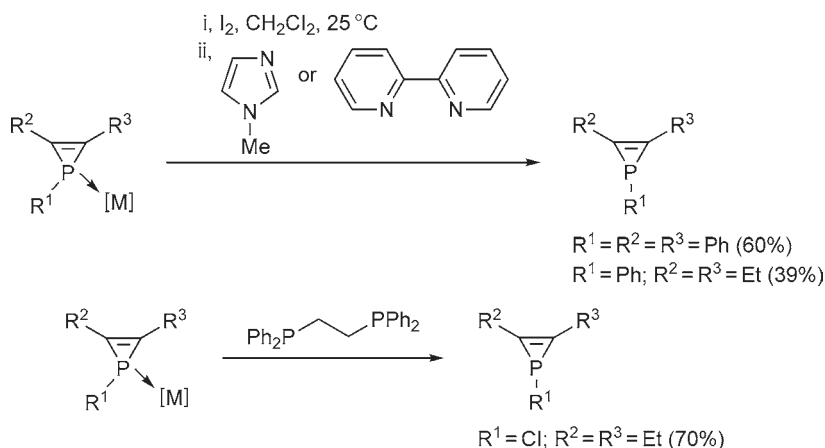
1.08.4.1 By Formation of Two P–C Bonds

The synthesis of phosphiranes or phosphirenes by the linkage of two P–C bonds requires a phosphorus fragment that can react with alkenes or alkynes in a [2+1] cycloaddition process. Phosphinidenes should logically serve as suitable building blocks, but their use is, however, strictly limited since their reaction behavior is dominated by oligomerization and polymerization reactions. An exception is the generation of mesitylphosphinidene by means of photolysis of 1-mesityl-1*H*-phosphirane in presence of hex-3-yne which furnishes 2,3-diethyl-1-mesityl-1*H*-phosphirene (Equation 23) <1992JA8526, 1994JA7899>; see also Equation (15).

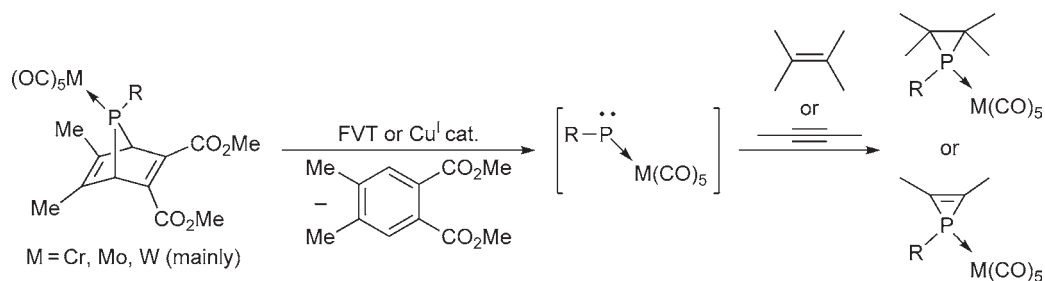


Phosphinidene complexes may be considered as synthetic equivalents; however, they have the disadvantage that the first formed phosphirane or phosphirene complexes must be transformed in an additional step to the desired uncomplexed phosphorus heterocycles. The complexed phosphiranes and phosphirenes can be easily decomplexed by several methods; Scheme 8 gives an overview <1996CHEC-II(I)297, 1995S941, 1997JA8432>. Initially halogenation, for example, with I₂, followed by displacement of the metal fragment by *N*-methylimidazole or 2,2'-biphenyl or decomplexation with 1,2-bis(diphenylphosphino)ethane, can be performed.

As mentioned above, phosphinidene complexes can play an outstanding role in the synthesis of phosphiranes and phosphirenes. They possess a singlet ground state which is reflected in their stereospecific cycloaddition reactions with alkenes and they possess an electrophilic character and react therefore especially readily with electron-rich alkenes or alkynes. Several starting compounds are available for the generation of phosphinidene complexes, among which the 7-phosphanorbornadiene complex and some derivatives play a major role (Scheme 9). The release of the phosphinidene fragment can be achieved either thermally or more gently with the aid of copper(I) catalysis. A theoretical investigation for the latter process is performed by Lammertsma *et al.* The calculations (DFT) give evidence for a solvent-aided catalytic mechanism <2003JA14750>.



Scheme 8



Scheme 9

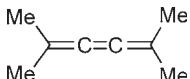
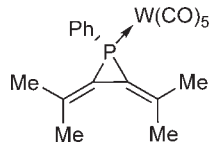
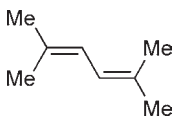
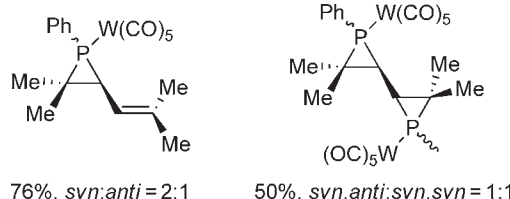
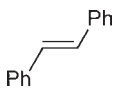
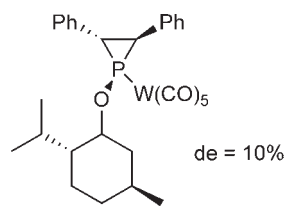
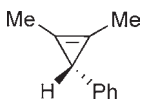
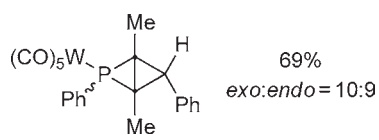
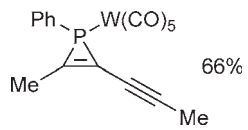
Many alkenes and alkynes as well as many substituents at phosphorus including alkoxy and amino groups have been successfully used in this cycloaddition process. [Table 3](#) gives a survey of newly synthesized phosphiranes and phosphirenes according to this method.

Table 3 Phosphirane and phosphirene complexes by cycloaddition reactions of terminal phosphinidene complexes with either alkenes or alkynes

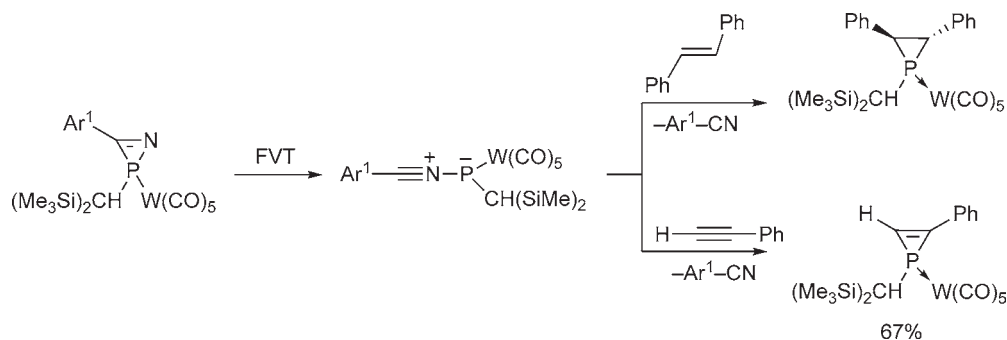
Alkene or alkyne	Phosphirane or phosphirene	Reference
	13% $\text{W}(\text{CO})_5$, Ph, Me, Cl, H	2000JOC652
	60% $\text{syn:anti} = 4:1$, $(\text{OC})_5\text{W}$, Ph	1996JA1690
	70% $\text{W}(\text{CO})_5$, Ph	1999JA11650

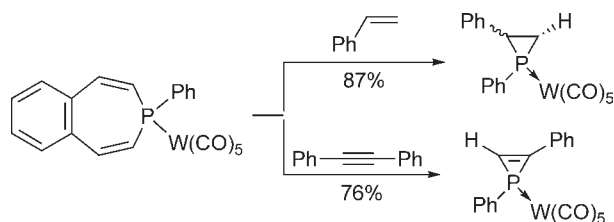
(Continued)

Table 3 (Continued)

Alkene or alkyne	Phosphirane or phosphirene	Reference
	 70%	2000JA12507
	 76%, <i>syn:anti</i> = 2:1 50%, <i>syn:anti:syn:syn</i> = 1:1	2000AGE2943
	 de = 10%	2002EJI1657
	 69% <i>exo:endo</i> = 10:9	2005AGE6579
	 66%	1999OM796

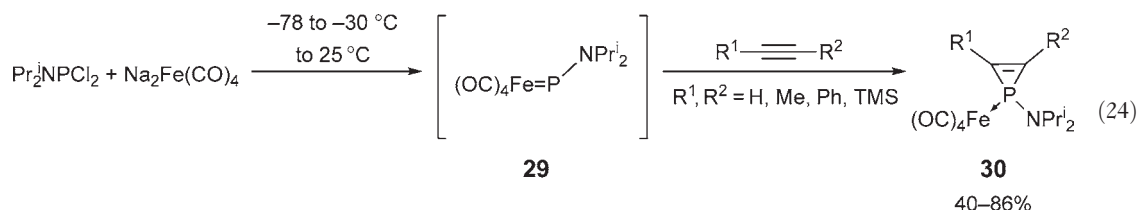
Besides the 7-phosphanorbornadiene complex, azaphosphirene complexes (**Scheme 10**) <1997AGE1492, 1997ZFA1897, 1999EJI1567, 1999OM5627, 1999ZFA102, 2001ZFA1135> and phosphepine complexes (**Scheme 11**) <2005JA5800> can serve as precursors for the generation of phosphiranes or phosphirenes, usually in complexed form.

**Scheme 10**

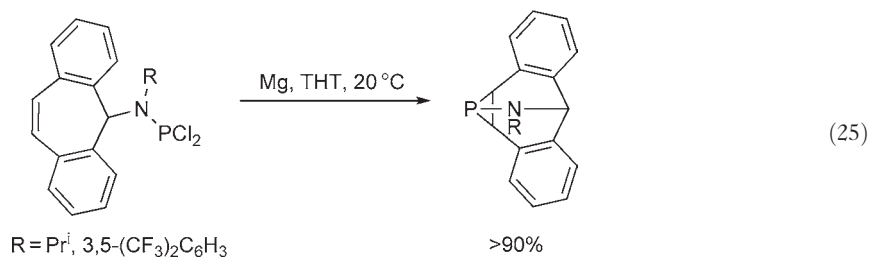


Scheme 11

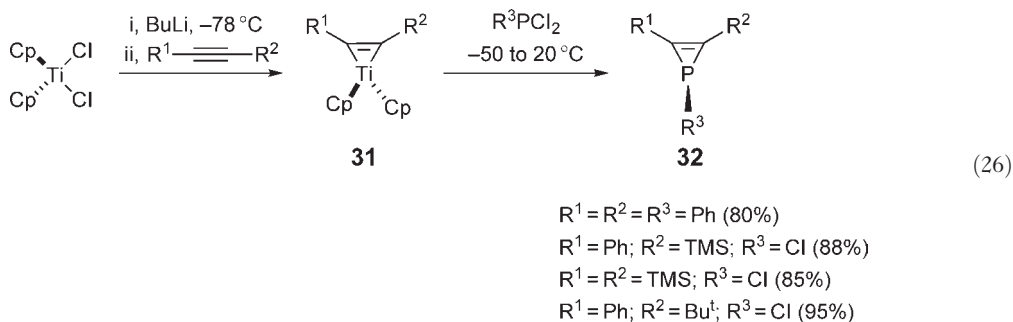
The electrophilic phosphinidene complex **29** can be generated *in situ* by the reaction of dichloro(diisopropylamino)phosphine with Collman's reagent. By trapping reactions with various alkynes, amine-substituted phosphirene complexes **30** are accessible (Equation 24) <2000T137>.

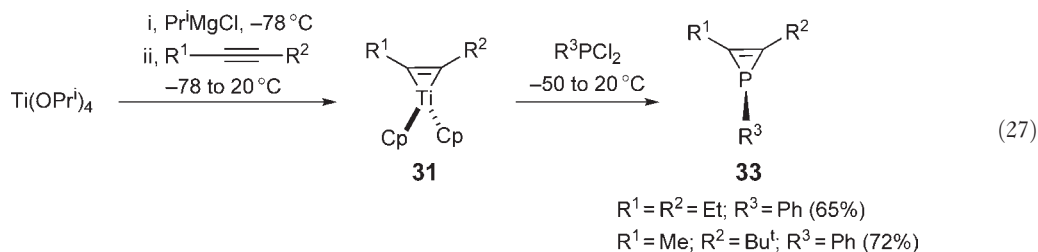


Very stable polycyclic phosphiranes were obtained by an intramolecular cycloaddition reaction of aminodichlorophosphines with the C–C double bond of 5*H*-dibenzo[*a,d*][7]annulene (dibenzocycloheptene) under the influence of Mg-turnings. Formally, these compounds are formed by an intramolecular [2+1] cycloaddition of an $\text{R}_2\text{N-P}$ phosphinidene unit to the C–C double bond of the central seven-membered ring. In analogy to the hydrocarbon ‘barbalan’ the amino compound is named BARBAR-Phos <1999AGE1623>. In a comparable reaction sequence, dibenzophosphasemibullvalene was obtained (Equation 25) <2003AGE3955>.

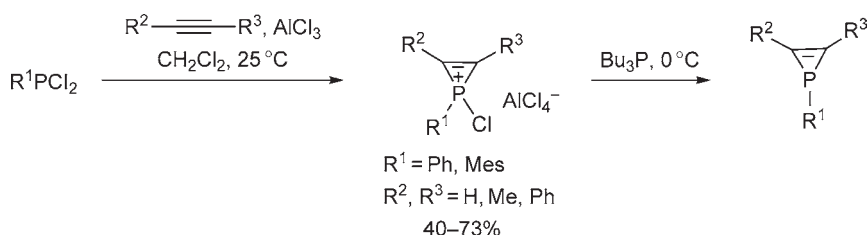


Titanacyclopropenes **31** reacts smoothly with dichlorophosphines or phosphorus trichloride with extrusion of the titanium fragment and formation of the phosphirenes **32** or **33**, respectively. The transition metal complexes themselves are generated *in situ* from either a dichlorotitanium complex (Equation 26) or tetraisopropoxytitanium (Equation 27) by reactions with alkynes <1998OM2677>. Analogous chemistry can be carried out with zirconacyclopropenes <1998CC1177>.



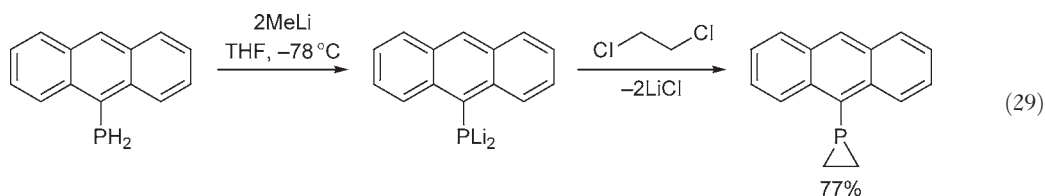
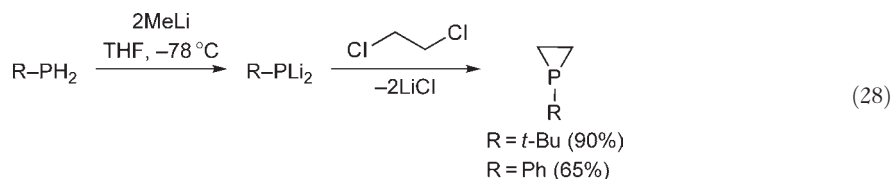


Another approach to the synthesis of phosphirenes by formation of two P–C bonds involves the electrophilic addition of halo- and dihalophosphine–AlCl₃ complexes with alkynes, yielding phosphirenium salts. In some cases, the use of thallium(I) triflate instead of AlCl₃ improves the method [<1997JOM\(529\)189>](#). In the normal case, the chlorophosphirenium salts are not isolated but rather immediately reduced with tributylphosphine to furnish the phosphirenes (**Scheme 12**) [<1996OM1597>](#).

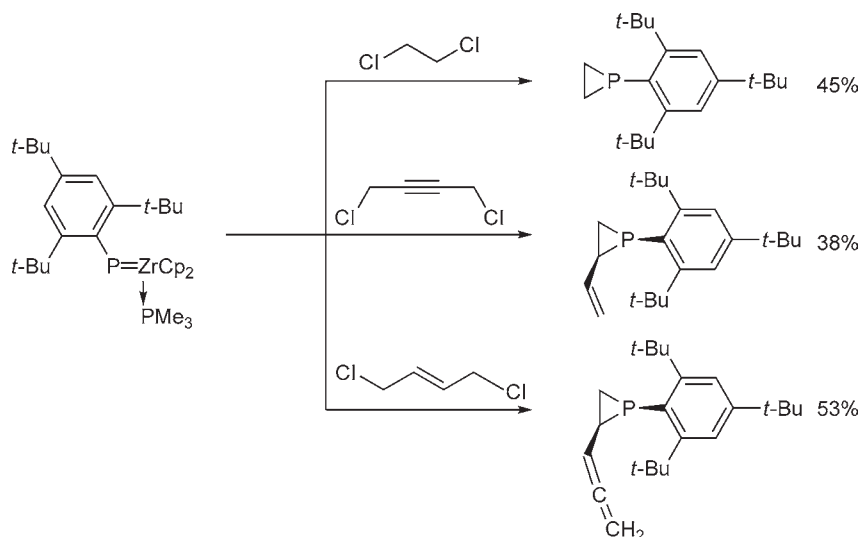


Scheme 12

The original synthesis of phosphiranes by Wagner *et al.* [<1967JA1102>](#) belongs to the category of the formation of two P–C bonds. The phosphorus component consists of a dimetalated phosphine which is allowed to react with a 1,2-dihaloethane derivative. Newer results for this method are represented in [Equations \(28\) <1996OM1301, 1997OM1526>](#) and (29) [<1999OM4222>](#).



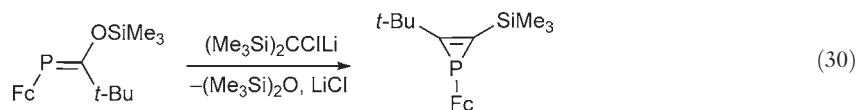
Related chemistry involves the reaction of a nucleophilic zirconocene–phosphinidine complex with 1,2-dichloroethane and related compounds (**Scheme 13**) [<1995JA11914>](#).



Scheme 13

1.08.4.2 By Formation of One P–C Bond and One C–C Bond

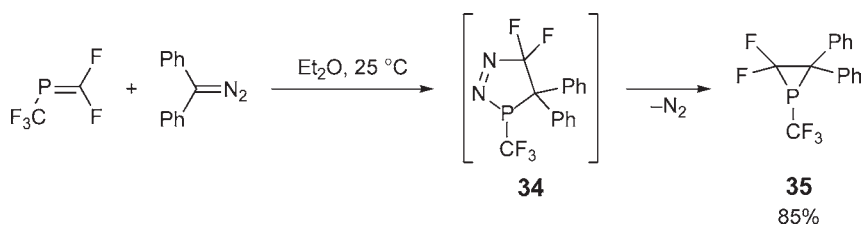
The availability of phosphaaalkenes and phosphaaalkynes has led to a further route for the synthesis of phosphiranes and phosphirenes by the formal addition of carbenes or carbenoids to P–C multiple bonds. An example already depicted in [Scheme 6](#) involved in the [2+1] cycloaddition reaction of a stable phosphinotrimethylsilylcarbene to *tert*-butylphosphaaalkyne [\[1995JA10785, 1999CEJ274\]](#). A carbenoid was also used in the synthesis of an unusual phosphirene from a siloxy-substituted phosphaaalkene ([Equation 30](#)) [\[1997JOM\(529\)127\]](#).



1.08.4.3 By Formation of One P–C Bond

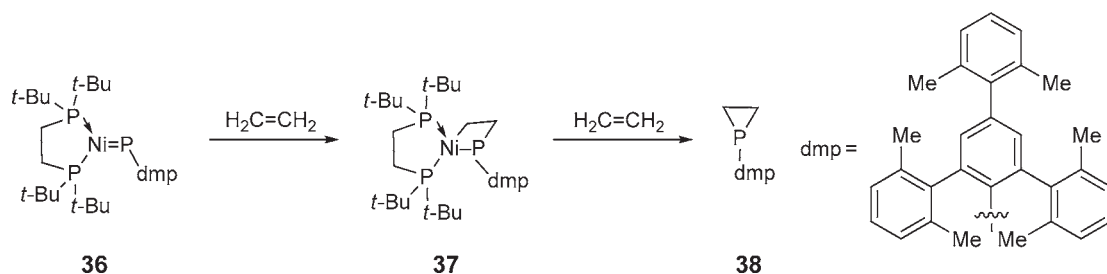
As shown in [Equation \(28\)](#), the synthesis of phosphiranes involves an intermediate secondary 2-chloroalkylphosphine. A preformed phosphine unit with a leaving group in the β -position is thus a potential phosphirane precursor [\[1998HAC607\]](#). This technique was optimized and used for the synthesis of chiral phosphiranes from optically pure 1,2-diols [\[1996JOC7702\]](#).

The 4,5-dihydro-3*H*-1,2,3-diazaphosphole **34** produced by a [3+2] cycloaddition reaction of diphenyldiazomethane with a phosphaaalkene is unstable and decomposes by extrusion of N_2 and formation of a new P–C bond yielding the phosphirane **35** ([Scheme 14](#)) [\[2001ZFA1241\]](#).



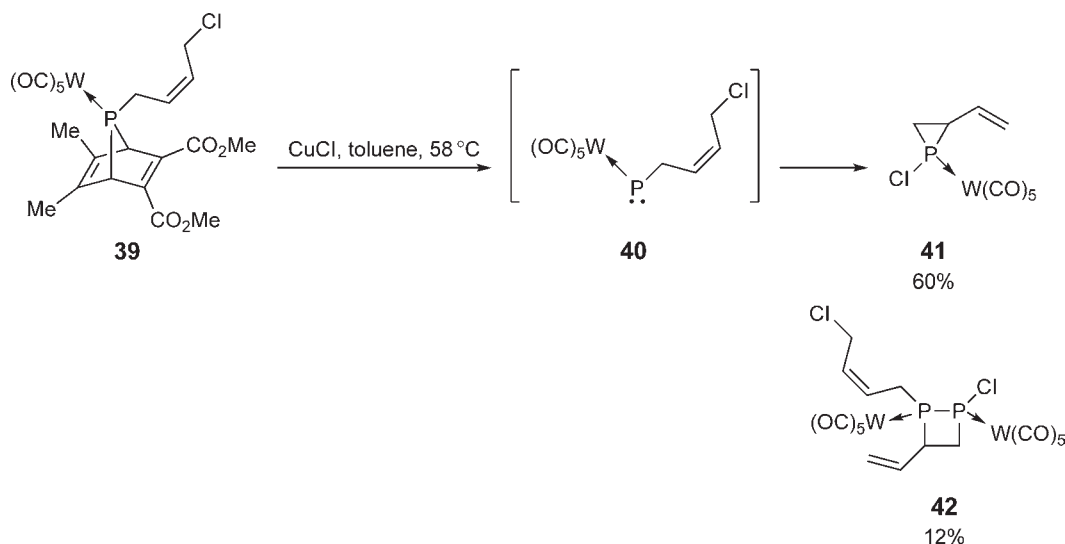
Scheme 14

The phosphinidene complex **36** reacts rapidly with ethylene to give the 2,6-dimesitylphenylphosphirane **38**; by monitoring the reaction at low temperature, an intermediate consistent with structure **37** is observed (Scheme 15) <2003JA13350>.



Scheme 15

Finally, the phosphinidene complex **40**, as generated from the appropriate 1-phosphanorbornadiene complex **39**, readily rearranges to give the 1-chloro-2-vinylphosphirane complex **41** and its formal dimer **42** (Scheme 16) <2005OM2930>.

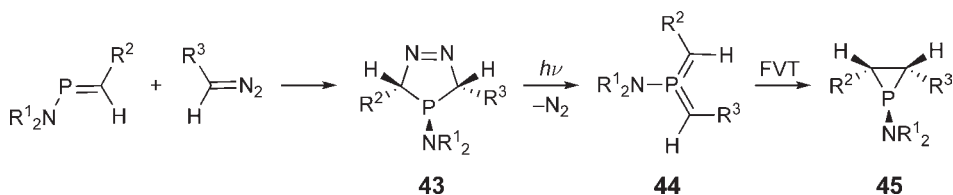


Scheme 16

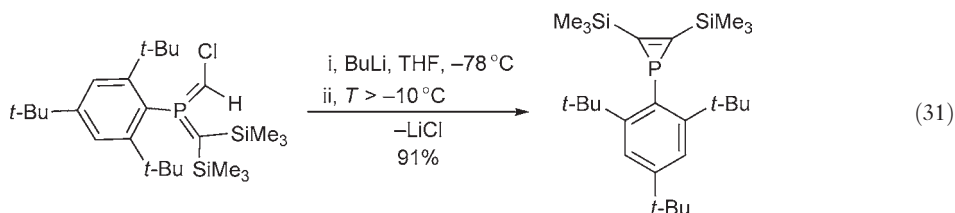
1.08.4.4 By Formation of One C–C Bond

The availability of phosphalkenes led to a second route to phosphiranes with diazoalkanes as cycloaddition partners; compare with Scheme 14. The first formed 4,5-dihydro-3*H*-1,2,4-diazaphospholes **43** decompose under the influence of light and extrusion of nitrogen to form the bis(methylene) phosphoranes **44**, which cyclize in a 4π -electrocyclic closure to the phosphiranes **45** (Scheme 17) <1996CHEC-II(I)298>. For the theoretical background, see Section 1.08.2.1.1, and for analogous reactions see <1995CC25> and <1997CB779>.

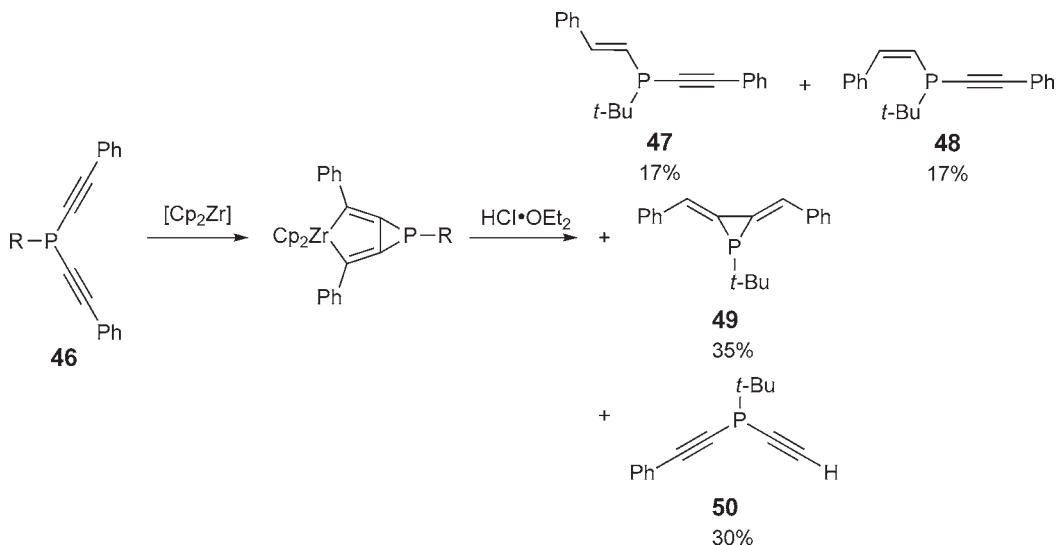
As is obvious from Scheme 17, thermal cyclization of bis-ylides like **44** can lead to the synthesis of phosphiranes or with appropriate substituted ylides to phosphirenes (Equation 31) <1995AGE1849, 1999JA5953, 2002OM4919>.



Scheme 17



Finally, dialkynylphosphines **46** are cleanly transformed into zirconacyclopentadiene phosphiranes when reacted with freshly prepared zirconocene. Addition of $HCl \cdot OEt_2$ to **46** ($R = t-Bu$) leads to a mixture of four products: the alkenyl-alkynyl phosphine **47/48**, the phospharadialene **49**, and the secondary phosphine **50** (Scheme 18) <1997OM3086>.



Scheme 18

1.08.5 The Chemistry of Arsiranes

In the chemistry of the heavier analogues of phosphiranes, no significant new features have been reported since CHEC-II(1996). Worthy of mention is a theoretical study of the rearrangement of arsirane oxides to As-hydroxy arsiranes in analogy to the rearrangement of phosphirane oxides; see Scheme 3 and <2000JOC8574>.

1.08.6 Conclusion

The chemistry of phosphiranes and phosphirenes and their derivatives comprehends theoretical questions, for example, antiaromaticity of phosphirenes, σ^* -aromaticity, reaction behavior like ring opening of vinylphosphiranes, complex building ability, and synthesis strategies. The cycloaddition reactions of transient phosphinidene metal complexes play an outstanding role.

1.08.7 Further Developments

1.08.7.1 Structure Data

High level *ab initio* calculations have been applied to estimate the ring strain energies of three-membered heterocycles, amongst other phosphorus three-membered heterocycles are included <2006JA4598>.

1.08.7.2 Reactivity

Alkylidenephosphiranes are able to undergo [3+2]-cycloaddition reactions with norbornene or dimethyl acetylenedicarboxylates <2007OM3614>. Anti-W(CO)₅-complexed 9-methyl-9-phosphabicyclo[6.1.0]nonatriene represents a covalently interlocked molecular bevel gear <2006JA128>. A stained phosphirene undergoes anionic ring opening polymerization upon initiation with *n*-butyllithium, to yield polyvinylphosphine, an unsaturated organophosphorus polymer <2006CC3332>.

1.08.7.3 Synthesis

2-Azaphosphirene complexes of W or Mo react with acetylenedicarboxylates yielding phosphirane complexes incorporated into cage compounds <2007OM1371>. Mo(CO)₄PMe₃-complexed phosphiranes and phosphirenes are smoothly decomplexed under mild CO-pressure <2006OM5286>. A further study deals with the intramolecular phosphinidene addition to the C=C bond of Mo complexed, seven-membered phosphorus heterocycles to afford bidentate phosphorus baskets <2006CEJ4333>.

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Biographical Sketch



Heinrich Heydt was born in 1945 at Sulzbach/Saarland and completed his undergraduate studies in chemistry at the Universität des Saarlandes, Saarbrücken, in 1972; he obtained his research diploma from the Universität des Saarlandes, Saarbrücken, under the supervision of Prof. M. Regitz, with a thesis entitled *Über die Reaktivität von Phosphono-Alkyl-Carbenen*. After the diploma in chemistry in 1972, he worked on his dissertation at the Technical University of Kaiserslautern under the supervision of Prof. M. Regitz, with a thesis entitled *Phosphoryl-3H-Pyrazole – Synthese und Reaktionen*, and in July 1976 he obtained Dr. rer. nat in Organic Chemistry. During 1976–77, he did postdoctoral research with Prof. M. Regitz at the TU Kaiserslautern.

He has worked as a senior teacher at the TU Kaiserslautern from September 1977 to April 2006; since May 2006, he is director of academic affairs at the TU Kaiserslautern.

1.09

Three-membered Rings with One Silicon, Germanium, Tin or Lead Atom

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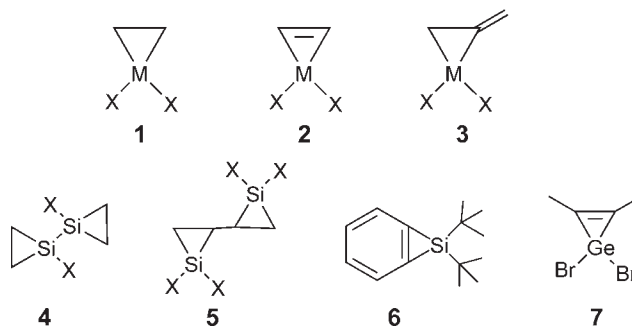
1.09.1 Introduction

1.09.1.1 Scope

Molecules with three rings containing one, two, or three heavier group 14 elements (silicon, germanium, tin, or lead) are challenging synthetic targets for chemists because they have interesting structures and a high reactivity. This chapter reviews the literature published between 1996 and 2005 concerning three-membered carbocycles containing one heavier group 14 element. Earlier work on these systems have been reviewed previously <1982COMC-I(2)86, 1982COMC-I(2)206, 1984CHEC-I(1)575, 1995COMC-II(2)1, 1996CHEC-II(1)305>. There are some reviews on these systems during the last decade; however, there are no comprehensive reviews on them in this range of time <2000AOC(46)1, 2001AOC(47)121, 2003CRV(103)1429, 2004AOC(50)145, 2004AHC(87)1>. This chapter explores several aspects related to the chemistry and properties of carbocycles containing tetravalent heteroatoms, giving special attention to the synthesis and reactivity of such compounds. As theoretical methods have achieved great levels of accuracy on the calculation of chemical properties, their application for the study of these systems is included. Not all three-membered ring compounds containing an atom heavier than silicon have been experimentally obtained and fully characterized. Emphasis is given to those compounds that have been isolated and characterized by several spectroscopic techniques, mostly the silicon derivatives. Many proposed reaction mechanisms involving sila-, germa-, or stannacyclopropanes are also discussed. Nowadays, systems containing one lead atom in a three-membered ring are still a synthetic and computational challenge.

1.09.1.2 Structural Types and Nomenclature

The heterocyclic ring systems reviewed in this chapter may be grouped into four main categories: those containing a saturated three-membered ring moiety **1**, with one silicon, germanium, tin, or lead atom that are called siliranes, germiranes, and stanniranes, and which also are found under their common names of silacyclopropanes, germacyclopropanes, or stannacyclopropanes, respectively. The second category includes all unsaturated three-membered rings **2**, such as silirenes, germirenes, and stannirenes, and also those that are commonly named as silacyclopropenes, germacyclopropenes, and stannacyclopropenes, respectively. Although no lead derivatives are known, their respective names may be written following the same rules as plumbanes or plumbacyclopropanes and plumbirenes or plumbacyclopropenes, respectively. Those molecules that contain an exocyclic double bond **3**, are commonly called alkylidene siliranes or allylidene silacyclopropanes and form a third category. The last category comprises molecules containing more than one three-membered ring with a silicon atom connected by an Si–Si **4** or a C–C **5** bond. When needed, common names will be used throughout the chapter, such as 1,2-di-*t*-butyl-silacyclobenzene **6** or 1,2-dibromo-2,2-dimethylgermacyclopropene **7**.



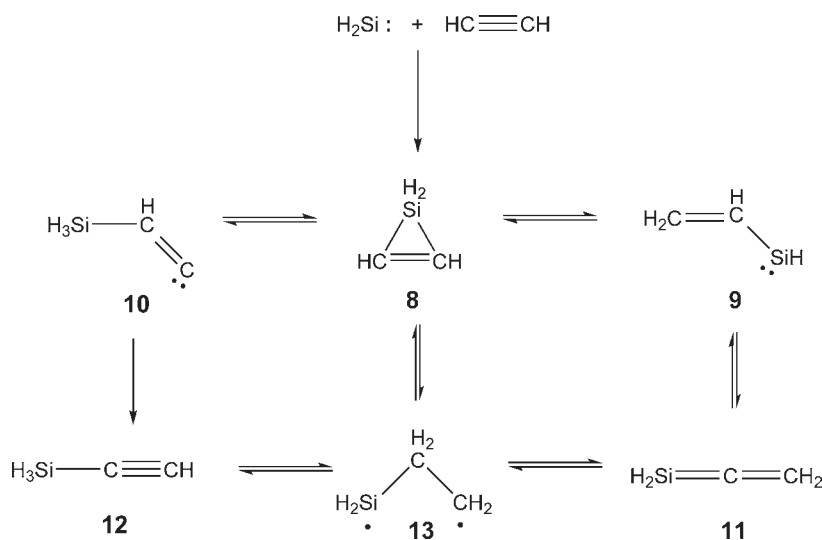
1.09.2 Theoretical Methods

Theoretical calculations provide the framework for a molecular level description of chemical structure and reactivity that forms the basis for interpreting the experimental data. Studies related to three-membered rings with silicon, germanium, and tin have been focused on the addition of carbene analogs into organic fragments. A nice example is the work of Gordon and Nelson. They studied the addition of SiF₂ and SiCl₂ to ethylene using MP4 and the 6-311(d,p) basis set at geometries determined with MP2 level of theory. In contrast to the earlier calculations on the

analogous SiH_2 addition which was found to proceed with no barrier, barrier heights of 18.4 and 4.5 kcal mol⁻¹ are predicted for the fluoro- and chlorosilylenes, respectively <1995OM1067>.

The addition of singlet carbene analogs MR_2 ($\text{M} = \text{C}, \text{Si}, \text{Ge}, \text{and Sn}$; $\text{R} = \text{H and F}$) on to ethylene has been investigated by *ab initio* methods <1996MP1567>. Sakai claims that the reaction mechanisms are two-step processes. The first step is complex formation, the C–M bond formation at one site, with the interaction between the empty p_π -orbital of carbene congeners and the π -orbital of ethylene, and the second is the other C–X bond formation with biradical coupling. The transition states correspond to the intermediate process between the first and the second steps <1998IJQ291>.

Skancke *et al.* have studied the barrier to the concerted ring opening of silacyclopropene **8** to give vinylsilylene **9** using CASPT2//CASSCF and hybrid DFT calculations. They found that this barrier is lower than the barrier to form silylacetylene **12**. The barriers, obtained by (12,12)CASPT2 calculations, are 32.2 and 38.7 kcal mol⁻¹, respectively. Rearrangement of **8** to silylvinylidene **10** is predicted to be the rate-determining step in the formation of **12**. The barrier to ring closure of **9** to **8** is computed to be 31.5 kcal mol⁻¹ by (12,12) CASPT2. The CASPT2 barrier height is essentially the same as that for rearrangement of **9** to 1-silaallene **11**. These results support the hypothesis that the formation of equal amounts of the two isotopomers of **8** from monodeuterated **9** is the result of a kinetically competitive equilibrium between **9** and **11**. Interconversion between **11** and **12** by two consecutive [1,2]-hydrogen shifts involving formation of the diradical **13** is found to be prevented by high-energy barriers (>70 kcal mol⁻¹) (Scheme 1) <1998ACT1180, 1999PCA4043, 2005CPH17>.

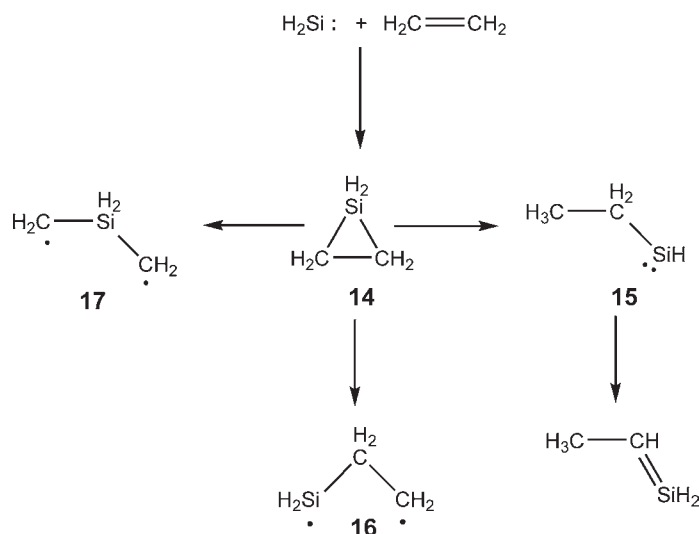


Scheme 1

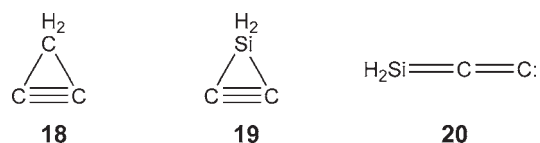
The same authors found that the transition state for hydrogen migration in concert with ring opening of silacyclop propane **14**, leading to ethylsilylene **15**, has an energy that is significantly lower than the energies of the 1-sila- and 2-silatrimethylene diradicals (**16** and **17**), formed by ring opening alone (Scheme 2) <1997JA8012>.

Interestingly, Pham-Tran *et al.* have pointed out the remarkably contrasting behavior of phosphirane and silirane in their ring-chain rearrangements <2001J(P2)766>.

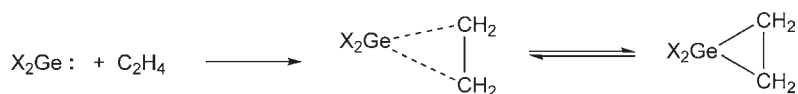
Sherrill *et al.* have used high-level *ab initio* methods to characterize silacyclop propyne **19**. The DZP CCSD(T) frequencies of **19** and **20** support Maier's identification of **19** by matrix isolation infrared spectroscopy. Because the experimental detection of **19** contradicted previous theoretical predictions, the authors reinvestigated the parent cyclopropyne **18** using a wide range of highly accurate *ab initio* methods. Although **19** is described reasonably well by a single electronic configuration, two configurations are required to obtain an acceptable zeroth-order wave function for **18**. At no level of theory does cyclopropyne become a minimum on the C_3H_2 surface. Structures **19** and **18** both exhibit weak triple bonds, but this bond appears somewhat stronger in **18**. The existence of silacyclop propyne as an isolable chemical species, in contradistinction with cyclopropyne, is explained as primarily due to the very high relative energy of the cumulated π -network of silapropadienyldiene **20** <1996JA7158>.



Scheme 2

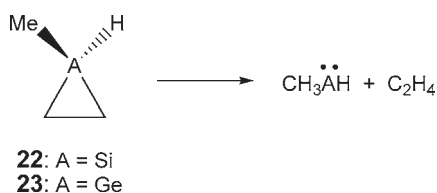


Su and Chu studied the potential energy surfaces for cycloaddition of germylene to the $\text{C}=\text{C}$ double bond of ethylene at the B3LYP/6-31G* level. They found that in contrast to the case of the carbene additions, a π -complex intermediate is formed between germylene and ethylene, which should play a key role in a subsequent polymerization. A major conclusion of this work is that germacyclop propane **21**, unlike cyclopropane, is quite an unstable compound, reverting thermally to its precursor and then polymerizing rapidly, or even reacting with a second molecule of olefin to yield a cyclic compound. Finally, the authors found that the cycloadditions of germynes to alkenes are more endothermic than the same reactions of carbenes, reflecting the weaker Ge–C versus C–C bond (Scheme 3) <1999JA11478>.



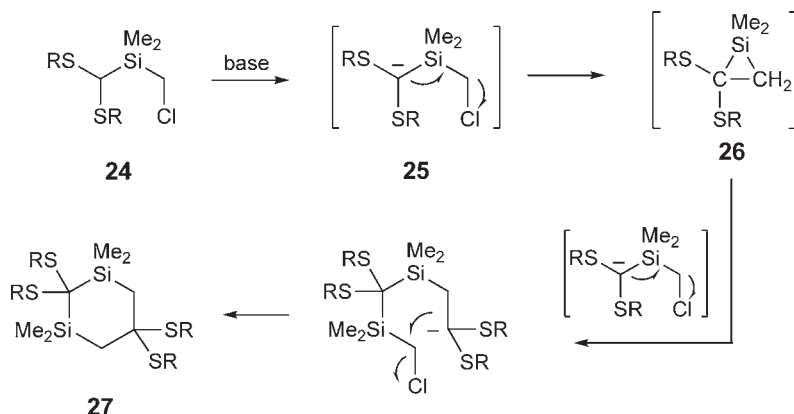
Scheme 3

Similar studies were carried out by Khabashesku *et al.* Using DFT calculations. They found that the germacyclop propane **23** is less thermostable than its silicon analog **22**, and methylgermylene extrusion was expected to proceed more easily. This study explains why the transient molecule **23** does not survive under vacuum pyrolysis experiments (Equation 1) <1998JA5005>.



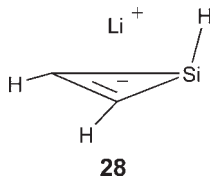
(1)

Shimizu *et al.* claim that formation of the 1,3-disilacyclohexane ring **27** may be understood in terms of a silacyclopropane intermediate **26**. The carbanion **25** formed by treatment of **24** with a base should generate silacyclopropane **26** by an intramolecular alkylation reaction. Since **26** should be highly reactive due to the strain energy, it should immediately be attacked at the silicon atom by another nucleophile **25** (Scheme 4) <1996CL1083, 1999ICA231>.



Scheme 4

Finally, it has been revealed by *ab initio* calculations at various levels that electropositive substituents (Li, BeH, and BH₂) on silacyclopropene do not form a bridged bond over the ring. Although in 1-lithiumsilylacyclopropene **28** the lithium occupies a position on the top of the ring, this structure, however, should be more appropriately described as a silacyclopropene anion Li⁺ ion pair, as shown by the MOs and Wiberg indices <1997PCA8565>.

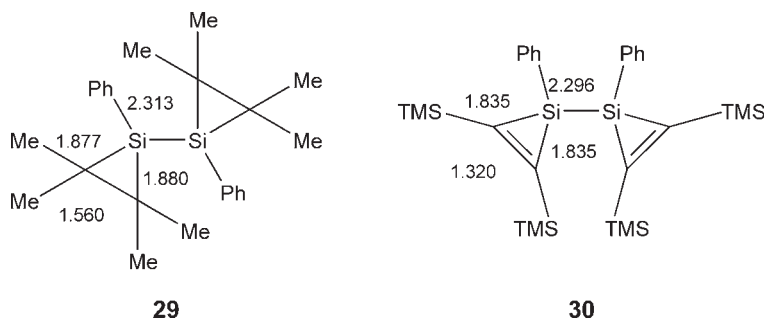


1.09.3 Experimental Structural Methods

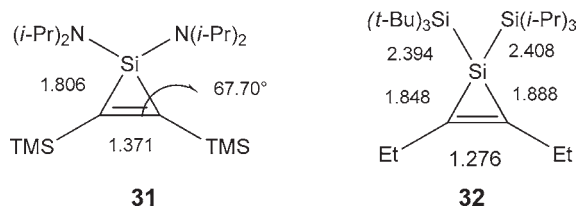
1.09.3.1 Spectroscopic Methods

1.09.3.1.1 X-Ray diffraction

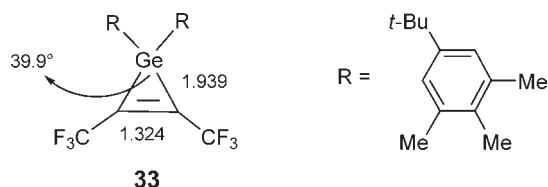
X-Ray diffraction studies have been carried out on several silacyclopropyl compounds, for example, **29** and **30** <1997JA3629>. The observed Si–Si bond distance in **30** is shorter than that expected for a single silicon bond (~2.34 Å).



An X-ray diffraction analysis of the deformation of the ring structure for 3,3-bis(diisopropylamino)-1,2-bis(trimethylsilyl)-3-silacyclopropene **31** gave the first experimental evidence of significant effects by the substituents. This structural change is a consequence of the interaction between the π -type σ^* -orbital of silicon–nitrogen bonds and the C=C π -bonding orbital <1998OM3819>. X-Ray analysis of **32** gave the Si–C bond distances ranging from 1.848 to 1.888 Å for a silacyclopropene, and C–C bond distance of 1.276 Å <2003OM2233>.

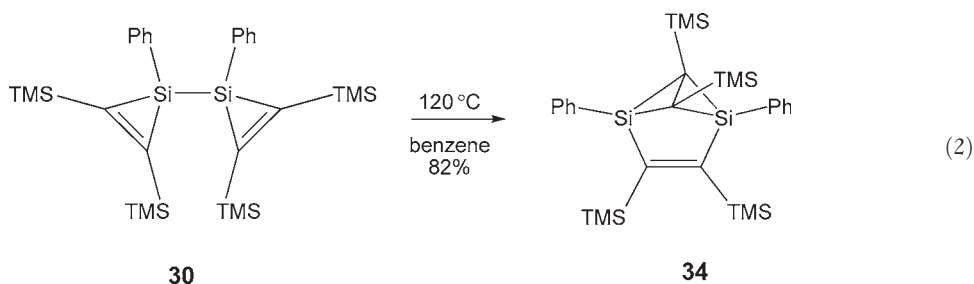


A germacyclopropane with electronegative groups at the ring carbon atoms, **33**, was obtained by the [1+2] cycloaddition reaction of tetrakis(2-*t*-butyl-4,5,6-trimethylphenyl)digermene with hexafluorobut-2-yne. A short C=C double bond (1.324(5) Å) and a sharp C–Ge–C bond angle of 39.93(14)° were determined by X-ray analysis <2002ZFA2821>.

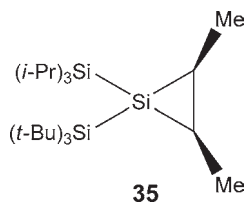


1.09.3.1.2 NMR studies

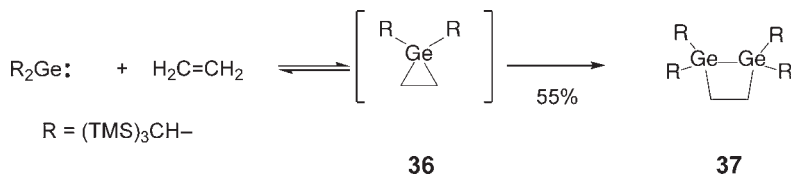
A highly unusual chemical shift value for ^{29}Si NMR of -143.2 ppm (silirenes ranges from -86 to -116 ppm) was observed for compound **30** <1997JA3629>. Compound **34**, a disilabenzvalene obtained by thermolysis of **30** in a degassed sealed tube at 120°C in benzene (Equation 2), presented an ^{29}Si NMR signal at -61.9 ppm, which is usual for siliranes.



A series of silacyclopropene derivatives, obtained by silver-catalyzed silylene transference to alkynes, presented ^{29}Si NMR signals ranging from -48.7 to -63.6 ppm <2005OM6212>. The silacyclopropane derivative **35**, showed an ^{29}Si NMR signal at -140.7 ppm, while for its analogous silacyclopropene derivative **32**, appeared at -152.3 ppm <2003OM2233>.

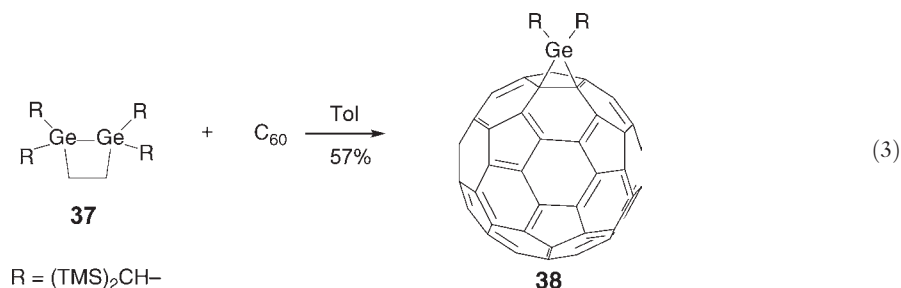


A germirane intermediate without substituents in the ring carbon atoms **36** was detected by ^1H NMR in the reaction of a stable germylene with ethylene to produce 1,2-digermacyclobutane. When the reaction mixture was allowed to stand for a few days, the intermediate germirane **36** gradually was converted into the product **37** (see Scheme 5). Attempts to isolate **36** were unsuccessful <1995OM2139>.

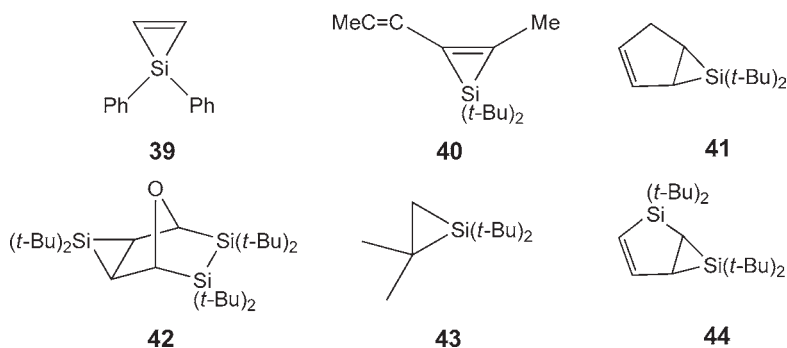


Scheme 5

Photolysis of several derivatives of 1,2-digermacyclobutane with bulky bistrimethylsilylmethyl groups in a toluene solution of buckminsterfullerene (C_{60}) afforded germacyclopropane **38** (Equation 3), a germylene adduct whose structure was analyzed using ^1H - and ^{13}C -NMR data <2001JOM82>. Nonequivalence on the signals corresponding to two disyl groups (disyl = $(\text{TMS})_2\text{CH}-$) at low temperatures and two methylene signals suggested that the adduct **38** is a germacyclopropane with a closed [6,6] bond on the C_{60} surface.



1,1-Diphenylsilirene **39** was characterized at -50°C by ^1H - and ^{13}C -NMR spectroscopy <1999OM2791>. The ^{29}Si NMR signal corresponding to a silacyclopropene **40**, obtained by photolysis of a cyclotrisilane, shifted to lower fields than observed with other siliranes (-63.78 ppm) <1998OM1237>. Compounds **41–44**, produced from reactions of five-membered ring compounds with a silylene precursor showed ^{29}Si NMR signals at -55.99 , -46.75 , -40.54 and -36.32 ppm, respectively <1995OM5695>.



1.09.4 Reactivity of Fully Conjugated Rings

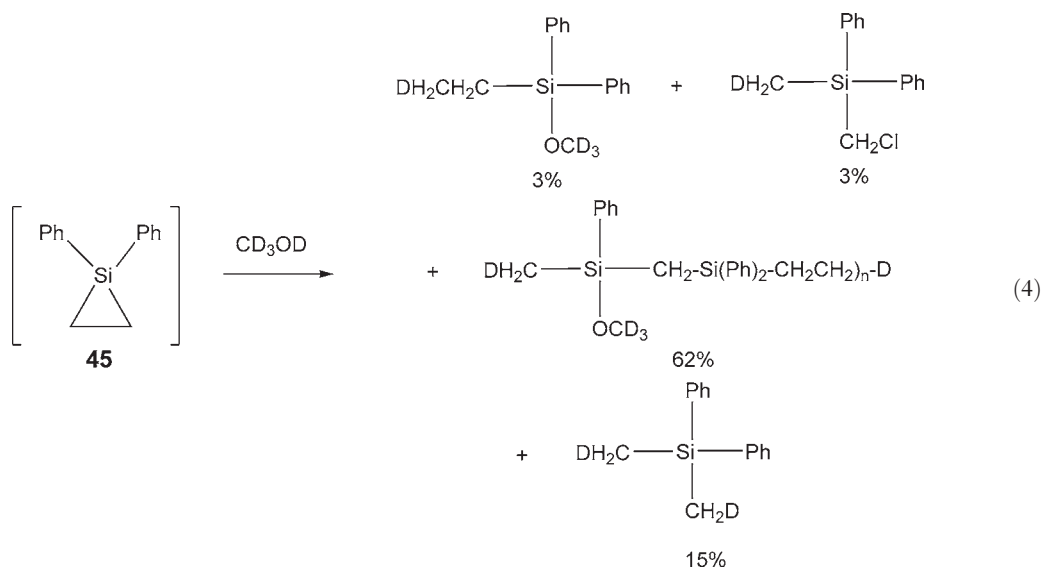
The first experimental evidence of the interaction between the acceptor σ^* -orbital of the silicon atom and the C=C π -bonding orbital was obtained from X-ray diffraction experiments of the deformation of the ring structure of 3,3-bis(diisopropylamino)-1,2-bis(trimethylsilyl)-3-silacyclopropene **31** <1998OM3819>. During the reaction of methoxy-[(trimethylsilyl)ethoxy]carbene with *N*-phenylmaleimide and C₆₀, a silacyclopropene carbocation was also suggested to be involved in the formation of the product. This conclusion was supported by evidence of scrambling of the CD₂ group as observed by ¹H NMR spectroscopy <2001JOC7496>.

1.09.5 Reactivity of Nonconjugated Rings

1.09.5.1 Silacyclopropanes

1.09.5.1.1 Ring-opening reactions

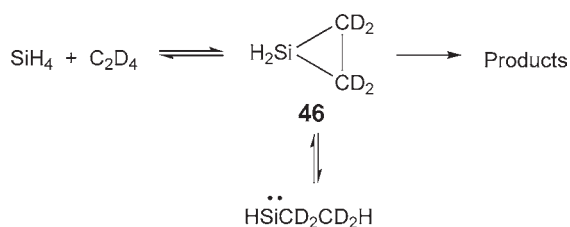
An intermediate, 1,1-diphenylsilacyclopropane **45**, derived from the reaction of Ph₂Si(CH₂Cl)₂ and magnesium, was trapped by a ring-opening reaction with deuterated methanol (Equation 4). The intermediate is part of the reaction pathway proposed by the authors as shown in Equation (5) <1998OM2404>.



Addition of several trapping agents (water, methanol, acetone, among others) represents a common method employed to obtain stable products that can be isolated and characterized. Several reactions use this kind of strategy in order to identify transient silacyclopropane intermediates that are not stable or readily isolable <2002PCP5072, 2004JOC4007>.

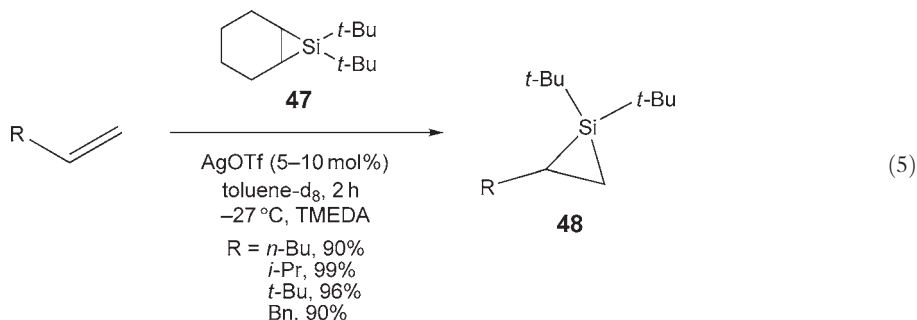
1.09.5.1.2 Generation of silylenes from silacyclopropanes

A reversible isomerization of a vibrationally excited silirane **46** to ethylsilylene was proposed to explain the large kinetic isotopic effects k_D/k_H in the SiH₂ + C₂D₄ reaction system (Scheme 6). Variations on the founded values may be caused by oversimplification of the model or greater mechanistic complexity <2002PCP5072>.

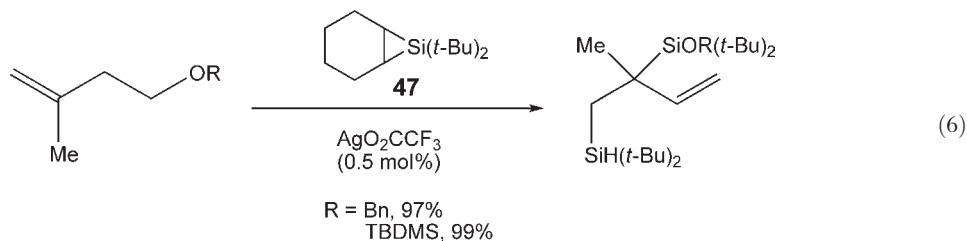


Scheme 6

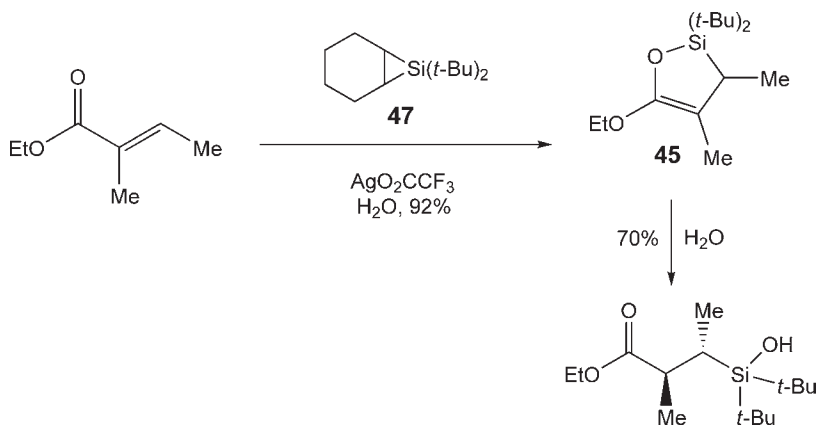
Cyclohexene silacyclopropane **47** undergoes silver-catalyzed silylene transfer, acting as an efficient method for silacyclopropane **48** synthesis (Equation 5) <2004JOC4007>. Kinetic studies of the transfer reaction suggested a possible mechanism for silver-mediated silylene transfer with a kinetic order of one for **47** <2004JA9993>.



When examining the silylene transfer to *gem*-disubstituted alkenes to form silacyclopropanes, an unprecedented reaction of homoallylic ethers was discovered. Two di-*t*-butylsilylene units were found to be incorporated into the molecule followed by a complete rearrangement of the carbon backbone (Equation 6) <2005OL5531>. This reaction opens a new route to prepare organic synthetically useful allylic silenes to be used in annulation reactions.

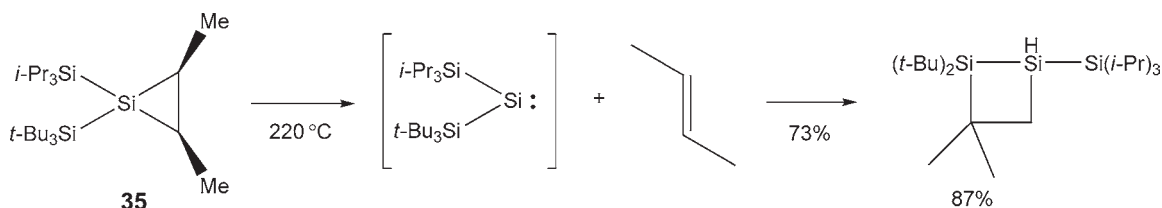


In a related work by Calad and Woerpel, siliranes have been used as transfer agents to carbonyl compounds (α,β -unsaturated esters) to produce oxasilacyclopentenones, providing a new effective method for regio- and stereoselective enolate formation. The oxasilacyclopentenones are useful synthetic intermediates that can undergo facile and selective Ireland–Claisen rearrangements and aldol addition reactions to provide products with multiple contiguous stereocenters and quaternary carbon centers (Scheme 7) <2005JA2046>.



Scheme 7

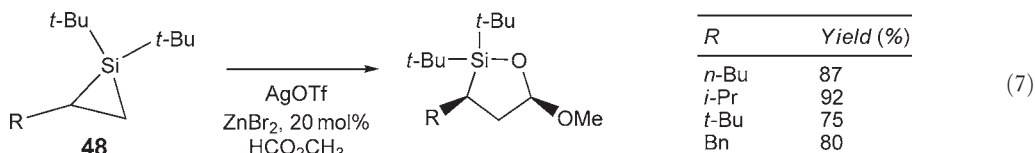
Thermolysis of **35** at 220 °C in benzene produces the corresponding silylene and *trans*-1,2-dimethyl ethylene. In the absence of trapping agents, the only product isolated in 87% yield is 1,1-di-*tert*-butyl-4,4-dimethyl-2-triisopropylsilyl-1,2-disiletane (Scheme 8) <2003OM2233>.



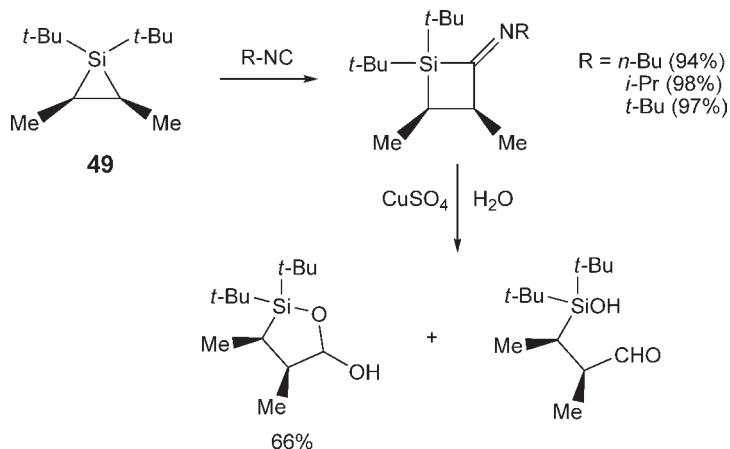
Scheme 8

1.09.5.1.3 One- and two-atom insertions

The silacyclopropanes **48** react readily with a wide range of carbonyl compounds, efficiently converting alkanes to oxasilacyclopentanes and providing a useful synthetic tool in organic synthesis (Equation 7) <2004JOC4007>.

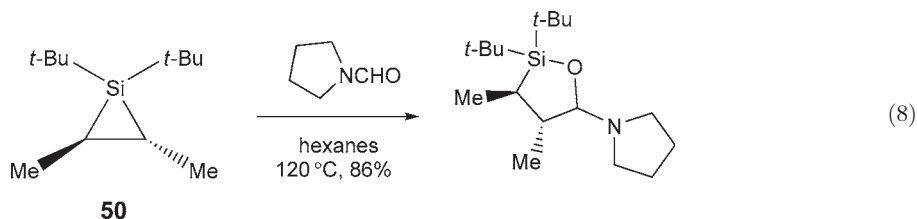


Siliranes **49** undergo a variety of stereospecific and regioselective one-atom insertion of isocyanides under mild conditions. The reaction is of synthetic utility in order to obtain oxasilacyclopentane hemiacetals, via thermal tautomerization of the iminosilacyclobutene to the corresponding ammosilacyclobutene and a ring-opening expansion promoted by acids (Scheme 9). Preparation of some derivatives using this method suggests broader use of silirane chemistry in organic synthesis <1999JOC1843>.

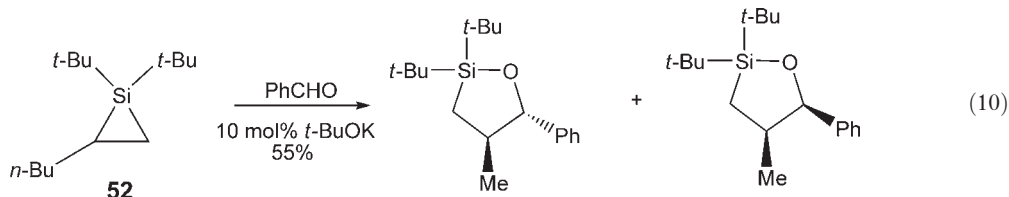
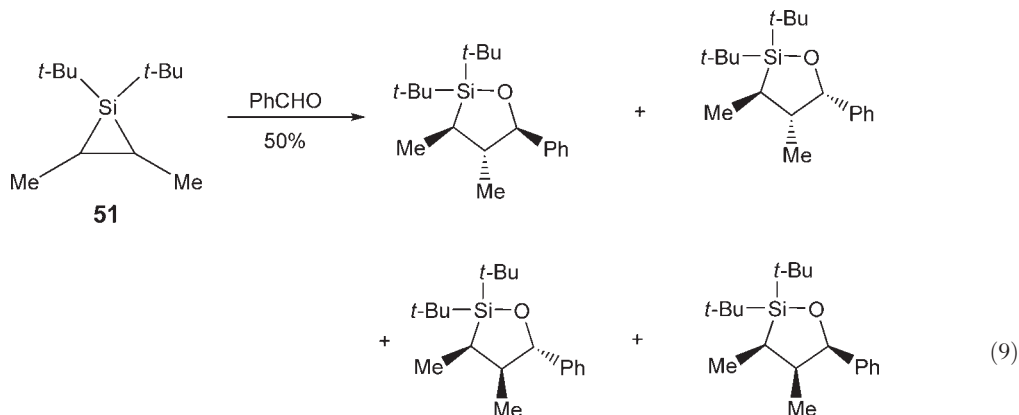


Scheme 9

Siliranes have been used as helpful intermediates in organic synthesis. *trans*-Insertion of formamides into a C–Si bond of silirane **50** provides a facile route to the oxasilacyclopentane acetate in 86% yield (Equation 8). The authors claim that the chemistry of siliranes will lead to new methods for the synthesis of polyoxygenated natural products <1997T16597>.



Silirane **51** undergoes stereo- and regioselective insertion of benzaldehyde to produce oxasilacyclopentane derivatives (Equation 9). Thermal reaction of **52** (>100 °C) proceeds through extensive decomposition and side products, while the reaction catalyzed with *t*-BuOK at <25 °C is cleaner and has a high degree of inversion (Equation 10) <1997JOC4737>. When CuI or CuBr₂ were used as catalysts, as well as ZnBr₂, insertion occurred with retention of configuration and, in the case of enols and formamides as substrates, with high diastereoselectivity at the newly formed stereogenic centers <1999JA949>.



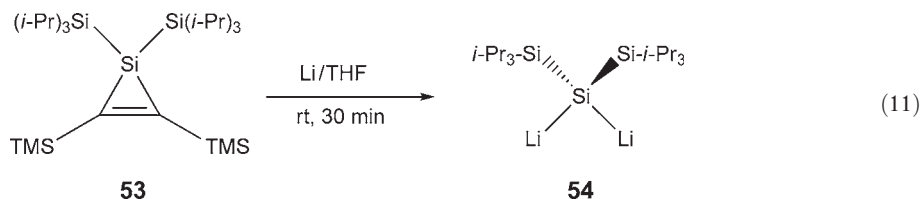
1.09.5.2 Silacyclopropenes

1.09.5.2.1 Review

Silacyclopropenes were reviewed as intermediates in the photolysis of several alkynyl-substituted disilane derivatives <1996CC2609>. Photolysis of the disilane derivatives gives highly reactive silacyclopropene intermediates.

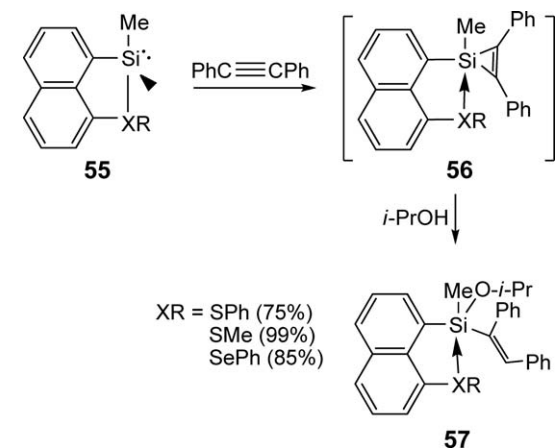
1.09.5.2.2 Ring-opening reactions

An organodilithiosilane **54** was unexpectedly obtained from silacyclopropane **53** by reacting it with an excess of Li, in dry oxygen-free tetrahydrofuran (THF), at room temperature for 30 min (Equation 11). There was no precedent for alkali metal-induced fragmentation of silirenes to dianionic silicon derivatives <1999JA10231>.

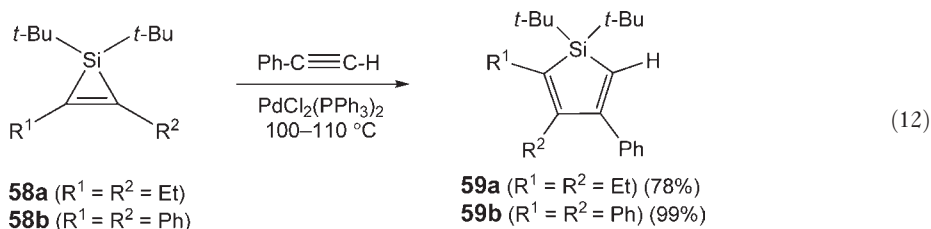


A silacyclopropene intermediate **56** was trapped by a reaction with 2-propanol during the thermal degradation of pentacoordinate disilanes **55** bearing an 8-thiona- or 8-seleno-1-naphthyl group and a methoxy group on the same silicon center. This reaction generates intramolecular sulfur- or selenium-coordinated silylenes **57** (Scheme 10) <2003OM3299>.

Silirenes **58a** and **58b** react with phenylacetylene in the presence of <3 mol% PdCl₂(PPh₃)₂ at 100–110 °C to give trisubstituted siloles **59a** (78%) and **59b** (99%), respectively (Equation 12) <1997OM4824>.



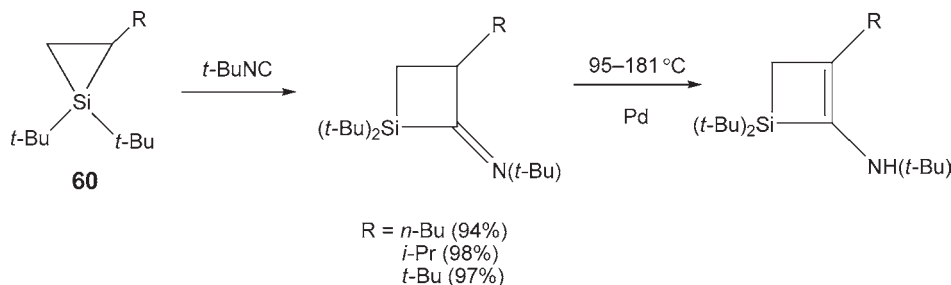
Scheme 10



Silylium ions stabilized by Si–X–Si three-center bonds (X = halogen or hydrogen) have been synthesized by the reaction of the corresponding 1-tris(trimethylsilyl)methyl-2,3-bis(trimethylsilyl)-1-silacyclopropene derivative with triethylsilylbenzenium tetrakis(pentafluorophenyl)borate <2004CL530>.

1.09.5.2.3 One- and two-atom insertions

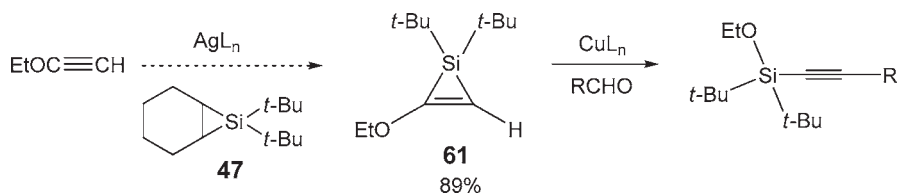
The insertion reaction of *p*-tolyl and *t*-butyl isocyanides into the more substituted Si–C bond of monosubstituted siliranes **60** produces the corresponding iminosilacyclobutanes with stereospecific retention of configuration. The regioselectivity diminishes with the increase of substitution on the silirane ring. When thermally activated, the iminocyclobutane undergoes tautomerization in the presence of a palladium catalyst to generate the thermodynamically more stable aminosilacyclobutene (Scheme 11) <1999JOC1843>.



Scheme 11

Silver phosphonate was also used as catalyst for silylene transfer to 1-heteroatom-substituted alkynes, resulting in alkoxy-, amino-, and alkylthiolate-substituted silacyclopropenes **61**. Silver-catalyzed silylene transfer to 1-halo- and 1-sulfonyl-substituted alkynes led to insertion of silylene into the carbon–heteroatom bond. Attempts of Cu-catalyzed

insertion of carbonyl compounds into heteroatom-substituted silacyclopropenes **61** led to rearrangement to produce Si-substituted alkynes with a silylene insertion into the carbon–heteroatom bond (Scheme 12) <2005OM6212>.

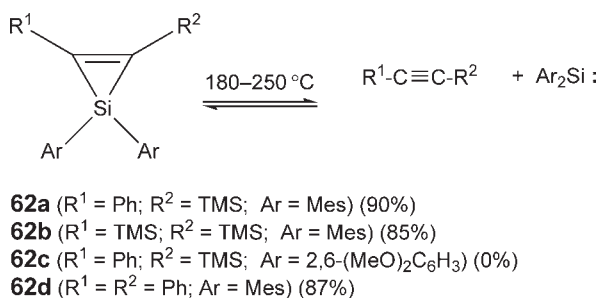


Scheme 12

1.09.5.2.4 Photo- and thermal-isomerization

Persilyl-substituted silacyclopropenes, $(R_3Si)_2SiC_2(SiMe_3)_2$ ($R_3Si = (Pr_3Si)-i\text{-Pr}$ or $(Bu_2MeSi)-t\text{-Bu}$), were photochemically isomerized to 1-silaallene derivatives, $(R_3Si)_2Si=C=C(SiMe_3)_2$, at wavelengths longer than 340 nm and further photoisomerized to acetylene derivatives, $(R_3Si)_2(TMS)SiC\equiv C-TMS$ as final products <2001CL1074>.

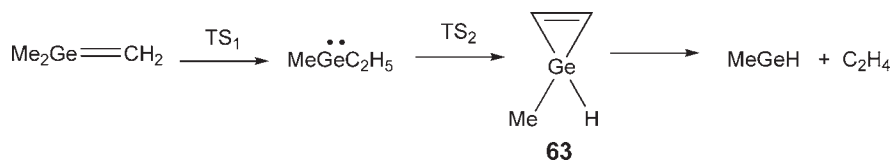
Ohshita *et al.* studied the rate of thermal silylene extrusion of silacyclopropenes **62a–d**. Substituents at the ring silicon and carbon atoms (Scheme 13) affect this rate. The origin of the effects has not been unambiguously explained yet <2003OM2436>.



Scheme 13

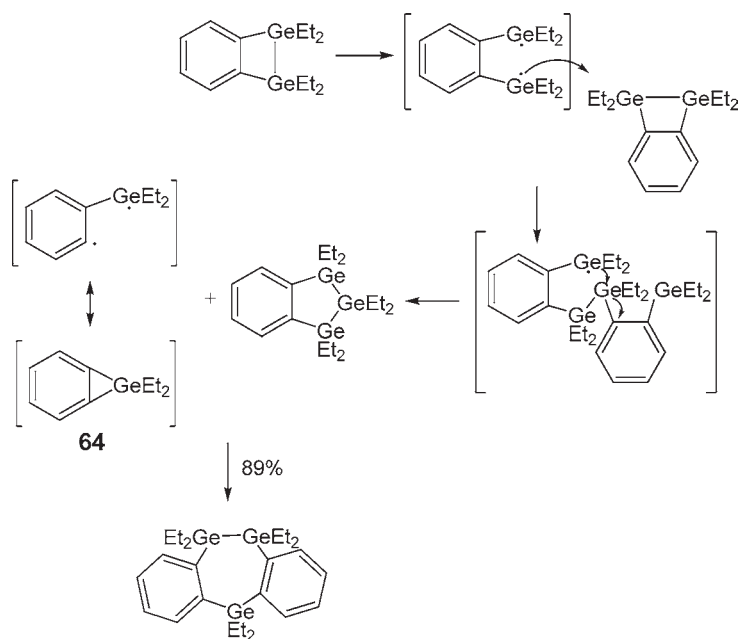
1.09.5.3 Reactions of Germacyclopropanes and Germacyclopropanes

An intermediate germacyclopropane was detected by $^1\text{H-NMR}$ spectroscopy while a germylene and ethylene reacted, forming 1,2-digermacyclobutane (Equation 2) <1995OM2139>. In another experiment, 1-methyl-1-germacyclopropane **63** was proposed as intermediate in the isomerization of the transient species 1,1-dimethyl-germene. Both were detected in the gas phase by electron impact mass spectrometry (EIMS) and in argon solid matrixes at 12 K by Fourier transform infrared (FTIR) spectroscopy. Further isomerization of the germacyclopropane **63** produces methylgermylene (Scheme 14) <1998JA5005>.



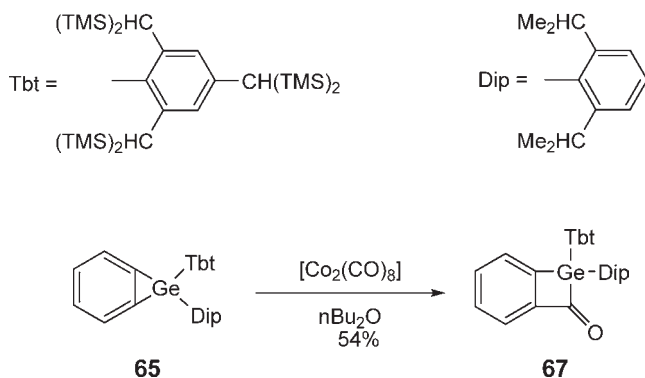
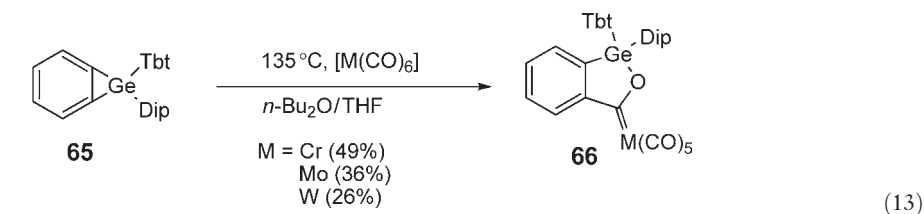
Scheme 14

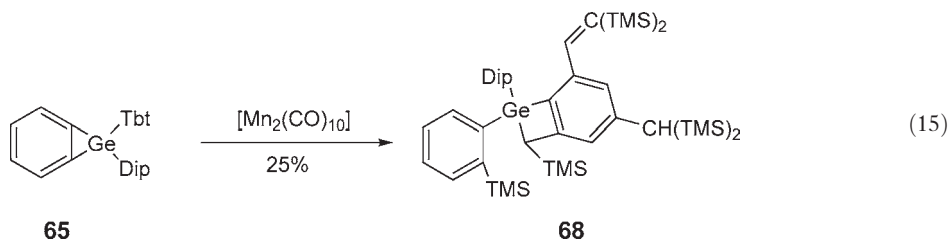
Benzogermacyclopropene **64** was suggested as an intermediate in the thermolysis of 3,4-benzo-1,1,2,2-tetraethyl-1,2-digermacyclobut-3-ene at 160 °C to form 4,5-benzo-1,1,2,2,3,3-hexaethyl-1,2,3-trigermacyclopent-4-ene in 89% yield (Scheme 15) <1996OM(15)2014>.



Scheme 15

The thermal reactions of an overcrowded germacyclopropabenzene **65** with a group 6 metal hexacarbonyl complexes $[M(CO)_6]$ ($M = Cr, Mo$ and W) resulted in the formation of novel Fischer-type carbene complexes **66** via the insertion reaction of a CO group to the Ge–C bond (Equation 13). Germacyclopropabenzene **65** reacts with $[Co_2(CO)_8]$ to give a germanium analog of benzocyclobutane **67** via the insertion reaction of a CO unit into the germacyclop propane ring (Equation 14). The reaction with $[Mn_2(CO)_{10}]$ resulted in the formation of the intramolecular cyclization product along with the migration of a trimethylsilyl group, a cyclobutabenzene derivative **68** (Equation 15) <2005AOM570>. The group of Tarima *et al.* is currently studying the structures and reactivity of metallocycloprobenzenes of the heavier elements from group 14.



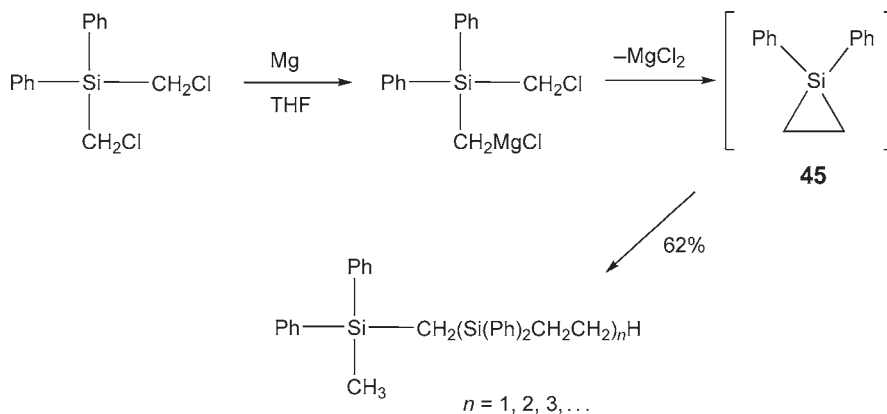


1.09.6 Synthesis of Three-Membered Rings with One Silicon Atom

1.09.6.1 Silacyclopropanes

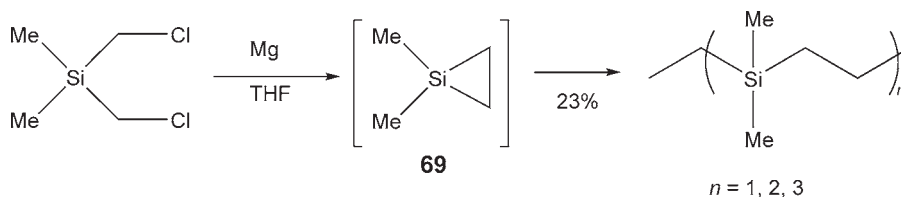
1.09.6.1.1 From acyclic compounds by formation of one C–C bond

An intermediate 1,1-diphenylsilacyclopropane **45**, derived from the reaction of $\text{Ph}_2\text{Si}(\text{CH}_2\text{Cl})_2$ and magnesium, was proposed and then trapped with deuterated methanol along with other deuterated products. The intermediate was compatible with a mechanism where a silacyclopentene is generated as part of the reaction pathway shown in [Schemes 4 and 16](#) <1998OM2404>.



Scheme 16

A silacyclopropane **69** was proposed as an intermediate in one of two possible pathways involving the Grignard reaction of bis(chloromethyl)dimethylsilane with trimethylchlorosilane in THF. The intermediate was obtained from the intramolecular cyclization of $\text{ClCH}_2\text{Me}_2\text{SiCH}_2\text{MgCl}$, which undergoes a ring-opening polymerization by nucleophilic attack ([Scheme 17](#)) <1999BKC422>.



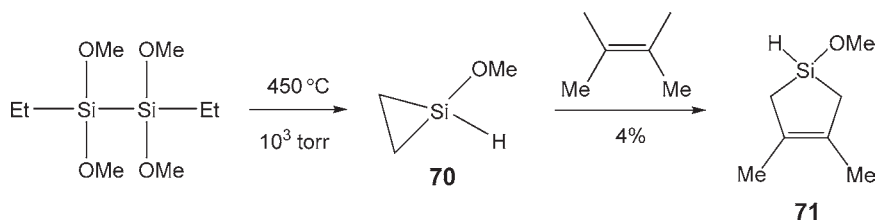
Scheme 17

1.09.6.1.2 Ring formation by [2+1] cycloaddition

The [2+1] cycloaddition of silylenes and alkenes is the most common preparative route to obtain silacyclopropanes.

1.09.6.1.2(i) Silylenes by thermolysis

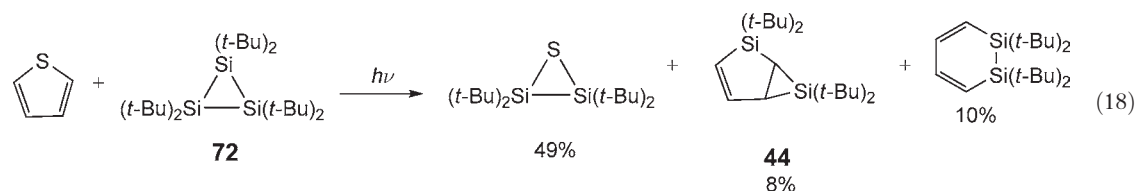
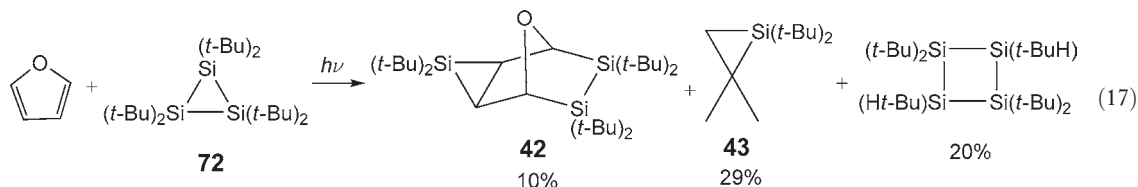
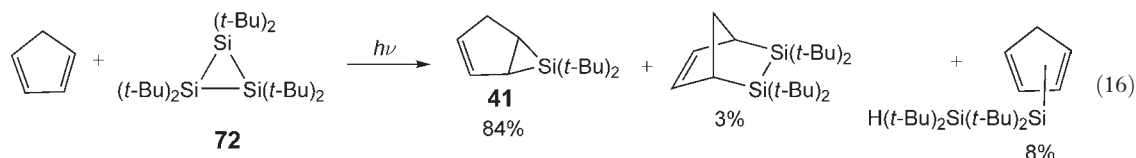
A 1-methoxy-1-silacyclopropane intermediate **70** has been suggested in order to explain the formation of 1-methoxy-3,4-dimethyl-1-silacyclopent-3-ene. Vacuum pyrolysis of 1,2-diethyl-1,1,2,2-tetramethoxydisilane in the presence of 2,3-dimethyl-1,3-butadiene, at 400–500 °C and 10^{-3} torr, in a vertical quartz tube, produces 1-ethyl-1-methoxy-, 1-ethyl-, and 1-methoxy-3,4-dimethyl-1-silacyclopent-3-ene. The 1-methoxy-1-silacyclopropane intermediate has been suggested in order to explain the formation of 1-methoxy-3,4-dimethyl-1-silacyclopent-3-ene along with ethyltrimethoxysilane. Product **71** was obtained via the proposed silacyclopropane intermediate **70** (Scheme 18), while the other products proceed via an oxasilacyclopropane intermediate <1997JOM219>.



Scheme 18

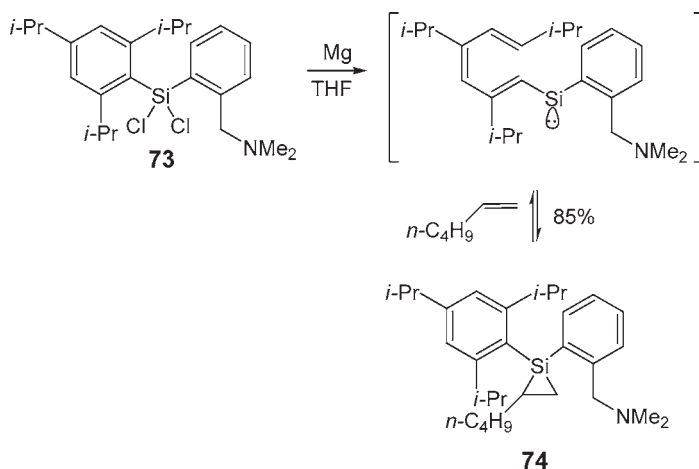
1.09.6.1.2(ii) Silylenes by photolysis

Photolysis of cyclotrisilane **72**, in the presence of five-membered ring compounds, produces 1,1-di-*tert*-butyl-2,2-dimethyl-1-silacyclopene **37** when reacted with cyclopentadiene (Equation 16), *exo*-3,3,6,6,7,7-hexa-*tert*-butyl-3,6,7-trisilacyclo-8-oxatricyclo[3.2.1.0^{2,4}]octane **38** and 1,1-di-*tert*-butyl-2,2-dimethyl-1-silacyclopene **39** when reacted with furan (Equation 17), and 2,2,6,6-tetra-*tert*-butyl-2,6-disilabicyclo[3.1.0]hex-3-ene **40** when reacted with thiophene (Equation 18), among other products <1995OM5695>. These products were characterized by ^1H , ^{13}C and ^{29}Si NMR, and for the furan derivative **38**, also by X-ray diffraction studies.



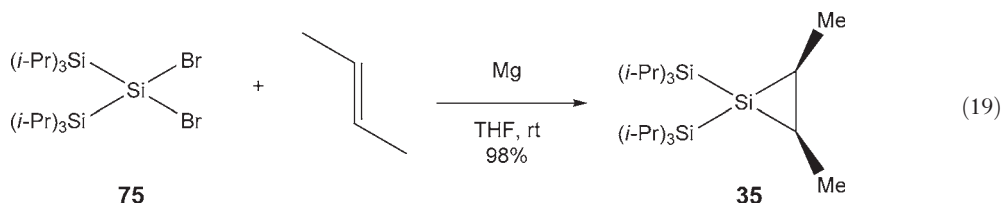
1.09.6.1.2(iii) Silylenes by reduction of dihalosilanes

The reductive dehalogenation of dichlorosilane **73** with magnesium in the presence of 1-hexene yields the corresponding 1-[2-(dimethylaminomethyl)phenyl]-1-[2,4,6-tris(isopropyl)phenyl]-2-*n*-butyl-1-silacyclopropane **74** (see Scheme 19) <1998CEJ852>.



Scheme 19

trans-2,3-Dimethyl-1-tri-*t*-butylsilyl-1-triisopropylsilylsilirane **32** was obtained in 98% yield by treating (*t*-Bu₃Si)(*i*-Pr₃Si)SiBr₂ **75** with activated magnesium in the presence of *trans*-2-butene (Equation 19). Trapping studies suggest that a silylene was extruded by thermolysis of the silirane. The kinetics of decomposition of the silirane was analyzed, and it was found to be stereospecific and proceeded in first order in benzene solution <2003OM2233>.



Two silacyclopropane derivatives, 2-*n*-butyl-1-*sec*-butyl-1-*tert*-butylsilacyclopropane **76a** and 2-*n*-butyl-1-*t*-butyl-1-isobutylsilacyclopropane **76b**, were recently synthesized by reacting *sec*-butyldichlorosilane or *t*-butylisobutyldichlorosilane with lithium in the presence of 1-hexene. They were polymerized via a ring-opening polymerization in the presence of hexamethylphosphoramide (HMPA) (hexamethylphosphoramide) with an *n*-BuLi initiator in THF at -78°C (Scheme 20). The polymers have high hydrophobicity <2003MM1474>.

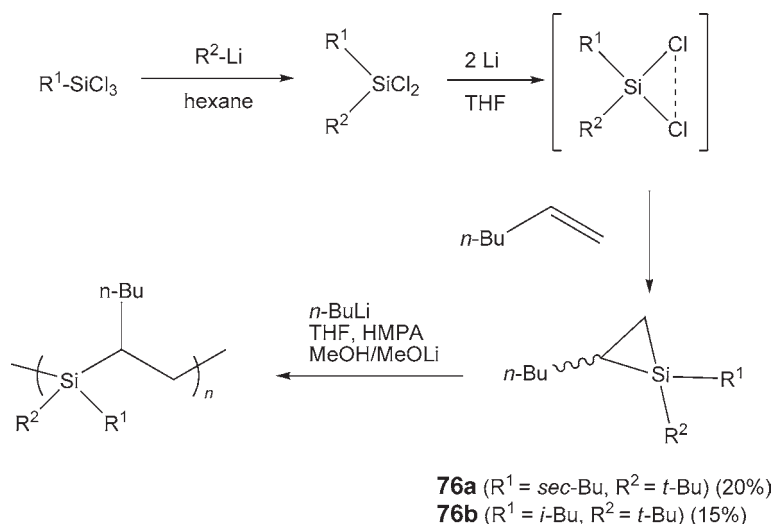
1.09.6.1.2(iv) Metal-catalyzed silylene transfer

Silver-catalyzed silylene transfer was developed as a mild and efficient method for silacyclopropane **48** synthesis. Employing low temperatures for the transfer improved diastereoselectivity and substrate compatibility compared to other methods of synthesis (Equation 5) <2004JOC4007>.

1.09.6.2 Silacyclopropenes

1.09.6.2.1 Ring formation by [2+1] cycloaddition

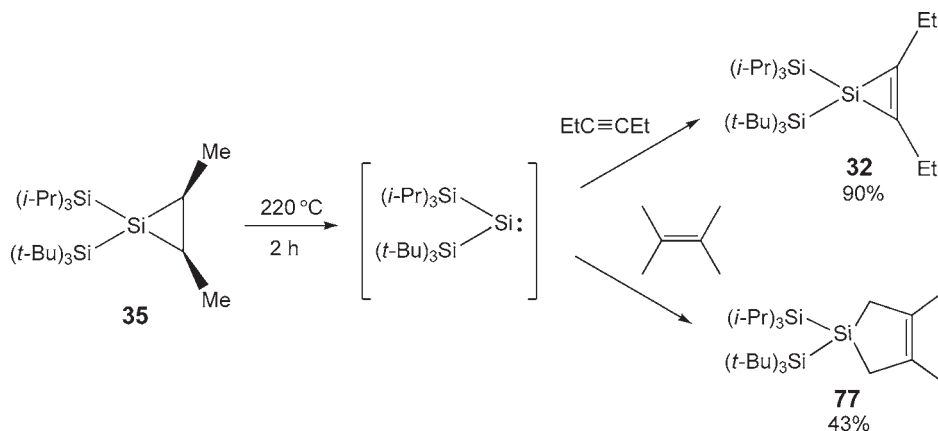
The most common way to prepare silacyclopropanes is by [2+1] cycloaddition of silylenes to alkynes. The corresponding silylenes can be prepared thermally, photochemically, by metal reduction or catalyzed by a metal.



Scheme 20

1.09.6.2.1(i) Silylenes by thermolysis

Thermolysis of **35**, in presence of $\text{EtC}\equiv\text{CEt}$ or 2,3-dimethylbut-2-ene, generates the corresponding 2,3-diethyl-1-tri-*tert*-butylsilyl-1-triisopropylsilylsilirene **32** or 3,4-dimethyl-1-tri-*tert*-butylsilyl-1-triisopropylsilyl-1-silacyclopent-3-ene **77** adducts in 87% and 43% yield, respectively (Scheme 21) <2003OM2233>.



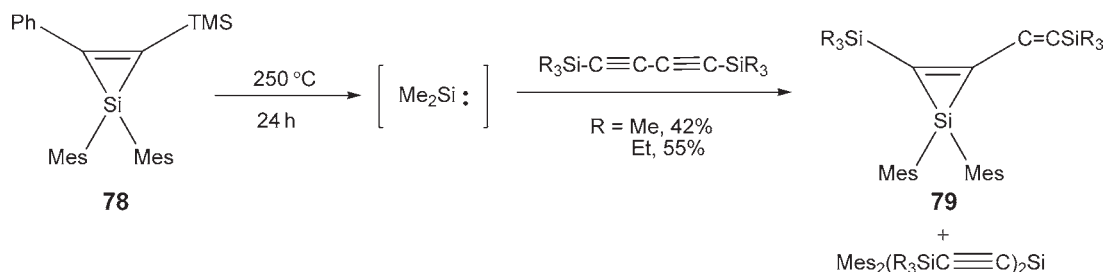
Scheme 21

Co-thermolysis of 1,1-dimesityl-3-phenyl-2-trimethylsilyl-1-silacyclopentene **78** with 1,3-bis(trimethylsilyl)- and 1,4-bis(triethylsilyl)butadiene at 250 °C for 24 h afforded 1,1-dimesityl-3-silyl-2-silylethynyl-1-silacyclopentenes **79** <1997JOM611>. Formation of this silacyclopentene can be understood in terms of silylene-transfer reaction from the initial silacyclopentene to the butadiene. Thermolysis of the resulting silacyclopentene gives ring-opening isomers produced from a 1,2-shift of the silyl group to the ring silicon atom (Scheme 22).

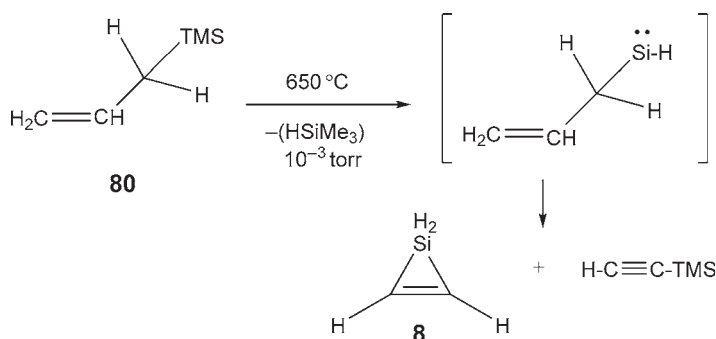
The first synthesis of unsubstituted silacyclopentene **8** was achieved recently, along with a novel route to obtain this class of substances. High vacuum pyrolysis of 1,1,1-trimethyl-2-vinylidisilane **80** produces the corresponding silacyclopentene by elimination of trimethylsilane (Scheme 23). A ring-opening reaction of the silacyclopentene produces the other product <1995AGE1439>.

Pulsed flash pyrolysis of 2-ethynyl-1,1,1-trimethylidisilane yields 1-silacyclopentenylidene **81** isolated in an argon matrix. It can further be isomerized by photolysis into ethynylsilanediyl **82**, vinylidenesilanediyl **83**, and

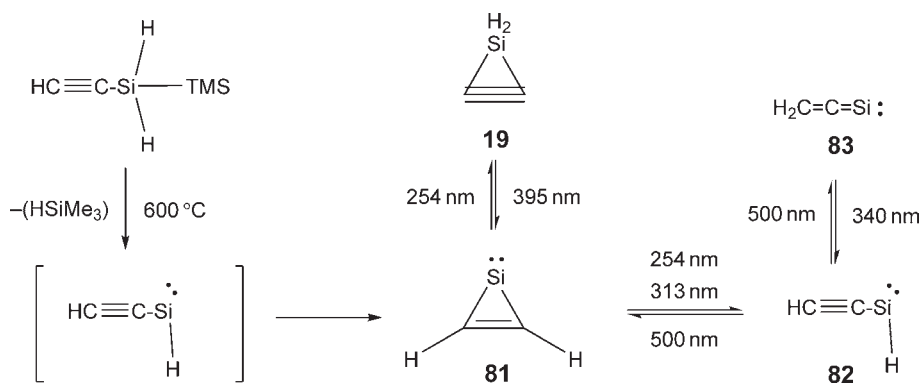
silacyclopropyne **19** (Scheme 24) <1995JA12712>. Comparing the experimental and calculated (MP2/6-31G**) infrared spectra for C_2H_2Si was used to identify the isomers.



Scheme 22

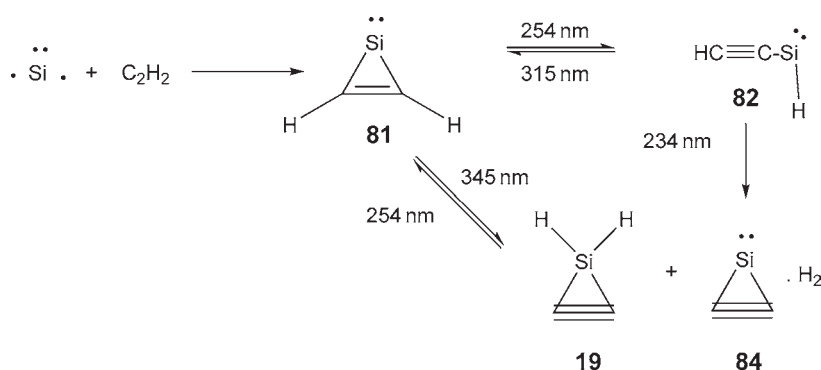


Scheme 23



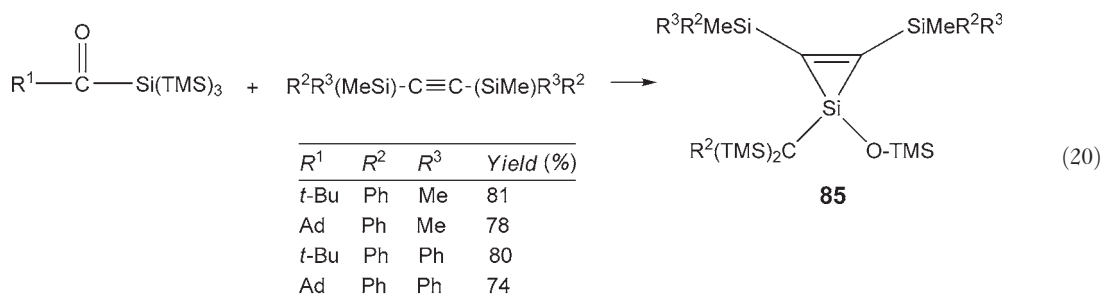
Scheme 24

In related work, evaporation of silicon and consecutive co-condensation of the generated atoms with acetylene in an argon matrix at 20 K yields also, as the primary product, silacyclopropenyldene **81**, which photochemically interconverts into the C_2H_2Si species, **82**, **19**, and **84** (Scheme 25) <1998EJO1313>. The photochemical interconversion of **81** into the other C_2H_2Si isomers, **82**, **19**, and **84**, was examined via infrared spectroscopy and found to be reproducible, as previously reported <1995JA12712>.



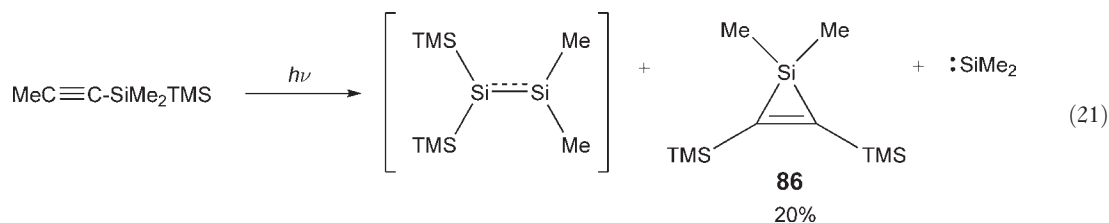
Scheme 25

Co-thermolysis of pivaloyl-adamantolyl(trimethylsilyl)-silanes with disubstituted acetylenes was carried out in a sealed glass tube, at 160 °C for 12 h, producing the corresponding silacycloprenes **85** in high yields ($\text{R}^1 = t\text{-Bu}$, Adamantyl; $\text{R}^2 = \text{phenyl}$; $\text{R}^3 = \text{Me}$, Ph) (Equation 20) <2000OM4921>. The products were characterized by ^{29}Si -NMR spectroscopy.

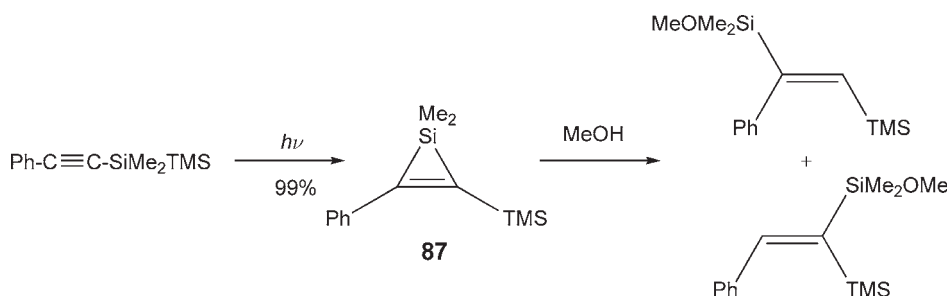


1.09.6.2.1(ii) Silylenes by photolysis

A mixture of reactive intermediates, including 1,1-dimethyl-3,3-bis(trimethylsilyl)-1-silaallene and dimethylsilylene, along with 1,1-dimethyl-2,3-bis(trimethylsilyl)-1-silacyclopene **86** were formed and detected from the direct irradiation of [(trimethylsilyl)ethynyl]pentamethyldisilane in hydrocarbon solution (Equation 21). These species were detected and identified using laser flash photolysis. They were trapped as their methanol adducts in steady-state irradiation experiments. Steady-state irradiation in the presence of methanol affords MeOH-addition products which are consistent with the formation of the silaallene, silacyclopene, and silylene along with bis(trimethylsilyl) acetylene as the major product <1997JA466>.

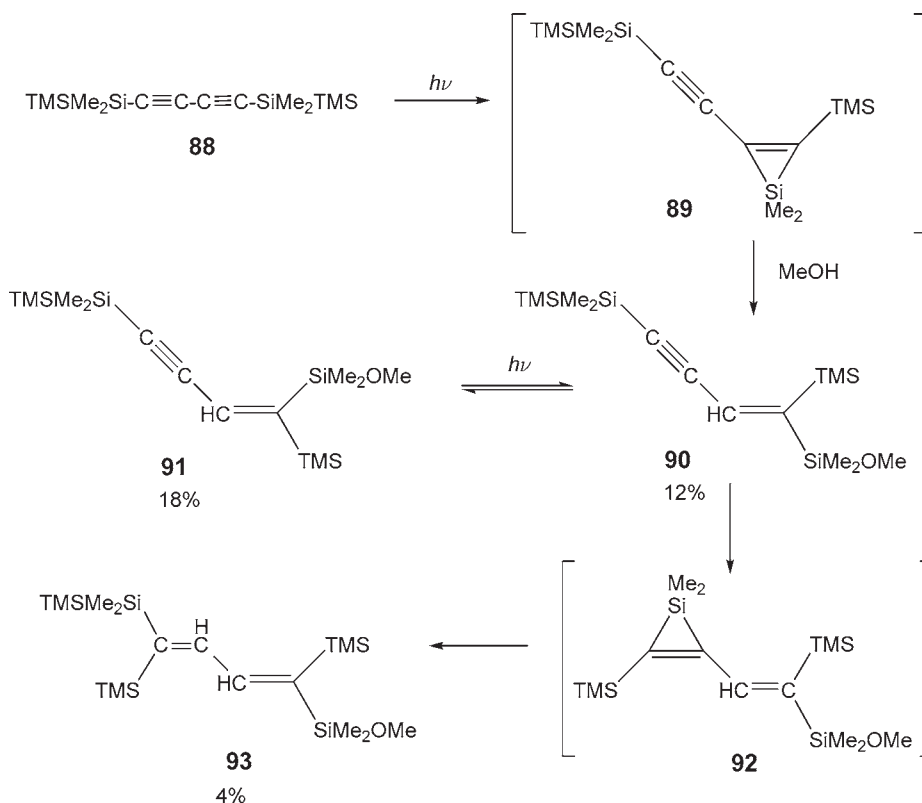


In a similar work, now carrying out the laser flash photolysis of pentamethyl(phenylethynyl)-disilane, the three intermediate products were determined to be stable on a millisecond time scale. The silacyclopene **87** was found to be stable for longer than 100 ms, based on its ultraviolet (UV) spectra (it presented a characteristic absorption band at 320 nm) and its reactivity toward various reagents, exposure to methanol affords two isomeric adducts (Scheme 26) <1997OM5804>.



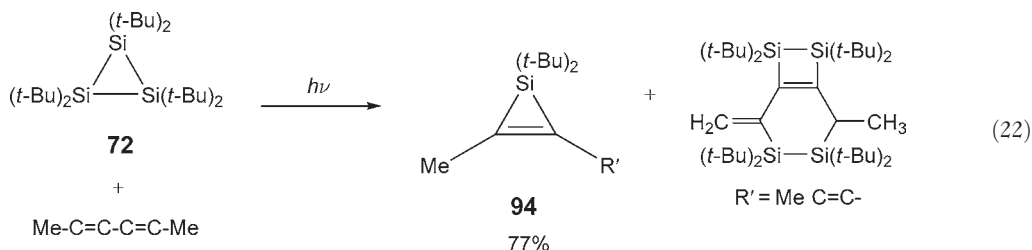
Scheme 26

Irradiation of 1,4-bis(pentamethyldisilanyl)butadiyne **88** in methanol yields two 1:1 photoaddition products **90** and **91** as well as one 1:2 photoadduct **93**. Adduct **90** is the primary photoproduct, while **91** and **93** are the secondary products. Structure **93** is formed via two silacyclopropene intermediates, **89** and **92** (Scheme 27). Irradiation of **88** with acetaldehyde and acetone in deaerated methylene chloride yields only the 1:1 photoadduct with a 1-oxa-2-silacyclopent-3-ene ring due to steric effects, preventing formation of a second silacyclopropene intermediate. Trapping experiments for the silacyclopropene intermediates with methanol were performed <1996OM2182>.



Scheme 27

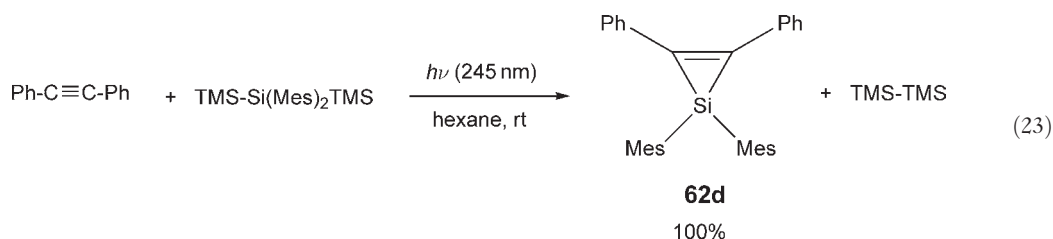
1-1-Di-*tert*-butyl-2-methyl-3-propynyl-1-silacyclopropene **94** was obtained by irradiating a solution of hexa-*tert*-butylcyclotrisilane **72** in the presence of an excess of hexa-2,4-diyne, giving in a 77% yield of a colorless, air-sensitive oil, which was characterized by ¹³C- and ²⁹Si-NMR spectroscopy (Equation 22) <1998OM1237>.



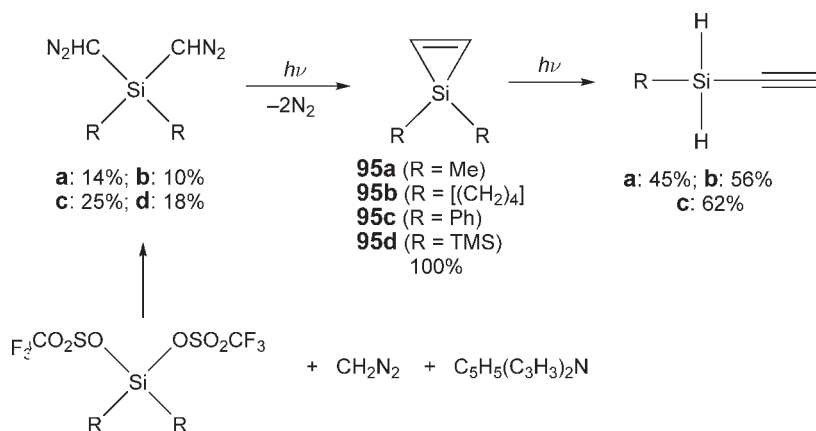
Several silacycloprenes **62a–c** were synthesized by photochemical isomerization of ethynyldisilanes (Scheme 28), while 1,1-dimesityl-2,3-diphenylsilacyclopentene **62d** was obtained by the reaction of the photochemically generated dimesitylsilylene with diphenylacetylene (Equation 23). All silacycloprenes are air stable and were characterized by ¹H- and ¹³C-NMR spectroscopy <2003OM2436>.



Scheme 28



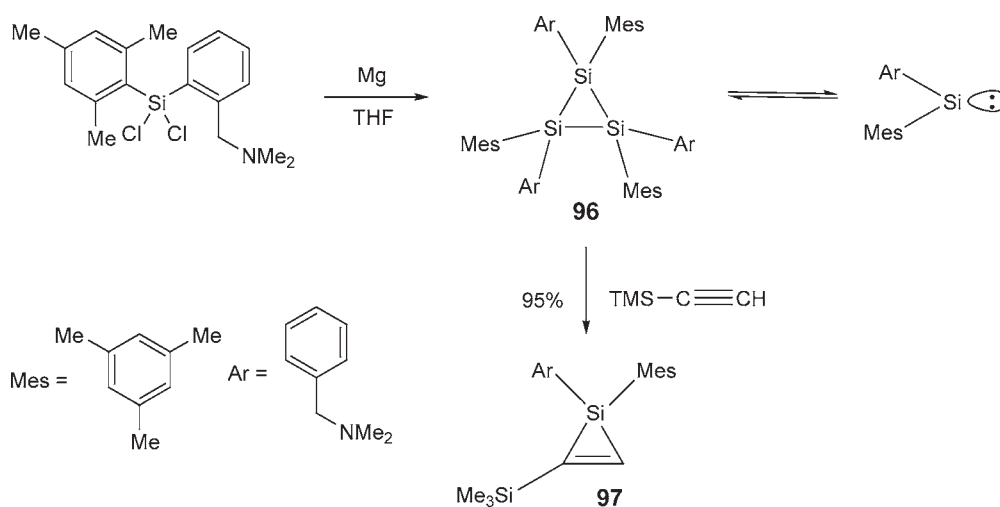
A novel synthesis of silirenes starting from bis(diazomethyl)silanes was described <1999OM2791>. Treatment of the corresponding triflates with diazomethane allowed the formation of the diazo compounds. Irradiation of alkyl- or phenyl-substituted diazo compounds in an argon matrix or organic glasses at cryogenic temperatures produced 1,1-disubstituted silirenes **95a–d** in high yields. They were characterized by comparison of the experimental IR spectra with DFT calculations. The silirene **95c** was stable enough, in solution below –50 °C, to be characterized by ¹H- and ¹³C-NMR spectroscopy. They suffer ring-opening reactions by UV irradiation, which leads to the formation of the corresponding ethynylsilanes (Scheme 29). The first silirenes without substituents at the double bond were produced using this method <1994AGE766>.



Scheme 29

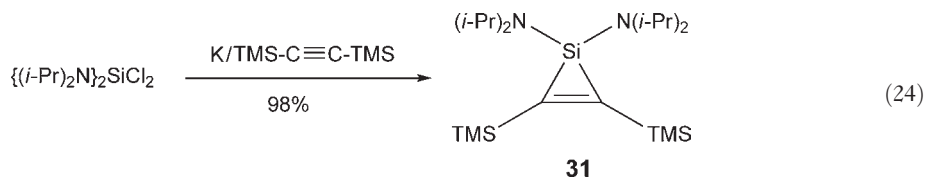
1.09.6.2.1(iii) Silylenes by reduction of dihalosilanes

Reductive dehalogenation of highly coordinated dichlorosilanes with magnesium yield cyclotrisilane **96**, which is in equilibrium with silylene and can be used as a versatile synthetic equivalent for this silylene. It was quantitatively converted to the corresponding silacyclopene **97** by treatment with an excess of trimethylsilylacetylene (Scheme 30) <1998CEJ852>.

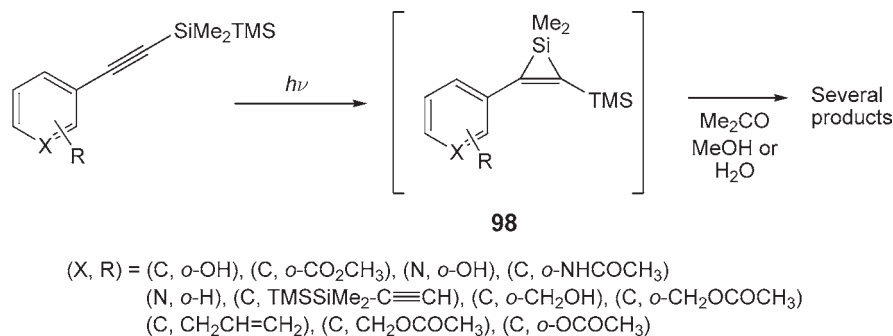


Scheme 30

3,3-Bis(diisopropylamine)-1,2-bis(trimethylsilyl)-3-silacyclopene **31** was synthesized by reacting a dihalogenated silane with potassium in the presence of an excess of bis(trimethylsilyl)acetylene in good yields (Equation 24) <1997BCJ253>. The molecular structure was studied by X-ray diffraction and the significant deformation of the ring structure was analyzed in terms of the substituent effects <1998OM3819>.



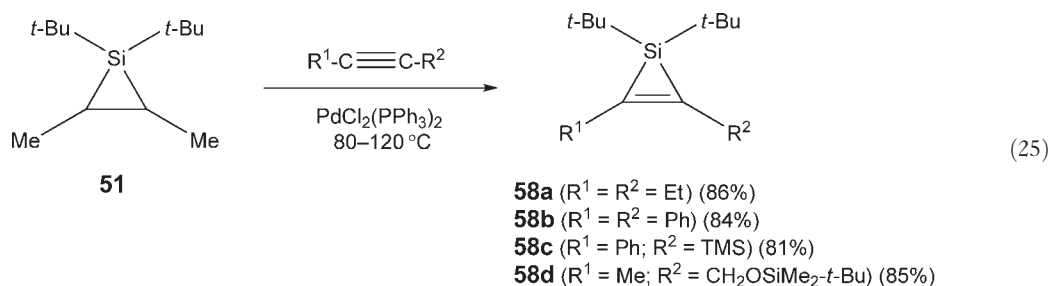
In a series of related papers, the group of Park and co-workers suggested a silacyclopropene intermediate as part of the concerted intramolecular cycloaddition process of the photoinduced reaction of several pentamethyldisilanyl-ethynyl derivatives. The intermediates, possessing a silacyclopropene moiety similar to **98**, were trapped, most of the times, as their photoadducts with acetone, methanol, and water (**Scheme 31**) <1998BKC686, 1999JPH67, 1999BKC547, 2000JPH155, 2000JPH219, 2001BKC1202, 2001JPH167, 2002JPH125, 2003JPH145, 2003JPH15, 2004JPH87>. In other work silacyclopropene intermediates were formed via the singlet excited state in the photolysis of 1-aryl-4-(pentamethyldisilanyl)but-1,3-diynes and trapped with methanol to give the corresponding photoadducts <1995BKC988>.



Scheme 31

1.09.6.2.1(iv) Metal catalyzed

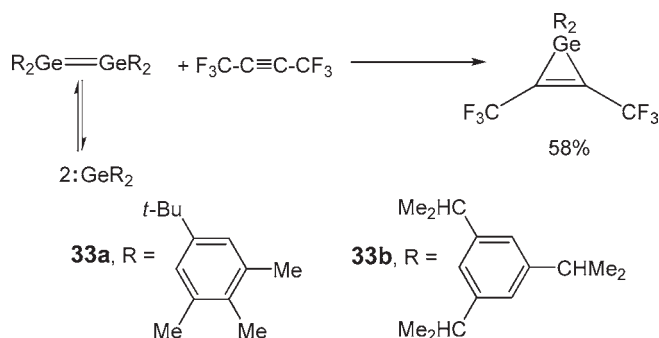
Thermally stable silirenes (**58a–d**) were produced in high yields (81–86%) by a Pd-catalyzed reaction of *cis*-1,1-di-*t*-butyl-2,3-dimethylsilirane **51** with disubstituted alkynes (alkyl-, aryl-, trimethylsilyl-, and heteroatom-substituted (**Equation 25**). Siliranes were then used to produce trisubstituted siloles (**Equation 12**) <1997OM4824>.



1.09.7 Synthesis of Three-Membered Rings with One Germanium or Tin Atom

1.09.7.1 Ring Formation by [2+1] Cycloaddition

Two germacycloprenes, **33a** and **33b**, were obtained from the reaction of tetrakis(2-*t*-butyl-4,5,6-trimethylphenyl)digermane and tetrakis(2,4,6-triisopropylphenyl)digermane with hexafluorobut-2-yne (**Scheme 32**). A short C=C double bond length (132.4 pm) and an acute bond angle were revealed by X-ray diffraction for **33a**. The short double bond may be the consequence of the strongly electronegative CF_3 groups. The molecule should be electron rich and be able to participate in reactions with numerous multiple bond systems <2002ZFA2821>.

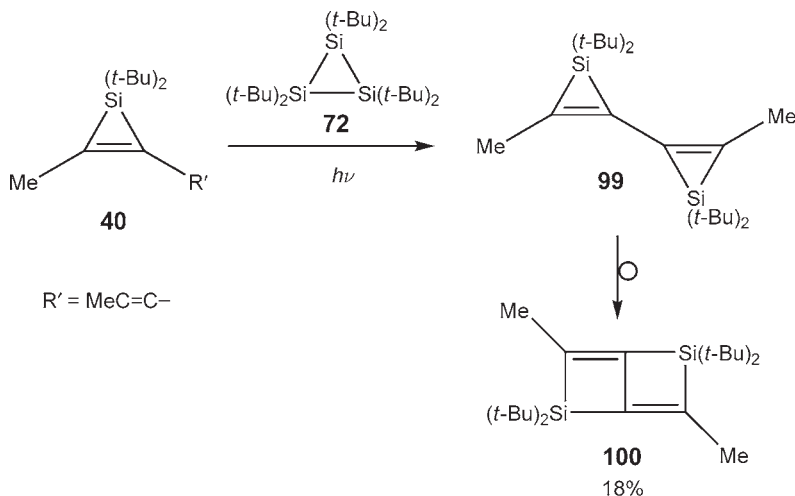


Scheme 32

1.09.8 Synthesis of Compounds Containing more than One Three-Membered Ring with One Silicon Atom

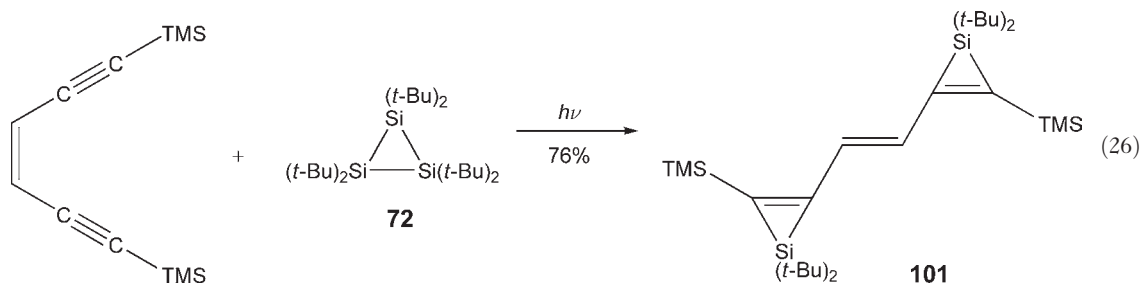
1.09.8.1 Three-Membered Rings Bridged by a C–C Bond

Further photolysis of silacyclopentene **40** with **72** produces a colorless crystalline solid: the bis(silirene) **99** (Scheme 33). The molecule is unstable in air and suffers a rearrangement to generate 2,5-disilobicyclo[2.2.8]hexa-1(6)-3-diene **100**, as confirmed by X-ray crystallography <1998OM1237>.

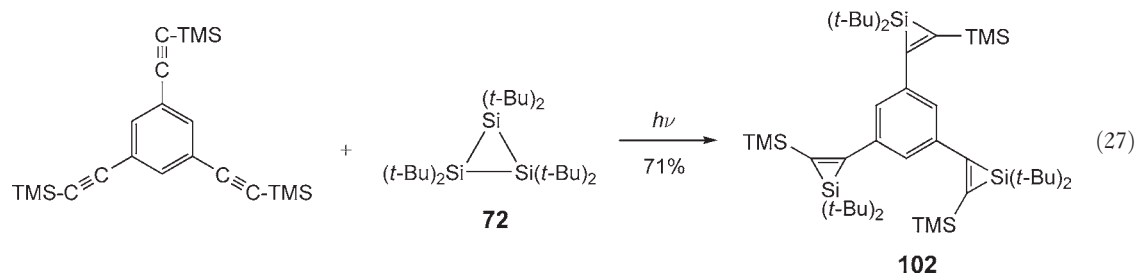


Scheme 33

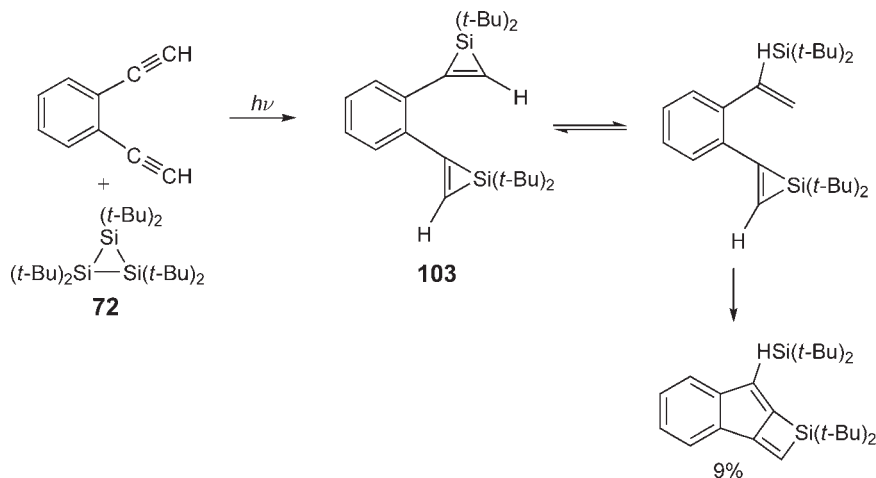
Photolysis of cyclotrisilane **72** in the presence of 1,6-bis(trimethylsilyl)-(Z)-3-hexene-1,5-diyne resulted in the formation of yellow crystals of bis(silirene) **101** with an olefinic double bond linkage in 76% yield (Equation 26) <2002OM636>.



When the photolysis is carried out in presence of 1,3,5-tris(trimethylsilyl)ethynylbenzene, colorless crystals of tris(silirenyl)benzene **102** were formed in 71% yield (Equation 27). Both products, **101** and **102**, were characterized by X-ray diffraction <2002OM636>.



Co-photolysis of the same silylene precursor, **72**, with 1,2-diethynylbenzene yields a tricyclic system with an exocyclic *t*-Bu₂SiH group via a bis(silirenyl)benzene **103** intermediate followed by a 1,2-hydrogen shift to give the vinyldiene derivative (Scheme 34) <2002OM636>.

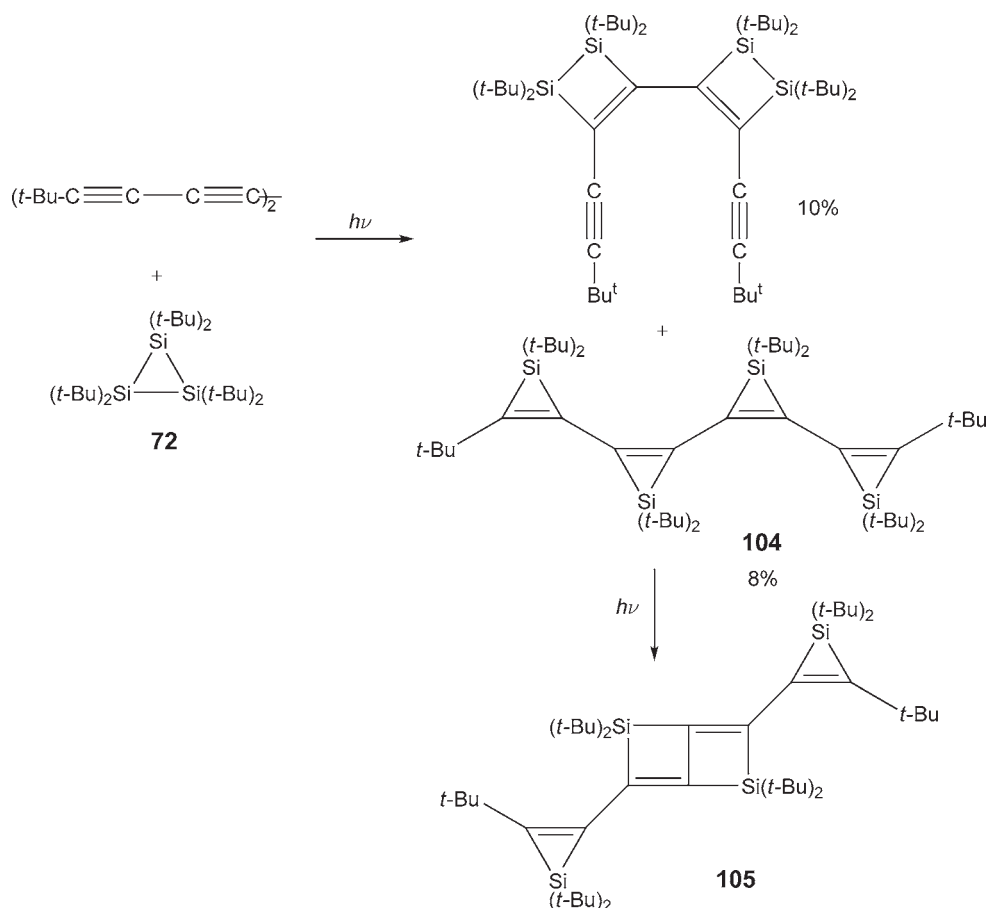


Scheme 34

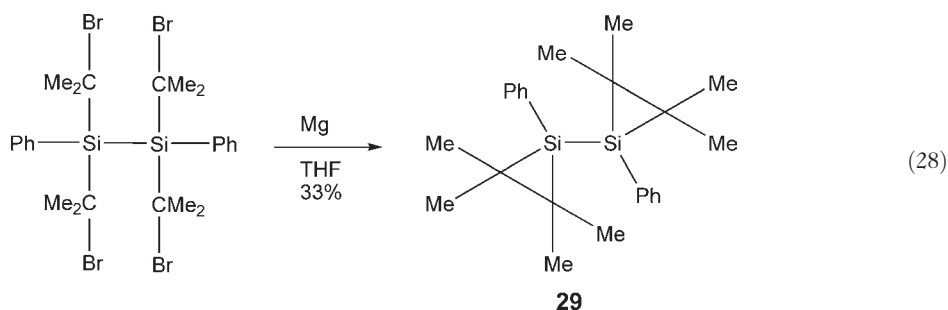
Co-photolysis of the precursor **72** and 2,2-11,11-tetramethyldodeca-3,5,7,9-tetrayne yields a mixture of products from which three homogeneous compounds were separated by fractional crystallization and isolated in yield ranging from 7% to 10% (Scheme 35) <2000OM(19)4938>. A quatersilirene **104** formed by [2+1] cycloaddition of the cyclotrisilane to all four C–C triple bonds was obtained and characterized by ²⁹Si-NMR and X-ray diffraction techniques. Bond lengths and angles are almost the same as those for similar molecules such as bis(silirenes). The third product, a 2,5-disilabicyclo[2.20]hexa-1(6),3-diene **105**, with two terminal silirene groups, produced by photochemical rearrangement of the quatersilirene, was also characterized by ²⁹Si-NMR spectroscopy and X-ray diffraction techniques.

1.09.8.2 Three-Membered Rings bridged by an Si–Si Bond

Bis(silacyclopropane) (see structure **29**) was synthesized by reacting diphenyltetrakis(1-bromo-1-methylethyl)-disilane with magnesium (Equation 28). This product is stable but it slowly decomposes or polymerizes in solution <1997JA3629>.



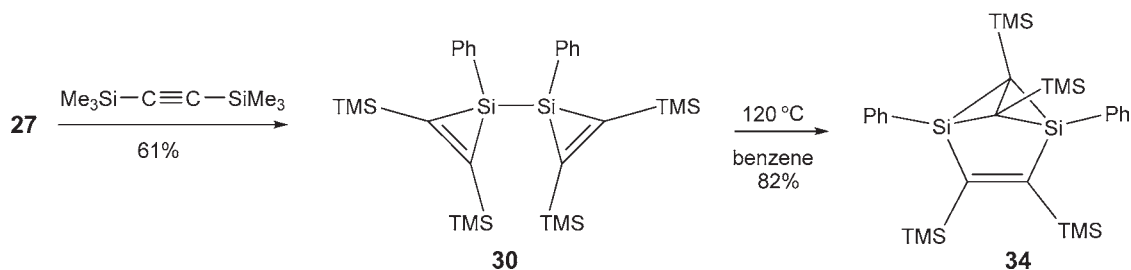
Scheme 35



Thermolysis of **29** in presence of bis(trimethylsilyl)acetylene at 60°C yields bis(silacyclopropane) **30** (61%), which is unstable to moisture and air oxidation [\[1997JA3629\]](#). Thermolysis of **29** in a degassed sealed tube produced the dimer disilabenzvalene **34** in 87% ([Scheme 36](#)).

1.09.9 Gas-Phase Studies

The group of Walsh has recently begun a series of gas-phase studies of the kinetics of SiH_2 and GeH_2 reactions by time-resolved means leading to the directly measured rate constants for these species. They found that GeH_2 insertion reactions have more negative activation energies than the analogous SiH_2 reactions. The investigations of reactions of GeH_2 are less extensive than those made for SiH_2 . Nevertheless, kinetic studies have been carried out for



Scheme 36

the insertion reactions GeH_2 into $\text{Ge}-\text{H}$ and $\text{Si}-\text{H}$, of the π -type addition reactions to C_2H_4 , C_2D_4 , $\text{CH}_3\text{CH}=\text{CH}_2$, and C_2H_2 . These studies were accomplished by the analysis of the reaction potential energy surface by quantum chemical calculations to see if there might be the possibility of an unusual mechanistic pathway <1995CPL513, 2001PCCP(3)2343, 2001JOM49, 2002PCP6001>.

Al-Rubaiey *et al.* reported time-resolved studies of silylene addition reactions ($\text{SiH}_2 + \text{C}_3\text{H}_6$, $\text{SiH}_2 + i\text{-C}_4\text{H}_8$, $\text{SiMe}_2 + \text{C}_2\text{H}_4$) over the pressure range 1–100 torr and at temperatures in the range 293–600 K, using laser flash photolysis techniques. All three reactions showed evidence of pressure dependence consistent with third-body assisted association reactions to form silirane products. The experimental ΔH° values yield strain energies of 190, 196, and 216 kJ mol^{-1} for 2-methyl-, 2,2-dimethyl-, 1,1-dimethylsilirane, respectively. Compared to the strain enthalpy of 167 kJ mol^{-1} for silirane itself, this shows that methyl substituents in the silirane products substantially increase the strain energies. G2 calculations support these conclusions <1998PCA8564, 1999PCA10945, 2002PCP5072>.

1.09.10 Further Developments

A recent review on sila- and germacyclopropabenzene has been published <2006OM3522>, and the use of silacyclopropanes as synthetic intermediates has been exploited in two recent works <2006OL4109, 2007JOC1027>.

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 1998EJO1313
 1998IJQ291
 1998JA5005
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 1998OM2404
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 1998PCA8564
 1999PCA522
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 2003JPH145
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1.10

Three-membered Rings with One Boron Atom

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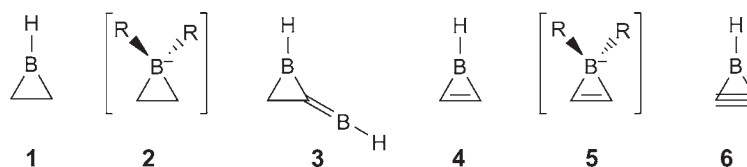
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1.10.1 Introduction

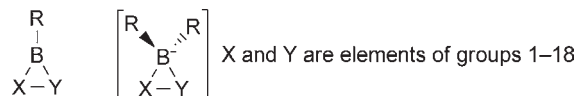
The present article covers synthetic methods, physicochemical properties, and spectroscopic measurements, as well as further applications of three-membered ring molecular systems with one boron atom, including both theoretical and experimental aspects. The survey encompasses the research in the field during the period between 1996 and 2006. In the past reviews of three-membered rings with one boron atom included in CHEC-II

* An important part of the current review was performed during a one-year stay at the Instituto de Química, UNAM, Mexico.

<1996CHEC-II(1)333>, molecules containing one boron and two carbons were systematically named as: borirane **1**, boratirane **2**, borirane-2-ylidene borane **3**, 1*H*-borirene **4**, boratirene **5**, and 1*H*-boryryne **6**.



Since these molecules represent the parent structures, we decided to follow this classification with the inclusion of heteroelements in the main three-membered ring, such as those belonging to groups 1–18, as depicted in the following scheme.



The structurally important ^{11}B nuclear magnetic resonance (NMR) data was thoroughly established in the previous chapter of CHECII <1996CHEC-II(1)333>. Since most of the structural evidence is based on ^{11}B NMR data, the values previously reported are given for comparison purposes. The ^{11}B chemical shifts for structures of type **1** are in the range from 70 to 73 ppm, for type **2** from –9 to –27 ppm, the type **3** compounds have values of 34–52 ppm, for **4** between 27–49 ppm, and for **5** between –10 and –20 ppm. Compound **6** was only determined theoretically.

Although this covers more extensively systems possessing one or no carbon elements, it can be mentioned that no free B–C–C systems were reported during the period covered herein. One additional restriction is the use of three-membered rings containing structures as simple as possible, to retain the distinctiveness of these small rings.

1.10.2 B–X–Y Rings and Recent Progress in Compounds 1–6

1.10.2.1 X and Y Are Elements of the Main Group

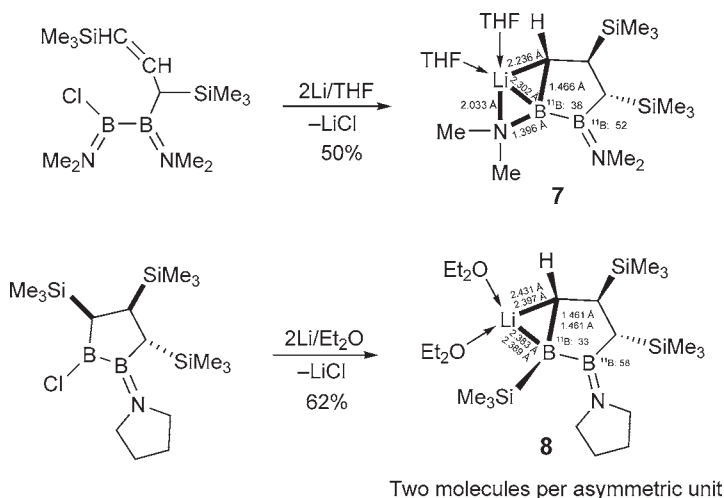
1.10.2.1.1 B–C–Li and B–N–Li systems

The reaction of the stereoisomeric mixture of (*E/Z*)-1-[1,3-bis(trimethylsilyl)allyl]-2-chloro-1,2-bis(dimethylamino)diborane with a previously formed green solution of lithium naphthalenate in tetrahydrofuran (THF), at room temperature produced, after work-up, the lithium 1,2-bis(dimethylamino)-4,5-bis(trimethylsilyl)diborolan-3-ide derivative **7** in 50% yield, as colorless crystals. This molecule presents two fused three-membered rings, formed by B–C–Li, lithium-boratirane, and B–N–Li, lithium-aza-boratirane. The X-ray structure of this derivative revealed that the nitrogen atom in the NMe_2 group prefers coordination with lithium, to form an allyl moiety analog, instead of the partial double bond formation with boron. The latter behavior was confirmed by the NMe_2 shifts in the ^1H and ^{13}C NMR spectra <2004EJI3063>. The formation of a C–B bond, carbanion stabilization by boron, and migration of a trimethylsilyl group were requirements for the formation of compound **7**. Moreover, the reaction of 1-chloro-2-piperidino-3,4,5-tris(trimethylsilyl)-1,2-diborolane in diethyl ether solution with lithium powder at room temperature, led to lithium 1-piperidino-2,4,5-*tris*(trimethylsilyl)-1,2-diborolan-3-ide **8** obtained in 62% yield as colorless crystals (Scheme 1).

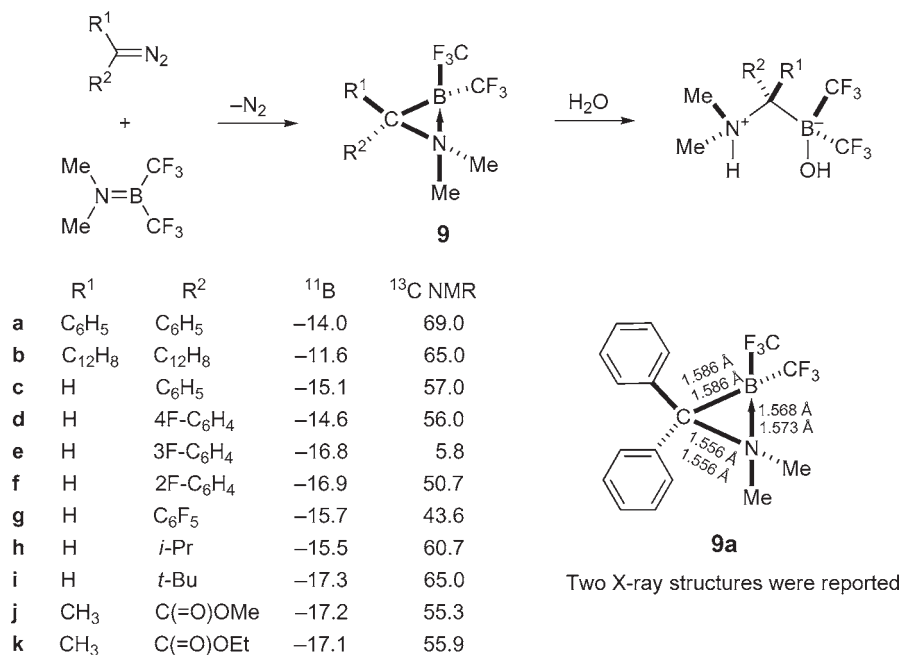
This molecule presents a lithium-boratirane (C–B–Li) ring formed by 1,2-migration of a trimethylsilyl group to a neighboring boron atom, generating a boron-stabilized carbanion. The X-ray structure of this derivative revealed two independent molecules per asymmetric unit. The two boratirane derivatives have been thoroughly characterized by multinuclear NMR and X-ray diffraction analysis.

1.10.2.1.2 B–C–N system

The reaction of a series of mono- and disubstituted diazomethanes with $(\text{F}_3\text{C})_2\text{BNMe}_2$ in pentane at -196°C led to 2,2-bis(trifluoromethyl)-2,3-dihydro-1,1-dimethyl-3,3-disubstituted-1,2-azaborirene derivatives **9a–k** as colorless solids <1999EJI255, 1996AOM147> (Scheme 2). Brauer *et al.* stated that all reactions are quantitative and the products are analytically pure.



Scheme 1

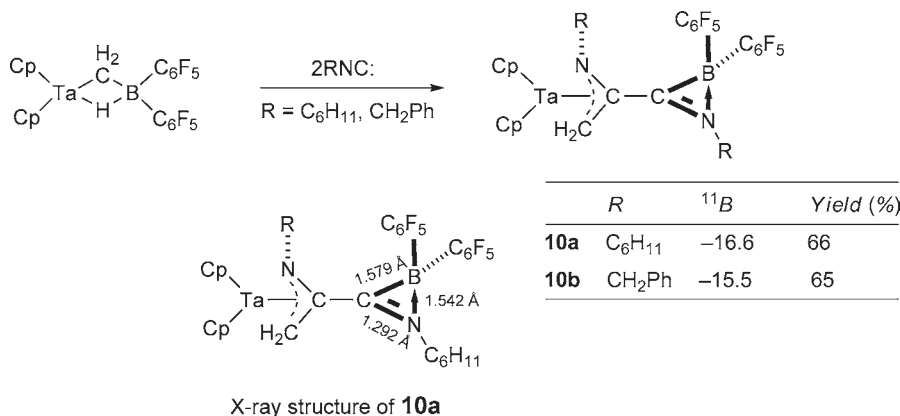


Scheme 2

All compounds of type **9** are sensitive to moisture with the exception of the R¹ = R² = C₆H₅ derivative **9a** due to decreased polarization of the N–B bond when compared with the rest of the series. The fact that these compounds hydrolyzed readily allowed to use them as synthons for the production of Me₂N⁺H–C(R¹)(R²)–B[–]–(CF₃)₂OH (as the zwitterionic species) by cleavage of the N–B bond. All three-membered ring derivatives were characterized through elemental analyses, ¹⁹F, ¹³C, ¹¹B, and ¹H NMR (CDCl₃ or CD₂Cl₂), mass spectra, and, in the case where R¹ = R² = C₆H₅, by single crystal X-ray diffraction. The ¹¹B chemical shifts appear between –17.3 and –11.6 ppm, depending on the R¹ and R² substituents. In all cases, the mass spectra clearly show the low-intensity molecular ion [M⁺], compared to the high intensity observed for the [M⁺–CF₃] and [M⁺–C₂F₅] fragments. For almost all cases, the base peak was found to be the [(CH₃)₂NCHR⁺] fragment.

1.10.2.1.3 B–C≡N system

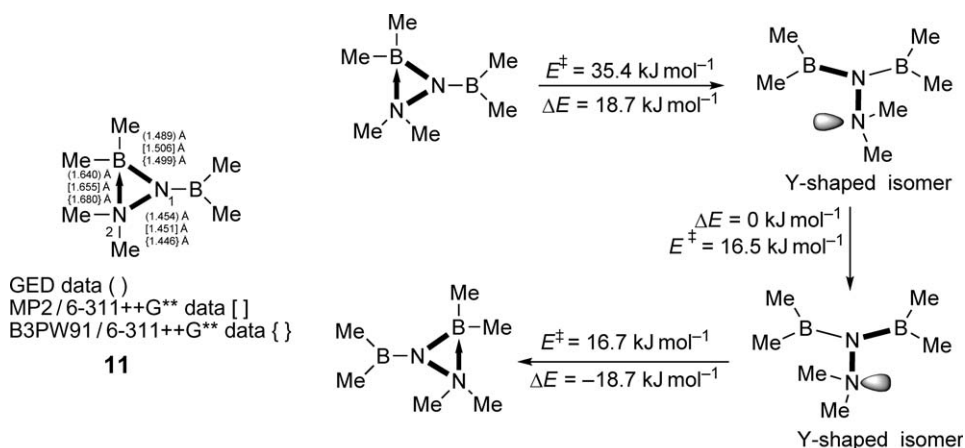
The reaction of $\text{Cp}_2\text{Ta}(\text{CH}_2\text{B}(\text{C}_6\text{F}_5)_2)(\mu\text{-H})(\text{CH}_3)$ with cyclohexyl or benzyl isocyanide, in THF under argon at -78°C and 1 atm pressure, formed the $\text{Cp}_2\text{Ta}^{\text{III}}(\eta^3\text{-(2-(2-substituted-azo-(dipentafluorophenyl)boratirenyl)-substituted)-azoallyl})$ compounds, where R = cyclohexyl (C_6H_{11}) **10a** or benzyl (CH_2Ph) **10b**; both derivatives contain the $\text{N}=\text{C}-\text{B}$ azo-boratirene subsystem <2002OM2422> and were characterized through elemental analyses, multi-nuclear NMR ($\text{THF-}d_8$), and, in the case where $\text{R}=\text{C}_6\text{H}_{11}$, by single crystal X-ray diffraction (Scheme 3).



Scheme 3

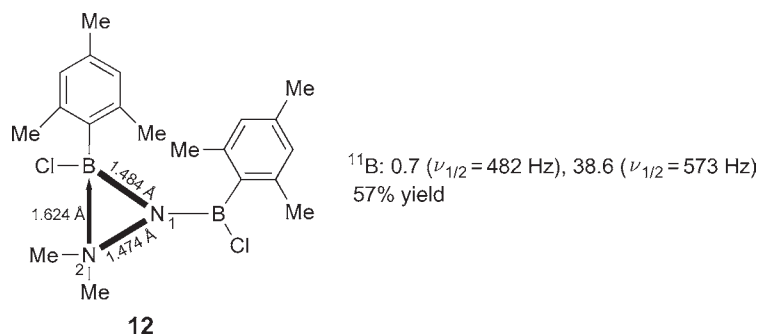
1.10.2.1.4 B–N–N systems

1,1-Bis(dimethylboryl)-2,2-dimethylhydrazine **11** was first synthesized in 1981 by Fußstetter and Nöth. <1981LA633>, who showed that the compound is stable below -70°C and is of monomeric nature in the gas phase, as demonstrated by mass spectrometry <2005DT2284>. This compound possesses a diazo-boratirene fragment and was characterized in 1955 by Bastiansen *et al.* using gas electron diffraction (GED) <1955ACS232, 2005DT2284>; its three-membered ring structure and some other possible 'Y'-type isomers were calculated through MP2/6-311++G** and B3PW91/6-311++G** levels of theory (Scheme 4) and the theoretical data compared with experimental evidence determined by Østby *et al.* <2005DT2284>. The ^1H , ^{13}C , and ^{11}B NMR spectra of this compound recorded at room temperature displayed only one peak which was assigned to the two equivalent dimethylboryl groups. The intramolecular rearrangement process and the two transition states, were computed at the B3PW91 level performing Hessian matrix calculations, showing one imaginary frequency to determine the first order saddle points, followed by further MP2 repetition of the structure optimizations.



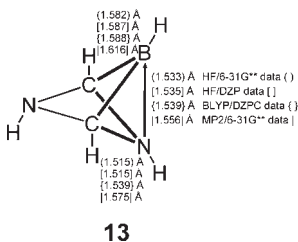
Scheme 4

Another example of a B–N–N system is that obtained by reaction of 1,1-dimethyl-2,2-bis(trimethylstannyl)hydrazine with dichloro-mesityl-borane giving, after removal of the solvents and sublimation of the Me_3SnCl , the 2,2-bis(chloromesitylboryl)-1,1-dimethylhydrazine **12** as a colorless powder; this compound possesses a diazaboratirane subsystem <1999EJI1765>. Compound **12** was characterized by multinuclear (^1H , ^{13}C , ^{11}B) NMR and infrared (IR) spectroscopies, mass spectrometry, single crystal X-ray diffraction, and elemental analysis. The shielding of the tetracoordinate boron atom suggests high electron density due to the high basicity of the hydrazine nitrogen atom bearing two methyl groups. The mass spectrometry data indicates that the molecular ion is also the base peak, due to stabilization of the positive charge by delocalization into the mesityl system attached to the boron atom, leading to few secondary fragments.



1.10.2.1.5 Bis B–C–N systems

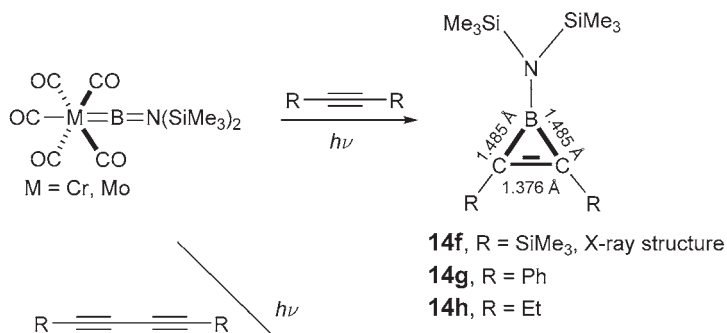
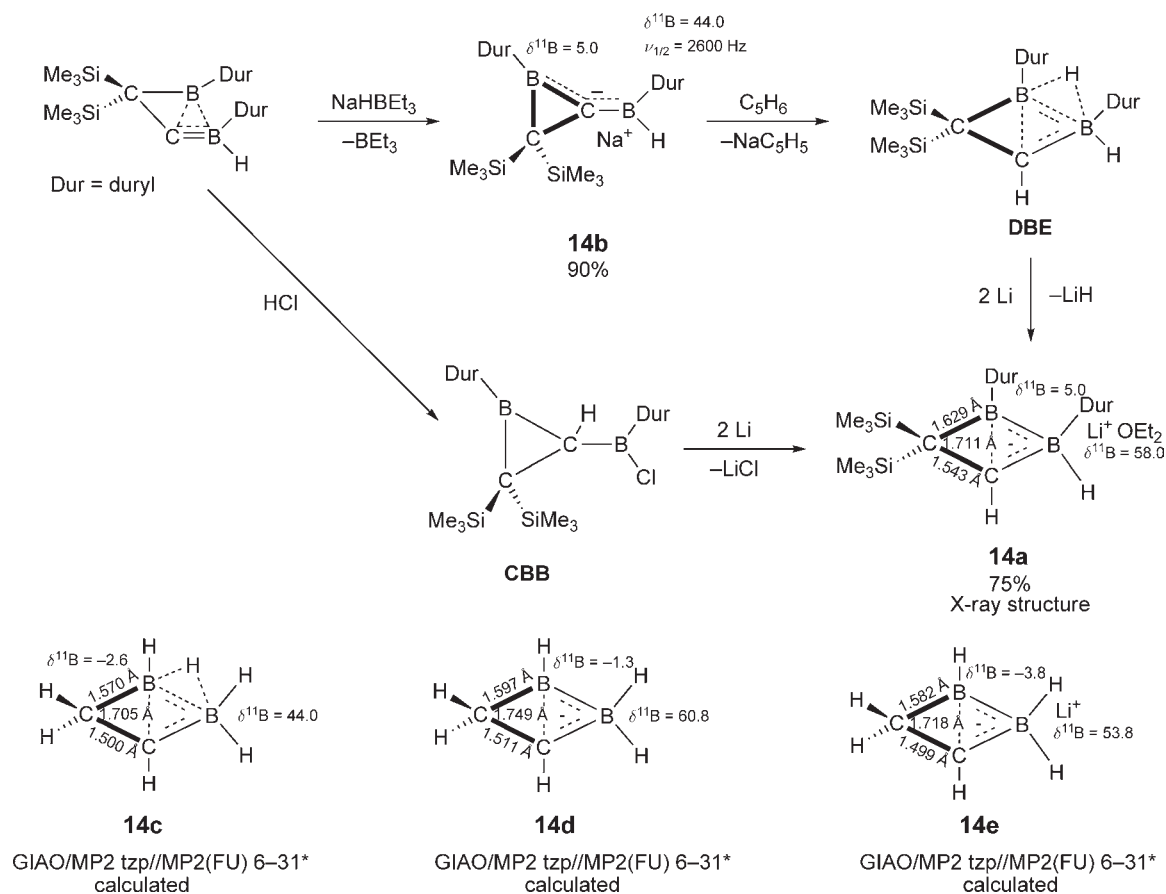
The azo-boratirane system, tetracyclo [4.4.4.4]-l-bora-3,5-diazapentane **13** (of pendulum type), has been predicted theoretically at the HF/6-31G**, HF/DZP, BLYP/DZP, and MP2/6-31G** levels of theory. The calculations show that the system undergoes rapid topomerization with a low-energy barrier of about 6.7–11.8 kcal mol^{−1} <1996CPL173>. The noncoordinated boron structure turned out to be the transition state, wherein all levels of theory show one imaginary frequency (188.2, 157.1, 269.7, and 299.8 cm^{−1}). In this compound, the boron coordinates with the nearest nitrogen through a dative bond, to give two faces of the system as the azo-boratirane subsystems. The low energy value for the topomerization process can be explained by the facile dissociation of the N→B bond in this strained molecule, as well as the presence of the neighboring donor site.



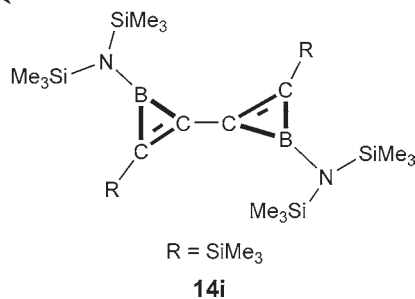
1.10.2.1.6 B–C–C, B–C=C, and bis(B–C=C) systems

There have been reported very few examples of systems containing the B–C–C three-membered ring and they are outlined in this section of the review. The group of Berndt <1996AGE1990> prepared and characterized compound **14a**, which was obtained through two different reaction pathways, one involving the formation of a nonclassical (homoaromatic) 1,2-diboretane (DBE) from **14b**; and the other route by the formation of a chloroborylborirane (CBB) (DBE and CBB were mentioned references cited in <1996AGE1990>). As underlined by the authors, the structure of **14a** was deduced from the experimental NMR data as well as the NMR/GIAO/MP2/tzp//MP2/6-31G* calculations of its homoaromatic unsubstituted DBE analogue **14c**, its unsubstituted anion **14d**, and its unsubstituted Li⁺ salt **14e**.

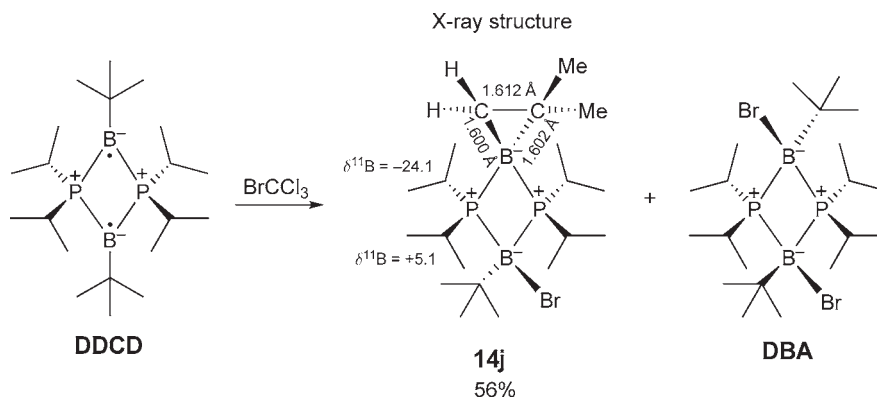
Some borirenes were reported recently by the group of Braunschweig <2005AGE7461>. The photolysis reactions of $[(\text{OC})_5\text{M}=\text{BN}(\text{SiMe}_3)_2]$ (M = Cr, Mo) <2006AGE5254>, as borylene moiety transfer reagent, in the presence of mono- and bis-alkynes produced the desired borirenes **14f–i** <2005AGE7461>. All reactions were monitored by ^{11}B NMR. The X-ray diffraction study for compound **14f** revealed the geometrical variables for this three-membered ring structure. As stated by Braunschweig <2005AGE7461, 2006AGE5254>, the previous synthetic routes to obtain these molecules were neither robust, nor simple or high yield, while the present strategy led to cleaner products in a single step with high yield.



Compound	$\delta^{11}\text{B}$ (ppm)	Yield (%)
14f	+33.2	82
14g	+25.0	88
14h	+25.0	100
14i	+28.0	11

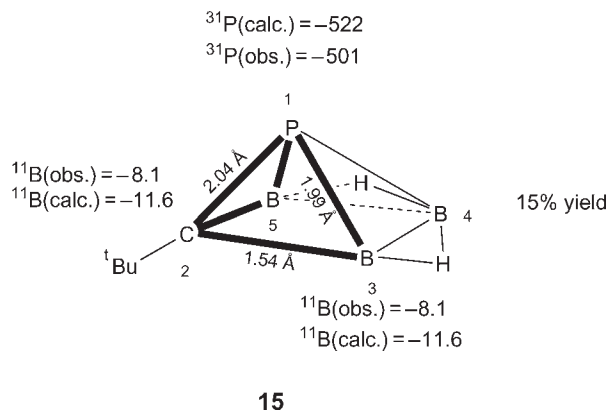


The boratirane **2** type molecule **14j** reported by Amii and co-workers <2004JA1344> was obtained, along with 1,3-dibromo adduct (DBA), during the reaction of 1,3-dibora-2,4-diphosphonio-cyclobutane-1,3-diyl (DDCD) with bromo-trichloro-methane evidencing the radical behavior of DDCD. This boratirane shows a novel spiro-B junction that preserves the four membered-ring present in DDCD as established by the X-ray structure of **14j**. The ^{11}B NMR data for **14j** presented a single broad signal for the B-spiro-boratirane at +24.0 ppm, while the bromine borate, appeared in -24.0 ppm.



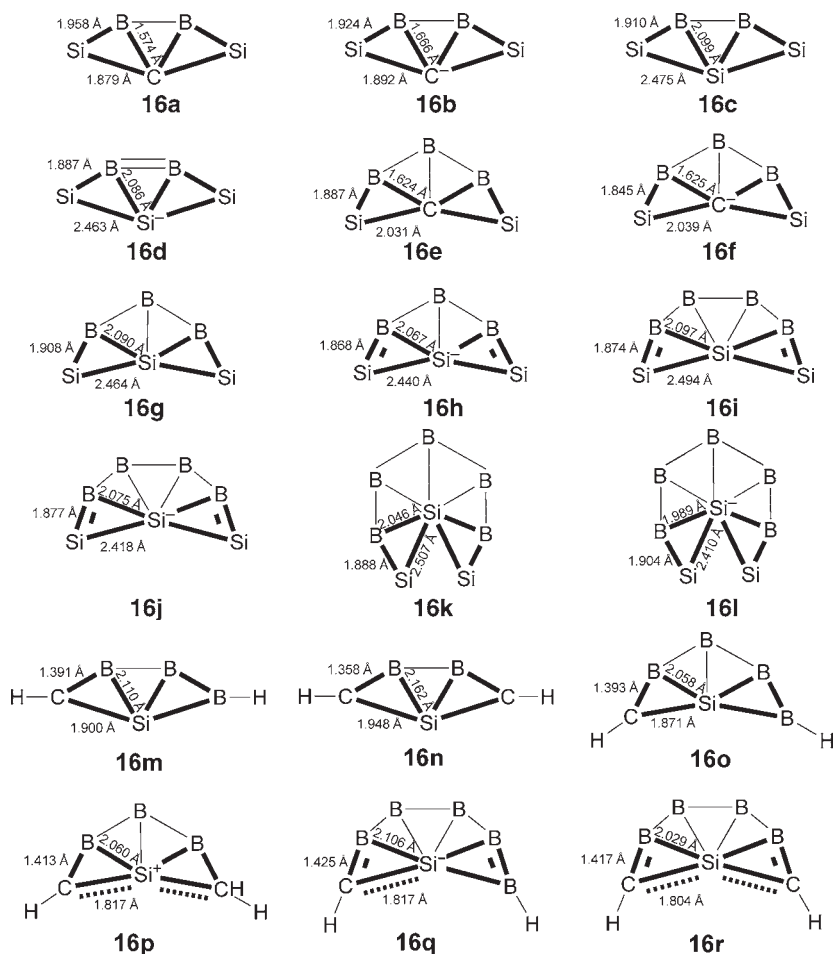
1.10.2.1.7 Bis B-C-P system

The gas-phase reaction between $\text{P}\equiv\text{C}/\text{Bu}$ (phosphaalkyne) and B_4H_{10} (tetraborane) led to 2-*t*Bu-1,2-PCB₃H₅ (*nido* five-vertex phosphacarborane, **15**) in which two equivalent faces gave three-membered rings with B-P-C, the phospho-boratirane subsystem <2002CC1448>. The unusual ^{31}P NMR chemical shift and two different ^{11}B resonances were indicative of the symmetry of the molecule. Theoretical calculations at the MP2/6-31G* level of theory evidenced that the minimum structure corresponds to the 2-*t*Bu-1,2-PCB₃H₅ compound, while the 1-*t*Bu-2,1-PCB₃H₅ isomer resulted ca. +2.3 kcal mol⁻¹ higher in energy. The calculated NMR data at the GIAO/B3LYP/6-311G*//MP2/6-311G are clearly in good agreement with the experimental values.



1.10.2.1.8 B-C-M (M = Si, Ge, and Sn) and B-Si-Si systems

Significant theoretical and experimental efforts to get a planar arrangement of atoms belonging to representative elements, which are included in simple and elaborate molecular entities, appeared in the last decade. Along this line, an interesting structural pattern **16a-r** has been presented by the group of Li, where planar central silicon and carbon atoms with tetra-, penta-, hexa-, and heptacoordination numbers were found for the former and tetra- and penta-coordination numbers for the latter <2004JA16227>.



The sila-, germa-, and stanna-boranes **16s–x**, possessing pyramidal boron atoms, were predicted theoretically <2003AGE539>; the sila-compound at the B3LYP/6-311+G** and CCSD(T)/6-311+G** levels of theory showed energy stabilizations of -2.4 and -4.1 kcal mol $^{-1}$, when compared with the system having a planar tricoordinate boron atom, which resulted to be the transition state in almost all cases (determined at B3LYP/6-311+G** with an imaginary frequency at 341 cm $^{-1}$). When the R substituent is fluorine **16v**, the most stable arrangement is the planar tricoordinate boron atom. These findings indicate that pyramidalization at the boron atom is highly dependent on stereoelectronic factors. The germa- and stanna-boranes were calculated at the B3LYP/LANL2DZ^C level of theory. According to the energies obtained for both, tricoordinate planar and pyramidal boron, these calculations clearly evidenced that when going down the column in group 14, the energy difference increases in favor of the pyramidal boron arrangement, even though the pyramidal boron is geometrically shorter. The geometric parameters for the germa- and stanna-boranes were not reported in the contribution.

	Calculated bond distances in Å at the B3LYP/6-311+G** () and CCSD(T)/6-311+G** [] levels of theory and preferred geometric arrangement of B			
		B–C	B–Si	C–Si
	s M=Si, R=H, pyramidal B	(1.481), [1.498]	(1.911), [1.912]	(2.109), [2.107]
	t M=Si, R=SiH ₃ , pyramidal B	(1.482)	(1.916)	(2.103)
	u M=Si, R=Me, pyramidal B	(1.502)	(1.943)	(2.023)
	v M=Si, R=F, planar B	(1.539)	(1.955)	(1.943)
	w M=Ge, R=H, pyramidal B			
	x M=Sn, R=H, pyramidal B			

These results were presented theoretically first at the B3LYP/Lan12dz and further optimized at the B3LYP/6-311++G(3df,p) level. All compounds **16** were minima verified through harmonic analysis of the optimized structures at the latter level of theory. The MP2 procedure, with the latter basis set, produced almost the same geometries with

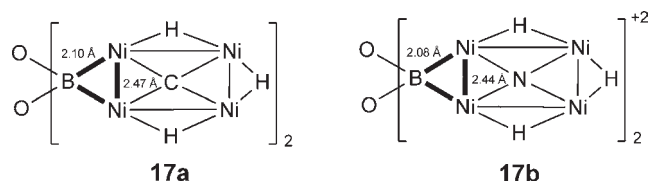
bond length differences smaller than 0.02 Å. All complexes included have the B–C–Si, siliconboratirane, or B–Si–Si, disiliconboratirane, systems. The molecular design of these compounds was systematic throughout the consecutive addition of boron atoms in the C_{2v} fan-type structures. The absence of the B_6Si_2Si derivative in the series is due to the instability of the planar octacoordinate geometry for the central silicon atom, thus hindering further study. All compounds have shown the lower frequency values greater than 100 cm^{-1} . Some other results along this line were published in 2005 by the same group <2005JPC(A)4133>.

1.10.2.2 X and Y Are Elements of the Transition Group

This type of boron-containing compound is named depending on the metallic substitution present in the system. A general example is (metal 1)–(metal 2)–borirane or –borirene (e.g., platinum–iron–borirane), where the metal with higher atomic number has been placed first. It is worth mentioning that the Braunschweig group has explored an important part of this boron chemistry employing transition group elements. Very recently, this group made use of the bridged borylene terminology in analogy with carbene-type structures <2003EJI393>. In this review, the first naming scheme has been used in order to maintain the nomenclature employed in the present contribution. Along this line, the calculated and experimentally obtained molecules are discussed in the following sections.

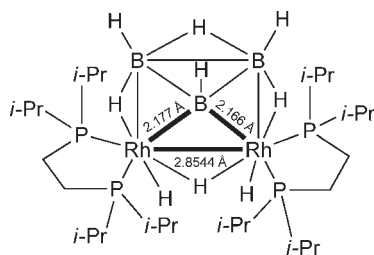
1.10.2.2.1 B–Ni–Ni system

Geometrical optimizations and electronic structural analyses of two $-O_2B_2-$ bridged hydrometal complexes $(Ni_4H_3X)_2B_2O_2^q$ ($X=C$, $q=0$; $X=N$, $q=+2$) **17a** and **17b**, which present the dinickel–boratirane subsystem, containing double tetracoordinate planar nonmetals (TPN = C, N) have been performed using the density functional theory at the B3LYP/6-311+G(d,p) level. Theoretical evidence of the possibility of two TPN centers coexisting in one planar molecule is presented <2005JPC259>. When the D_{2h} planar symmetry was maintained, an imaginary frequency was found for the N_{TPN} molecule, while the relaxation of the geometry (without symmetry restraints) led to the minimum energy structure.



1.10.2.2.2 B–Rh–Rh systems

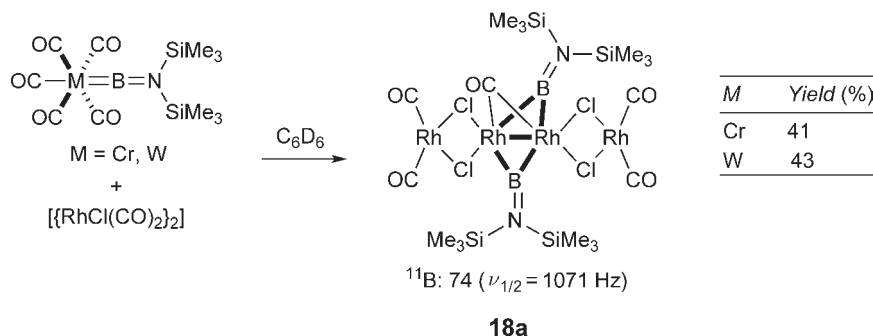
The reaction of $[Rh(IH)(DiPPE)]_2$ ($DiPPE = 1,2\text{-bis}(\text{diisopropylphosphino})\text{ethane}$) with 3 equiv of borane dimethylsulfide gave the *nido*-metallaborane $[RhH(DiPPE)]_2B_3H_7$ **18** <2004POL2665>; the yield of the product was not determined. The ^1H , ^{11}B , and ^{31}P NMR spectra (at -80°C) were recorded for the present compound showing the expected shifts for the observed nuclei. Suitable amber monocystals of $[RhH(DiPPE)]_2B_3H_7$ were used for the X-ray diffraction.



^{31}P : 106.5, 98.8 (br, d); 106.5 (dd, $J(^{187-185}Rh-^{31}P) = 169\text{ Hz}$, $^2J(P-P) = 29\text{ Hz}$); 98.4 (dd, $J(^{187-185}Rh-^{31}P) = 194\text{ Hz}$, $^2J(P-P) = 29\text{ Hz}$)
 ^{11}B : 26.7; 26.7 (dq, $J(^{11}B-^1H) = 63, 62.5\text{ Hz}$)
 ^1H : 2.7 (br, 4H, $Rh-H-B$ and terminal $B-H$), 10.0 (ttt, $Rh-H-Rh$)

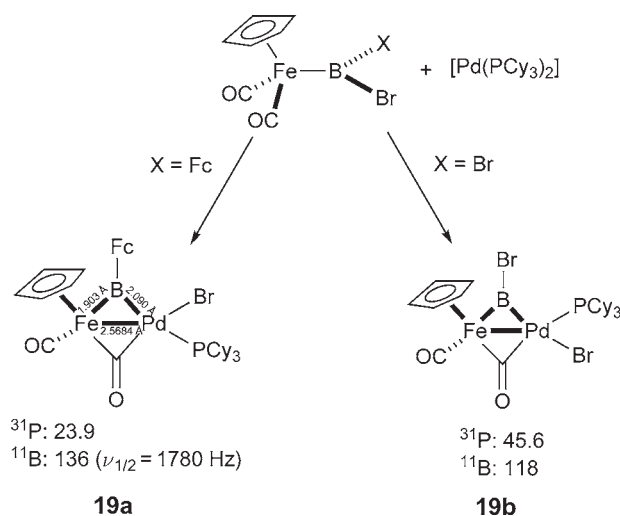
The structure of **18** turned out to be a distorted square pyramidal cluster which retained the chemical connectivity established by the NMR observations, as well. This structure is in accordance with Wade's rules of electron counting where each RhH(DiPPE) fragment is isolobal with a B–H vertex, contributing two electrons to cluster bonding.

The reaction of the terminal borylene $[(OC)_5M=B=N(SiMe_3)_2]$ ($M = Cr, W$) compounds with $[RhCl(CO)_2]_2$ in deuterated benzene for a few minutes led to formation of a tetranuclear rhodium bis-borylene compound as black crystals **18a**. The bis-borylene derivative possesses two fused B–Rh–Rh, dirhodium-borane rings $<2006AGE2132>$. Compound **18a** was characterized by multinuclear NMR and infrared spectroscopy, elemental analysis and single crystal X-ray diffraction. The ^{11}B NMR (C_6D_6) spectrum presents a single signal at 74 ppm, a low frequency shift when compared with similar systems, which normally appear between 98 and 120 ppm.



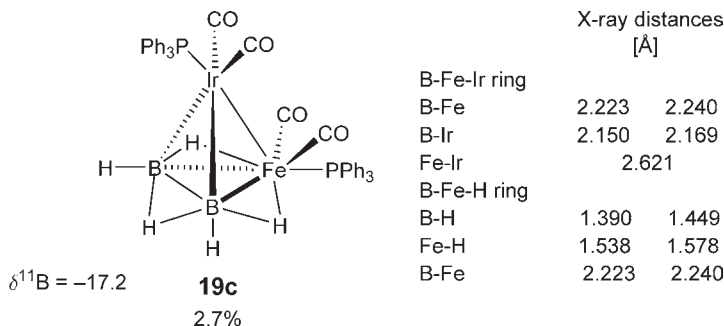
1.10.2.2.3 B–Fe–M ($M = Pd$ and Ir) systems

Recent results in the chemistry of transition metal haloboryl compounds indicate a feasible synthetic approach, where the boron atom of a specific haloboryl compound is linked to a molecular entity of electron-rich transition metal nature. The linking occurs through oxidative addition to the B–X ($X = \text{halogen}$) of the $(\eta^5-C_5Me_5)(OC)_2Fe\{B(X)Br\}$ species ($X = Br, Fc$ ($Fc = (\eta^5-C_5H_4)Fe(\eta^5-C_5H_5)$)), to the palladium center at the $[Pd(PCy_3)_2]$ molecule $<2005JA1386>$. Thus the synthesis occurs through oxidative addition of $[(\eta^5-C_5Me_5)(CO)Fe(\mu-CO)(\mu-BFc)Pd(Br)(PCy_3)]$ **19a**, a heterodinuclear bridged borylene species and the report describes the isolation, full analytical and spectroscopic characterization of $[(\eta^5-C_5Me_5)(CO)Fe(\mu-CO)(\mu-BBr)Pd(Br)(PCy_3)]$ **19b**, which represents the only example of a transition metal complex featuring the reactive B–Br bond. In these derivatives, the presence of the Pd–Fe–B (palladium–iron–borirane) ring is established also by NMR measurements (toluene- d_8). The molecular geometry of the B–Fc-substituted compound suggests a pronounced asymmetry in the bridging coordination of this group which prefers a strong interaction with iron instead of the palladium center. As has been observed, the vacant coordination site was occupied by the bridging coordination of the carbonyl ligand to produce two fused three-membered rings in both derivatives. The yields of **19a** and **19b** were not reported within the communication (Scheme 5).



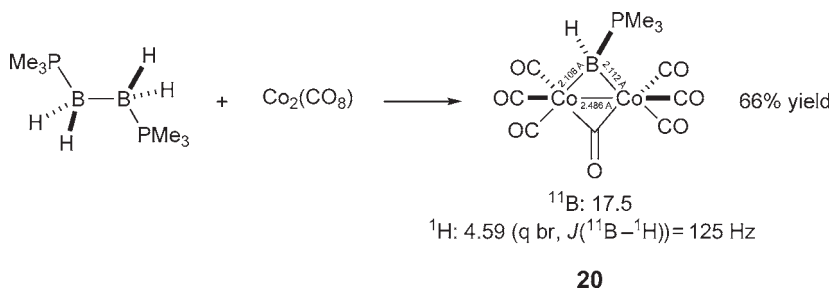
Scheme 5

Another bimetallic borirane, was prepared by reaction of $[\{\mu\text{-Fe}(\text{CO})_4\}\text{B}_6\text{H}_9]^-$ and *trans*- $\text{Ir}(\text{CO})\text{Cl}(\text{PPh}_3)_2$ in THF, forming the *nido*-[1,1,2,2-(CO)₄-1,2-(PPh₃)₂-1,2-FeIrB₂H₅] (**19c**) orange-red air stable compound in 2.7% yield <1996IC35>. Compound **19c** was characterized by NMR, IR, MS, elemental analyses and X-ray diffraction data. According to the characterization of the title compound it possesses two symmetric and fused B–Fe–Ir and B–Fe–H three-membered ring cores, which form a triangular pyramid. The $^1\text{H}\{^{11}\text{B}\}$ NMR data indicated the presence of the B–Fe–H triangular moiety showing a single signal at -13.77 ppm. The ^{11}B NMR data evidenced a broad signal at -17.2 ppm. The X-ray structure of **19c** was determined and its geometrical parameters ascertained the stated, almost symmetric, structure and the fusion scheme of the three-membered rings.



1.10.2.2.4 B–Co–Co system

The reaction of octacarbonyl dicobalt ($\text{Co}_2(\text{CO})_8$) with a two fold excess of bis(trimethylphosphine)diborane ($\text{B}_2\text{H}_4 \cdot 2\text{PMe}_3$) at -196°C was warmed to -15°C in hexane with the evolution of carbon monoxide to yield the $[\mu\text{-BH}(\text{PMe}_3)\text{-}\mu\text{-CO}\{\text{Co}(\text{CO})_3\}_2]$ compound **20** as yellow crystals, after separation of trimethylphosphine by sublimation <1998JA4222>. The B–Co–Co, dicobalt–boratirane, compound was characterized by multinuclear NMR (C_6D_6 and toluene- d_8), IR, mass spectrometry, and elemental analyses. According to the authors, the reaction course depends on the initial dissociation of $\text{B}_2\text{H}_4 \cdot 2\text{PMe}_3$ into $\text{BH}_3 \cdot \text{PMe}_3$ and $\text{BH}\cdot\text{PMe}_3$ where the latter species is the isoelectronic boron counterpart methylene and acts as the bridging moiety. The X-ray diffraction analysis could also be obtained and the geometrical parameters evidenced asymmetric bridging coordination for both the CO and $\text{BH}\cdot\text{PMe}_3$ substituents to the Co–Co core (Scheme 6).

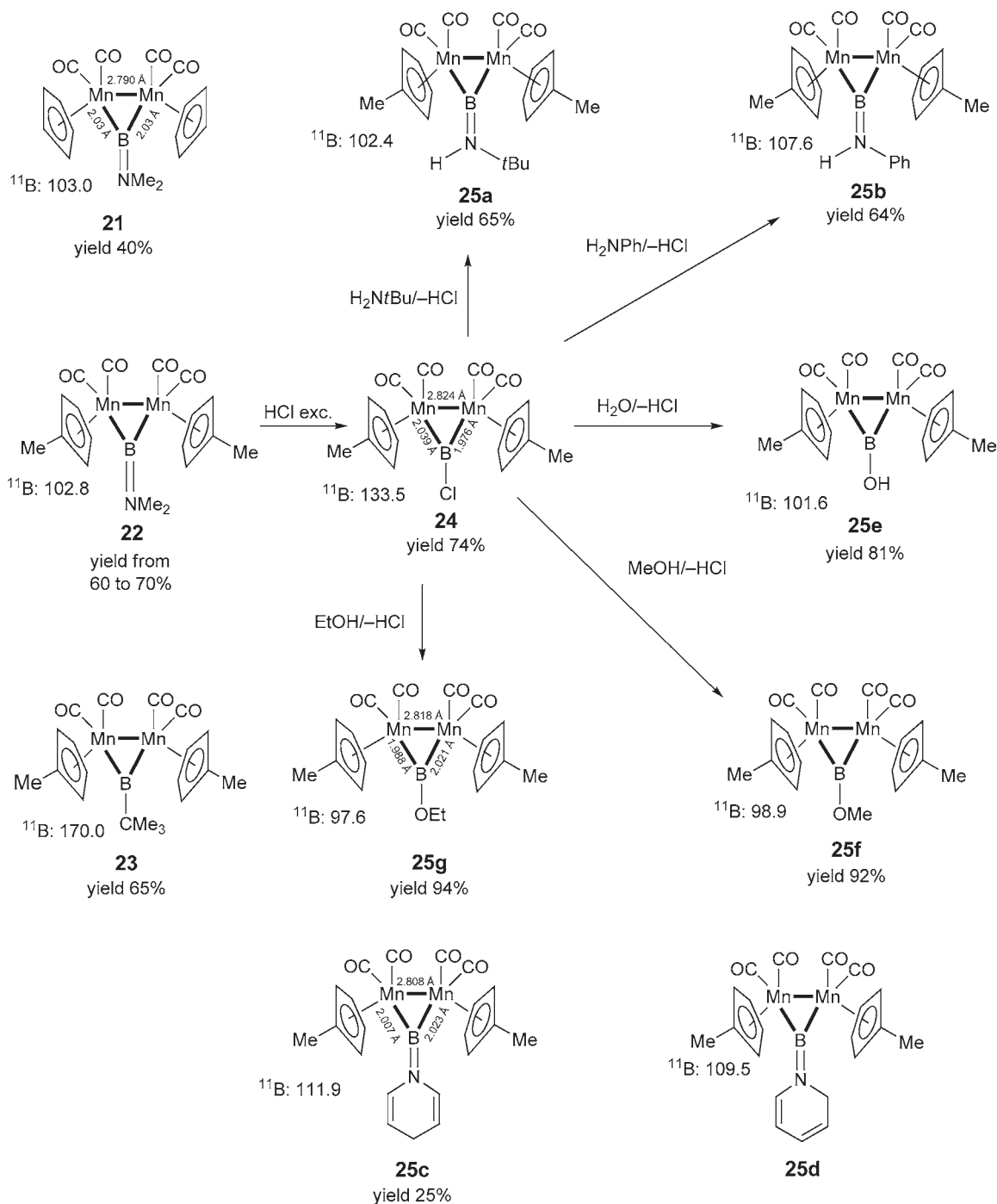


Scheme 6

1.10.2.2.5 B–Mn–Mn systems and production of B–Mn–Pd and B–Pd–Pd systems

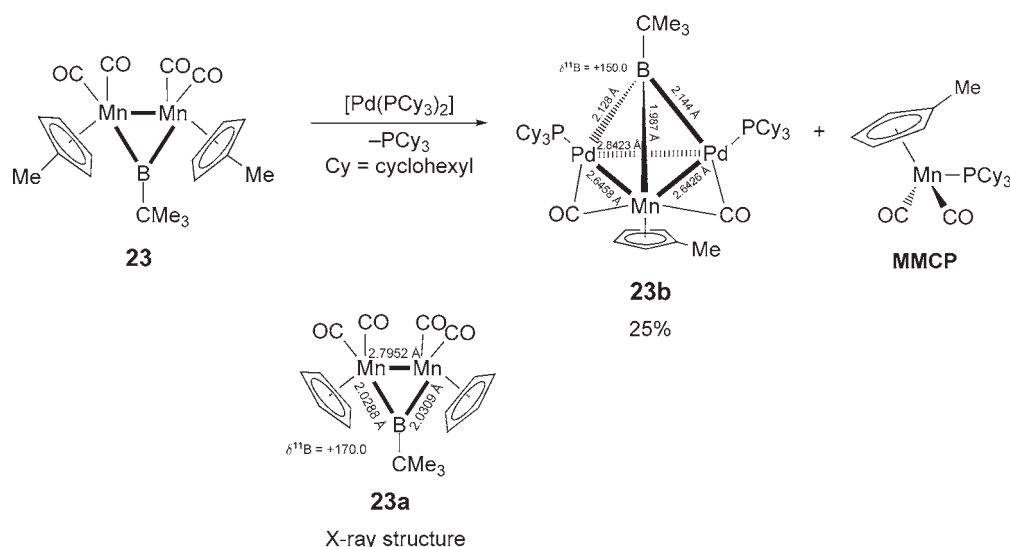
The preparation and characterization of the first bridged borylene compounds was described in 1995 by Braunschweig. The compounds obtained were $[\mu\text{-B}(\text{NMe}_2)\{(\eta^5\text{-C}_5\text{H}_5)\text{Mn}(\text{CO})_2\}_2]$ **21**, $[\mu\text{-B}(\text{NMe}_2)\{(\eta^5\text{-C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ **22**, and the $[\mu\text{-B}(t\text{Bu})\{(\eta^5\text{-C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ **23**, all three with a B–Mn–Mn dimanganese–borirane central ring. An improved synthetic approach, through the optimization of the starting material, was also reported in 1997 by Braunschweig <1997JOM163>. During the research, related references and a review have appeared <2001CCR1>. The milestone for further reactions was provided by the possibility of activation of the borylene precursor. This activation was achieved as follows: the reaction of **22** with a solution of hydrochloric acid in diethyl ether provided the $[\mu\text{-B}(\text{Cl})\{(\eta^5\text{-C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ compound **24**, containing a B–Mn–Mn, dimanganese–borirane central ring, with a chlorine substituent at boron <1997CB1295, 2002AGE1359>. At this stage, reactions involving replacement of the chlorine atom in the **24** system, with primary amines, pyridine, alcohols, and water,

produced the $[\mu\text{-B(X)}\{(\eta^5\text{-C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ derivatives, where X = NH*t*Bu **25a**, NPh **25b**, (4-hydro)pyridyl **25c**, (2-hydro)pyridyl (**25d**) (two pyridyl isomers) <2003IC941, 2004ICA1822>, OH **25e**, OMe **25f**, and OEt **25g** radicals. All compounds were characterized by multinuclear NMR (C_6D_6), IR, and elemental analyses with the exception of B = (2-hydro)pyridyl due to difficulties in the separation from its isomer; therefore, its yield was reported to be 58.6% in a 2:1 mixture (**Scheme 7**). A variation in the procedure led to exclusive formation of **25c** 25% yield. For **21**, **24**, **25c**, and **25g**, the single crystal X-ray diffraction analyses were also performed.

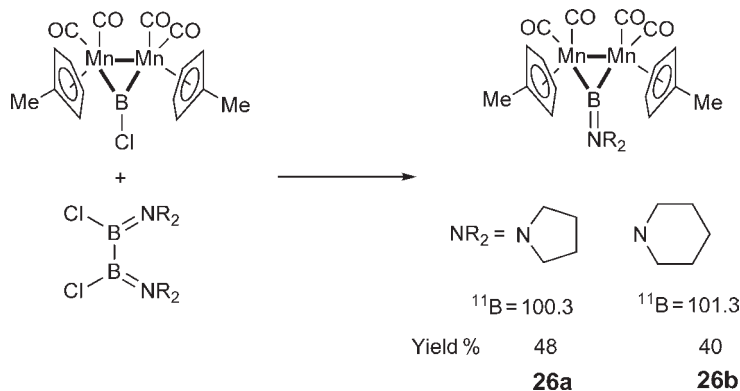


Scheme 7

Type **23** compounds remain unique examples since they are alkylborylene molecules where the unstable unsaturated structure confers the boron atom special reactivity <2001ICH1295, 2002OMC213>. Along this line, the X-ray structure of type **23** compounds <1997JOM163, 2001CCR1> was obtained <2006AGE4352> by preparing an unsubstituted analogue **23a**, according to a variant of the procedure stated earlier in this section <1997JOM163>, from $K[(\eta^5\text{-C}_5\text{H}_5)\text{Mn}(\text{CO})_2]\text{H}$ and $\text{B}_2/\text{Bu}_2\text{Cl}_2$ and recrystallizing in hexanes at -35°C . The geometrical parameters in this structure are closely related to the parent π -stabilized, amino and chloro, counterparts **21** and **24** even though such stabilization is missing in this case. Moreover, in order to track the reactivity of this type of structures, the reaction of compound **23** with $[\text{Pd}(\text{PCy}_3)_2]$ (Cy = cyclohexyl) during three days led to the preparation of more elaborated bimetallic boriranes <2006AGE4352> such as the trimetallic species $[(\mu_3\text{-B}/\text{Bu})\{(\eta^5\text{-C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})\}[\text{Pd}(\text{PCy}_3)_2]]$ **23b** obtained as red crystals with the concomitant formation of $[(\eta^5\text{-C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2]\text{PCy}_3$ (MMCP). Compound **23b** is the first example of a heterometallic μ_3 -borylene molecule, an example of homometallic μ_3 -borylene molecule will be discussed later in Section 1.10.2.2.9. The characterization of **23b** through NMR, X-ray diffraction data and DFT calculations revealed a single ^{11}B signal at +150.0 ppm, 20 ppm shielded compared to that of **23** (+170.0 ppm), as well as an interestingly localized bonding scheme albeit the charge count of this metallaborane is two electrons short of a *closo* species, which can be explained by the presence of two Mn–B–Pd 3 center 2 electron bonds. The parameters of the geometrical B–Pd–Pd three-membered ring core were measured and stated in the present contribution.



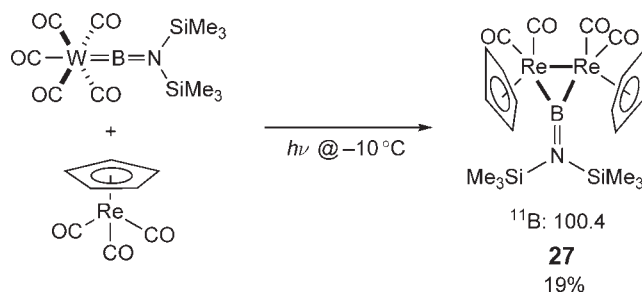
Another B–Mn–Mn example is, the boron–boron cleavage reaction of an anionic manganese compound of the $2\text{K}[(\text{C}_5\text{H}_4\text{Me})\text{MnH}(\text{CO})_2]$ type with two 1,2-diaminodichlorodiboranes, $\text{B}_2(\text{NC}_4\text{H}_8)_2\text{Cl}_2$ and $\text{B}_2(\text{NC}_5\text{H}_{10})_2\text{Cl}_2$, which yielded the bridged borylene crystalline materials $[\mu\text{-B}(\text{NR}_2)\{(\eta^5\text{-C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\}_2]$ ($\text{NR}_2 = \text{NC}_4\text{H}_8$ **26a**, NC_5H_{10} **26b**). These two borylenes possess a B–Mn–Mn, dimanganese–borirane, central ring <1999JOM231>. The reported compounds were characterized by multinuclear NMR (CDCl_3), IR, and elemental analyses (Scheme 8).



Scheme 8

1.10.2.2.6 B–Re–Re, B–Cr–Cr, B–Re–Co and B–Cr–Co systems

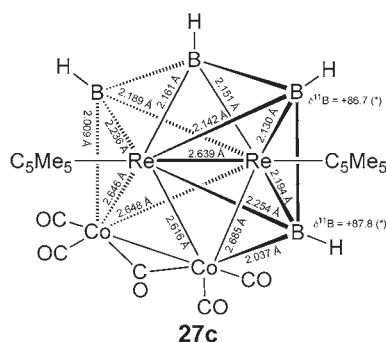
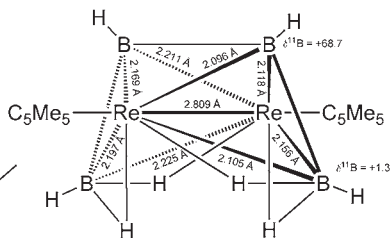
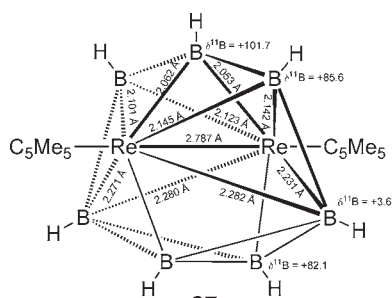
Irradiation of $[(\eta^5\text{-C}_5\text{H}_5)\text{Re}(\text{CO})_3]$ with $\text{W}(\text{CO})_3\text{BN}(\text{SiMe}_3)_2$ in hexane for 5 days afforded the $[\mu\text{-B}(\text{N}(\text{SiMe}_3)_2)(\eta^5\text{-C}_5\text{H}_5)\text{Re}(\text{CO})_2]_2$ compound **27** as yellow crystals. Photolysis during the last day did not significantly change the observed NMR signals. This borylene possesses a B–Re–Re, dirhenium–rhenium borirane central ring $\langle 2001\text{AGE}2298 \rangle$. Compound **27** was characterized by multinuclear NMR (C_6D_6) and mass spectrometry (Scheme 9).



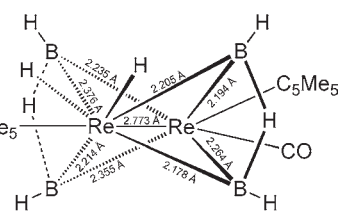
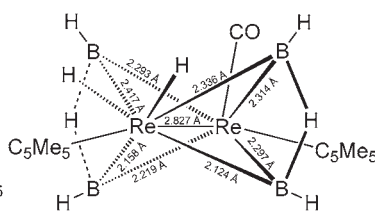
Scheme 9

Molecular systems comprising the B–Re–Re three-membered ring as a core embedded in metallaboranes were firstly reported by the group of Fehner $\langle 1998\text{CC}1787 \rangle$ and further studied systematically $\langle 1999\text{OM}853, 2000\text{JOM}614, 1999\text{JA}7451, 2000\text{AGE}2900, 2000\text{IC}5373, 2001\text{AGE}1125, 2001\text{JA}9188, 2004\text{JA}3203 \rangle$. The addition of $\text{BH}_3 \cdot \text{THF}$ to $\text{C}_5\text{Me}_5\text{ReCl}_4$ provided $(\text{C}_5\text{Me}_5\text{Re})_2\text{B}_7\text{H}_7$ (**27a**) possessing five B–Re–Re three-membered rings fused in a radial fashion at the Re–Re core, as a pale yellow solid in 66% yield $\langle 1998\text{CC}1787, 1999\text{OM}853 \rangle$. Compound **27a** was characterized by NMR, MS and single crystal X-ray diffraction analysis. The ^{11}B NMR spectrum displays four signals at +101.7 (one central BRe_2B_2 moiety), +85.6 (two symmetric BRe_2B_2 moieties), +82.1 (two symmetric BReB_3 moieties) and +3.6 ppm (two symmetric BRe_2B_2 moieties), with an integral ratio of 1:2:2:2. The signals are interestingly distributed over a large chemical shift range of ca. 100 ppm, and were unambiguously assigned through the ^{11}B – ^{11}B correlation spectroscopy (COSY) experiments $\langle 1999\text{OM}853 \rangle$. The B–Re distances, 2.053–2.280 Å, are slightly larger in average, than the range of observed B–Ni (2.10, 2.08), B–Mn (1.988–2.039), B–Rh (2.177, 2.166), B–Co (2.108, 2.112), B–Fe (1.903) and B–Pd (2.090) bonds (bond distances in Å) in the simpler bimetallic three-membered rings. Similar B–Re–Re three-membered ring derivatives were prepared by the reaction of $\text{C}_5\text{Me}_5\text{ReCl}_4$ with boron hydrides. An example was obtained by addition of a five-fold excess of LiBH_4 to $\text{C}_5\text{Me}_5\text{ReCl}_4$ $\langle 1998\text{JCD}1525 \rangle$ providing $(\text{C}_5\text{Me}_5\text{Re})_2\text{B}_7\text{H}_7$ (**27b**) in 32% yield as orange-yellow crystals. This compound has four B–Re–Re three-membered rings fused as in **27a** $\langle 2000\text{JOM}614 \rangle$ and was obtained after separation of rhenium hydride by-products. The characterization of **27b** was accomplished by NMR, IR, MS and X-ray crystallography. The bridging hydrogen atoms in B–H–Re moieties behave as metallic hydrides according to ^1H and ^{11}B NMR data, unfortunately they were not found in the structural analysis, precluding the geometrical measurements of these mono-metallic three-membered rings. Compound **27b** was employed as starting material for the production of more elaborate B–Re–Re systems by reacting it with a twofold excess of $\text{Co}_2(\text{CO})_8$ and constructing the $(\text{C}_5\text{Me}_5\text{Re})_2\{\mu\text{-}\eta^6\text{-B}_4\text{H}_4\text{Co}_2(\text{CO}_5)\}$ (**27c**) compound obtained as brown crystals in 75% yield $\langle 1999\text{JA}7451, 2001\text{IC}5373 \rangle$. This substance was characterized by NMR, IR, MS and X-ray diffraction analyses. The ^{11}B NMR spectrum revealed two double signals at +87.8 and +86.7 ppm of equal intensities indicative of the symmetry of the molecule in solution (the assignments may be interchanged). In addition to the four B–Re–Re systems there were formed four B–Re–Co three-membered rings, as determined by X-ray diffraction analysis. Subsequent reaction of **27b** with CO gave a mixture of *cis* and *trans* CO addition stereoisomers (**27d** and **27e**) in 75% yield $\langle 2000\text{AGE}2900, 2000\text{IC}5373 \rangle$. Their NMR data as well as the X-ray crystallography were determined for the 1:1 mixture. The mixture of **27d** and **27e** was heated leading to a single derivative, the $[(\text{C}_5\text{Me}_5\text{ReH}_2)(\text{C}_5\text{Me}_5\text{Re}(\text{CO}))(\text{B}_4\text{H}_4)]$ (**27f**) *trans* stereoisomer, obtained by removal of a hydrogen molecule in 78% yield. This compound was characterized by NMR, MS, IR and X-ray crystallography. The ^{11}B NMR spectrum clearly evidenced two signals, one at +87.2 and the other at –11.7 ppm.

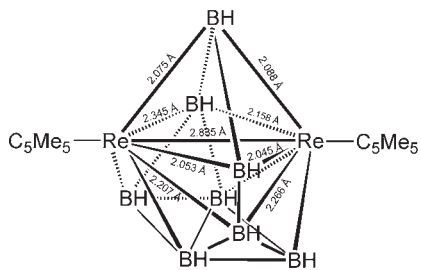
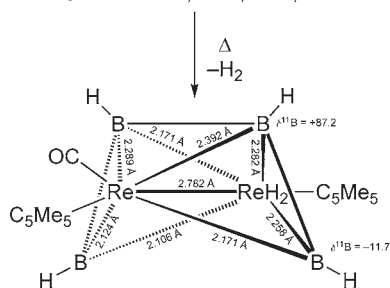
Another systematic study comprising the B–Re–Re core was developed through the incorporation of an eight-fold excess of $\text{BH}_3 \cdot \text{THF}$ to **27b** $\langle 2001\text{AGE}1125, 2004\text{JA}3203 \rangle$. This reaction led to **27a** in 17% yield, and three other byproducts $[(\text{C}_5\text{Me}_5\text{Re})_2\text{B}_8\text{H}_8]$ **27g** in 38% $[(\text{C}_5\text{Me}_5\text{Re})_2\text{B}_9\text{H}_9]$ (**27h**) in 10%, and $[(\text{C}_5\text{Me}_5\text{Re})_2\text{B}_{10}\text{H}_{10}]$ (**27i**) in 7%. The three derivatives were characterized by NMR, MS, IR and X-ray crystallography.



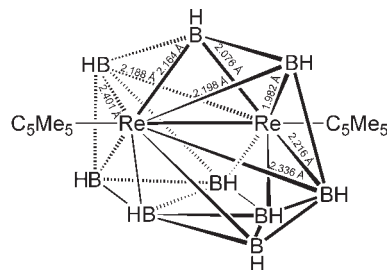
(*) The assignments may be interchanged



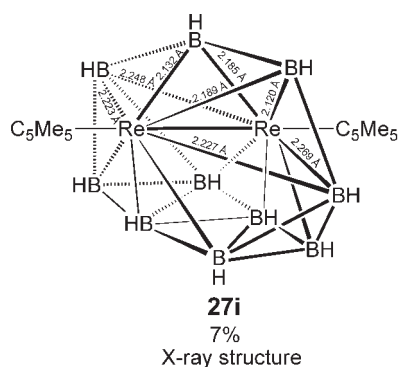
75% as the mixture as well as in the X-ray structure
 $\delta^{11}\text{B} = +13.6, -1.9, -7.7, -20.1$



$\delta^{11}\text{B} = +97.9$ (2B), $+65.8$ (4B), $+21.9$ (2B)



$\delta^{11}\text{B} = +94.1$ (2B), $+76.2$ (2B), $+35.5$ (2B), $+1.1$ (2B), -28.7 (1B)



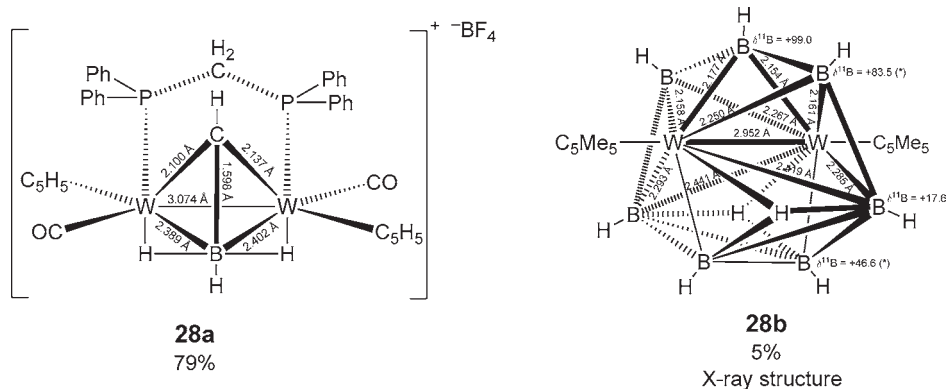
$$\delta^{11}\text{B} = +60.0 \text{ (2B)}, +50.4 \text{ (2B)}, +16.1 \text{ (2B)}, -10.8 \text{ (2B)}, -22.9 \text{ (2B)}$$

Similar B–Cr–Cr three-membered rings have been reported by the group of Fehlners <2000IC5373, 1999JA7451>.

1.10.2.2.7 B–W–W systems

One of the first molecular systems including the B–W–W three-membered ring core was prepared by Alvarez and co-workers <1996AGE102> from $[\text{W}_2(\mu\text{-COMe})(\text{CO})_2(\mu\text{-Ph}_2\text{PCH}_2\text{PPh}_2)(\text{C}_5\text{H}_5)_2]\text{BF}_4$ (**28a**) and a 20 fold excess of $\text{BH}_3\cdot\text{THF}$. The X-ray structure of **28a** confirmed the presence of the B–W–W core and two B–C–W three-membered rings. This compound was also characterized by IR, ^1H and ^{13}C NMR spectroscopy.

Fehlners' group has also developed metallaboranes with the B–W–W moiety <1998CC1787, 1999OM853>. One example of this is the analogue system of **27a**, which was prepared from the pyrolysis reaction of $\text{C}_5\text{H}_5\text{WH}_3\text{B}_4\text{H}_8$ in toluene at 100°C , thus yielding $(\text{C}_5\text{H}_5)_2\text{B}_7\text{H}_9$ (**28b**) in 5% yield <1998CC1787>. This compound was thoroughly characterized by ^1H and ^{11}B NMR, MS, IR and by single crystal X-ray diffraction analysis. The $\mu^3\text{W-B-B}$ nature of two hydrogen atoms was confirmed by the ^1H NMR shift of a single signal which integrates for two boron atoms at -8.8 ppm (Scheme 10).

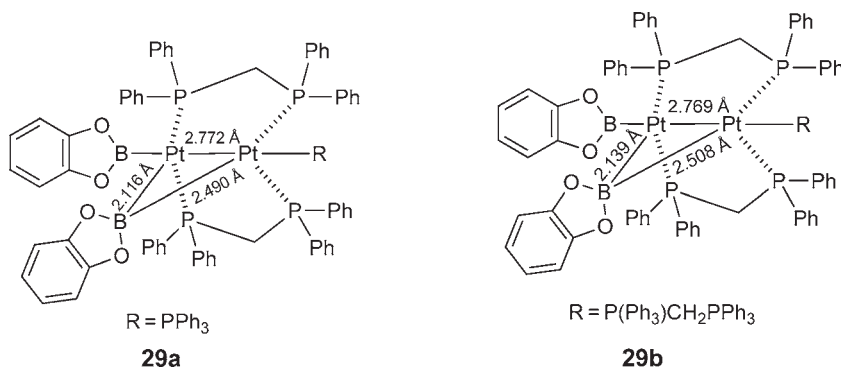


Scheme 10

1.10.2.2.8 B–Pt–Pt system

The platinum(II) bis(boryl) compound with the formulas $\text{cis-}[\text{Pt}(\text{PPh}_3)_2(\text{B}(1,2\text{-O}_2\text{C}_6\text{H}_4))_2]$ was added to an NMR tube with 1.1 equiv of the [bis(diphenylphosphino)methane] (dppm) and both compounds were dissolved in CD_2Cl_2 to afford an orange solution which became red over time <1999JCD1687>. Based on multinuclear (^{31}P and ^{11}B) NMR experiments, recorded at -90°C and room temperature, the main product resulted in the $\text{cis-}[\text{Pt}(\text{dppm})(\text{B}(1,2\text{-O}_2\text{C}_6\text{H}_4))_2]$ compound **29a**. Moreover, when the solution was layered with hexane and solvent diffusion was allowed to occur for days at room temperature, red crystals of $[\text{Pt}_2(\text{PPh}_3)(\mu\text{-dppm})_2(\text{B}(1,2\text{-O}_2\text{C}_6\text{H}_4))(\mu\text{-B}(1,2\text{-O}_2\text{C}_6\text{H}_4))]$ and a small quantity of orange crystals characterized as $[\text{Pt}_2(\text{PPh}_3)(\kappa^1\text{-dppm})(\mu\text{-dppm})(\text{B}(1,2\text{-O}_2\text{C}_6\text{H}_4))(\mu\text{-B}(1,2\text{-O}_2\text{C}_6\text{H}_4))]$ **29b** were obtained. These compounds possess the Pt–Pt–B, diplatinum–boratirane, three-membered rings. In order to

increase the yields for the latter two derivatives, 2.6 equiv of dppm was added, increasing the yield of $\text{Pt}_2(\text{PPh}_3)(\kappa^1\text{-dppm})(\mu\text{-dppm})(\text{B}(1,2\text{-O}_2\text{C}_6\text{H}_4))(\mu\text{-(B}(1,2\text{-O}_2\text{C}_6\text{H}_4)))$, although the overall yield for the two boron-bridged compounds was maintained but not reported within the contribution. Both diplatinum–boratiranes were characterized by single crystal X-ray diffraction analysis as their CH_2Cl_2 and $0.15\text{ C}_6\text{H}_{14}\cdot 0.69\text{ CH}_2\text{Cl}_2$ solvates, respectively. The observation of the NMR spectra of the pure substances was precluded by the low yields and co-crystallization.



1.10.2.2.9 B–Fe–Fe and B–Ru–Ru systems

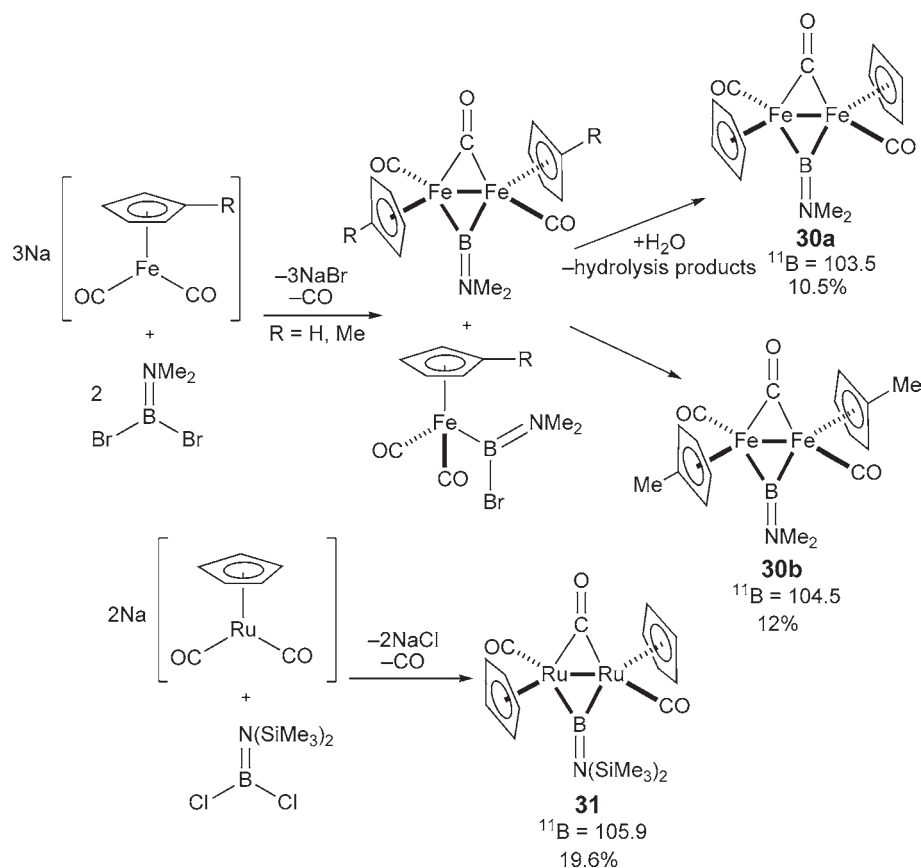
The salt elimination reactions employing strong nucleophilic compounds of Fe and Ru produced B–Fe–Fe, diiron–borirane, or B–Ru–Ru, diruthenium–borirane, rings, as reported by Braunschweig in 1999 <1999EJI1523>. Two independent diiron–boriranes of the $[\mu\text{-B}(\text{NMe}_2)\text{-}\mu\text{-CO}\{(\eta^5\text{-C}_5\text{H}_4\text{R})\text{Fe}(\text{CO})_2\}]_2$ type ($\text{R} = \text{H}$ **30a**, Me **30b**) were prepared as 1:1 dark red powder mixtures with $[(\eta^5\text{-C}_5\text{H}_4\text{R})(\text{CO})_2\text{Fe}\{\text{BBr}(\text{NMe}_2)\}]$ when Me_2NBBR_2 and a threefold excess of $\text{Na}[(\eta^5\text{-C}_5\text{H}_4\text{R})\text{Fe}(\text{CO})_2]$ were employed. Samples of pure diiron–boriranes were obtained when the mixture was dissolved in diethyl ether and water. Instead of the by-products present in the iron derivatives, the diruthenium–borirane, $[\mu\text{-B}(\text{N}(\text{SiMe}_3)_2)\text{-}\mu\text{-CO}\{(\eta^5\text{-C}_5\text{H}_5)\text{Ru}(\text{CO})_2\}]_2$ **31**, species was formed by the reaction between $\text{Na}[(\eta^5\text{-C}_5\text{H}_5)\text{Ru}(\text{CO})_2]$ and $(\text{Me}_3\text{Si})_2\text{NBCl}_2$. All three compounds were characterized by multinuclear NMR (C_6D_6), IR, and elemental analyses (Scheme 11).

An interesting set of reactions to functionalize tri-ruthenium clusters, $[(\text{C}_5\text{Me}_5)\text{-Ru}]_3(\mu\text{-H})_6]^-$, with NaBRH_3 ($\text{R} = \text{H}$, CN) led to the formation of two new reagents of the type $\{(\text{C}_5\text{Me}_5)\text{-Ru}\}_3(\mu\text{-H})_3(\mu_3\text{-BR})$ ($\text{R} = \text{H}$, **31a**, $\text{R} = \text{CN}$, **31b**) that were used for further substitution reactions <2001OM4772>. From **31a** or **31b**, using excess of methanol or ethanol, it was feasible to obtain the B–R ($\text{R} = \text{OMe}$, **31c**, $\text{R} = \text{OEt}$, **31d**) tri-ruthenium clusters possessing also three-fused B–Ru–Ru rings, in a pyramidal structure <2001OM4772>. The exposure of **31a** to benzothiophene led to an interesting reaction product with the activation of the S-five-membered ring, but the $[(\text{C}_5\text{Me}_5)\text{-Ru}]_3(\mu\text{-H})_6]^-$ resulted more efficient in the activation of this heterocycle. As stated previously in Section 1.10.2.2.5, these systems are examples of homometallic μ_3 -borylene molecules.

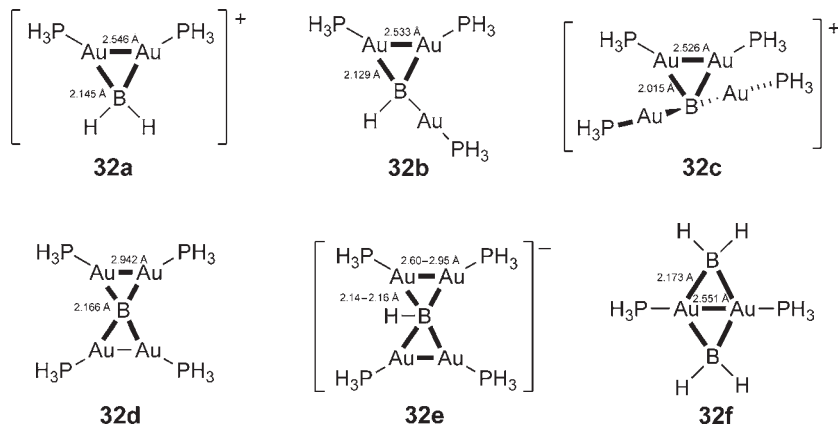
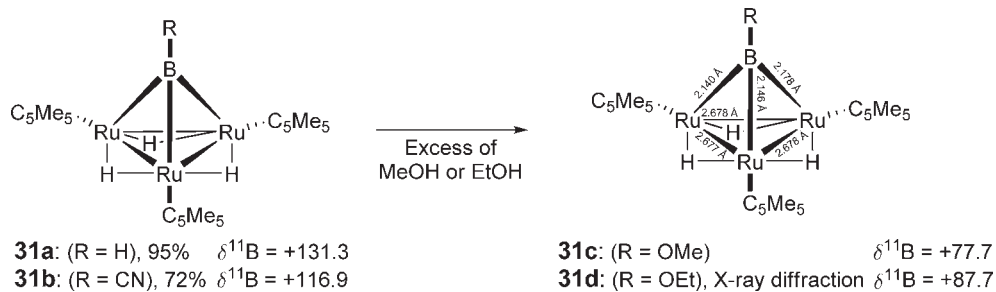
Some other three-membered rings comprising B–Fe–Fe cores were reported by the group of Aldridge in 2002 and 2003 <2002JCD3851, 2003OM4213> and B–Ru–Ru cores by the group of Kawano and Shimoi, as well as by Housecroft and co-workers, both in 2000 <2000OM5575, 2000JOM89>.

1.10.2.2.10 B–Au–Au systems

Theoretical evidence for the energy stabilization of three-membered B–Au–Au-bearing systems **32a–f** was reported in 2000 by Tamm and Pyykko. <2000THA399>. The theoretically predicted molecules belong to two specific groups: the first is named six-electron three-ligand molecules, and the latter is eight-electron four-ligand series. The first five compounds, **32a–e**, belong to the first type, and only **32f** belongs to the latter description. These compounds were calculated using MP2 level of theory employing the resolution of identity (RI-MP2). According to this, the theoretical methods employed herein consisted of the Stuttgart relativistic effective core potentials of Bergner type for boron and phosphorus atoms, and Andrae type for the gold atoms. The basis sets were modeled with the Huzinaga 2s/4s basis except for the hydrogen atoms. Polarization functions were added to all atoms. The values of the geometry optimizations are expected to be bracketed within HF and MP2 approaches according to previous results referenced by the authors. Since at least two gold atoms are present, the ‘aurophilicity’ term was therefore employed. The theoretical values were compared with previously reported experimental data and reproduced well the trends, providing an inexpensive methodology to overcome the gold-containing systems.



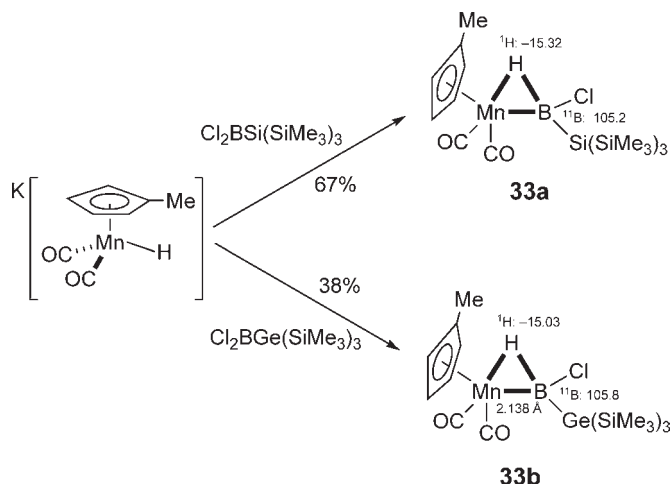
Scheme 11



1.10.2.3 X and Y Belong to Elements of the Main and Transition Groups, Respectively

1.10.2.3.1 B–Mn–H system

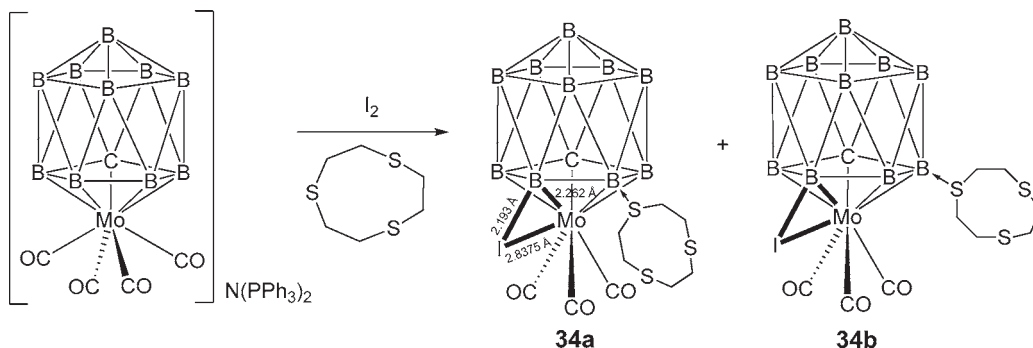
The parallel reactions of $K[(\eta^5\text{-C}_5\text{H}_4\text{Me})\text{Mn}(\text{CO})_2\text{H}]$ with dichloro{tris(trimethylsilyl)M}borane, where $M = \text{Si}$ and Ge , produced [chloro{tris(trimethylsilyl)M}boryl]dicarbonyl-(η^5 -methyl-cyclopentadienyl)- μ -hydrido-manganese compounds, $M = \text{Si}$ **33a** and Ge **33b** <2002JCD2289>. These two compounds have the same three-membered ring core, the B–Mn–H, manganese–hydrido–boratirane (Scheme 12). The compounds were characterized by multinuclear NMR, IR, and elemental analyses. Important spectroscopic evidence for the B–Mn μ -H structures was obtained by recording ^{11}B coupled and ^1H decoupled resonances, where the latter exhibits a sharp signal due to irradiation of the ^{11}B atom bonded to the μ -H. The X-ray diffraction analysis of the $\text{Ge}(\text{SiMe}_3)_2$ -bearing derivative allowed to establish the structure but the quality of the reflections collected did not allow to localize the exact position of the B–Mn μ -H.



Scheme 12

1.10.2.3.2 B–Mo–I system

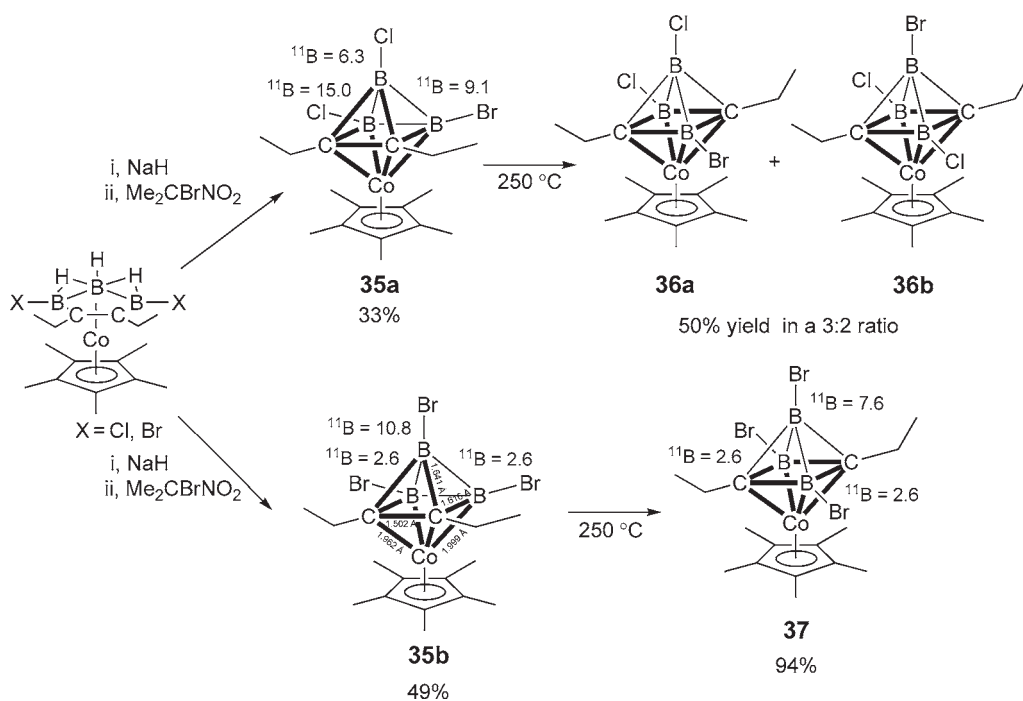
The reaction of $[2,2,2,2\text{-(CO)}_4\text{-closo-2,1-MoCB}_{10}\text{H}_{11}]\text{N}(\text{PPh}_3)_2$, the cyclo-1,4,7- $\text{S}_3(\text{CH}_2)_6$ thioether, and I_2 generated two distinct products, **34a** and **34b**, and in both derivatives an iodine atom acts as a bridge for the B–Mo fragment. The two μ -I compounds were obtained in a 7:1 isomeric ratio with a 35% overall yield <2001JCD2791>. The ratio of isomers was determined through ^{11}B NMR signal integration. The isomerism present in the mentioned compounds is dependent on the coordination site of the thio-macrocyclic ligand, as evidenced at the 7- **34a** or 11- **34b** sites of the carborane skeleton. Both derivatives present the B–Mo–I three-membered ring system (Scheme 13). The two μ -I compounds were characterized by multinuclear NMR, IR, and elemental analyses; moreover, for the first and more abundant isomer, substituted at the 7-position, the X-ray diffraction analysis was obtained, showing the μ -I character.



Scheme 13

1.10.2.3.3 B–C–Co system with fused B–C–C ring

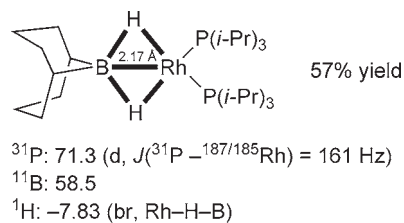
The deprotonation reaction of 4,6-dichloro- or dibromo-*nido*-cobaltacarboranes with sodium hydride in THF was followed by addition of 2-bromo-2-nitropropane. The corresponding crude product was purified by column chromatography on silica producing the *closo*-[1,2,3-Cp*Co(Et₂C₂B₃-4,6-Cl₂-5-Br)] **35a** and *closo*-[1,2,3-Cp*Co(Et₂C₂B₃Br₃)] **35b**; both gave orange crystals, as has been thoroughly reported by Schanz <2001AGE2705>. These two cobaltacarboranes were characterized by ¹H, ¹³C, and ¹¹B NMR, mass spectrometry, and the X-ray structure for the tribromide compound. These evidences allowed establish of an octahedral cluster geometry constructed through the B₃C₂Co core. The first two compounds presented two three-membered rings constituted by B–C–Co, which are occupying two of the eight faces of the figure in the B₃C₂Co octahedron, as well as a B–C–C ring in another face of the octahedron. Thermal rearrangement of **35a** *in vacuo* at 250 °C led to a 1:1 mixture of constitutional isomers **36a** and **36b** where the carbon atoms of the octahedron in both of the newly formed compounds are placed, in a *trans*-disposition. When the starting material was **35b**, a single product, **37**, was formed, in quantitative yield, also placing the two carbon atoms in a *trans*-arrangement. This derivative was again thoroughly characterized. The thermal rearrangements and further characterization of the products obtained are strong evidence of the thermodynamic preference of these isomeric derivatives to place the carbon atoms away from each other (Scheme 14).



Scheme 14

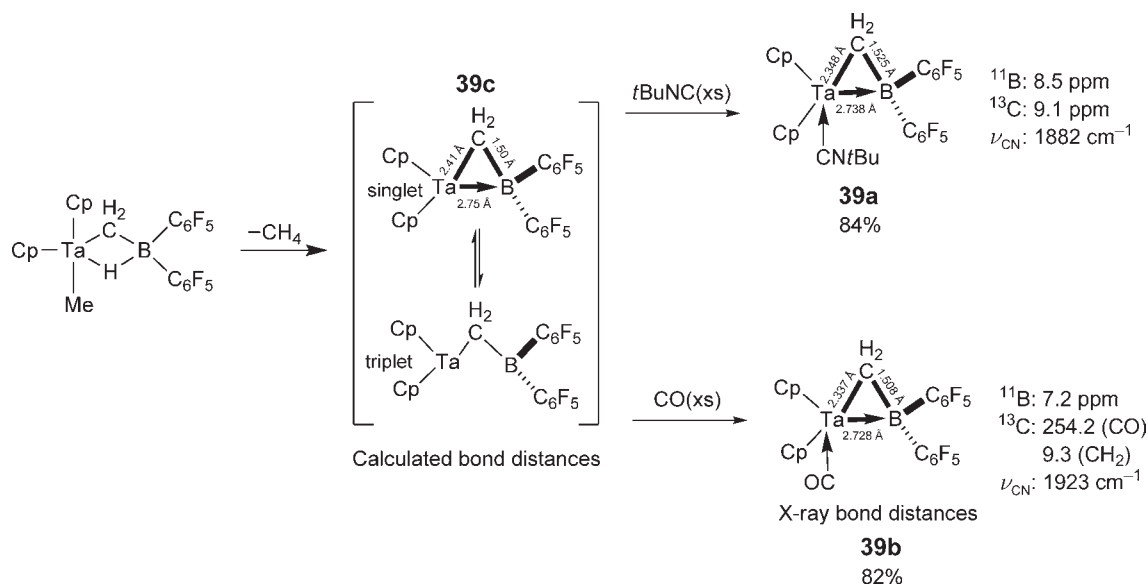
1.10.2.3.4 B–Rh–H system

The reaction between 0.5 equiv of 9-*H*-BBN and *trans*-RhH(N₂)(P(*i*-Pr)₃)₂ gave compound Rh(μ_2 -H₂BC₈H₁₄)(P(*i*-Pr)₃)₂ **38** as orange crystals <2004POL2665>. The spectroscopic characterization was accomplished through ¹H and ¹¹B NMR, while the results of single crystal X-ray diffraction confirmed the spectroscopic evidences for the proposed structure. The molecular structure consists of a 16-electron square planar Rh(I) center with the disubstituted borohydride ligand bonded to the metal center in a μ_2 -fashion.

**38**

1.10.2.3.5 B-Ta-C system

The trapping reaction at -78°C between $\text{Cp}_2\text{Ta}(\text{CH}_2\text{B}(\text{C}_6\text{F}_5)_2)(\mu\text{-H})(\text{CH}_3)$ with at least a three-fold excess of *tert*-butyl isocyanide, or pressurization at 1 atm with carbon monoxide, underwent methane loss while the mixture was maintained 1.5 h under vigorous stirring at room temperature. The products of the corresponding reactions were the $\text{Cp}_2\text{Ta}(\eta^2\text{-CH}_2\text{B}(\text{C}_6\text{F}_5)_2)(\text{L})$ compounds, where L = *tert*-butyl isocyanide (*t*BuNC) **39a** or carbon monoxide (CO) **39b** ligands. The molecules reported contain the Ta-C-B, tantalum-boratrane subsystem, reported in the original reference as the asymmetric η^2 -binding-mode compounds <2001OM3927>. Both derivatives were characterized through elemental analyses, multinuclear NMR (CD_2Cl_2 and THF- d_8), IR, and by single crystal X-ray diffraction. The authors claim that they were not able to isolate the green paramagnetic material which arises by loss of methane from the $\text{Cp}_2\text{Ta}(\text{CH}_2\text{B}(\text{C}_6\text{F}_5)_2)(\mu\text{-H})(\text{CH}_3)$ starting material; nevertheless, the experimental and computational evidences strongly indicate the formation of the borataalkene compound **39c** (three-membered structure in brackets of singlet nature), which also contains the Ta-C-B, tantalum-boratrane, subsystem. Additionally, the paramagnetic nature of the intermediate green solution evidences the presence of the triplet, open form for the borataalkene compound. The unrestricted theoretical calculations at the BP86VWN/IV(Ta)/III level of theory were utilized (IV is a triple- ζ basis set used for Ta, III is a double- ζ basis set used for the remaining elements) to calculate the singlet and triplet states for the intermediate mixture. In fact, a slight energetic preference, ca. 1.5 kcal mol^{-1} , for the formation of triplet instead of the singlet structure was reported. These findings allowed determination of the contribution of the two intermediates at ambient temperature and, thus, the trapping reaction led to L-stabilized compounds of type **39** (Scheme 15).



Scheme 15

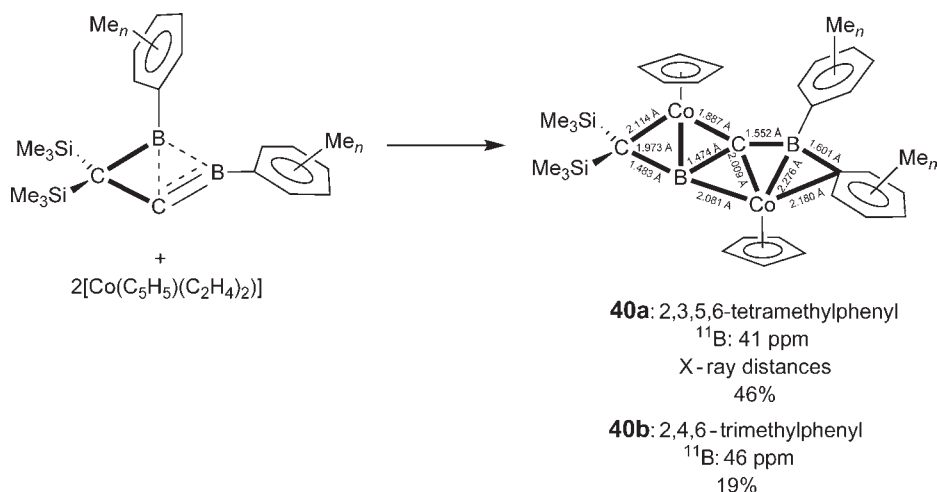
1.10.2.3.6 B-C-Co systems

The reactions of B-duryl- (B-(2,3,5,6-tetramethylphenyl)) and B-mesityl-substituted boriranylideneboranes with $[\text{Co}(\text{C}_5\text{H}_5)(\text{C}_2\text{H}_4)_2]$ in hexane produced the μ -[didurylborylbis(trimethylsilyl)methyleneborylcarbene]bis(η^5 -pentadienyl)dicobalt **40a** and μ -[dimesitylborylbis(trimethylsilyl)methyleneborylcarbene]bis(η^5 -pentadienyl)dicobalt **40b**, respectively, as stated by Gunale *et al.* in 1998 <1998CEJ44>. The two reported compounds present five fused three-membered rings with common cores of B-C-Co atoms, thus presenting the cobalt-boratrane system five times. These compounds were characterized by multinuclear NMR (THF- d_8) and mass spectrometry. Additionally, in the case of **40a**, the X-ray diffraction analysis could be determined (Scheme 16).

1.10.3 Applications

As has been stated throughout the review, the small three-membered rings bearing one boron atom are useful synthons for the preparation of more elaborate compounds. The use of simpler C-C-B boratiranes to produce metal-substituted boratiranes such as B-Co-C <1998CEJ44> or B-Mn-Mn boratiranes to produce substituted analogs

preserving the three-membered ring core has been stated <1999JOM231, 1997CB1295, 2002AGE1359, 2003IC941>. Moreover, these small rings are precursors of important zwitterionic species such as the ammonium borates reported by Pawelke and co-workers <1999EJI255, 1996AOM147>. There are other reports where the authors employ B–Mn–Mn cycles in the preparation of metalloboranes <2002AGE1359>. Additionally, these B–Mn–Mn molecules were used for the preparation of boron-containing compounds with three different transition metal atoms in its surroundings <2006AGE1066>. Other techniques for the observation of these derivatives include their transformation into more stable substances, such as borylene complexes stabilized by transition metal bases <2005AGE3763>.



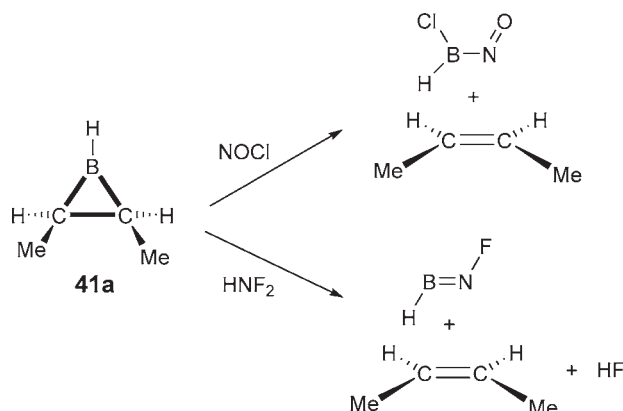
Scheme 16

1.10.4 Perspectives

The systematic theoretical investigation of boron compounds is of great value to predict the geometry, thermodynamic stability, and reactivity of three-membered heterocycles. Experimental work in the field has allowed chemists to prepare boron heterocycles containing different elements within the ring. These new compounds not only increase our knowledge of boron chemistry but also show the versatility of this small element in organic chemistry. In this area, both theoretical as well as experimental work is of importance, as the results of these studies can be applied to several research and technological fields, such as materials chemistry, catalysis, electronic molecular materials, as well as boron-assisted organic and inorganic synthesis, medicinal chemistry, etc. It is also worthy to note that while three-membered ring systems containing one boron atom represent an interesting research field, this area is attracting a good deal of attention recently as a consequence of the involvement of the organic chemistry community in the study of these intriguing heterocyclic ring systems.

1.10.5 Further Developments

The ring opening reactions of 2,3-dimethyl-borirane **41a** with NOCl and HNF_2 have been explored yielding the corresponding alkenes <2007IJQC1590>. The compounds were studied by means of B3LYP and HF methodologies employing the 6-31G(d) basis set for geometry optimizations. Single point calculations for these geometries were computed at the MP2/6-31G(d) and MP2/6-311G(d,p), as well as with the B3LYP/6-311G(d,p) levels of theory. The results of this research reveal that the reaction pathway for the ring opening reaction of **41a** passes through the formation of a prereactive complex, and proceeds to a transition state that leads to the *cis*-2-butene with the same stereochemistry as that present in **41a**, independently of whether the NOCl or HNF_2 cleaving reagent are used. The energy analyses revealed that these reactions are highly exothermic. The calculations performed for solution phase (polarized continuum model (PCM) with acetonitrile and CCl_4 as implicit solvents at the SCRFB3LYP/6-31G(d) level) do not alter the results obtained in gas phase, thus the observed trend is that HNF_2 is more efficient for the borirane cleavage reaction than NOCl .



As further development, in our opinion, one could expect functionalization of porous materials or metal-organic frameworks (MOFs) with these small molecules in order to trap hydrogen and maintain it stable to develop storage systems. This could have important economic implications. The rational design of functional materials within the confinement of these small three-membered rings containing boron (coupled with main group or transition block elements) would encourage the preparation of new substances with interesting properties and applications.

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Biographical Sketch



Hiram I. Beltrán was born in 1975 in México City, México. He received his B.Eng. degree (chemical engineering) from ESQIE-IPN in 1998. The same year he joined the research group of Professor N. Farfán at the Centro de Investigación y de Estudios Avanzados del IPN (CINVESTAV-IPN) where he obtained his Ph.D. in 2002 for his work in the field of boron and tin chemistry. Then he joined the Molecular Engineering Program at the Mexican Institute of Petroleum as a postdoctoral fellow between 2003 and 2005. In 2005, he worked as research associate in the Chemistry Institute at the UNAM. In 2006 he was appointed Full-time Researcher in the Natural Sciences Department at the Universidad Autónoma Metropolitana (DCNI, UAM), Cuajimalpa. His present research is focused in the field of synthesis and characterization of bioactive compounds, in particular the biochemistry of molecules containing representative elements.



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1.11

Diaziridines and Diazirines

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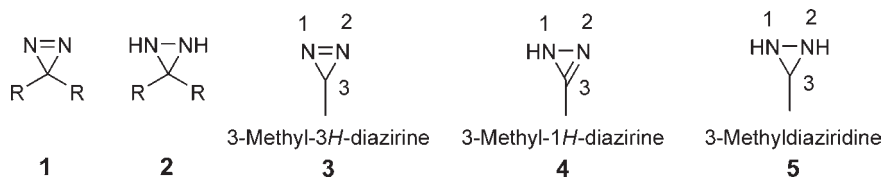
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1.11.1 Introduction

Diaziridines and diazirines were first prepared by Abendroth and Henrich <1959AGE283>, Schmitz <1959AGE127>, and Paulsen <1960AGE781> at the turn of the 1960s. Nearly 50 years later, both diaziridines and diazirines have seen tremendous utility in synthetic chemistry and biochemistry. In particular, diazirines have been widely used as photochemical and thermal precursors of carbenes in their primary role as photoaffinity tags. Unlike diazo compounds, diazirines are reasonably stable and have been used extensively in both photolysis and thermolysis.

1.11.2 Scope and Nomenclature

This chapter focuses on publications since 1995 and builds on the corresponding chapter in the previous editions <1984CHEC(7)195, 1996CHEC-II(1A)347>. In this chapter, the discussion of diazirine **1** systems is followed by diaziridine **2** systems. The nomenclature of both saturated and unsaturated systems follows the Hantzsch–Widman convention and is exemplified here by structures **3**–**5**. The presence of the diaziridine group has often been indicated by the prefix ‘azi’ (e.g., azi-adamantane <2001TL9161, 1998JA11627>), and this nomenclature has been employed when used in source reference.

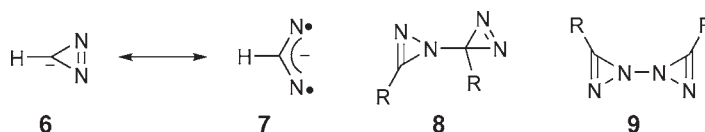


1.11.3 Theoretical Methods

During the last decade, important theoretical studies have been carried out for diazirines and diaziridines. The absolute gas-phase acidity of diazirine was calculated using *ab initio* molecular orbital (MO) calculations at the G2 and G2(MP2) levels of theory <1995AJC401>. The calculated gas-phase acidity for diazirine (1667 kJ mol^{-1}) agreed with experiment ($1678 \pm 13 \text{ kJ mol}^{-1}$ <1990JA9024>), although the calculated value was toward the lower end of the range of experimental values. Accurate calculation of the nitrogen nuclear magnetic resonance (NMR) parameters of diazirine has been achieved through density functional theory (DFT) methods at the B3LYP/6-311+G(d,p) level of theory <2005HC84>. Values for chemical shifts and indirect nuclear spin–spin coupling constants compared favorably with experimental data.

The recently defined concept of ultradiagonal strain energy <1996JST(374)29> has been applied to diazirine using *ab initio* calculations <1999JOC6361>. Very good agreement was observed between theoretical and experimental data for total molecular energy and structural parameters. The low-lying electronic states of diazirine and 3,3'-dimethyldiazirine have been studied by high-level *ab initio* quantum chemistry methods <1999BKC1281>. Optimization of the equilibrium geometries of the ground state and the first excited singlet and triplet states was performed using the Hartree–Fock (HF) and complete active space SCF (CASSCF) methods, as well as using the Møller–Plesset second-order perturbation (MP2) theory and the single CI (CIS) theory. The computed transition energies, particularly by MCQDPT2, were in accordance with the experimental observations.

Several theoretical studies of diazirinyl radicals have been undertaken. Multiconfiguration self-consistent field (MCSCF) calculations have been used to investigate the stability of, and isomerization between, the diazirinyl anion **6** and the open-chain biradical anion **7** (Scheme 1) <1995JPC6548>. Dimerization of aryldiazirinyl radicals has been explored by computational and experimental methods <2004PCCP756>. Both approaches support the predominance of the N–N dimer **9** over the isomeric C–N form **8**. Furthermore, bimolecular dimer decomposition was shown to be considerably more favorable than the alternative unimolecular pathways.



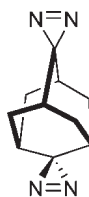
Scheme 1

Carbene generation is the cornerstone of diazirine reactivity and a number of modeling studies have been performed in this area. Complete-basis-set *ab initio* computational studies were performed in order to evaluate the aromatic character (stability) of cyclopropene, diazocyclopropene, and diazocyclopropane carbenes <1999JMT(491)33>. Cyclopropene and diazocyclopropene carbenes are found to be aromatic, while the diazocyclopropene-hydrogenated isomer should be aromatic, both as a singlet and as a triplet. A related study investigated the minimum energy path for the reaction of singlet methylene with N_2 <1995JCP4930>. Carbene formation from photoexcited 3*H*-diazirine has been modeled in its lowest singlet state in a combined CASPT2 and *ab initio* direct dynamics trajectory study <2002JA1728>.

The reactivity of palladium and copper cluster models toward diazirine has been compared using the LCGTO-MCP-LSD method <1996SUS11>; such calculations were performed to give an insight into the differential bond scission experimentally observed in the thermal decomposition of diazirine on palladium and copper surfaces. Stronger chemisorption was evident with palladium and furthermore, partial diazirine lowest-unoccupied molecular orbital (LUMO) occupation only occurred for the copper cluster model systems. The calculated N–N bond order was significantly decreased in the copper complexes of excited state diazirines, whereas palladium complexes remained unperturbed.

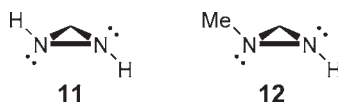
With the advent of the state-of-the-art theoretical methods, it is now possible to carry out accurate quantum-chemical *ab initio* calculations of diazirine's molecular parameters, and other related properties, to spectroscopic accuracy. For instance, an *ab initio* study, using the coupled-cluster method, enabled the calculation of the equilibrium structure and molecular properties of diazirine, diazirinyl radical, and their related cations H_2CN_2^+ and HCN_2^+ <2004JST(695)203, 2004CP131>. The calculated results for the equilibrium geometry, dipole moment, ionization potential, and quadruple coupling tensors were closely correlated to the experimental data. In another case, high-level theoretical calculations and a single crystal X-ray diffraction study were conducted for 2,6-diaziadamantane **10**

<2003JOC2129>. B3LYP/6-311+G* and MP2/6-311+G* calculations, exploring the interaction between carbon–nitrogen and nitrogen–nitrogen covalent bonds, and diazirine ring electron density, suggested limited diazirine strain and this conclusion was corroborated by the X-ray diffraction study.



10

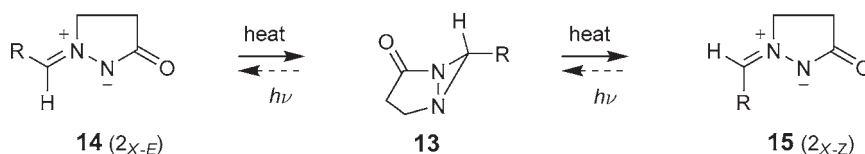
The N-inversion, ring opening, and thermochemistry of diaziridines have been investigated using high-level *ab initio* methods <1998PCA3193>, with the heat of formation of *trans*-diaziridine **11** calculated to be $\Delta H_f^\circ_{298.15} = 55.8 \text{ kcal mol}^{-1}$. High-level *ab initio* methods have also been used in the calculation of the relative energies of the zwitterionic forms of diaziridine by cationization in the gas phase <1998JMT(433)217>. *Ab initio* theoretical $[\alpha]_D$ values of *trans*-diaziridine **11** and (1*S*,2*S*)-methyldiaziridine **12** were calculated to be +41.6 and +2.9, respectively, using the 6-31G* method. However, they were found to be –18.4 and +18.4, respectively, by the double-zeta plus polarization (DZP) method <1999CPH(240)1>.



11

12

The electrocyclic thermal cleavage of four bicyclic (*S*)-diaziridines **13** to their corresponding (*E*)- and (*Z*)-imides **14** and **15** has been studied (Scheme 2). *Ab initio* calculations were carried out at UB3LYP/6-311++G (3df, 2p) levels of theory with the most favored product being **14** (2_{X-E}) <2006JMT(770)7>.



R = H, Me, *t*-Bu, Ph

Scheme 2

1.11.4 Experimental Structural Methods

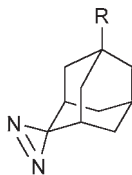
Experimental methods have been extensively employed to elucidate structural parameters such as molecular geometry, bond connectivity, and the absolute configuration of diazirines and diaziridines and this is covered in detail in previous editions <1984CHEC(7)195, 1996CHEC-II(1A)347>.

1.11.4.1 Diazirines

In the last decade, experimental structural methods have been applied in specialized facets of diazirine chemistry, particularly with regard to supramolecular diazirine species and a detailed examination of diazirine decomposition.

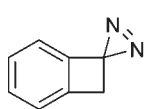
Various diazirine species have been trapped within cyclodextrins, wherein their supramolecular reactivity differs from that observed in solution phase <1993AGE1344>. A contemporary challenge, therefore, has been the structural determination of diazirine–cyclodextrin inclusion complexes, to give insight into this modification of diazirine behavior. Complexes of aziadamantanes **16a–c** with α -, β -, and γ -cyclodextrins have been studied using induced circular dichroism (ICD), UV–Vis (UV – ultraviolet) and 1- and 2-D NMR spectroscopy, as well as X-ray diffraction. Determination of host–guest stoichiometry and association constants has been achieved through ICD and ^1H NMR

spectroscopy <2001TL9161>; moreover, a combination of ICD and UV–Vis techniques yielded information about the supramolecular alignment of host and guest and the microenvironment of the bound diazine <1998JA11627>. A similarly detailed structural analysis has been achieved using rotating frame Overhauser effect spectroscopy (ROESY) and, in the solid state, by single crystal X-ray diffraction <2000TL5663>.

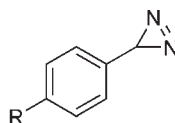


16a: R = H
b: R = OH
c: R = NH₂

Hemicarcerands have been used to encapsulate the aryldiazirines **17**, and **18a** and **18b** and thereby to investigate inner-phase diazine decomposition <2002AGE96>. Detailed ¹H NMR studies allowed the preferred inner-phase orientation of the guests to be deduced.



17



18a: R = H
b: R = Me

Dimethyldiazirine **19** has been analyzed by fluorescence excitation spectroscopy of a gaseous, jet-cooled sample <1997JPH123>. Relatively strong bands in the fluorescence excitation spectrum were assigned to specific vibrational modes of the S₁ state <1998BKC1042>; lower-frequency bands have been assigned to vibrational modes associated with the CH₃ torsional motion <1999BKC365>. Model calculations, assuming a sinusoidal function for the potential shape along the CH₃ torsional angle, agree well with experimental values and suggest that, in the electronically excited state of dimethyldiazirine, the methyl group has near free rotation with respect to the rest of the molecule. Fluorescence spectroscopy was also employed to analyze adamantyldiazirine **16a** <1997JA3580>. The fluorescence lifetime of the primary decay component was measured as 240 ps at ambient temperature and the rate-limiting barrier for activated processes in the diazine excited state was found to be between 2.7 and 2.9 kcal mol^{−1}.

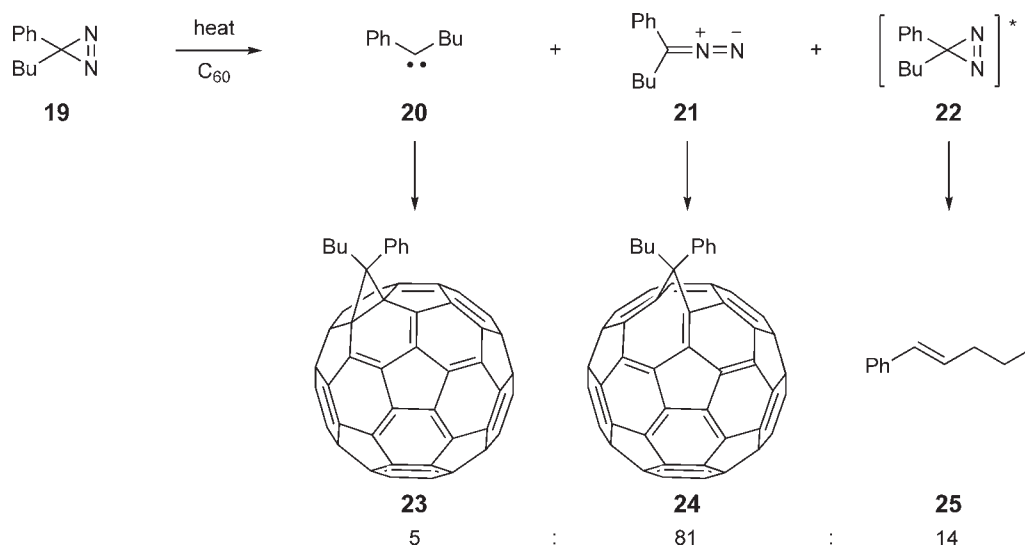


19

High-resolution gas-phase infrared (IR) spectroscopy was employed in rovibrational analysis of the ν_2 band of diazirine-*d*₂ (D₂CN₂) <2001JSP(205)86>, with the aim of providing accurate data for comparison with state-of-the-art quantum-chemical *ab initio* calculations. The ν_2 vibrational mode can be approximated to N=N stretching; at a resolution of ~ 0.005 cm^{−1} this was widely perturbed. A pentad model was employed to take into account the possible perturbors.

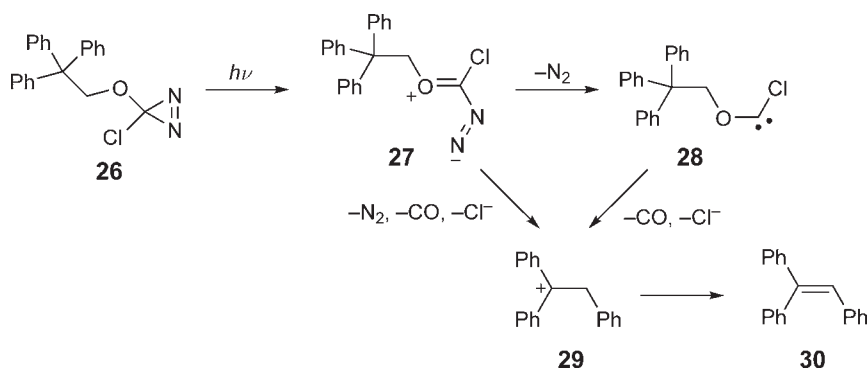
Diazirines are commonly used as carbene precursors via photolytic cleavage. This process has been the source of much experimental and theoretical research <1996CHEC-II(1A)347>. At present, three elementary processes are known in diazine photolysis (Scheme 3): (1) the generation of a carbene (e.g., **20**), (2) the generation of a diazoalkane (e.g., **21**), and (3) the rearrangement of the excited state of the diazirine (e.g., **22**) <B-2002MI27>. A nonspectroscopic method has been developed which can distinguish between these pathways by means of a fullerene probe (Scheme 3) <2000JA7134>. Fullerene will react with carbenes to give methanofullerene (e.g., **23**) and, complementarily, with diazo compounds to give fulleroids (e.g., **24**). Excited state diazine rearrangement does not interact with fullerene but produces olefinic rearrangement products (e.g., **25**). Consequently, cleavage of

diazirines, in the presence of C_{60} , generates a ratio of isolable products which directly reflects the relative occupancy of the diazirine decomposition pathways. Using this method, substituent effects on both photochemical <2002JA9465> and thermal decomposition <2003JOC7471> of diazirines have been studied.



Scheme 3

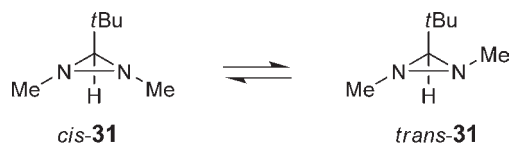
Ultrafast (pico- and femtosecond, ps and fs) laser flash photolysis (LFP), combined with UV–Vis spectroscopy, has been employed to study carbene generation in α -halodiazirines <2006OL4807>. Photolysis of 3-(2,2,2-triphenylethoxy)-3-chlorodiazirine **26** (Scheme 4) produced 1,1,2-triphenylethene **30** via the carbene **28** and the cation **29**. Studies employing ps and fs LFP detected the highly transient diazirine excitation product **27**; moreover, it was found that up to 25% of the cationic intermediate **29** can arise directly from **27**. The zwitterionic (or tautomeric diradical) structure of **27** was tentatively proposed, as it would represent the ultimate product of the S_1 state of a diazirine. Similar results have been reported from ultrafast LFP of related arylmethoxybromodiazirines <2004OL3353>, arylhalodiazirines <2006JA16446>, and diaryloxydiazirines <2003OL5027>, all of which corroborate the proposed zwitterionic/diradical excited species. LFP has also been employed in the identification of carbene–diazirine ylides as side products in diazirine photolysis <2000PCA4115> and in the calculation of the quantum yield of formation of diazo compounds from diazirine photolysis <1996JA7229>.



Scheme 4

1.11.4.2 Diaziridines

^{13}C NMR experiments on 1,2-dimethyl-3-*tert*-butyldiaziridine **31** have shown that, as solvent polarity increases, the population of the 1,2-*cis*-form also increases (Scheme 5). However, only the 1,2-*trans*-form is observed when the *tert*-butyl is replaced by other R groups (Me, Et, *i*-Pr, Ph) <1998MC113>.



Solvent	<i>cis</i> - 31 : <i>trans</i> - 31
D ₂ O	2:1
CDCl ₃	0.05:1
C ₆ D ₆	0.03:1

Scheme 5

Diaziridines are bidentate molecules and can form coordination polymers with silver nitrate producing stable 1:1 complexes. X-Ray analysis of these complexes has shown that the silver ions are coordinated to the *trans*-orientated lone pairs of the nitrogen atoms (Figure 1). These complexes can be homochiral or pseudo-racemic depending on the substitution around the ring, and can form coordination polymer chains with other diaziridine molecules <2000MC44, 1995MC218>. The structure of complexes with transition metals has also been studied <2000RCB1882>.

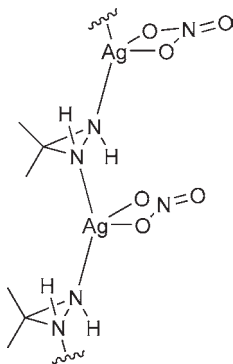
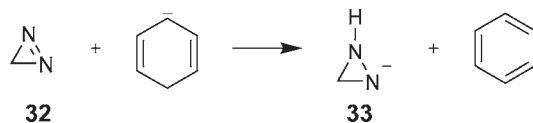


Figure 1

Photoelectron spectroscopy (PES) has shown that in the case of tri- and tetra-alkylated diaziridines, all compounds exist in the *trans*-configuration, with a lone pair–lone pair dihedral angle of 100–110° <1994J(P2)2059>.

The *N*-diaziridinyl anion **33** has been generated from diazirine **32** in a Fourier transform mass spectrometer by reduction of the diazirine (Scheme 6). The acidity of its conjugate acid and the electron affinity of its corresponding radical were measured and used to calculate the N–H bond strength in *trans*-diaziridine ($88 \pm 4 \text{ kcal mol}^{-1}$) <1999IJM179>.



Scheme 6

1.11.5 Thermodynamic Aspects

In the last decade, limited research has been published on the thermodynamic properties of diazirines and diaziridines. Extensive coverage of this topic was presented in CHEC-II(1996) <1996CHEC-II(1A)347>.

As mentioned in previous editions, the inversion of nitrogen atoms in diaziridines has been actively studied since 1967, when it was discovered that nitrogen inversion is slow on the NMR timescale <1967CB1778>. NMR methods have also been used to determine the inversion barriers (108–113 kcal mol⁻¹) <1969AGE212>, and in all known examples, the inversion barrier does not exceed 117 kcal mol⁻¹ <B-1992MI105>. However, the inversion barriers in 3,3-unsubstituted diaziridines were not measured until recently, and it was found that the values were generally much higher <2004CEJ951>. The enantiomers of 1,2-di-*tert*-butyldiaziridine **34** (Scheme 7) were separated, and the stopped-flow multidimensional gas chromatographic method (sfMDGC) used to determine the enantiomerisation rate constant. From this, the inversion barrier was calculated as 135.8 ± 0.2 kcal mol⁻¹ (at 150.7 °C). This represents the highest value found for nitrogen inversion in a three-membered ring compound.

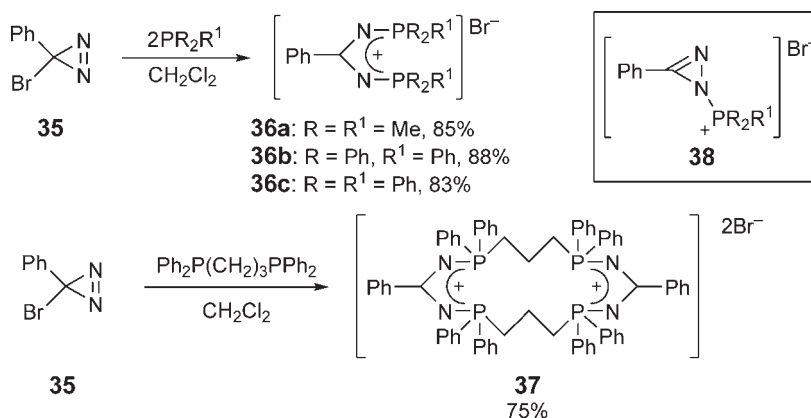


Scheme 7

1.11.6 Reactivity of Diazirines

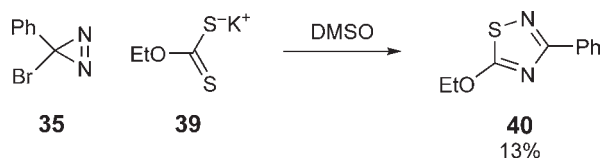
As in prior editions, the reactivity of diazirines is categorized as proceeding with or without ring cleavage; discussion here follows this respective order.

In the last decade, several examples of nucleophilic cleavage of diazirines have been reported. Previously, nucleophilic attack upon diazirines was known to proceed without cleavage, providing a convenient method of C-3 substitution <1983JA6513> or addition to the N=N bond without ring cleavage <1996CHEC-II(1A)347>. Treatment of bromophenyldiazirine **35** with 2 equiv of trimethyl-, diphenylmethyl-, or triphenylphosphine gave the cationic bis-adducts **36** (Scheme 8) <1996JA1060>. The reaction was extended to diphosphines, where interesting products such as the 16-membered dicationic macrocycle **37** were produced in good yield. Initial S_N2' phosphine attack on the diazirine is thought to give the intermediate 1*H*-diazirine **38** (consistent with related mechanistic studies <1989TL4901, 1990JA368>), whereby S_N2 attack of a second phosphine on nitrogen gives the product cation.

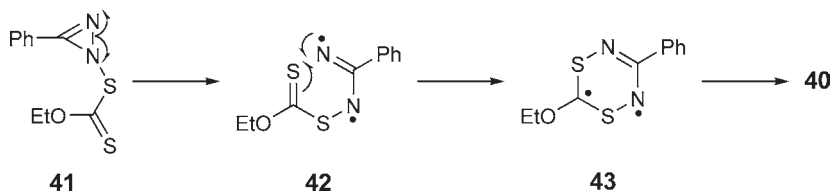


Scheme 8

Cleavage of bromophenyldiazirine **35** with a xanthate nucleophile has allowed the synthesis of a novel heterocycle (Scheme 9) <1999TL29>. Exposure of **35** to potassium ethyl xanthate **39** produced the adduct **40** in low yield. The reaction may proceed via S_N2 cleavage of the intermediate 1*H*-diazirine **41** (similar to **35** → **36**); however, a radical mechanism was also proposed (Scheme 10) in which fragmentation of **41** preceded cyclization and sulfur extrusion.

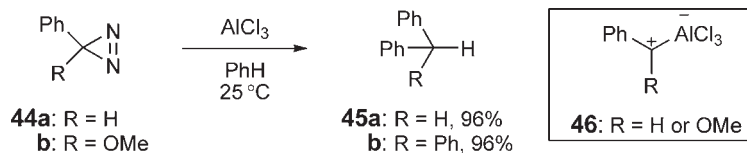


Scheme 9



Scheme 10

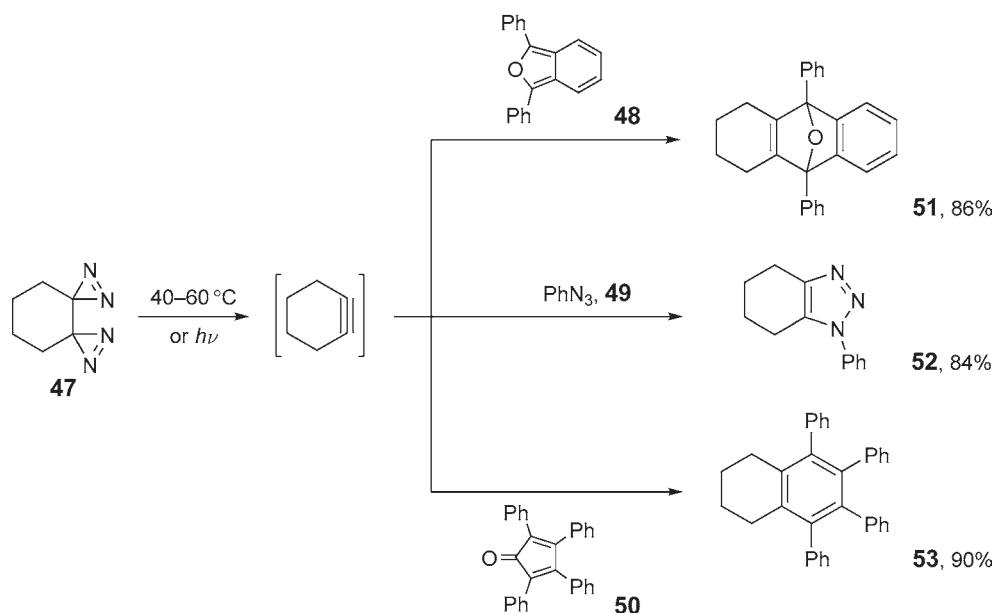
Obviously, carbene generation is a facet of diazirine reactivity involving ring cleavage. Earlier literature is well covered in the previous editions [<1984CHEC\(7\)195, 1996CHEC-II\(1A\)347>](#) and is the subject of an excellent review [<2006ACR267>](#), and recent mechanistic investigations are detailed in [Section 1.11.4.1](#). Common applications of diazirine-generated carbenes are documented in [Section 1.11.9](#). Two recent, interesting examples of diazirine carbenes in synthesis are outlined here. Carbene formation from diazirines can be thermolytic, photolytic, or mediated by Lewis acid. The appropriate choice of Lewis acid has enabled tandem carbene generation and Friedel–Crafts reaction of aryldiazirines to be performed [<2000JA9878>](#). Treatment of the diazirines **44a** and **44b** with aluminium trichloride in benzene gave the phenylmethane derivatives **45a** and **45b** ([Scheme 11](#)). Compound **45b** is the product of two benzene alkylations; the second alkylation is possible due to the lability of the methoxy substituent. The reaction is thought to proceed via the alkylating electrophile **46**, generated by combination of a carbene and aluminium trichloride.



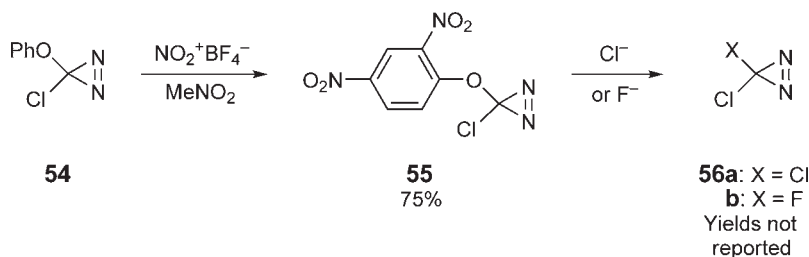
Scheme 11

Bidiazirin-3-yls cleave thermally or photolytically to generate the corresponding alkyne [<2006AGE309>](#). Although more convenient methods of $\text{C}\equiv\text{C}$ bond formation exist, bi-3*H*-diazirin-3-yls (e.g., **47**) are powerful precursors to highly strained cycloalkynes, requiring only mild propagation conditions. Such cycloalkynes are inevitably unstable and, hence, are trapped *in situ*. Thermolysis or photolysis of the bi-3*H*-diazirin-3-yl **47** in the presence of the reaction partners **48–50** gave the alkyne cycloaddition products **51–53** in good yields ([Scheme 12](#)) [<2006AGE309>](#).

In the last decade, little new methodology has been developed which involves reactions of diazirines which proceed without ring cleavage. However, a variation of the diazirine exchange reaction [<1983JA6513>](#) has been investigated; consequently, the scope of this reaction has been extended to conveniently synthesise previously hard-to-obtain diazirines. Originally, the diazirine exchange reaction allowed haloalkyl-, -aryl-, -alkoxy-, or -aryldiazirines to be substituted with a variety of nucleophiles [<1983JA6513>](#). By generating haloaryloxydiazirines where the lability of the aryloxy substituent exceeds that of the halogen, dihalodiazirines have been synthesized [<2005JA2409>](#). Phenoxychlorodiazirine **54** underwent dinitration to give the diazirine **55**; attack with either chloride or fluoride leads to the dihalodiazirines **56a** or **56b** ([Scheme 13](#)) [<2007JA5167>](#). Previous syntheses of difluoro- and chlorofluorodiazirine, via fluorinated nitrogenous intermediates, are described as ‘shatteringly explosive’ [<1973JOC1065>](#).



Scheme 12

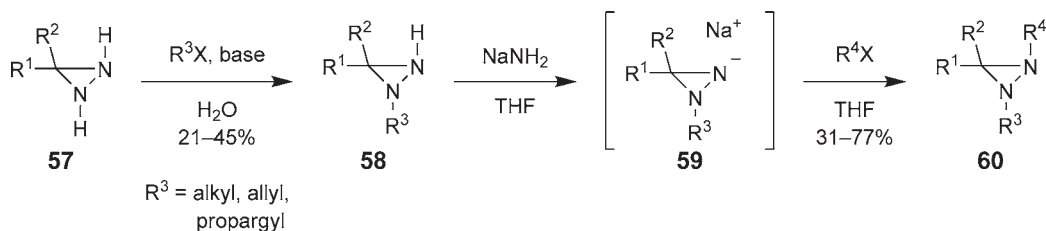


Scheme 13

1.11.7 Reactivity of Diaziridines

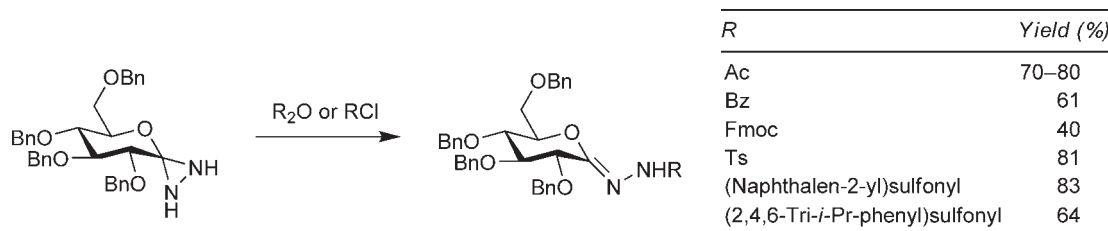
As before, the reactions of diaziridines can be split into two classes: reactions without ring cleavage, and those with ring cleavage/expansion.

Although N-alkylation is usually incorporated from the starting aldehyde or amine when the diaziridine is synthesized [\[1996CHEC-II\(1A\)347\]](#), both nitrogens of the preformed diaziridine **57** can be alkylated sequentially with alkyl halides ([Scheme 14](#)) [\[1999MC112\]](#). Note the need for a strong base in the second alkylation step. Treatment of **58** with a mild base and alkylating agent gives rise to a quaternary diaziridinium species which rapidly decomposes.



Scheme 14

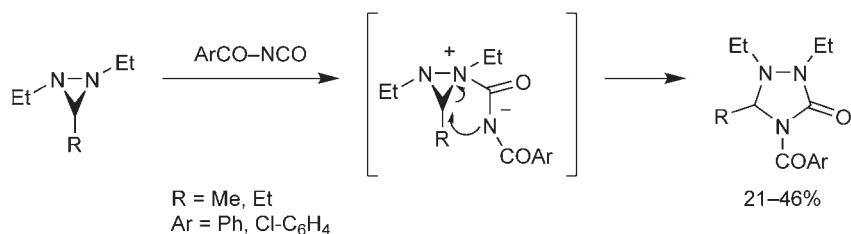
In the case of acylating or sulfonylating electrophiles, however, the acyl (sulfonyl) diaziridinium intermediate rearranges to give acyl (sulfonyl) hydrazones (**Scheme 15**) <2003HCA2490>.



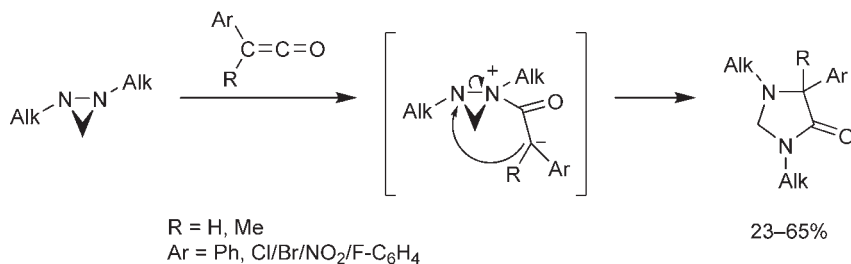
Scheme 15

Ring cleavage can either be through (1) C–N or (2) N–N cleavage (**Scheme 16**). Reaction with isocyanates or ketenes can lead to rearrangement of the N-acylated intermediates, giving rise to ring-expanded heterocycles <2006RCB554, 2005RCB1021, 2006JHC881, 2003MC221>.

(1) C–N cleavage

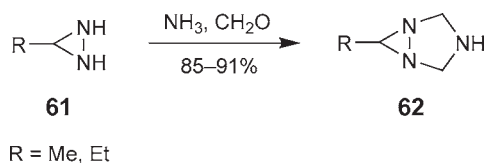


(2) N–N cleavage



Scheme 16

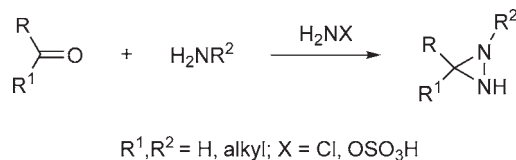
In addition, unsubstituted diaziridines can undergo Mannich-type reactions to give bicyclic diaziridines **62** (**Scheme 17**) <2003RCB2282, 2002RCB1497, 1993RCB2004>.



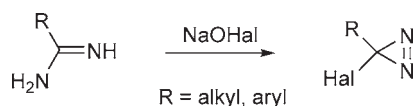
Scheme 17

1.11.8 Synthesis

The syntheses of diazirines and diaziridines are closely related due to the relative ease of interconversion between the species by reduction/oxidation <1996CHEC-II(1A)347>. Consequently, diazirines and diaziridines are both commonly synthesized by the well-established methods of Schmitz <1961CB2166> (**Scheme 18**) and Graham <1965JA4396> (**Scheme 19**), and these are described in previous editions <1984CHEC(7)195, 1996CHEC-II(1A)347>.

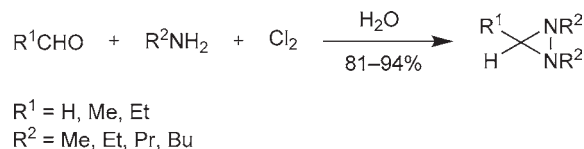


Scheme 18

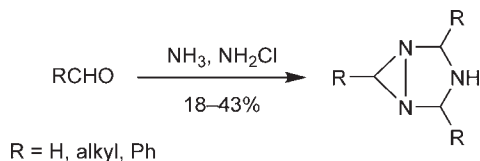


Scheme 19

Recent advances in diazirine/diaziridine synthesis have extended the scope of the standard Schmitz or Graham procedures by various modifications. Among these, the use of electrochemical methods <2002RJE1220>, and the dimerization of perfluorinated imines <1998JFC(89)111>, while efficient, may not find wide use. Of the more conventional methods described, a simple procedure for the synthesis of symmetrical diaziridines is shown in **Scheme 20** <2006RCB2056>. This is an extension of the Schmitz procedure, but without the need for an electrophilic aminating agent. Bicyclic diaziridines can also be synthesized directly from the corresponding aldehydes by reaction with ammonia <1993RCB1602> (**Scheme 21**).

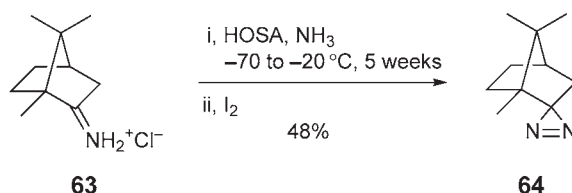


Scheme 20



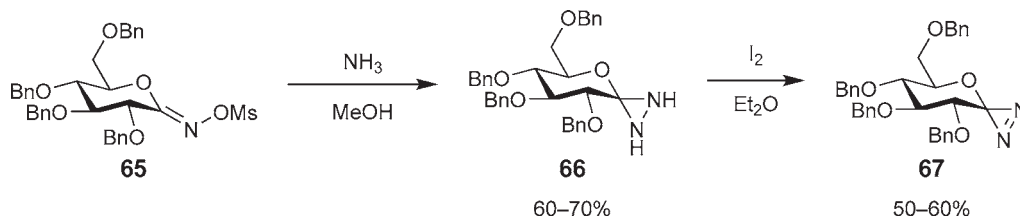
Scheme 21

The Schmitz reaction can be unsuccessful in sterically demanding environments; in such circumstances, the electrophilic aminating agent reacts faster with ammonia than with hindered ketones <1965JA2665>. Consequently, the synthesis of 2-azi-camphane **64**, a compound which is unobtainable under standard conditions <1996TL6647>, was achieved by slow diaziridination of camphor imine hydrochloride **63** (rather than camphor itself) with hydroxylamine-*O*-sulfonic acid (HOSA)–ammonia, followed by iodine-mediated oxidation (**Scheme 22**) <2001S379>.



Scheme 22

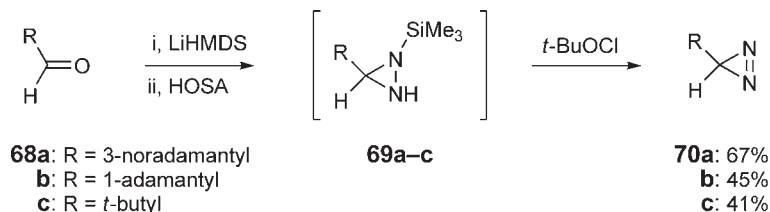
A similar method has been used to synthesize spirocyclic glycosyl diaziridines and diazirines (e.g., **66** and **67**), which are used as glycosylidene carbene precursors. The diaziridine is made by reaction of the sulfonylated oxime **65** with ammonia, followed by oxidation to the diazirine with iodine (Scheme 23).



Scheme 23

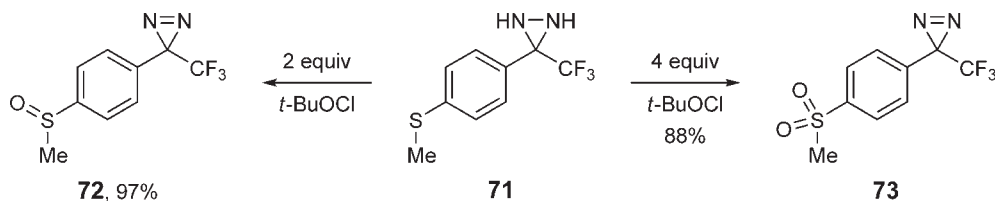
The stereoselectivity of the addition of ammonia has been studied [\[2003HCA1488\]](#), along with the thermolysis of the diazirine products [\[1994HCA2335\]](#). The addition of the corresponding carbenes to, among others species, alcohols and buckminsterfullerene (C_{60}) has been fully investigated [\[1993HCA2847\]](#).

Some aldehyde-derived diaziridines are unstable and hamper the Schmitz synthesis of the corresponding diazirines [\[1975J\(P2\)686\]](#). A one-pot derivative of the standard Schmitz reaction has been developed to circumvent such problems, in which an intermediate diaziridine is stabilized by a trimethylsilyl group [\[2000TL795\]](#). Treatment of the aldehydes **68a–c** with LiHMDS, then HOSA, gave the silicon-stabilized diazirines **69a–c**. *In situ* oxidation with *t*-butyl hypochlorite generated the diazirines **70a–c** in moderate yields (Scheme 24).



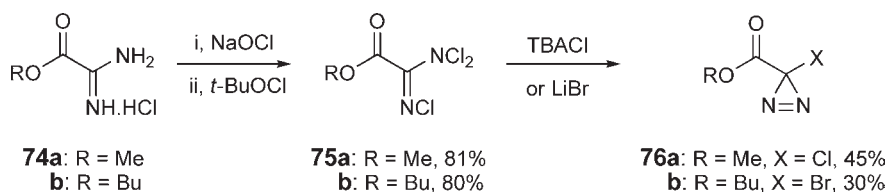
Scheme 24

Methodology has been developed in which simultaneous oxidation of a compound containing diaziridine and sulfide groups can lead to either a diazirine–sulfoxide or a diazirine–sulfone, dependent on oxidant stoichiometry [\[1995S553\]](#). Treatment of the diaziridine **71** with 2 equiv of *t*-butylhypochlorite gave the diazirinylsulfoxide **72**, whereas application of 4 equiv gave the diazirinylsulfone **73** (Scheme 25).



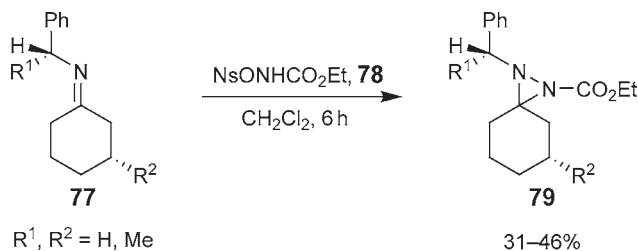
Scheme 25

An extension of the Graham method of diazirine synthesis has enabled the first synthesis of 3-carboalkoxy-3-halodiazirines (e.g., **76**) <2004JOC7359>. Conversion of the amidines **74a** and **74b** into the corresponding *N,N,N'*-trichloroamidines **75a** and **75b** was achieved through successive chlorination steps; reductive dechlorination with bromide or chloride gave the diazirines **76a** and **76b** (Scheme 26).



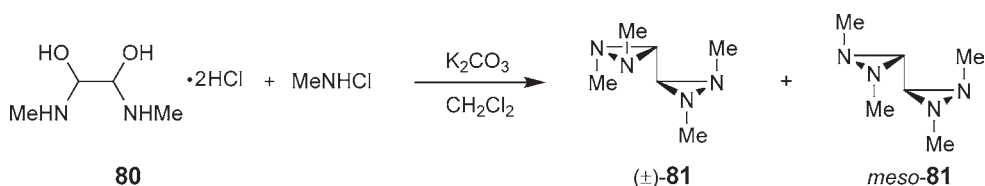
Scheme 26

Spirocyclic, chiral diaziridines **79** can be made by reaction of a chiral-substituted imine **77** with ethyl *N*-[(4-nitrobenzenesulfonyl)oxy]carbamate (NsONHCO₂Et, **78**) (Scheme 27) <1998TL6391>. Interestingly, this reaction does not proceed when using the more traditional tosyl-substituted aminating agent.



Scheme 27

An alternative approach from a noncarbonyl precursor starts from 1,2-bis(methylamino)ethane-1,2-diol dihydrochloride **80**, and is used to prepare racemic and meso-bidiaziridine **81** (Scheme 28) <2004RCB641>.



Scheme 28

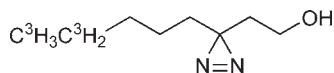
1.11.9 Important Compounds and Applications

1.11.9.1 Diazirines

Diazirines are a reliable source of carbenes, and this property has dominated their application in the last decade. In particular, there has been considerable use of diazirines in macromolecular systems, both chemical and biological, and this is the subject of a recent review <2005SFM178>. Synthetic applications are documented in Section 1.11.6.

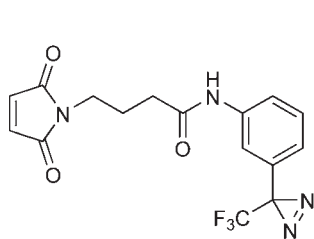
Diazirines exhibit low biological activity; hence, they have been frequently employed as carbene progenitors in biochemical applications such as photoaffinity labeling and as cross-linking reagents <2002CTM271>. For example, tritiated 3-diazirinyloctanol **82** was synthesized as a radiolabeled, photoactivable mimetic of conventional general anesthetics <1999JME3300>. *In vitro* and *in vivo* analysis confirmed the anesthetic properties of **82**, which was then

photoincorporated into nAcChoR-rich membranes. The radiolabeled incorporation sites were readily identified and marked the location of anesthetic action. A recent advance in photoaffinity labeling has been the development of biotinyl diazirine probes [<2005TCR385>](#), which improve labeled fragment isolation: biotinylated fragments can be rapidly isolated via their high-affinity binding with tetrameric avidin [<1990JCH\(510\)3>](#).

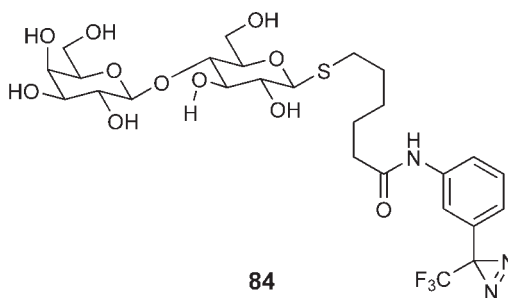


82

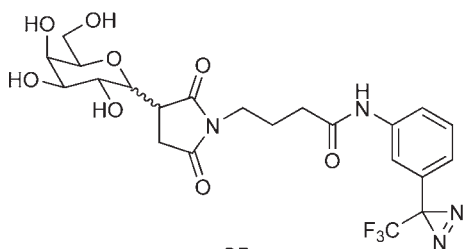
The diazirinylmaleimide **83** has been successfully applied in surface bioengineering as a photoactivable linker. Photoactivation of **83** leads to effective grafting via carbene insertion on to silicon, silicon nitride, and diamond surfaces [<1998SIA783>](#). Immobilization of F(ab') fragments, by covalent binding to the grafted linker molecules, generated a bioactive silicon nitride surface [<1997SAB38>](#). Similarly, the saccharide-bearing diazirinylmaleimides **84** and **85** were photoactively immobilized on diamond [<1999BCC169>](#) and polystyrene [<2001BMC2943>](#) surfaces, respectively. Surface modification of nylon-6,6 has been achieved through attachment of the diazirinylfluor-enone **86** via photoinduced carbene generation [<2006NJC53>](#). In the pursuit of novel cosmetic formulations, diazirines have been used as photoactivatable linkers for the attachment of compounds to keratinic polymers [<EP1362851>](#).



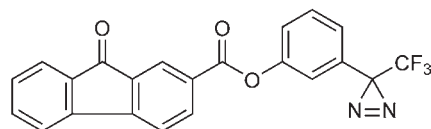
83



84



85

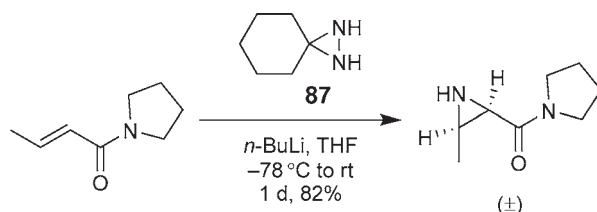


86

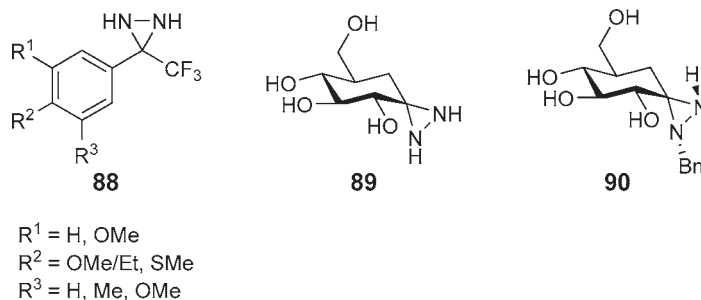
1.11.9.2 Diaziridines

Besides being precursors to diazirines (and by extension, carbenes), diaziridines have found application as aziridinating agents [<2002HCA4272, 1999TL5207>](#). 3,3-Pentamethylenediaziridine **87** was found to aziridinate α,β -unsaturated amides in good yield, and with high diastereoselectivity. This diastereoselectivity was found to be independent of the substrate geometry (**Scheme 29**).

In addition, diaziridines have also been shown to possess biological properties. Substituted phenyl diaziridines **88** can cause inactivation of human cytochrome P4502B6 [<2006DMD2102, 2006DMD1849, 2004DMR343>](#), while carbasugar-derived spirocyclic diaziridines **89** and **90** have been evaluated as glycosidase inhibitors [<2003HCA2210>](#).



Scheme 29



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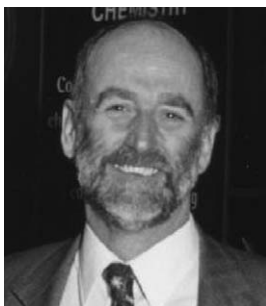
Biographical Sketch



Graeme McAllister was born in Bellshill, Scotland in 1974. His undergraduate studies were carried out at the University of Glasgow, where he received his BSc (Hons.) in 1996. He stayed at the University of Glasgow to join the research group of Richard C. Hartley, conducting research into the total synthesis of chalcocoracin, and the identification/isolation of a Diels–Alderase enzyme. In 1999, he joined the research group of Professor Richard Taylor at the University of York, initially as a postdoctoral researcher and latterly as experimental officer, where he has carried out research, primarily into novel applications of the Ramberg–Bäcklund reaction, as well as developing new one-pot tandem methodology processes and investigating natural product syntheses.



Alexis Perry conducted his undergraduate studies at the University of Glasgow, where he obtained his MSci in 2001. He joined the research group of Prof. Adam Nelson at the University of Leeds, where he developed methodology for the synthesis of C-linked azasaccharides and obtained his PhD in 2005. After a year of postdoctoral research into porphyrin-based molecular memory with Prof. Maxwell Crossley (University of Sydney), he accepted a further postdoctoral position in the research group of Prof. Richard Taylor at the University of York, where he is involved in the development of tandem reactions and their application in natural product synthesis.



Richard Taylor obtained BSc and PhD (Dr. D. Neville Jones) from the University of Sheffield. Postdoctoral periods with Dr. Ian Harrison (Syntex, California) and Prof. Franz Sondheimer (University College London) were followed by lectureships at the Open University and then UEA, Norwich. In 1993 he moved to a chair at the University of York. Taylor's research interests center on the synthesis of bioactive natural products and the development of new synthetic methodology. His awards include the Royal Society of Chemistry's Pedlar Lectureship (2007). Taylor is the immediate past-president of the RSC Organic Division and an editor of *Tetrahedron*.

1.12

Oxaziridines and Oxazirines

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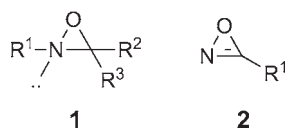
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1.12.1 Introduction

Oxaziridines and oxazirines are the smallest heterocyclic compounds having three electronegatively different oxygen, nitrogen, and carbon atoms in a three-membered ring system. Oxaziridines are saturated molecules, whereas oxazirines are unsaturated as shown by the general structures [1](#) and [2](#).



Since their discovery, oxaziridines **1** have been extensively explored because of their unusual reactivity. This is undoubtedly related to the strained three-membered ring and relatively weak N–O bond in the molecules **1**.

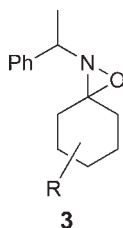
Oxazirines **2**, on the other hand, are only observed as unstable and transient or postulated reaction intermediates, with little known of their chemistry [<1978JA3674, 2004JOC8583, 2005EJO4521>](#). Theoretically, oxazirines were found to collapse with little or no activation to more-stable structures (e.g., isocyanates), and there is no theoretical evidence that any substituted oxazirines would be kinetically stable compounds [<1978JA3674>](#).

Oxaziridines have been the subject of a number of general reviews by Emmons [<1956JA6208>](#), Horner and Jurgens [<1957CB2184>](#), Schmitz [<1984CHEC\(7\)195>](#), Haddadin and Freeman [<B-1985MI\(42\)283>](#), and Davis and Sheppard [<1989T5703>](#). A number of more specialized reviews dealing with their ability to function as electrophilic aminating [<1991S327>](#) and hydroxylating reagents [<1992CRV919, 2003OR1>](#) have also appeared. Other specific reviews were also published by Petrov and Resnati focusing solely on the synthesis and reactivity of polyfluorinated oxaziridines [<1996CRV1809>](#) and by Aube on oxaziridine rearrangements in asymmetric synthesis [<1997CSR269>](#). In addition, critical reviews of the oxaziridine literature from 1996 to 1999 have also appeared in *Progress in Heterocyclic Chemistry* [<1996PHC\(8\)44, 1998PHC\(10\)49, 1999PHC\(11\)66>](#). This chapter updates our earlier account on oxaziridine chemistry in CHEC-II(1996) [<1996CHEC-II\(1A\)365>](#), with particular emphasis on their synthetic utilities. Some overlap with earlier discussions of oxaziridine chemistry is necessary for the sake of continuity.

1.12.2 Structure of Oxaziridines and Oxazirines

Both theoretical and experimental studies on the structures of oxaziridines and oxazirines have been discussed in detail previously [<1996CHEC-II\(1A\)365>](#). Spectroscopic studies using X-ray, nuclear magnetic resonance (NMR), and circular dichroism (CD) excitation chirality methods have been used to determine the configurational stability of the oxaziridine nitrogen atom and their chiral optical properties which have also been reviewed earlier [<1996CHEC-II\(1A\)365>](#). These studies indicated that *N*-alkyl oxaziridines show a high degree of configurational stability of the pyramidal nitrogen atom with inversion barriers of 31–33 kcal mol^{−1}. Pyramidal inversion in *N*-sulfonyloxaziridines is also high because chiral nonracemic oxaziridines were isolated [<1996CHEC-II\(1A\)365>](#).

More recently, Usuki *et al.* studied, using NMR techniques, the conformation of spirocyclic oxaziridines **3** derived from substituted cyclohexanones [<1995JOC8028>](#). Depending on substitution and on the stereochemistry, these compounds exhibit a substantial upfield shift of the cyclohexyl methylene or methane protons with a 1,3-diaxial relationship to the oxaziridine N-substituent. This effect is ascribed to a conformation that places an aromatic group over the plane of the cyclohexane ring. This conformation has also been observed in the solid state by X-ray crystallography and is further supported by molecular mechanics calculations.



1.12.3 Reactivity of Oxaziridines

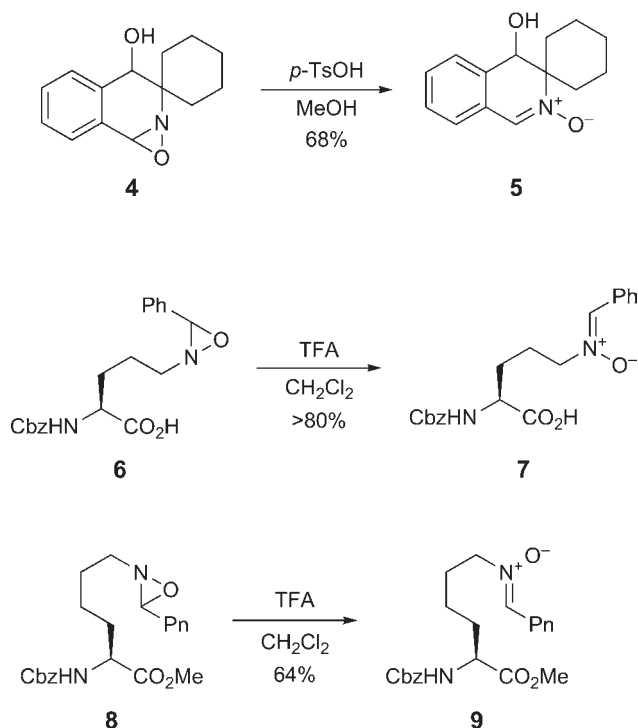
As expected, reactions involving oxaziridines take place at the ring carbon, nitrogen, and oxygen atom depending on the substitution pattern and the reaction conditions. Photo- and thermo-rearrangement of oxaziridines affords isomeric amides or nitrones, while treatment with acid can give hydroxyl amines. The preparatively most useful reactions of oxaziridines, however, are their ability to act as electrophilic aminating and oxidizing reagents. Much of

the reactions related to oxaziridines have been reviewed and the reader is directed to CHEC-II(1996) for details <1996CHEC-II(1A)365>. Synthetically important examples of these transformations and new chemistry are illustrated in the following sections.

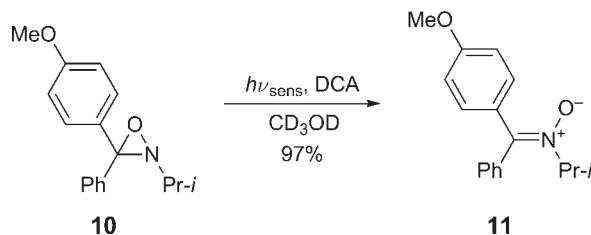
1.12.3.1 Rearrangement Reactions of Oxaziridines

1.12.3.1.1 Rearrangement to nitrones

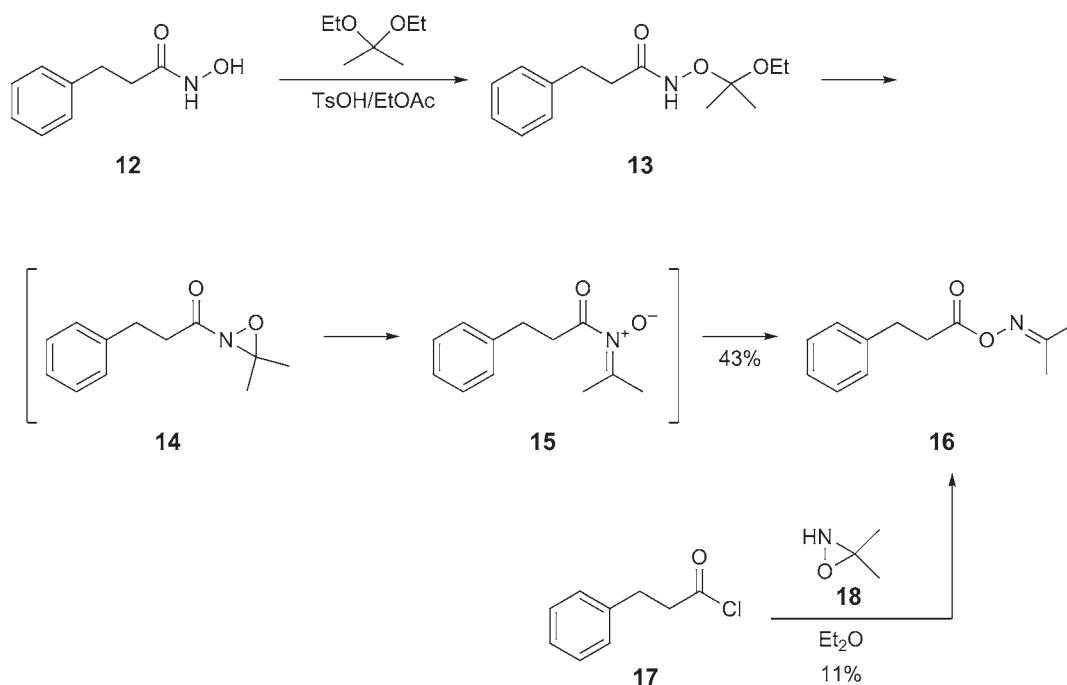
Thermal and acid-catalyzed rearrangement of oxaziridines involving cleavage of the C–O bond to nitrones has been reviewed <1996CHEC-II(1A)365>. More recently, it was reported that treatment of oxaziridine **4** with *p*-TsOH in methanol gave nitron **5** in 68% yield <1996JME4997>. Other acids can also be used for this rearrangement; for example, reaction of oxaziridine **6** with trifluoroacetic acid (TFA) in methylene chloride afforded nitron **7** in >80% <1999JOC7451>. Similarly, treatment of **8** with TFA in methylene chloride gave nitron **9** in 64% yield <2001JOC8282>.



Iwano *et al.* reported the stereoselective isomerization of geometrically constrained oxaziridines to the corresponding nitrones by photosensitized electron transfer <1995CL67>. For example, irradiation of oxaziridine **10** in *d*₄-methanol in the presence of 9,10-dicyanoanthracene (DCA) gave (*E*)-nitron **11** in 97% yield.

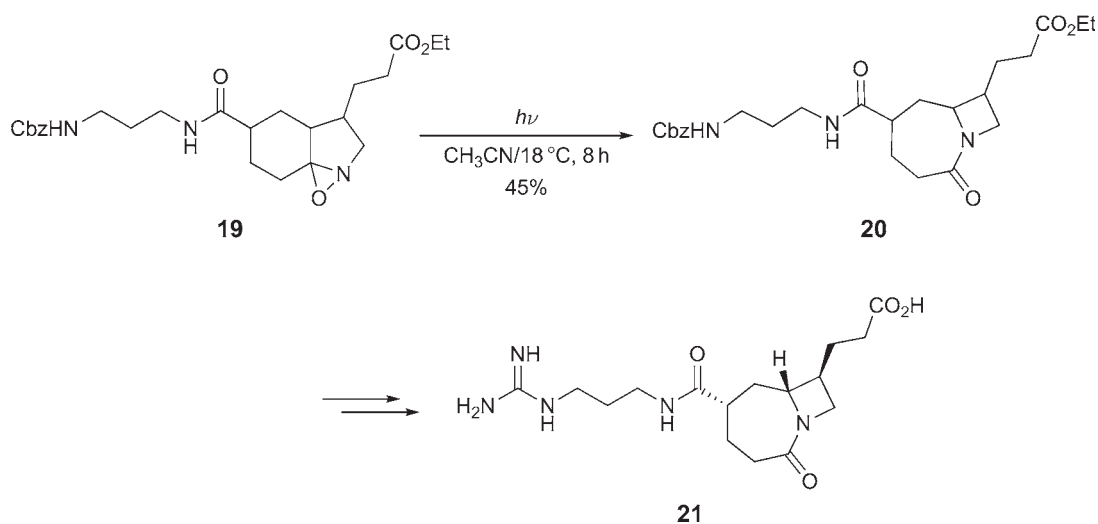


Reaction of hydroxamic acid **12** with acetone ethyl acetal gave rise to acetylated acetone oxime **16** in 43% yield along with other products <2002JOC4833>. It was postulated that the reactions went through an *N*-acyloxaziridine **14** which rearranged to nitron **15** leading to oxime product **16**. This hypothesis was supported by the reaction of the acyl chloride **17** with dimethyloxaziridine **18**, generated *in situ*, which also gave the *O*-acyl acetone oxime **16** in 11% yield.



1.12.3.1.2 Rearrangement to amides

Photochemical isomerization of oxaziridines is also known to give rise to amides. The reaction takes place with concomitant cleavage of the N–O bond and migration of one of the C-3 substituents to nitrogen. This rearrangement has been cleverly used in the synthesis of medium- to large-size lactams [<1996CHEC-II\(1A\)365, 2001OL3067>](#). More recently, Bourguet *et al.* successfully applied this methodology to the synthesis of lactam **20**, a precursor in the preparation of **21**, a nonpeptide GRD antagonist [<2003BML1561>](#). Oxaziridine **19** upon ultraviolet (UV) irradiation at 18 °C for 8 h afforded lactam **20** in 45% yield.

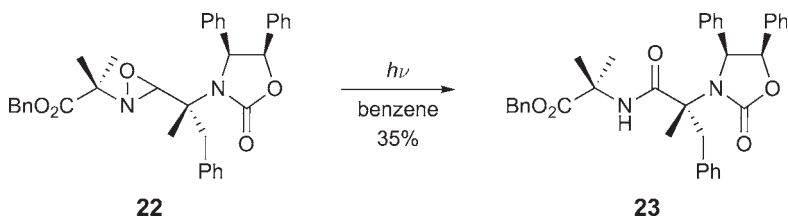


Irradiation of spiro oxaziridines gives rise to various cyclic lactams as summarized in [Table 1](#).

Table 1 Irradiation of spiro oxaziridines to cyclic lactams

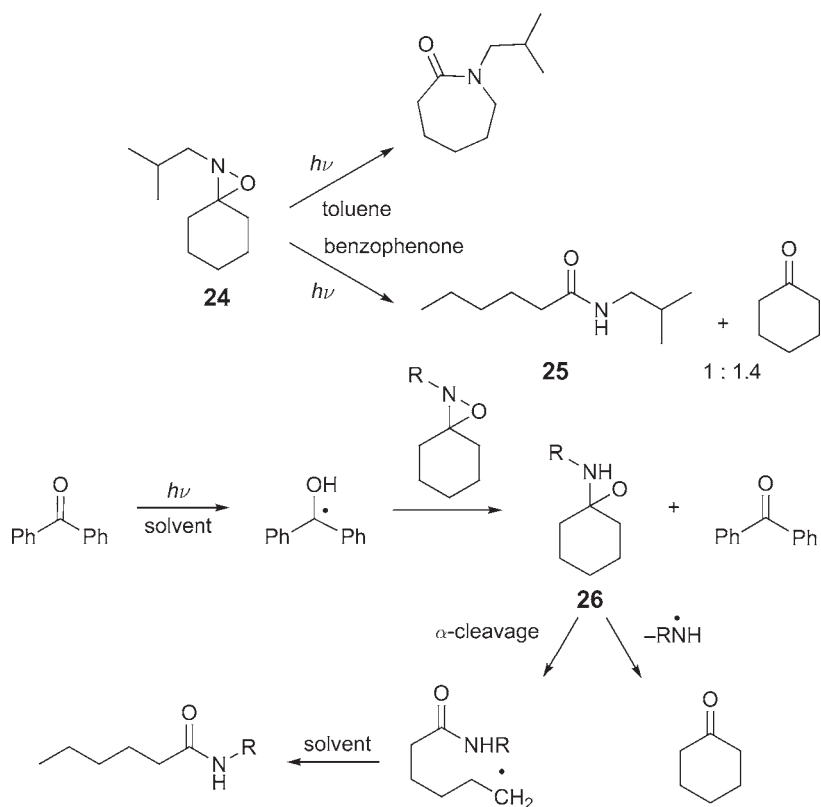
<i>Oxaziridine</i>	<i>Lactam</i>	<i>Yield (%)</i>	<i>References</i>
		53	1995JA5169
		79	2001JOC2636
		79	1997JOC654
		57	2001TA3293
		69	1999TL991, 2001J(P1)1153

The photolytic oxaziridine rearrangement was used by Wenglowsky and Hegedus to prepare sterically demanding dipeptides <1998JA12468>. For example, irradiation of oxaziridine **22** afforded amide **23** in 35% yield.

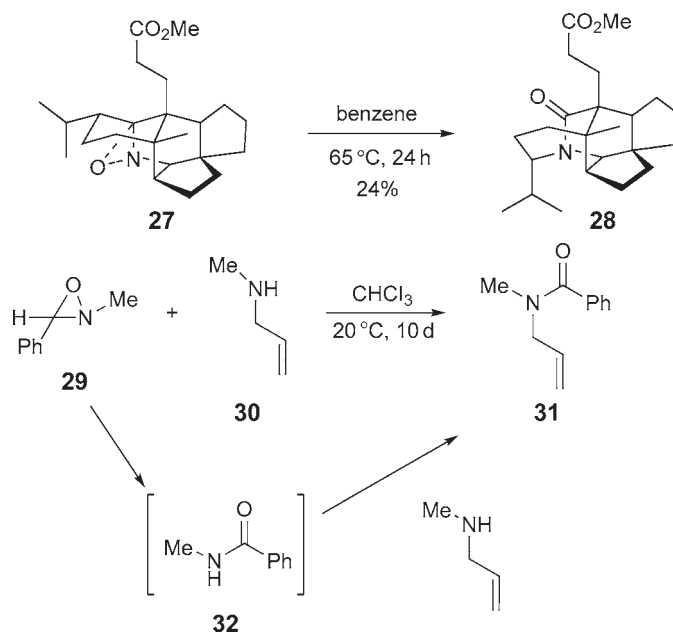


Irradiation of oxaziridine **24** in the presence of benzophenone, a classic triplet sensitizer, underwent reaction by two pathways to give a mixture of amide **25** and cyclohexanone products <1995JA7812>. It was proposed that ketyl radicals **26** are involved in the 'triplet' sensitization chemistry of the oxaziridine and a mechanism was proposed as shown in **Scheme 1**.

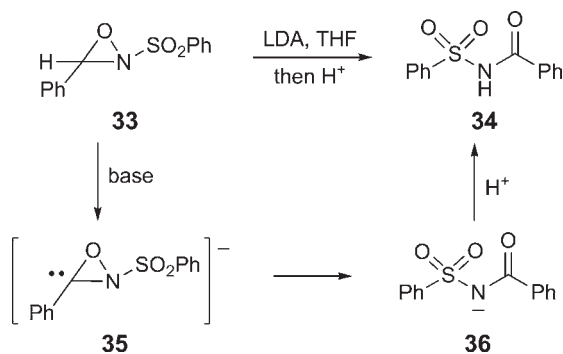
Thermal rearrangement of oxaziridine **27** to amide **28** was reported by Heathcock and Joe <1995JOC1131>. Reaction of oxaziridine **29** with *N*-methylallylamine **30** in chloroform, after 10 days at 20 °C, gave *N*-allylamide **31** as the only product <1997TL8545>. Formation of amide **31** was believed to result from an oxaziridine-to-amide rearrangement to give *N*-methylbezamide **32** and subsequent transamination with *N*-methylallylamine.



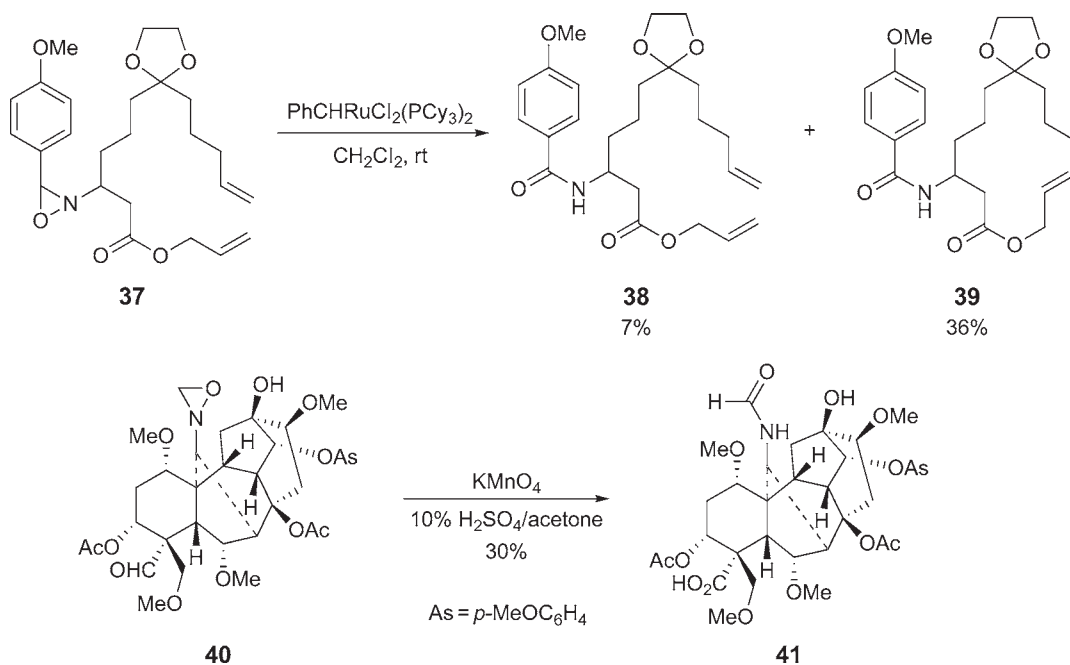
Scheme 1



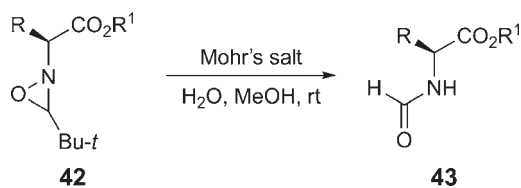
Stojanovic and Kishi reported a novel light-emitting reaction of *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** <1995JA9921>. When treated with more than 2 equiv of a strong base such as lithium diisopropylamide (LDA), **33** underwent spontaneous decomposition with emission of intense yellow light. *N*-Benzoylbenzenesulfonamide **34** was the only isolable product on acidic workup of this chemiluminescent reaction at -78°C . A mechanism involving the generation of species **35** was proposed to account for this reaction.



White *et al.* reported that ring-closing metathesis (RCM) of oxaziridine diene **37** afforded amide **38** and cycloalkene **39** in 7% and 36% yields, respectively [\[2001OL413\]](#). Under these conditions, oxaziridine-to-amide rearrangement is promoted. On reaction of oxaziridine **40** with $KMnO_4$ in acetone in the presence of 10% H_2SO_4 , formamide acid **41** was isolated in 30% yield [\[2002T9431\]](#).



With ammonium ferrous sulfate hexahydrate (Mohr's salt) 3-*tert*-butyl oxaziridines **42** derived from amino acids, gave *N*-formyl α -amino esters **43** in 90–99% yields ([Table 2](#)) [\[1998S297\]](#). This procedure represents a mild method for formylating amino esters without using a formylating reagent.



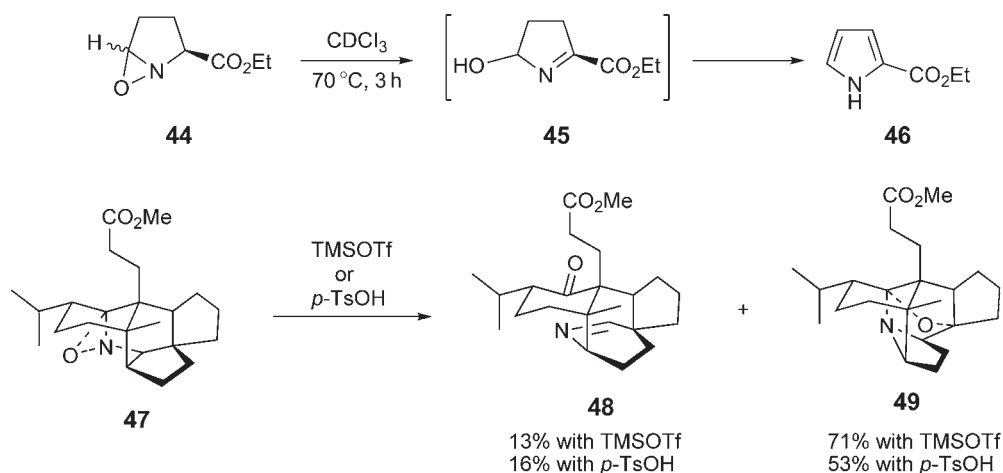
1.12.3.1.3 Miscellaneous rearrangement reactions

Heating a mixture of diastereomeric oxaziridine **44** at $70^\circ C$ for 3 h resulted in formation of pyrrole ester **46** as the only product [\[2002TA437\]](#). Hydroxy imine **45** was suggested as an intermediate with transformation. Treatment with

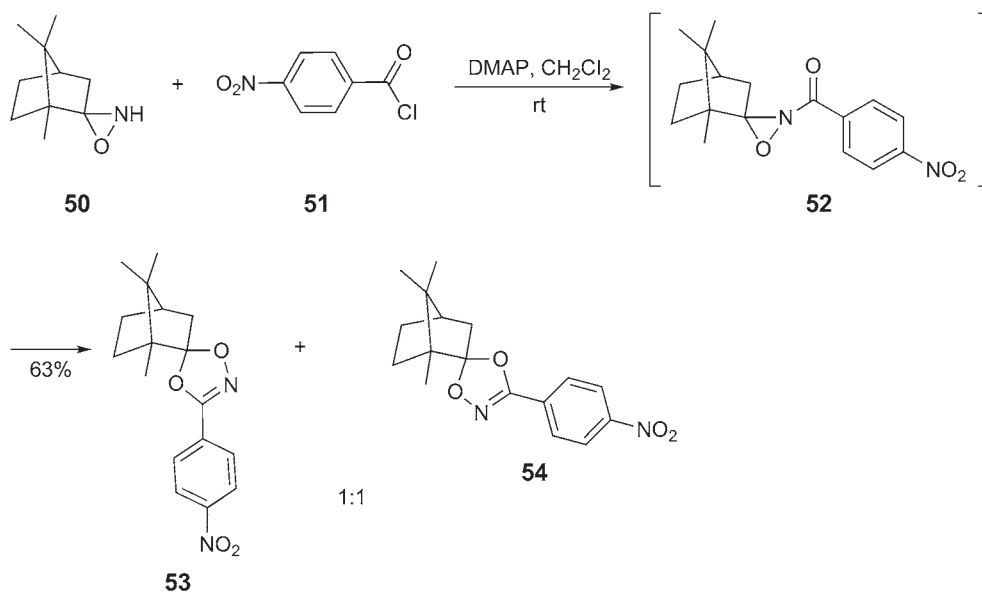
trimethylsilyl trifluoromethanesulfonate (TMSOTf) or *p*-toluenesulfonic acid (*p*-TsOH) oxaziridine **47** produced a mixture of the keto imine **48** and the isomeric amino ether **49** with the latter being the major product in both reactions <1995JOC1131>.

Table 2 Preparation of *N*-formyl α -amino esters **43**

Entry	<i>R</i>	<i>R</i> ¹	Yield (%)
1	Me	Bn	87
2	<i>i</i> -Pr	Bn	89
3	<i>i</i> -Pr	<i>t</i> -Bu	90
4	<i>i</i> -Bu	Bn	82
5	<i>s</i> -Bu	Me	99
6	Bu	Bn	84
7	Bn	<i>t</i> -Bu	96

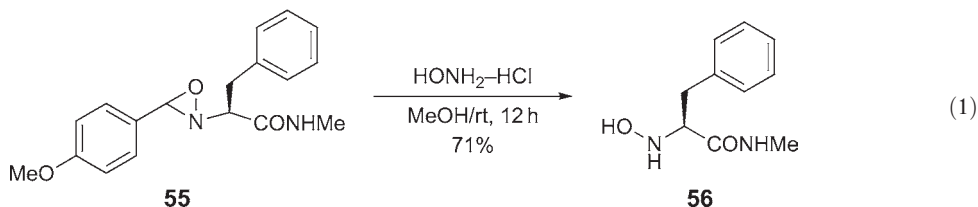


Treatment of NH-oxaziridine **50** with *p*-nitrobenzoyl chloride **51** in methylene chloride in the presence of DMAP at room temperature resulted in dihydrodioxazoles **53** and **54** in 63% yield as a 1:1 mixture of diastereoisomers <2000JOC4204>. *N*-Acyl oxaziridine **52** was believed to have been formed first which rearranged to products **53** and **54**.

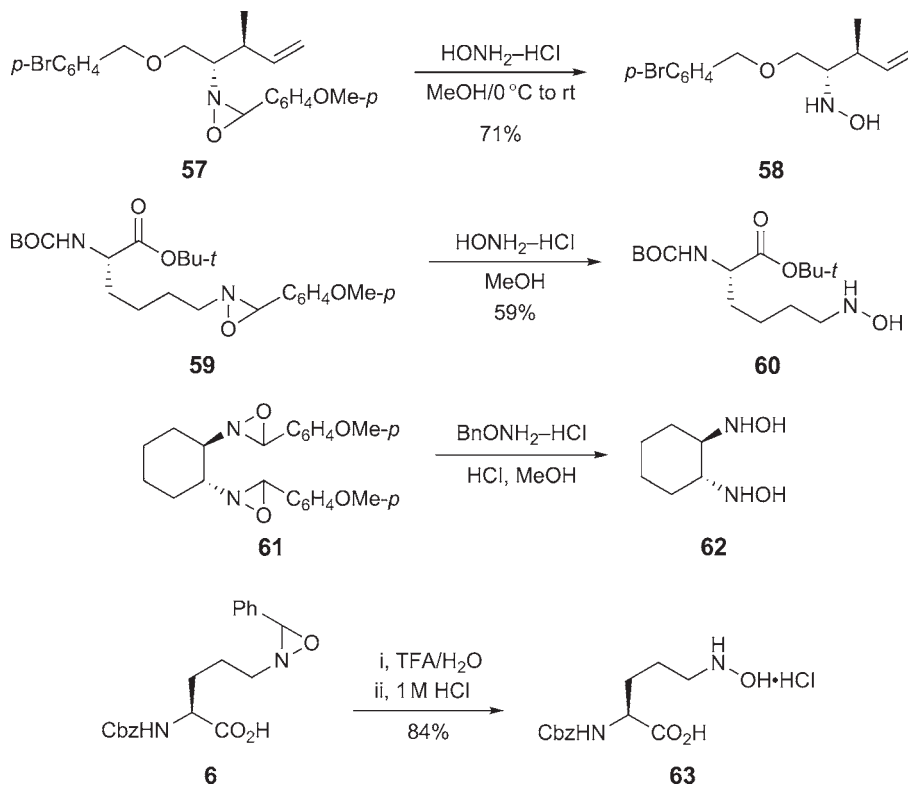


1.12.3.2 Acid-Catalyzed Hydrolysis

3-Aryloxaziridines with acid and hydroxylamine give *N*-alkyl hydroxylamine exclusively through N–O bond cleavage. This is particularly true when the 3-aryl group is a carbocation stabilizing group such as *p*-MeOC₆H₄, which stabilizes the developing carbocation on the oxaziridine carbon atom <1996CHEC-II(1A)365>. This transformation has been successfully applied to the synthesis of *N*-hydroxy amino acid derivatives by first converting the amino acids into oxaziridines, followed by the acid-catalyzed reaction with hydroxylamine <1996CHEC-II(1A)365>. A recent example is shown in Equation (1), where (*S*)-2-(hydroxyamino)-*N*-methyl-3-phenylpropanamide **56** was isolated in 71% yield from oxaziridine **55** <2003BMC2421>.



Treatment of oxaziridine **57** with HONH₂–HCl in methanol afforded hydroxylamine **58** in 61% yield <2002JA4950, 2005JOC1963>. Similar transformations have been used in the synthesis of 5-lipoxygenase inhibitors <1997JME819>. Reaction of oxaziridine **59** with HONH₂–HCl in methanol afforded hydroxylamine **60** in 59% yield <2006JME3003>. Reaction of bis-oxaziridine **61** with BnONH₂–HCl in methanol gave bis-hydroxylamine **62** <2005AGE4389>. Oxaziridine **6** on reaction with TFA/H₂O gives hydroxylamine **63** directly <1999JOC7451>.

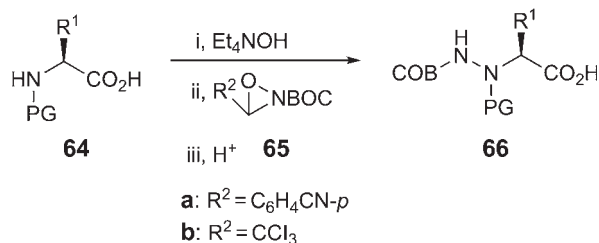


1.12.3.3 Amination Reactions of Oxaziridines

Vidal *et al.* have recently reviewed the use of *N*-alkyloxycarbonyl-3-aryloxaziridines as electrophilic aminating reagents <1997CEJ1691>. These reactions are believed to take place by attack of the nucleophile at the oxaziridine nitrogen atom.

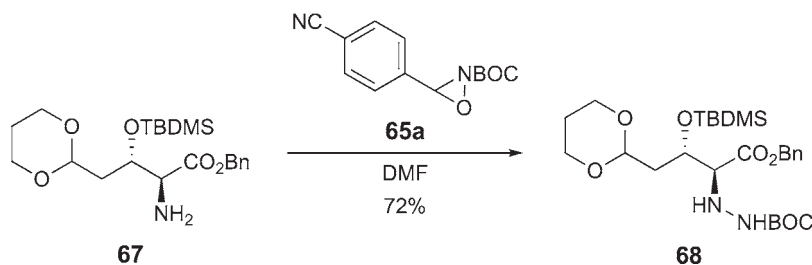
1.12.3.3.1 Amination of *N*-nucleophiles

Electrophilic amination of *N*-benzylamino acids (**64**; PG = Bn) with *N*-BOC-4-cyanophenyloxaziridine (**65a**; R² = PhCN-*p*) is a convenient method for the preparation of *N*-orthogonally diprotected hydroazino acids **66** (BOC = *t*-butoxycarbonyl) <1998TL8845, 1998JME4833, 2003HCA4152>. The reaction is quite efficient and accommodates various functional groups encountered in amino acid side chains (Table 3). *N*-BOC-3-trichloromethyloxaziridine (**65b**; R² = CCl₃) has also been used in similar manner (Table 3) <2004JOC2367>. With these aminating reagents, *N*-unsubstituted amino acids gave lower yields (Table 3).

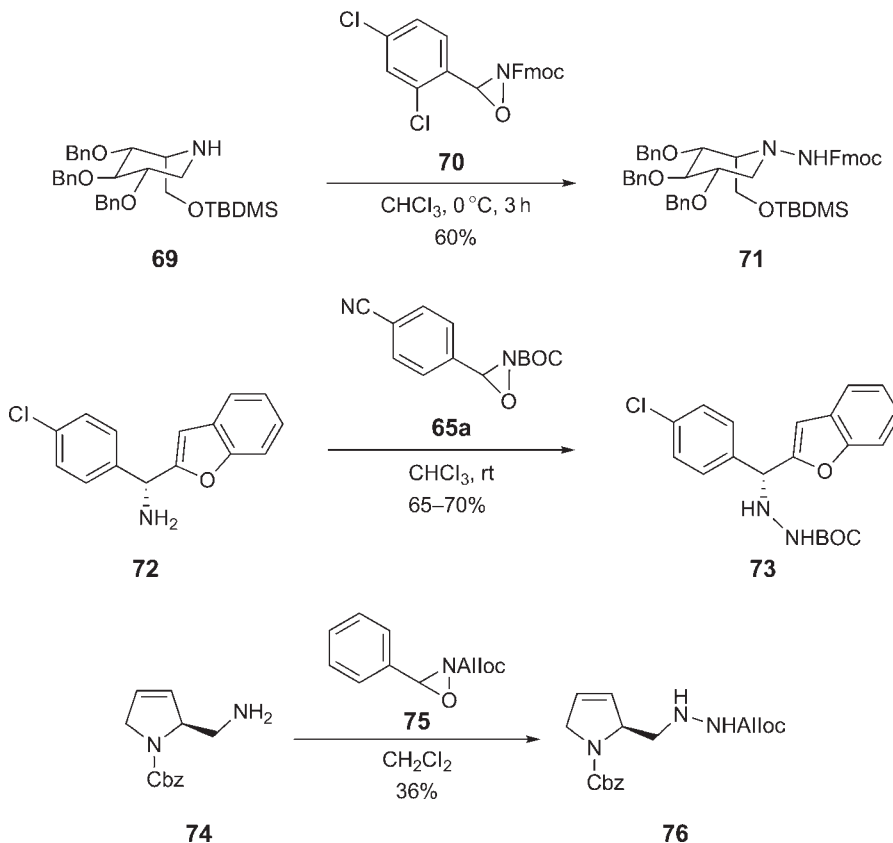
**Table 3** Preparation of α -hydrazino acids **66**

Entry	R ¹	PG	R ²	Yield (%)	Reference
1	CH(CH ₃) ₂	H	4-NCC ₆ H ₄	21	1998JME4833
2	CH(CH ₃) ₂	Bn	4-NCC ₆ H ₄	65–69	1998JME4833
3	CH(CH ₃) ₂	Bn	CCl ₃	48	2003HCA4152
4	CH ₃	H	4-NCC ₆ H ₄	50	2004JOC2367
5	CH ₃	Bn	4-NCC ₆ H ₄	88–91	1998JME4833
6	CH ₃	Bn	CCl ₃	81	2003HCA4152
7	(<i>S</i>)-CH(CH ₃)CH ₂ CH ₃	H	4-NCC ₆ H ₄	0	2004JOC2367
8	(<i>S</i>)-CH(CH ₃)CH ₂ CH ₃	Bn	4-NCC ₆ H ₄ h	75–88	1998JME4833
9	(<i>S</i>)-CH(CH ₃)CH ₂ CH ₃	Bn	CCl ₃	52	2003HCA4152
10	3-Methyleneindole	Bn	CCl ₃	63	2004JOC2367
11	(CH ₂) ₄ NHCO ₂ Bn	Bn	CCl ₃	40	2004JOC2367
12	CH ₂ C ₆ H ₄ -OBn- <i>p</i>	Bn	CCl ₃	71	2004JOC2367
13	(CH ₂) ₃ S(O)CH ₃	Bn	CCl ₃	91	2004JOC2367
14	CH ₂ CONH ₂	Bn	CCl ₃	41	2004JOC2367
15	(CH ₂) ₂ CO ₂ H	Bn	CCl ₃	46	2004JOC2367
16	(CH ₂) ₂ CO ₂ CH ₃	Bn	CCl ₃	71	2004JOC2367
17	CH ₂ CO ₂ Bn	Bn	CCl ₃	56	2004JOC2367
18	CH ₂ OH	Bn	CCl ₃	57	2004JOC2367
19	(CH ₂) ₃ OH	Bn	CCl ₃	60	2004JOC2367
20	–CH ₂ CH ₂ CH ₂ –		4-NCC ₆ H ₄	95	1998JME4833

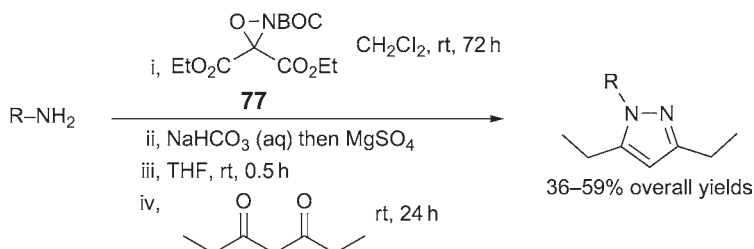
Treatment of amino ester **67** with *N*-BOC oxaziridine **65a** afforded α -hydrazino carboxylic acid **68** in 72% yield <1998JOC6421>. This compound is a precursor to (3*S*,4*S*)-4-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid, important structural units found in the potently antitumor antibiotic luzopeptins.



Electrophilic amination of azasugar **69** with *N*-fluorenylmethoxycarbonyl-3-(2,4-dichlorophenyl)oxaziridine **70** furnished *N*-Fmoc-protected *N*-amino azasugar **71** <2002TL2215>. Similar amination of amines **72** and **74** with oxaziridines **65a** and **75** gave hydrazines **73** and **76**, respectively <2000TA4895, 2005BML1327>. N-Electrophilic amination of the ϵ -amino group of lysine in peptides with 2-BOC-3-(4-cyanophenyl)oxaziridine **65a** has also been described <1999TL7315>. N-Amination of amino acid derivatives has been used in the synthesis of N-terminal α -hydrazinoacetylpeptides <2000TL45>. The synthesis of hydrazinopeptides using solid-phase N-electrophilic amination and this oxaziridine has been described by Klinguer *et al.* <1996TL7259>.



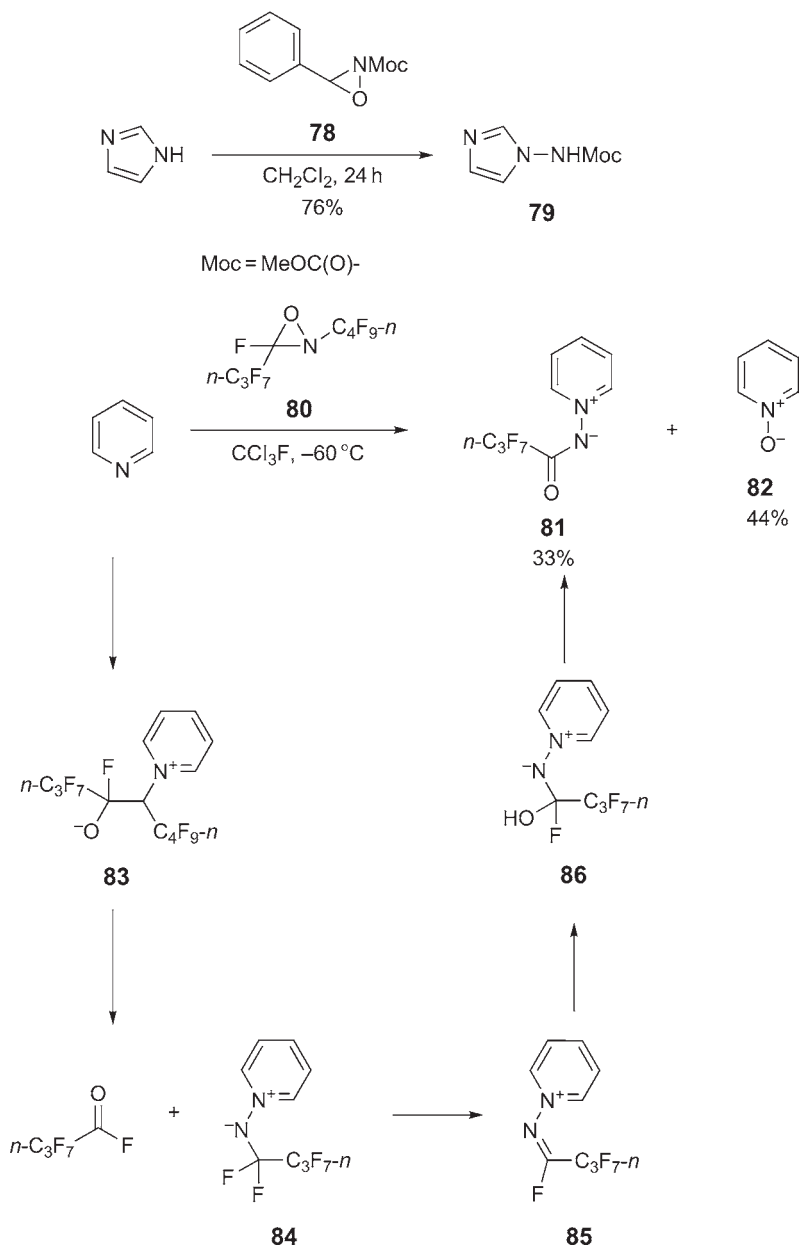
More recently, Armstrong *et al.* reported the use of the diethylketomalonate-derived oxaziridine **77** for the amination of primary amines affording the *N*-BOC hydrazines in good to excellent yields <2005OL713>. This method allows a one-pot synthesis of pyrazoles from primary amines as shown in Scheme 2.



Scheme 2

Imidazole reacts with *N*-Moc oxaziridine **78** to give the corresponding hydrazine **79** in 76% yield <1997CEJ1691>. With perfluorinated oxaziridine **80**, pyridine gave the perfluoroacetylpyridiniumaminide **81** in 33% yield along with the normal oxidation product, pyridine *N*-oxide **82** <1996J(P1)2517>. The formation of **81** was believed to result from

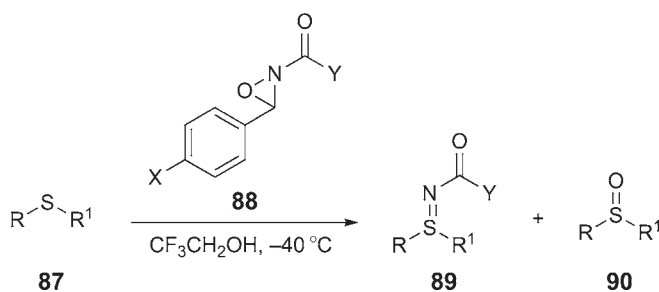
the attack of the pyridine nitrogen on the oxaziridine nitrogen generating an oxy anion **83** that was suggested to undergo a series of fragmentations via species **84–86** to give the products (**Scheme 3**). Pyridazines and quinoxalines show similar reactivity.



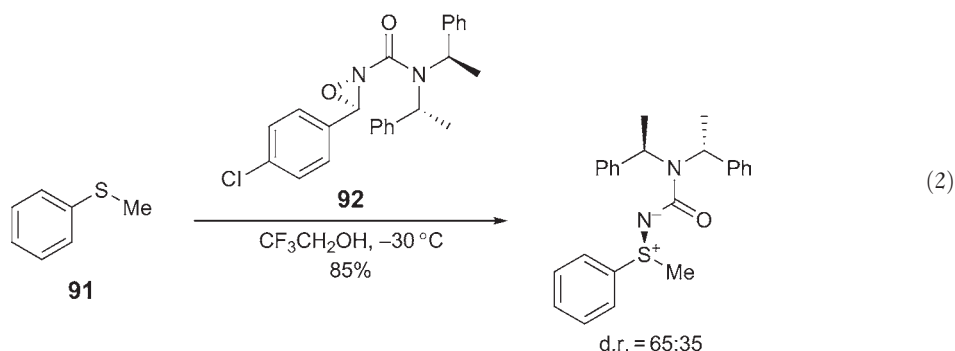
Scheme 3

1.12.3.3.2 Amination of S-nucleophiles

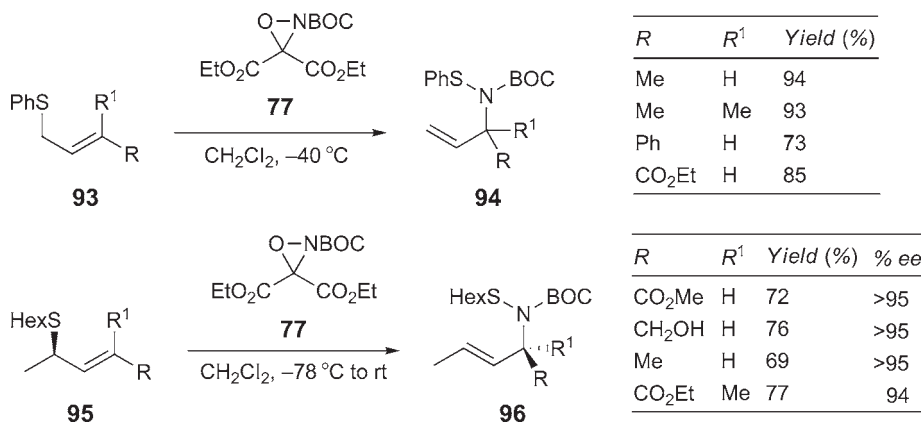
Armstrong *et al.* reported the amination of various sulfides with *N*-acyloxaziridines <2002CCC904, 2003TL5335>. Treatment of various sulfides **87** with **88** in trifluoroethanol afforded sulfimides **89** and sulfoxides **90**, with the former predominating (**Table 4**). Asymmetric sulfimidation with a chiral oxaziridine **92** gave low diastereoselectivities (**Equation 2**) <2003TL5335>.

**Table 4** Amination of sulfides with *N*-acyloxaziridines **88** <2003TL5335>

<i>R</i>	<i>R</i> ¹	<i>X</i>	<i>Y</i>	[<i>N</i>]:[<i>O</i>]	Yield [<i>N</i>] (%)	Yield [<i>O</i>] (%)
Ph	Me	Cl	NEt ₂	>10:1	99	
Ph	Bn	Cl	NEt ₂	>10:1	94	6
Bu- <i>t</i>	Me	Cl	NEt ₂	3:1	72	^a
Ph	Me	CN	OBu- <i>t</i>	10:1	87	5
Ph	Bn	CN	OBu- <i>t</i>	3:1	75	22
Bu- <i>t</i>	Me	CN	OBu- <i>t</i>	1:1	49	^a

^aVolatile product not isolated.

Treatment of allylic sulfides **93** with *N*-BOC-oxaziridine **77** gives *N*-thio allylic amines **94** in good to excellent yields through S-amination followed a [2,3]-sigmatropic rearrangement of the resulting sulfimides <2002CC904>. Reaction of chiral branched allylic sulfides **95** with **77** gave *N*-thio allylic amines **96** in high yields and excellent ee <2006JOC4028>. The reaction results from a [2,3]-sigmatropic rearrangement of the intermediate allylic *N*-BOC-sulfimides with high level of chirality transfer. The first example of formation of quaternary stereocenter using this transformation was also reported.



1.12.3.3.3 Amination of O-nucleophiles

Electrophilic O-amination of alkoxides with trichloromethyloxaziridine **65b** gave *N*-BOC-*O*-alkylhydroxylamines **97** in good to excellent yields <2000CC975>. The reaction takes place smoothly with lithium alkoxides with transfer of the NHBOC functional group to the alkoxide oxygen. Phenol and carboxylic acid oxygens underwent similar O-aminations (Table 5, entries 7 and 8).

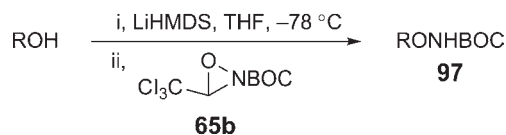
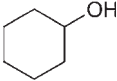
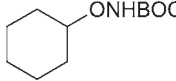
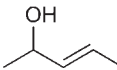
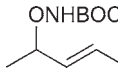
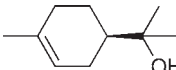
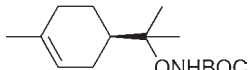
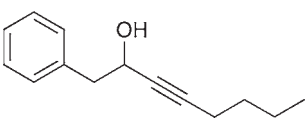
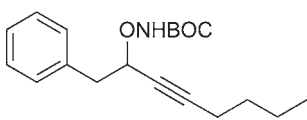
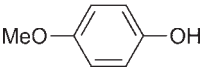
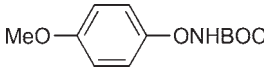
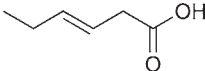
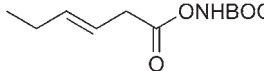
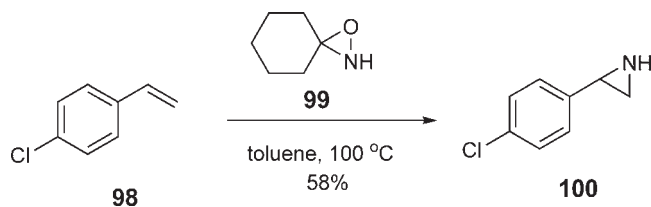


Table 5 O-Amination of hydroxy compounds to hydroxylamines **97** <2000CC975>

Entry	ROH	Product	Yield (%)
1	BnOH	BnONHBOC	>95
2	PhCH ₂ CH ₂ OH	PhCH ₂ CH ₂ ONHBOC	80
3			85
4			96
5			50
6			50
7			87
8			80

1.12.3.3.4 Amination of C-nucleophiles

Treatment of chlorostyrene **98** with oxaziridine **99** in toluene at 100 °C gives aziridine **100** in 58% yield <2003JOC6497>. Similar reaction of styrene **101** with oxaziridine **102** at 50 °C for 50 h afforded the aziridine **103** in 52% yield (Equation 3) <2005TL2207>.





<2005T8423>. In a similar manner, the lithium enolate of **106** afforded **107** in 50–70% yield <2005T8423>.

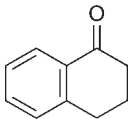
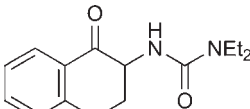
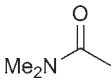
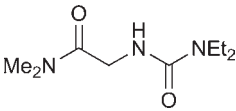
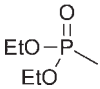
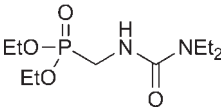
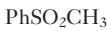
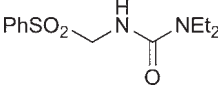
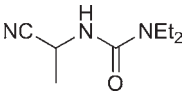


phosphonate-, and nitrile-stabilized carbonions underwent the desired amination (**Table 6**).

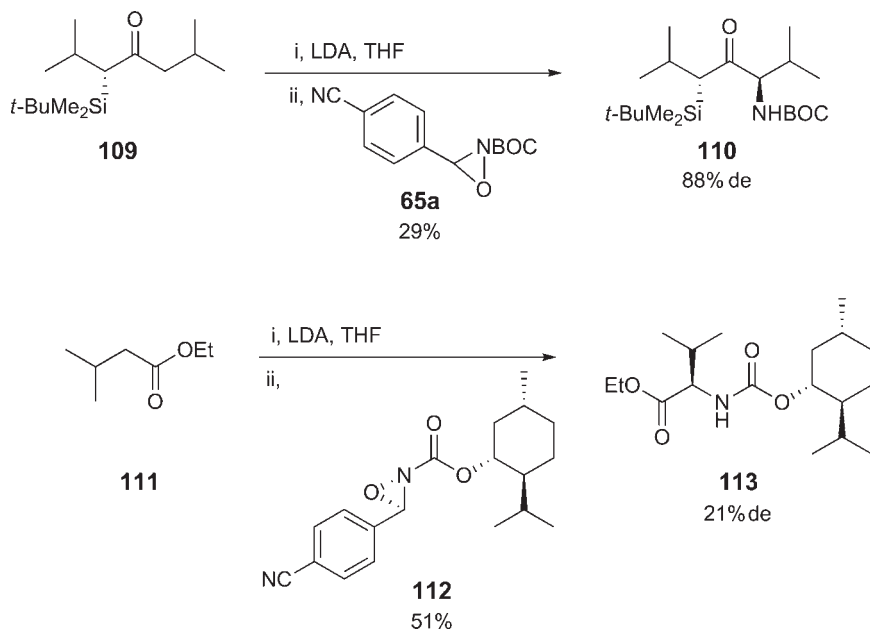
**Table 6** Carbanion amination using 3-(2-cyanophenyl) oxaziridine **108**(Continued)

(Continued)

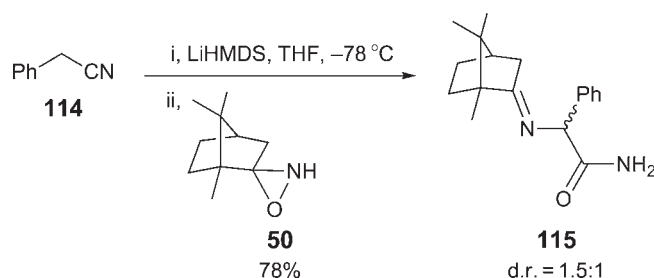
Table 6 (Continued)

Entry	Substrate	Product	Yield (%)
4			59
5			51
6			51
7			43
8			56

Asymmetric α -amination of enolates has also been described. For example, treatment of α -silyl ketone **109** with LDA followed by addition of oxaziridine **65a** gave the *N*-BOC-amino ketone **110** in 29% yield and 88% de [<1998TA3709>](#). Asymmetric amination of the prochiral enolate of **111** with chiral nonracemic oxaziridine **112** afforded amino ester **113** in 51% yield and 21% de [<2001TA535>](#).



Chiral NH-oxaziridines such as **50**, introduced by Page *et al.*, act as an electrophilic source of nitrogen upon reaction with various carbon nucleophiles. Nitrogen is transferred, together with the camphor unit, on reaction with the enolates of esters, malonates, and nitriles [<2000JOC4204, 2002JOC7787>](#). For example, deprotonation of phenylacetonitrile **114** with LiHMDS and subsequent treatment with **50** provided a 78% yield of **115** as a mixture of diastereomers (d.r. = 1.5:1) at the new stereogenic center [<2000JOC4204>](#).



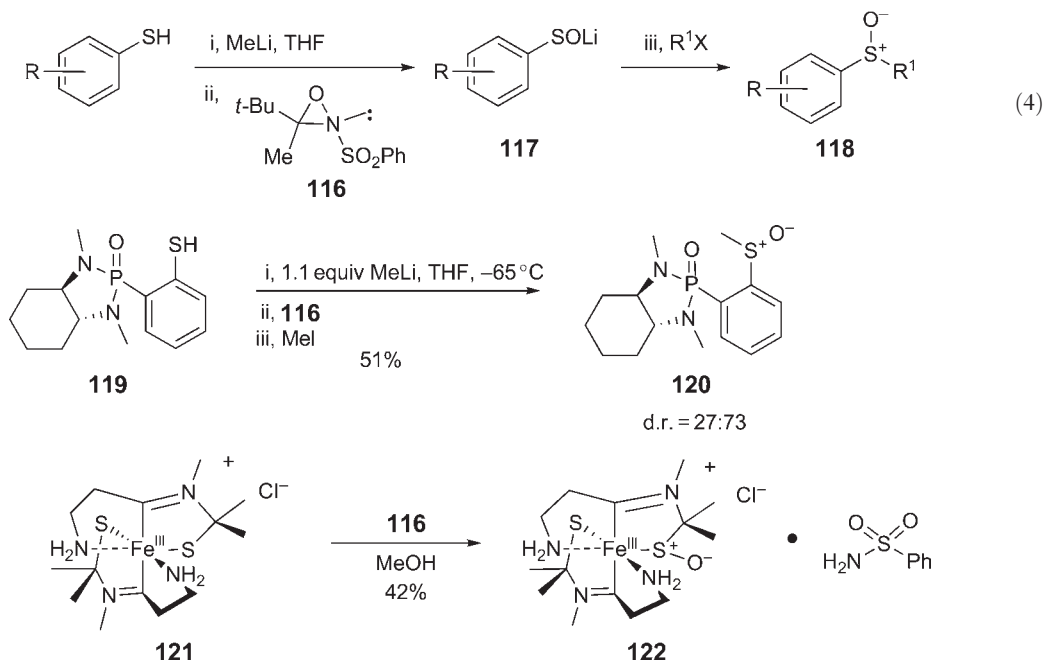
1.12.3.4 Oxygen-Transfer Reactions of Oxaziridines

By far the most widely used synthetic application of the oxaziridines is oxidation. The aprotic *N*-sulfonyl- and peroxaziridines transfer oxygen at rates comparable to peracids via a mechanism where the nucleophilic species attacks the electrophilic oxaziridine oxygen atom in an $\text{S}_{\text{N}}2$ -type fashion [\[1996CHEC-II\(1A\)365\]](#).

1.12.3.4.1 Oxidation of organosulfur compounds

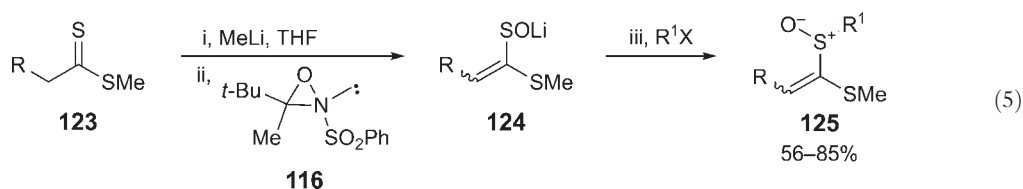
1.12.3.4.1(i) Oxidation of thiols

Lithium aryl thiolates, prepared by reaction of aryl thiols with MeLi, on oxidation with *N*-sulfonyloxaziridine **116**, give sulfoxides **118** on alkylation in good to excellent yields (Equation 4) [\[1997JOC8626, 1999PS\(153\)381, 2004JOC6916\]](#). Sulfenate anions **117** are suggested to be intermediates in this transformation. Diastereomerically enriched sulfoxides have been prepared by alkylation of sulfenate anions generated from chiral thiols [\[2002OL3619\]](#). Similar transformations using thiol **119** gives mixtures of sulfoxides **120** and was described by Mauger *et al.* [\[2004TL3855\]](#). Oxidation of thiolate-ligated ion complex **121** with **116** gave the sulfenate **122** in 42% yield [\[2006JA11211\]](#). Its structure was determined by X-ray crystallography.



1.12.3.4.1(ii) Oxidation of enethiols

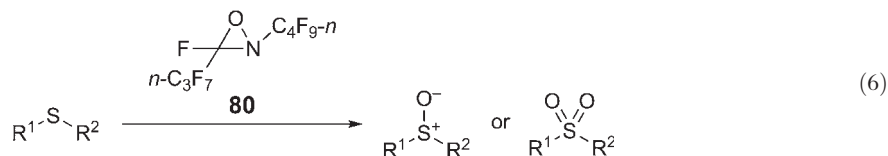
Oxidation of enethiolates derived from dithioesters **123** with *N*-sulfonyloxaziridine **117** gave the corresponding vinyl sulfenates **124**. Subsequent alkylation with alkyl halides led to ketene dithioacetal *S*-oxides **125** in good to excellent yields (Equation 5) [\[2004JOC6916\]](#).

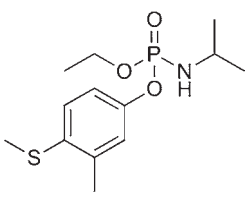
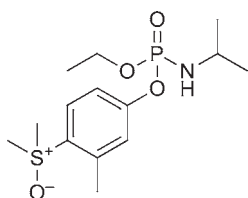
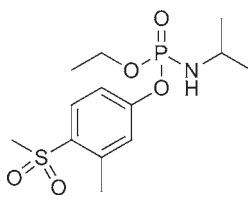
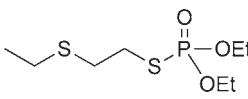
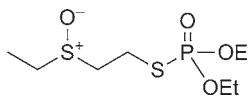
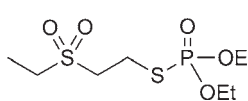
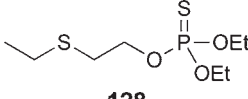
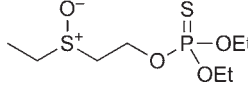
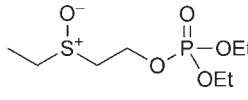


1.12.3.4.1(iii) Oxidation of sulfides

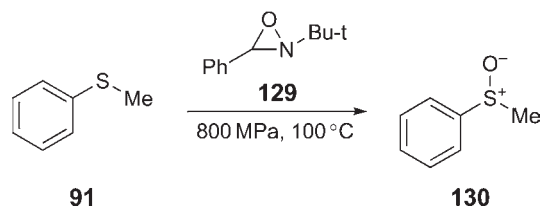
1.12.3.4.1(iii)(a) Oxidation of sulfides to sulfoxides

The selective oxidation of sulfides to sulfoxides by *N*-sulfonyloxaziridine continues to be an important and widely used transformation <1996CHEC-II(1A)365>. For example, Terreni *et al.* reported the chemoselective sulfur oxygenation of various phosphoramidates, thionophosphates, and thiophosphates using perfluorinated oxaziridine **80** (Equation 6; Table 7) <1995T7981>. Treatment of sulfide **126** with 1 equiv of oxaziridine **80** gave the corresponding sulfoxide in >98% yield, and with 2 equiv of **80** the sulfone was formed quantitatively. Similarly, reaction of thiophosphate thioether **127** with 1 equiv of **80** gave the sulfoxide in >98% yield, and with 2 equiv of **80** the sulfone was formed. It was interesting to note that under these conditions the thionic sulfur of **128** was not oxidized with 1 equiv of the oxaziridine. However, desulfurization occurred on treatment with 2 equiv to give the sulfoxide phosphonate (Table 7).

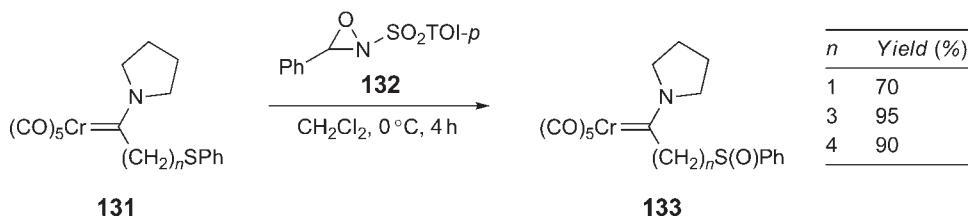
**Table 7** Oxidation of sulfides with perfluorooxaziridine **80** <1995T7981>

Sulfide	Equiv of 80	Product	Yield (%)
 126	1		98
	2		100
 127	1		98
			82
 128	1		>98
	1		95

Earlier 3-phenyl-2-*tert*-butyloxaziridine **129** was reported not to be able to oxidize sulfides to sulfoxides even on heating and to undergo thermal rearrangement to *N*-*tert*-butyl- α -phenylnitrone. However, Shimizu *et al.* demonstrated that under 800 MPa at 100 °C, this oxaziridine behaves as an oxidant and was able to oxidize thioanisole to the sulfoxide <1997J(P1)3491>.



Oxidation of pentacarbonyl[amino(arylthioalkyl)carbene]chromium(0) complexes **131** with *N*-sulfonyloxaziridine **132** afforded the corresponding sulfoxides **133** in good to excellent yields <1995SL666>. The oxidation is chemoselective, affording only sulfoxide products whereas the use of dimethyloxirane resulted in overoxidation to sulfones.



Perfluorinated oxaziridine **80** oxidizes 1-trifluoromethyl vinyl sulfides **134** to the corresponding sulfoxides **135** in high yields at -50 °C (Table 8) <1996S399>. However, at room temperature, sulfones are formed exclusively.

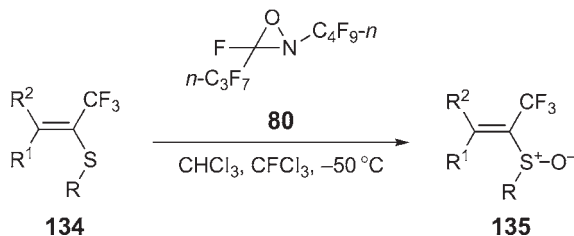
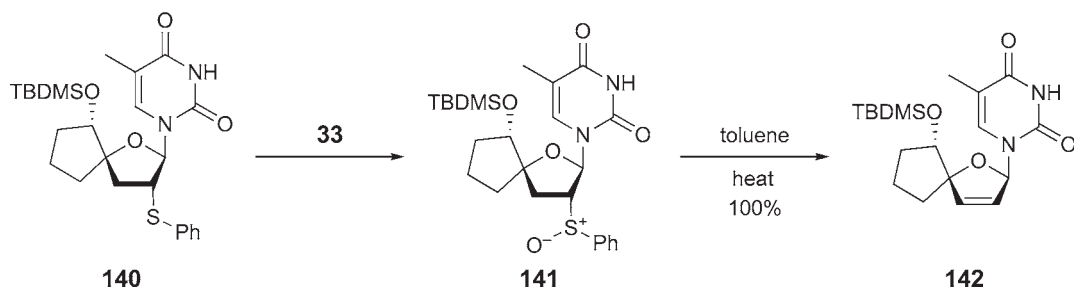
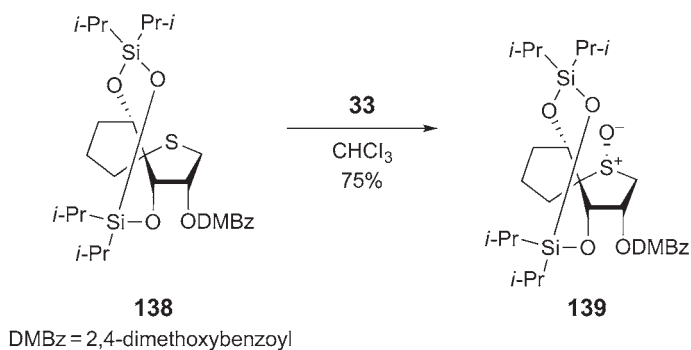
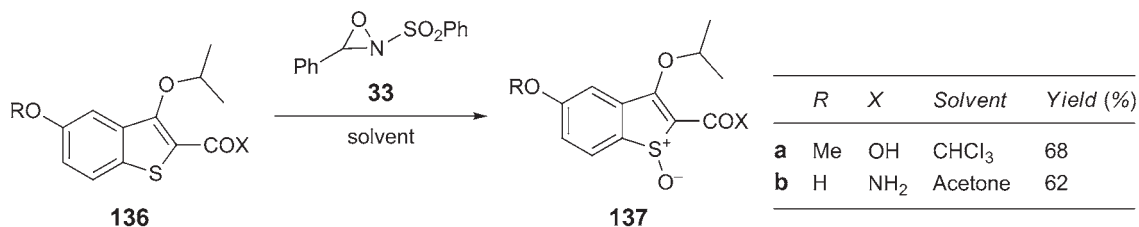


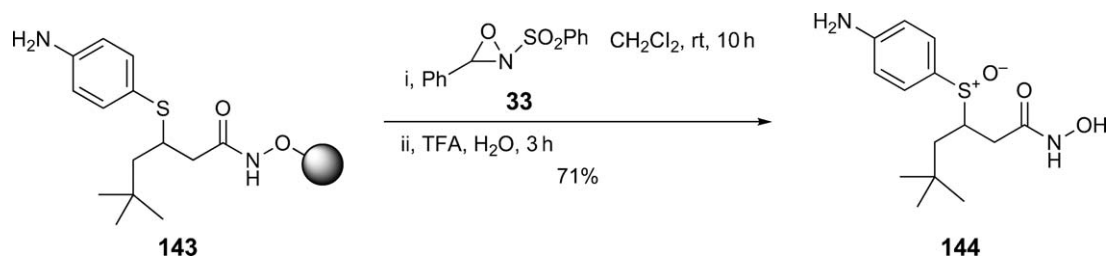
Table 8 Oxidation of 1-trifluoromethyl vinyl sulfides **134** with perfluorinated oxaziridine **80** <1996S399>

Entry	R	R ¹	R ²	Yield (%)
1	Et	Ph	H	87
2	Et	3,4-Cl ₂ C ₆ H ₃	H	95
3	Et	PhCH ₂ CH ₂	H	>98
4	Et	Cyclohexyl	H	95
5	Et	H	Cyclohexyl	87
6	Et	H	Ph	87
7	Et	H	3,4-Cl ₂ C ₆ H ₃	87
8	Hexyl	PhCH ₂ CH ₂	H	95
9	Et	CH ₂ -cyclohexyl	H	82

Oxidation of benzothiophene carboxylic acid **136a** with *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** in chloroform gave **137a** in 68% yield <1995JME4597>. Similarly, the benzothiophene amide **136b** afforded **137b** in 62% yield. Oxidation of chiral sulfide **138** with *N*-sulfonyloxaziridine **33** in chloroform furnished a pair of diastereomeric sulfoxides, with the major one, **139**, being isolated in 75% yield <2005JOC5655>. Selective oxidation of **140** with **33** gave the corresponding sulfoxide **141** in good yield <2003JOC8614>. On heating, **141** gave the conformationally restricted nucleoside **142** quantitatively.

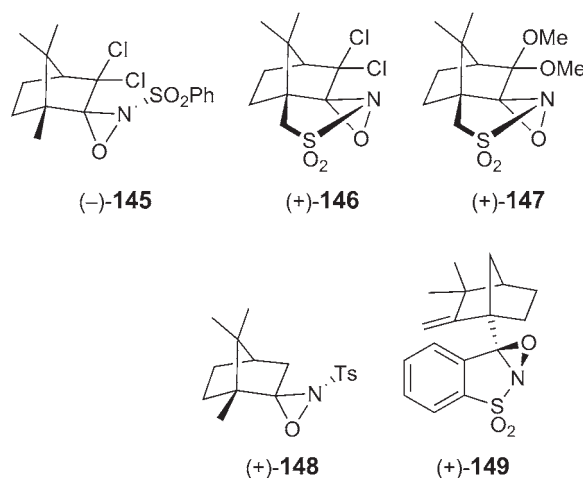


Rosse *et al.* described the oxidation of the resin-bound β -sulfenyl hydroxamic acids *N*-sulfonyloxaziridines <2001SL538>. For example, oxidation of **143** with **33** afforded the corresponding sulfoxide **144** in 71% yield after cleavage of the resin with TFA. Apfel *et al.* in the preparation of some potent peptide deformylase inhibitors and antibacterial agents employed a similar transformation <2000JME2324>.



1.12.3.4.1(iii)(b) Asymmetric oxidation of sulfides to sulfoxides

The asymmetric oxidation of sulfides with enantiopure *N*-sulfonyloxaziridines continues to be an important method to prepare enantiomerically enriched sulfoxides, valuable synthons, and auxiliaries used in asymmetric synthesis <1996CHEC-II(1A)365>. The ee's are dependent on the reaction conditions (temperature and solvent), the substrate, and oxaziridine structure. The mechanism for these oxidations is generally considered in terms of an S_N2-type attack of the sulfide sulfur on the oxaziridine oxygen atom and is controlled by steric factors. This means that the absolute stereochemistry of the product is predictable and the desired enantiomer can be obtained by choice of the appropriate reagent. A number of enantiopure *N*-sulfonyloxaziridines, most derived from camphor, have been used for this purpose as shown in Scheme 4. Of these reagents, the (–)-*N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine **145** generally gives the highest ee's. Representative examples of asymmetric oxidations employing these reagents are given in Table 9.



Scheme 4

Table 9 Asymmetric oxidation of sulfides to sulfoxides

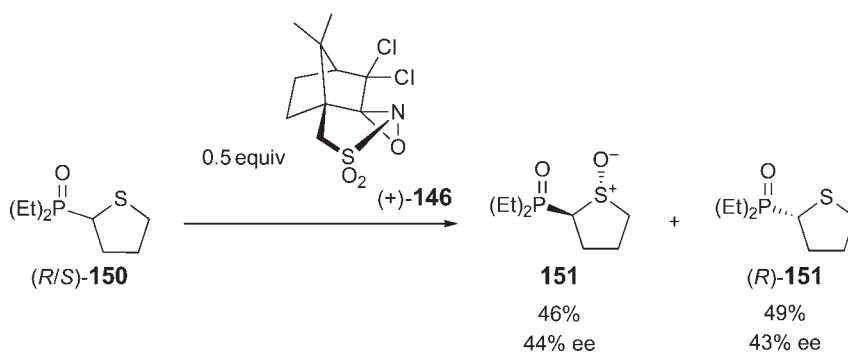
Sulfide	Oxaziridine	Sulfoxide ee (%), Yield (%)	Reference
	(–)- 145	d.r. 99:1, 74	2004TL3855
	(–)- 145	75, 90	1995TA131
	(–)- 145 (+)- 147	74, 90 96, 95	1998TA2567
	(+)- 146	73, 82	2001TA167
	(+)- 146	>98, 76	2005TA651

(Continued)

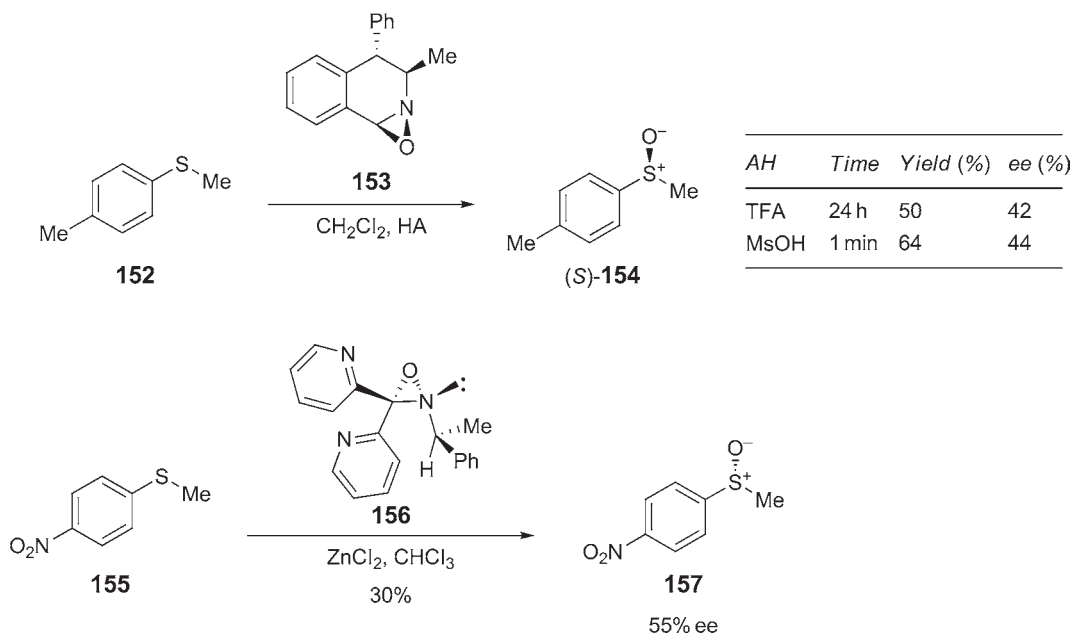
Table 9 (Continued)

Sulfide	Oxaziridine	Sulfoxide ee (%), Yield (%)	Reference
	(+)- 146	75, 95	2000TA3455
	(+)- 146	59, 67	1999T525
	(+)- 148	97, 55	2001T2597
	(+)- 149	19, 100	2000JOC6756
	(+)- 147	98, 100	1995TA2911

Kielbasinski *et al.* reported that enantiomerically enriched 2-phosphonothiolane sulfoxides are obtained by diastereoselective S-oxidation combined with a kinetic resolution using chiral oxaziridines <2005TA651>. For example, treatment of racemic **150** with 0.5 equiv (+)-(dichlorocamphorsulfonyl)oxaziridine **146** afforded sulfoxide **151** in 46% yield and 44% ee.

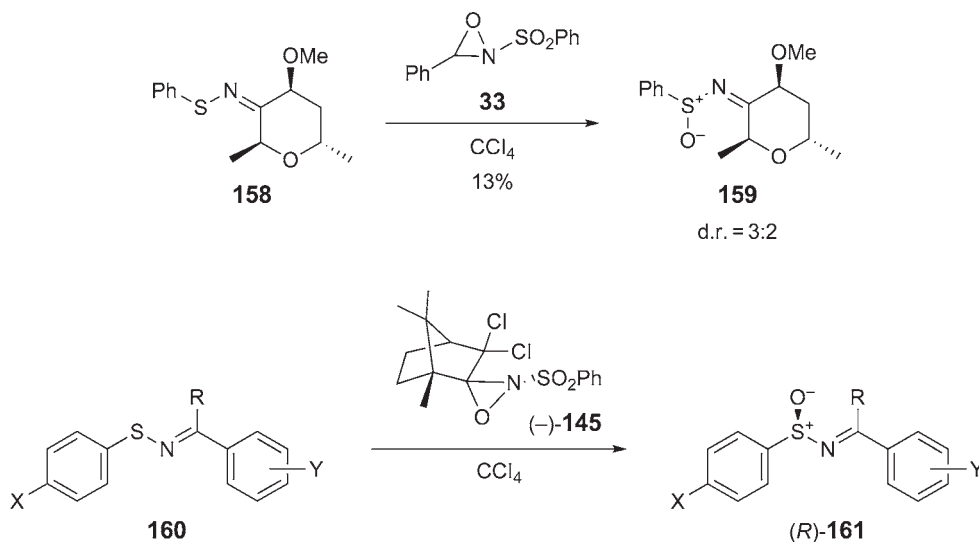


Asymmetric sulfide oxidations are reported using oxaziridines other than *N*-sulfonyloxaziridines, but it is necessary to use a protic acid or Lewis acid to increase their reactivity. For example, *p*-tolyl methyl sulfide **152** with bicyclic oxaziridine **153** in the presence of TFA gave the (*S*)-sulfoxide **154** in 50% yield and 42% ee in 24 h <1999T155>. It is interesting to note that use of MsOH resulted in much faster reaction with the oxidation complete in less than a minute. Similarly, sulfide **155** with chiral oxaziridine **156** in the presence of zinc chloride afforded sulfoxide **157** in 30% yield and 55% ee <2005JOC301>.



1.12.3.4.1(iv) Oxidation of sulfenimines

Treatment of chiral sulfenimine **158** with *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** gave sulfinimine **159** in 13% yield as a mixture of diastereoisomers <2006TL5657>. Enantioselective oxidation of prochiral *N*-sulfenimines **160** with (–)-*N*-(phenylsulfonyl)-1-(3,3-dichlorocamphoryl)oxaziridine **145** in CCl_4 gave the enantiomerically enriched sulfinimine **161** in 87–90% ee, which could be further upgraded to >97% ee by crystallization (Table 10) <1997JOC2555>. The stereochemistry of the oxidation was controlled by the configuration of the oxaziridine with (–)-**145** giving (*R*)-**161** and (+)-**145** affording the (*S*)-isomer.



1.12.3.4.1(v) Oxidation of sulfenic acids

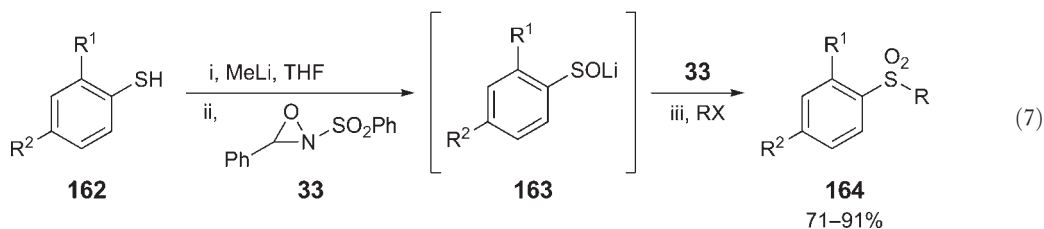
As discussed previously, treatment of thiolates generated from thiols and MeLi with sterically hindered *N*-sulfonyloxaziridine **116** gave the corresponding sulfenate intermediates which were alkylated to afford sulfoxides **118** (Equation 4) <1997JOC8626, 1999PS(153)381, 2004JOC6916>. Oxidation of thiolates generated from aryl thiols

162 and MeLi with the less sterically hindered *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33**, on the other hand, resulted in further oxidation of the initially formed sulfenate intermediates **163** to give sulfinates which on alkylation afford sulfones **164** (Equation 7) <1999OL1177>. As expected, more than 2 equiv of the oxaziridine is required for optimum yields. This method has been used in the synthesis of [^{11}C]-labeled sulfones <2006JOC210>.

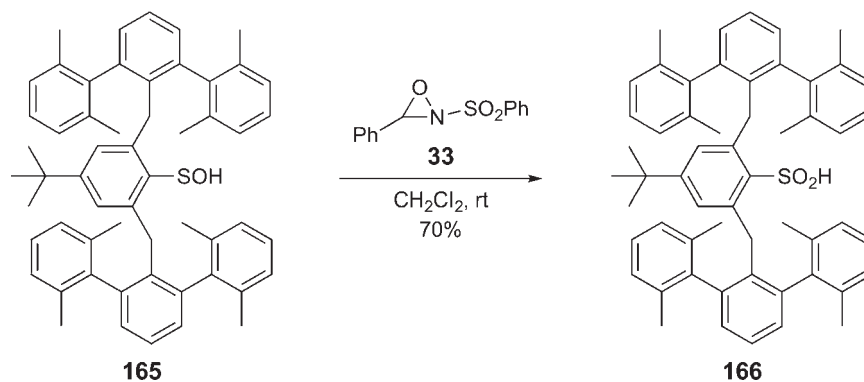
Table 10 Asymmetric oxidation of sulfinimines **160** to sulfinimines **161** using (–)-*N*-sulfonyloxaziridine (–)-**145** <1997JOC2555>

Entry	X	Y	R	Yield (%)	ee (%)
1	H	H	H	95	88[>97] ^a
2	H	<i>o</i> -MeO	H	89	85[>97] ^a
3	H	<i>p</i> -MeO	H	95	89[>97] ^a
4	Me	H	Me	90	87[>97] ^a

^aEnantiomeric purity after crystallization.



Goto *et al.* reported that oxidation of the hindered, stable, sulfenic acid **165** with *N*-sulfonyloxaziridine **33** in methylene chloride at room temperature gave the corresponding sulfinic acid **166** in 70% yield <1997JA1460>.



1.12.3.4.1(vi) Oxidative desulfurizations

Sochacka and Fratzak reported recently an efficient desulfurization of 2-thiopyrimidine nucleosides **167** to the corresponding 4-pyrimidinone analogues **168** using *N*-sulfonyloxaziridine **33** <2004TL6729>. The reaction is facile, affording the desulfurized products **168** in good to excellent yield as shown in Table 11.

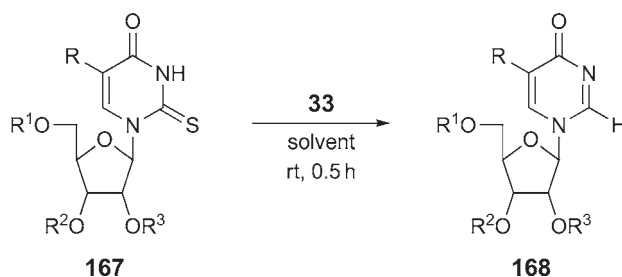
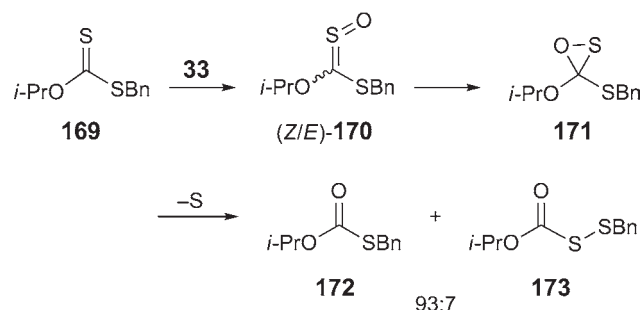


Table 11 Desulfurization of 2-thiopyrimidine nucleosides **167** with *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** <2004TL6729>

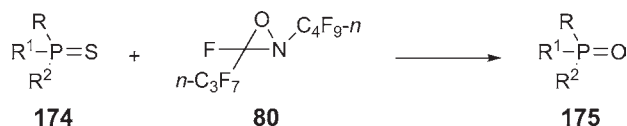
<i>R</i>	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>Solvent</i>	<i>Yield (%)</i>
H	H	H	H	Pyridine	81
H	H	H	H	CH ₃ CN	79
CH ₂ NHCH ₃	H	H	H	Pyridine	100
CH ₂ CO ₂ CH ₃	H	H	H	Pyridine	100
H	PhCO	PhCO	PhCO	CH ₂ Cl ₂	100

It was suggested that the desulfurization of 2-thiopyrimidine nucleosides **167** with *N*-sulfonyloxaziridine **33** proceeds via the initial formation of a sulfur oxyacid followed by subsequent decomposition to **168** and sulfur dioxide. This was confirmed by the experiment where, 2',3',5'-*O*-tribenzoyl-2-thiouridine was treated with 2 equiv of **33** in methylene chloride under argon. The emerging argon was analyzed and found to contain sulfur dioxide as the only gaseous reaction product. Moreover, workup of the reaction mixture resulted in the isolation of tribenzoyl uridine together with the sulfonimine (PhSO₂N=CHPh) in quantitative yields.

Xanthate **169** with oxaziridine **33** gave *S*-benzyl *O*-isopropyl carbonothioate **172** and *SS*-benzyl *O*-isopropyl carbonodithioperoxoate **173** in a ratio of 93:7 <1997J(P1)2019>. The reaction is believed to go through sulfur oxidation to give sulfine intermediate **170** that rearranges to an oxathiirane **171** intermediate (Scheme 5).

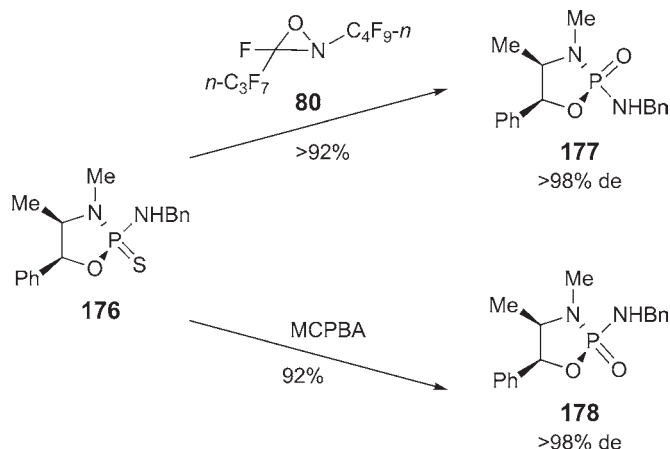
**Scheme 5**

With perfluorooxaziridine **80**, thiophosphoryl substrates **174** underwent facile desulfurization <1996TL4707, 1997JOC6401>. The reaction is quite general, giving the desulfurized products **175** in good to excellent yields (Table 12).

**Table 12** Desulfurization of thiophosphoryl substrates **174** with perfluorooxaziridine **80**

<i>R</i>	<i>R</i> ¹	<i>R</i> ²	<i>Yield (%)</i>	<i>Reference</i>
<i>i</i> -Bu	<i>i</i> -Bu	<i>i</i> -Bu	95	1997JOC6401
Ph	Ph	Ph	95	1997JOC6401
EtO	EtO	CF ₂ Br	94	1997JOC6401
MeO	MeO	4-NO ₂ -C ₆ H ₄ O	82	1997JOC6401
MeO	MeO	EtS(O)CH ₂ CH ₂ O	93	1997JOC6401
BnO	BnO	C ₉ H ₁₉ (CH ₃)CH	92	1996TL4707
BnO	BnO	<i>n</i> -Bu ₃ Sn	91	1996TL4707
Et ₂ N	4-NO ₂ -C ₆ H ₄ O	4-NO ₂ -C ₆ H ₄ O	80	1997JOC6401

Treatment of 1,3,2-oxazaphospholidine 2-sulfide **176**, bearing two amino residues at phosphorus, with oxaziridine **80** gave 1,3,2-oxazaphospholidine 2-oxide **177** in 92% yield [<1997JOC6401>](#). It was interesting to note that the desulfurization occurred with complete stereoselectivity (>98% de) and with inversion of the configuration at the phosphorus, whereas use of *m*-chloroperbenzoic acid (MCPBA) resulted in retention of configuration affording **178** (**Scheme 6**).

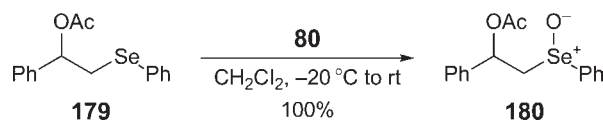


Scheme 6

1.12.3.4.2 Oxidation of organoselenium compounds

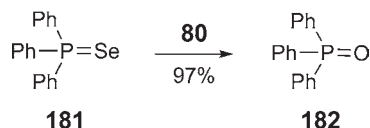
1.12.3.4.2(i) Oxidation of selenides

Reaction of selenide **179** with perfluorinated oxaziridine **80** in methylene chloride at -20°C gave selenoxide **180** in quantitative yield as a mixture of diastereomers in a 1:1 ratio [<1998CBL39>](#). This transformation has been employed in glycosylation reactions using intermediate oxaziridine-generated selenoxides [<1998CBL39>](#).



1.12.3.4.2(ii) Oxidative Deselenizations

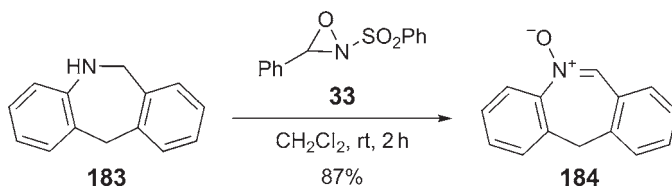
Oxidative deselenizations have also been described. For example, reaction of triphenylphosphorus selenide **181** with perfluorooxaziridine **80** resulted in complete deselenization affording triphenylphosphine oxide **182** in 97% yield [<1997JOC6401>](#).



1.12.3.4.3 Oxidation of organonitrogen compounds

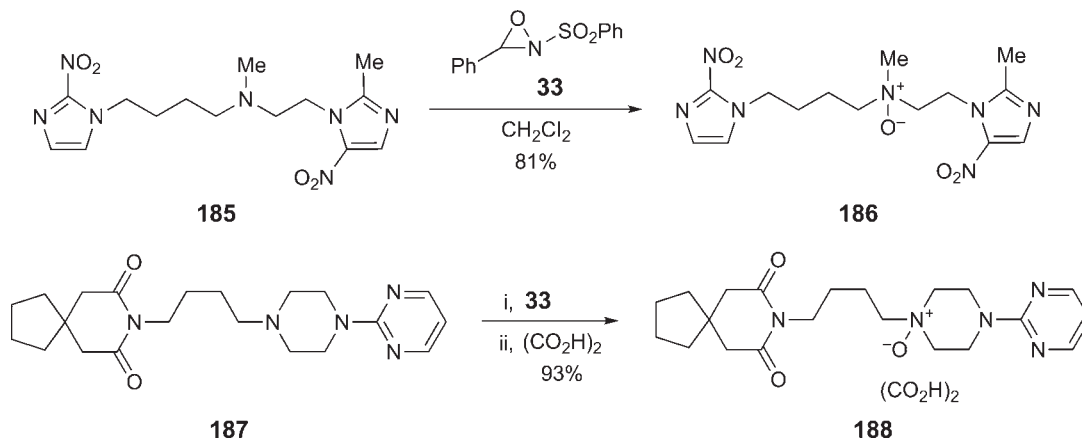
1.12.3.4.3(i) Oxidation of amines

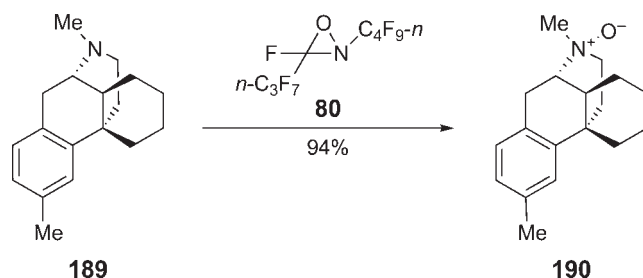
Oxidation of amines with oxaziridines gave rise to different products depending on the nature of the starting amines and the oxaziridines [<1996CHEC-II\(1A\)365>](#). For secondary amines, the reaction usually affords nitrones, and it is a mild method for their preparation. For example, oxidation of 5,6-dihydromorphanthridine **183** with *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** in dichloromethane at room temperature gave nitron **184** in 87% yield [<2002BML243, 2002OPD911>](#). Compared to other reagents such as MCPBA, *N*-sulfonyloxaziridine **33** afforded the highest yields under mild aprotic reaction conditions. Other examples can be found in [Table 13](#).

**Table 13** Oxidation of secondary amines with *N*-sulfonyloxaziridine **33**

Amine	Nitron	Yield (%)	Reference
		100	2002TL9357
		54	2001J(P1)3409
		79	1999S2036

Tertiary amines with *N*-sulfonyloxaziridines give the corresponding *N*-oxides. For example, **185** with *N*-sulfonyloxaziridine **33** gave the corresponding *N*-oxide **186** in 81% yield [\[1995JME1928\]](#). Similarly, buspirone **187** with **33** gave *N*-oxide **188**. The reaction is highly chemoselective, giving **188** as the sole product in 93% yield isolated as oxalate [\[1996OPP115\]](#). Arnone *et al.* studied the oxidation of tertiary amines with various perfluorinated oxaziridines such as **80**. For example, treatment of dextromethorphan **189** with **80** gave *N*-oxide **190** in 94% yield [\[1998T7831\]](#). Pyridines are also oxidized to the *N*-oxides [\[1998T7831\]](#) as well as other heteroaromatic nitrogen compounds [\[1996JFC\(80\)31\]](#).





Chiral tertiary allylic amines **191** with *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** also gave rise to amine *N*-oxides **192**, which underwent the [2,3]-Meisenheimer rearrangement to hydroxylamines **193** with a high level of stereoselectivity (Table 14) <1999J(P1)2327>. Reduction of **193** gave the corresponding allylic alcohols **194**.

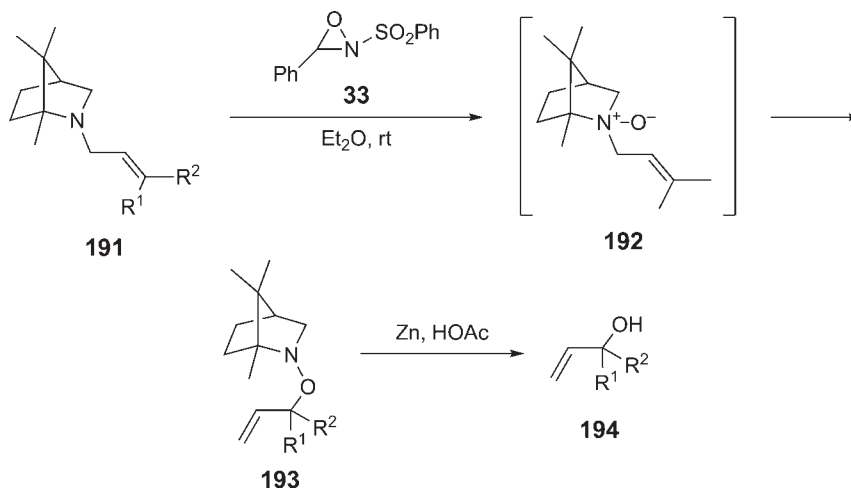
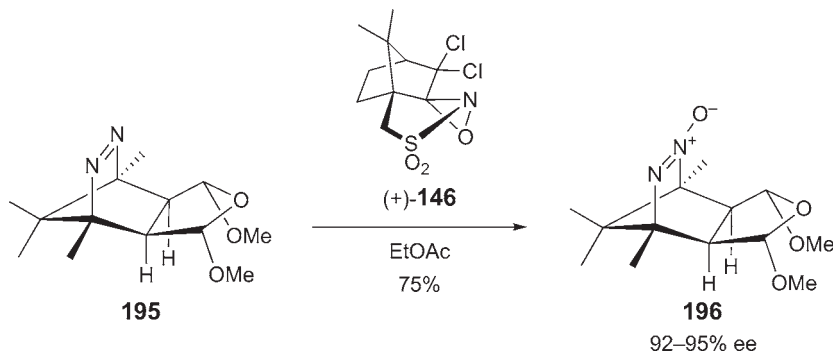


Table 14 Oxidation and rearrangement of amines **191** using *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** <1999J(P1)2327>

<i>R</i> ¹	<i>R</i> ²	Yield 194 (%)	<i>de</i> (%)
H	Et	48	86
Me	CH ₂ CH ₂ CH=CMc ₂	25	65
H	Me	19	94
Me	H	19	50

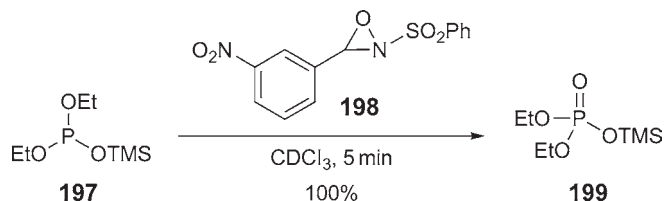
1.12.3.4.3(ii) Oxidation of diazenes

Asymmetric oxidation of diazene **195** with (+)-(dichlorocamphorsulfonyl)oxaziridine **146** in EtOAc gave the corresponding *N*-oxide **196** in 75% yield. The reaction is highly enantioselective, affording the product in 92–95% ee <1998CC749>.

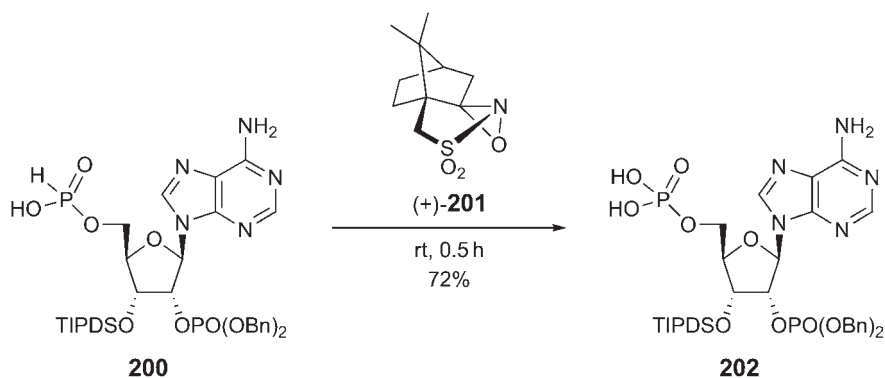


1.12.3.4.4 Oxidation of organophosphorus compounds

Wada *et al.* found that 2-phenylsulfonyl-3-(3-nitrophenyl)oxaziridine **198** is an effective reagent for the oxidation of silyl phosphates to the corresponding silyl phosphonates under neutral and anhydrous conditions <1997JA12710>. For example, diethyl trimethylsilyl phosphonate **199** was obtained in quantitative yield within 5 min on oxidation of **197**. Oxidations using *t*-BuOOH and its derivatives resulted in much lower yields and longer reaction times.



Hydrogen phosphonate **200** with (+)-(camphorsulfonyl)oxaziridine **201** gave phosphonate **202** in 72% yield <2004AGE4637>. This oxaziridine was also used by Manoharan *et al.* for the preparation of inter-nucleotide phosphate linkages in oligonucleotide synthesis <2000OL243>. Other reports using oxaziridines in oligonucleotide synthesis have also appeared <1995TL2047>.



TIPDS = 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene)

1.12.3.4.5 Hydroxylation of unactivated C–H bonds

The perfluorooxaziridines are among the few reagents available for the insertion of an oxygen atom into an unactivated C–H bond. A concerted 'oxenoid' O-atom-type insertion mechanism for the oxidation has been proposed <1996CHEC-II(1A)365>. Sorochinsky *et al.* for example, studied the oxyfunctionalization of bridgehead adamantane derivatives **203** using perfluorinated oxaziridine **80** <1997T5995>. The process was found to proceed with excellent regioselectivity affording 3-substituted adamantan-1-ols **204** in good to excellent yields (Table 15). The reaction tolerates various functional groups such as halogen, haloalkyl, hydroxyl, carboxyl, and carboalkoxyl.

Adamantane **205** reacts with oxaziridine **206** at 22 °C to give 1-adamantanol **207** in 73% yield <2005JA15391>. A catalytic version of this oxidation has been developed using catalytic amounts of the imine **208** and diselenide **209** with excess urea- H_2O_2 (UHP) as the oxidant.

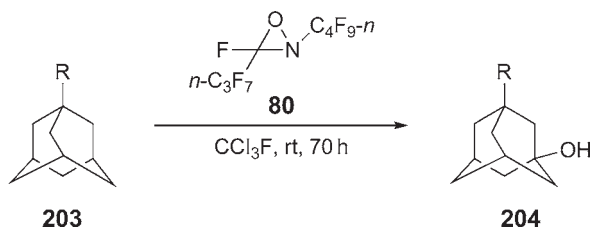
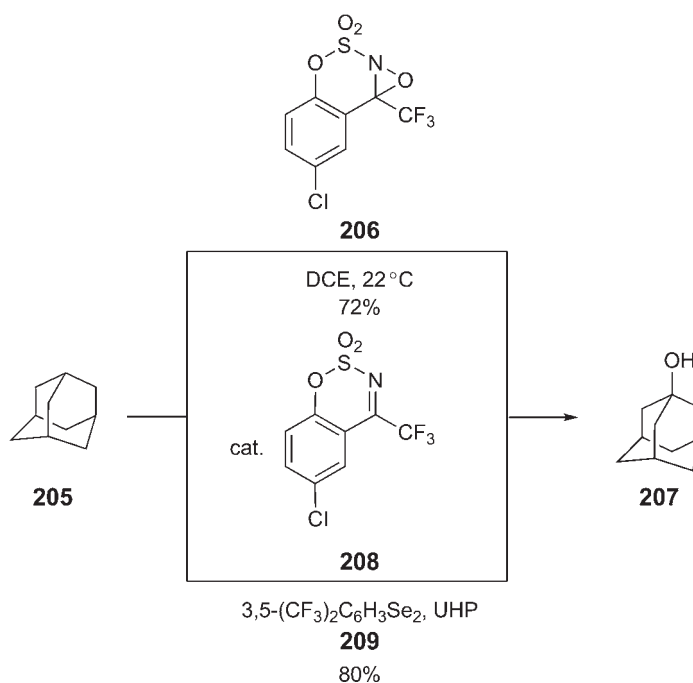


Table 15 Oxyfunctionalization of 1-substituted adamantanes **203** with perfluorooxaziridine **80** <1997T5995>

Entry	R	Yield (%)
1	CH ₂ Br	94
2	F	82
3	Cl	85
4	Br	89
5	OH	85
6	CH ₂ CO ₂ H	90
7	CO ₂ H	82
8	CO ₂ Me	85



Nonactivated tertiary hydrocarbon sites of enantiopure compounds **210** are oxyfunctionalized enantiospecifically by perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine **80** under remarkably mild reaction conditions (Equation 8) <1999OL281>. The reaction occurs with retention of the configuration at the oxidized stereogenic center and the enantiospecificity is highly independent of both the carbon framework of the substrate as well as functional groups (Table 16).

1.12.3.4.6 Oxidation of methyl ethers

Reaction of methyl ethers **212** with perfluorinated oxaziridine **80** gives ketones **213** (Equation 9) <1995JOC2314>. The reaction is highly chemoselective and tolerates a number of functional groups such as ketones, acids, and esters (Table 17).

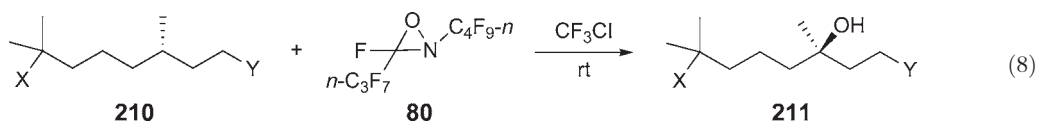
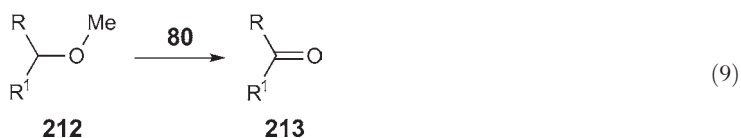


Table 16 Enantiospecific oxyfunctionalization of citronellyl derivatives **210** with perfluorooxaziridine **80** <1999OL281>

<i>X</i>	<i>Y</i>	<i>Time (h)</i>	<i>Added salt</i>	<i>ee (%)</i>		<i>Configuration retention (%)</i>
				210	211	
H	H	1		81	78	96
H	H	9		81	48	59
H	H	1	KF (1 equiv)	81	79	97
H	H	9	KF (1 equiv)	81	78	96
H	H	9	CsF (1 equiv)	81	72	89
H	H	9	CsF (1 equiv)	81	71	88
Cl	Br	30		99	97	98
OH	Br	21		99	96	97

**Table 17** Selective oxidation of methyl ethers **212** to carbonyl compounds with perfluorooxaziridine **80** <1995JOC2314>

<i>Substrate</i>	<i>Product</i>	<i>Yield (%)</i>
		88
		91
		82
		84
		91

(Continued)

Table 17 (Continued)

Substrate	Product	Yield (%)
		78
		79

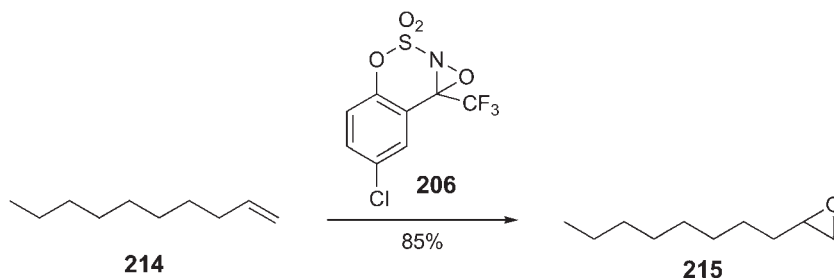
1.12.3.4.7 Oxidation of carbon–carbon double bonds

1.12.3.4.7(i) Epoxidation of alkenes

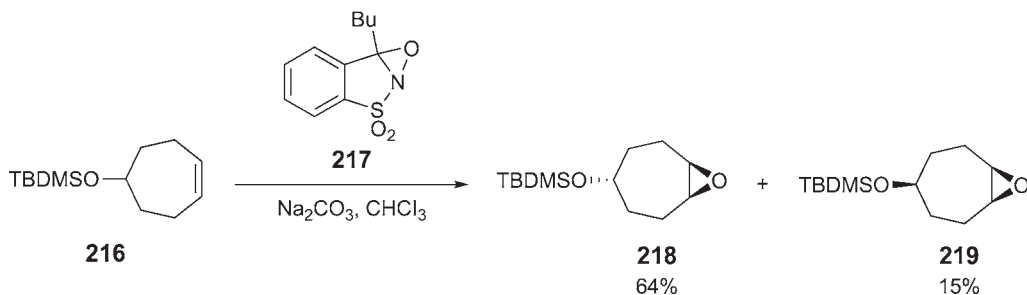
Epoxidation of alkenes with oxaziridines gives the corresponding epoxides in a *syn*-stereospecific manner and has been the subject of several reviews [\[1996CHEC-II\(1A\)365, 1999RCR183\]](#).

The transition state for oxygen transfer from *N*-sulfonyloxaziridines to alkenes was studied by Anderson *et al.* using the endocyclic restriction test [\[1999OL1415\]](#). In this study, molecules containing both the oxaziridine and alkene functionalities were prepared, and the ability of each system to intramolecularly transfer oxygen was evaluated. The results are consistent with a transition state in which N–O bond cleavage is more advanced than C–O bond cleavage.

More recently, it was reported that treatment of alkene **214** with oxaziridine **206** at 22 °C afforded epoxide **215** in 85% yield [\[2005JA15391\]](#). A catalytic variant of this reaction has been devised. Epoxidation of alkenes with *N*-phosphinoyloxaziridines has also been described [\[2003SL121\]](#).



Epoxidation of alkene **216** with *N*-sulfonyloxaziridine **217** gave *trans*-epoxide **218** and *cis*-epoxide **219** in 64% and 15% yield, respectively [\[1999TL8637\]](#). Use of methyl(trifluoromethyl)dioxirane exhibited no selectivity.



Arnone *et al.* studied the epoxidation of various olefins **220** with perfluorinated oxaziridine **80** (Equation 10) <1996JOC8805>. Alkyl-substituted olefins are epoxidized with this oxaziridine under particularly mild conditions. Electron-deficient substrates can also be epoxidized, and the more electron deficient the double bond is, the more severe the reaction conditions become. The reaction is chemoselective and stereoselective, with *cis*-alkenes affording *cis*-epoxides. Various complex and polyfunctionalized substrates of natural origin (monoterpenes, sesquiterpenes, and steroids) have been epoxidized effectively with this reagent (Table 18).

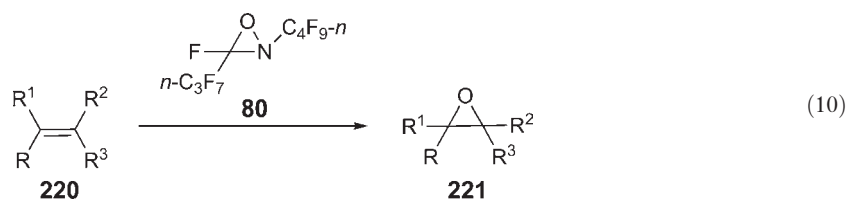


Table 18 Epoxidation of olefins **220** with perfluorinated oxaziridine **80** <1996JOC8805>

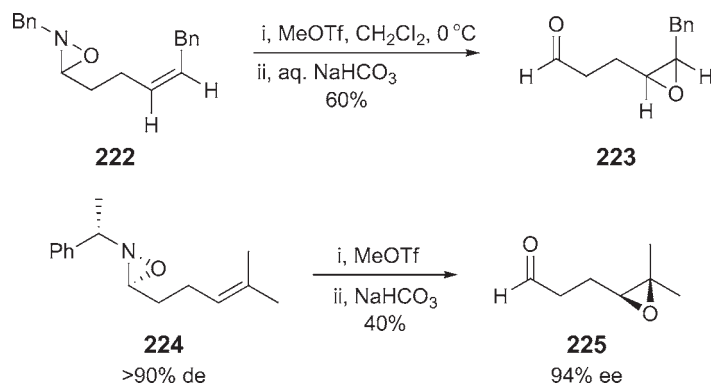
Substrate	Product	Yield (%)	de (%)
		80	
		85	
		82	
		60	
		88	0
		75	0
		87	>98

(Continued)

Table 18 (Continued)

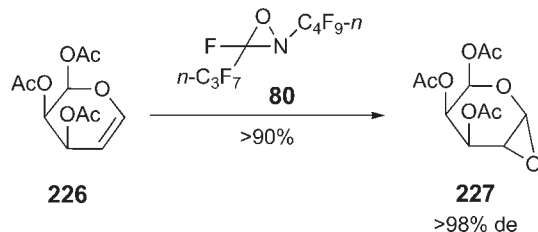
Substrate	Product	Yield (%)	de (%)
		82	50
		84	66
		44	26

Intramolecular epoxidation of unsaturated oxaziridines was studied by Armstrong and Draffan [<1998SL646, 2001J\(P1\)2861>](#). For example, treatment of oxaziridine **222** with MeOTf in methylene chloride at 0 °C followed by aqueous NaHCO₃ afforded epoxy aldehyde **223** in 60% yield [<2001J\(P1\)2861>](#). It should be pointed out that the epoxidation could also be intermolecular if the double bond and the oxaziridine ring are spaced in such a way that the geometric constraints prevent the intramolecular epoxidation from occurring [<2000PAC2259>](#). Intramolecular epoxidation of unsaturated oxaziridines has also been developed in an asymmetric fashion. Oxaziridine **224**, for example, underwent intramolecular epoxidation to yield the *S*-epoxide **225** with 94% ee [<1999TL4453, 2000JA2948, 2001J\(P1\)2861>](#).



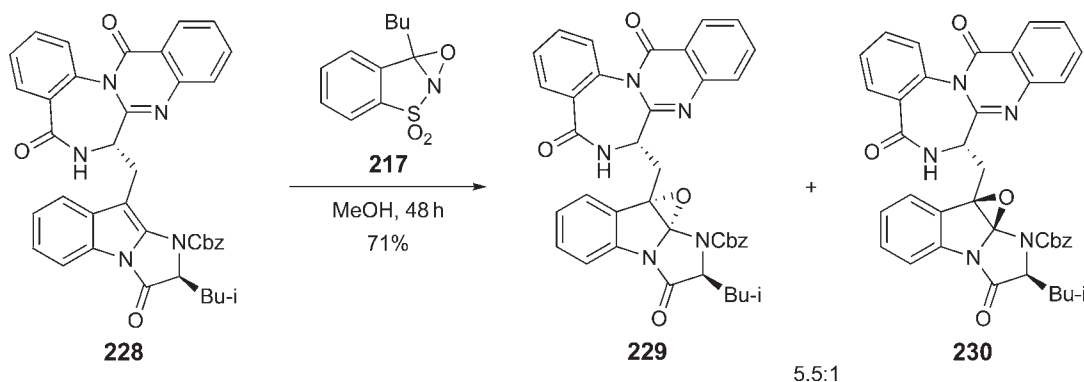
1.12.3.4.7(ii) Epoxidation of silyl enol ethers

Perfluorinated oxaziridines epoxidize glycols to give the corresponding 1,2-anhydrosugars in high yield and moderate to complete diastereoselection [<1995CC901>](#). For example, treatment of **226** with **80** in chloroform afforded **227** in >90% yield and >98% de.



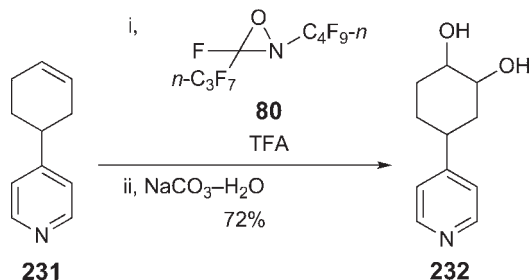
1.12.3.4.7(iii) Epoxidation of enamines

Indole **228** with oxaziridine **218** gave epoxides **229** and **230** as a 5.5:1 mixture of diastereomers. The major product **229** is formed from epoxidation on the face opposite the isobutyl group [<1998JA6417>](#).



1.12.3.4.7(iv) Dihydroxylation of alkenes

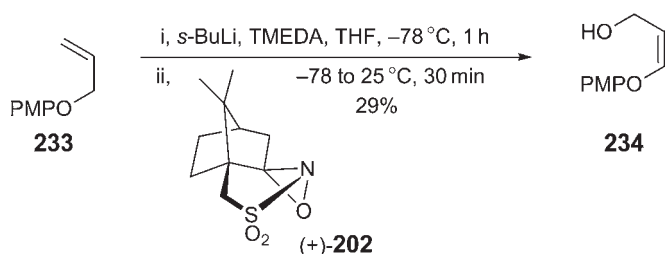
Treatment of pyridinyl cyclohexene **231** with perfluorinated oxaziridine **80** in TFA afforded dihydroxy product **232** in 72% yield [<1998T7831>](#). The pyridine nitrogen is not oxidized under these conditions because TFA protonates the pyridine nitrogen atom.



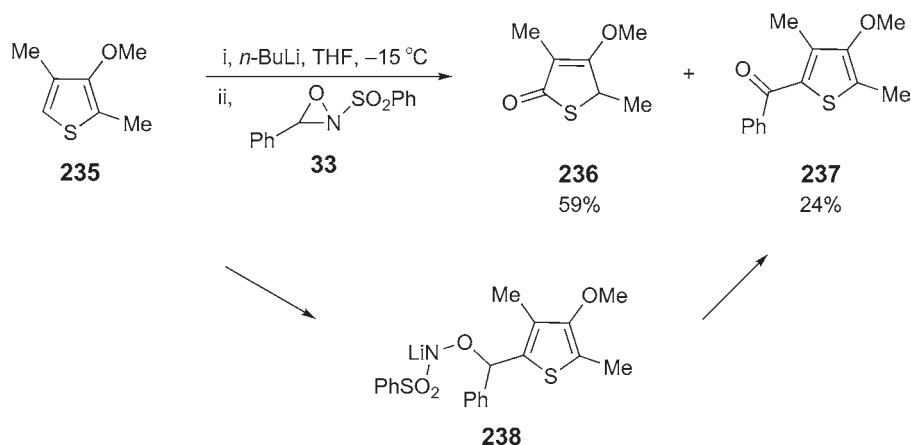
1.12.3.4.8 Oxidation of carbanions

1.12.3.4.8(i) Hydroxylation of lithium and Grignard reagents

Deprotonation of allyl ether **233** with *s*-BuLi in the presence of tetramethylethylenediamine (TMEDA) followed by reaction with (camphorsulfonyl)oxaziridine **202** produced alcohol **234**. The product was isolated in 29% yield as the sole geometrical isomer [<2005TL3465>](#). An advantage of using the (camphorylsulfonyl)oxaziridines for these hydroxylations is that the *N*-sulfonylimine by-product is resistant to addition of the organometallic reagent [<1987TL5115>](#).

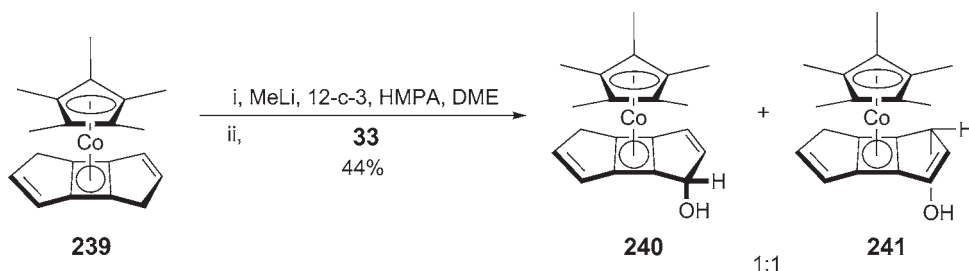


Thiophene **235** was reacted with *n*-BuLi and *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** to give a mixture of products **236** and **237** in 79% and 24% yield, respectively (Scheme 7) <1997TL183>. Compound **236** is the expected hydroxylation product as a consequence of attack at the oxygen atom. It is believed that **237** is a result of anion attack at the oxaziridine carbon atom with formation intermediate **238**, which then gives rise to ketone **237**.

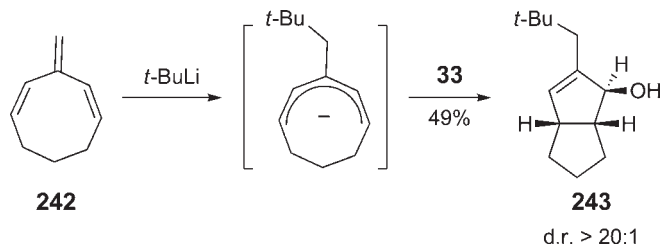


Scheme 7

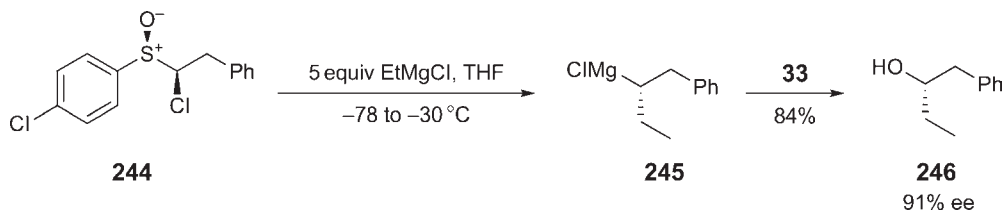
Treatment of the anion generated from the diene cyclobutadiene–cobalt complex **239** and MeLi with racemic oxaziridine **33** gave hydroxyl products **240** and **241** in 44% yield <2004JOC2516>. These products were obtained as a $\sim 1:1$ mixture of diastereomers arising from *exo*-face addition of the oxygen electrophile to the π -allyl anion.



Cascade carbolithiation–hydroxylation of **242** with *t*-BuLi and *N*-sulfonyloxaziridine **33** gave bicyclic allylic alcohol **243**. The alcohol was isolated in 49% yield and $>20:1$ d.r. <2004JA3434>.



The Grignard reagent **245** generated by treatment of optically active α -chlorosulfoxide **244** with ethylmagnesium chloride is hydroxylated by oxaziridine **33** to give secondary alcohol **246**. The product was obtained in 80% yield and 91% ee <2000AGE3072>.



1.12.3.4.8(ii) Hydroxylation of α -stabilized carbanions

Phosphonate anions of **247** react with (+)-(dichlorocamphorylsulfonyl)oxaziridine **146** to give the corresponding α -hydroxy phosphonates **248** in reasonable yields and ee's (Table 19) <1997TL3495, 1999JOC388, 2003TA265, 2003BML3351>. Use of (camphorsulfonyl)oxaziridine **202** gave lower enantioselectivities <1997TL3495>.

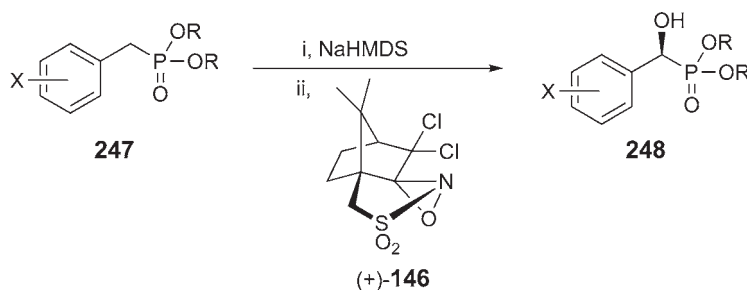
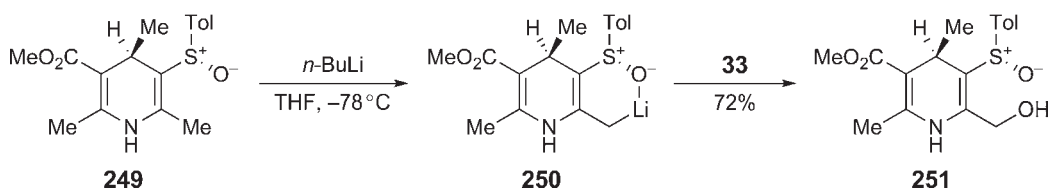


Table 19 α -Hydroxylation of phosphonates **247** using (+)-(dichlorocamphorsulfonyl)oxaziridine **146**

Entry	R	X	Yield (%)	ee (%)	Reference
1	Me	H	70	93	1999JOC388
2	Me	4-NO ₂	54	80	1999JOC388
3	Me	4-MeO	60	81	1999JOC388
4	Et	H	45	>99	2003TA265
5	Et	3-CF ₃	45	98	2003TA265
6	Allyl	H	36	96	2003TA265
7	Allyl	3-CF ₃	47	98	2003TA265

Sulfoxide **249** reacts with 2 equiv of *n*-BuLi and was treated with *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** to give hydroxyl product **251** in 72% yield <1996CPB457>. None of the regioisomeric compounds was detected in the crude reaction mixture. Carbanion stabilization via formation of the chelation structure with the neighboring sulfinyl group as shown in **250** is thought to be responsible for the observed regioselectivity.



1.12.3.4.8(iii) Hydroxylation of enolates

The most widely used application of *N*-sulfonyloxaziridines is the α -hydroxylation of metal enolates to give α -hydroxy carbonyl compounds, an important structural unit found in many biologically important molecules. Enolate hydroxylation by *N*-sulfonyloxaziridines has been the subject of several reviews <1995HOU(E21e)4494, 1996CHEC-II(1A)365>. The most recent and comprehensive of these reviews is found in *Organic Reactions* <2003OR1>. Because this review contains so many examples, the subject is only briefly presented below.

Many metal enolate α -hydroxylations have been performed with racemic *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** because it is more reactive than the enantiomerically pure camphor-derived *N*-sulfonyloxaziridines (Equation 11). Examples are given in Table 20.

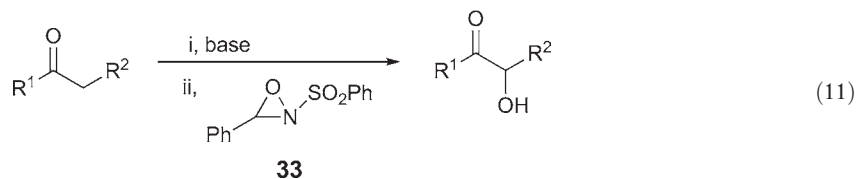
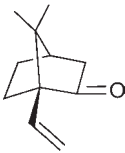
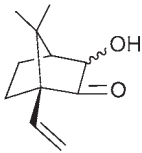
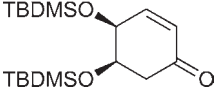
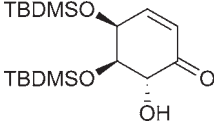
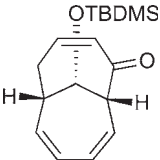
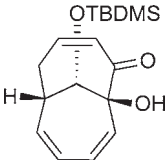


Table 20 Hydroxylation of metal enolates to α -hydroxy carbonyl compounds with *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** at -78°C

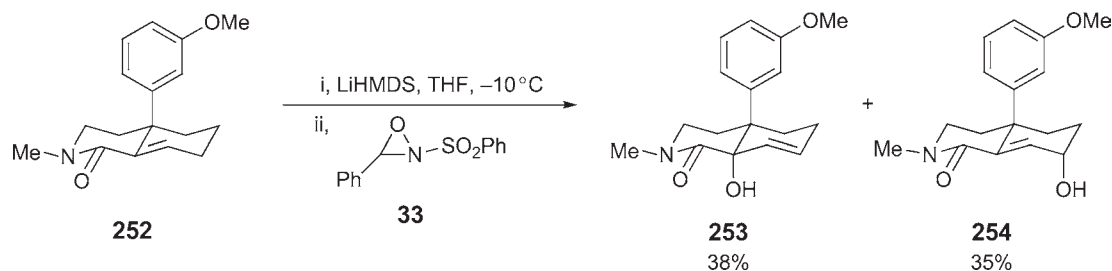
Ketone/ester	Base	Product	Yield (%)	References
	KOBu-t		75	1996JOC7373
	NaHMDS		66	2004OL4057
	NaHMDS		64	1995CC123
	NaHMDS		71	1999JOC684, 2001JA5407
	NaHMDS		84	2001JOC7832
	LDA 0°C		70	1998TL5895

(Continued)

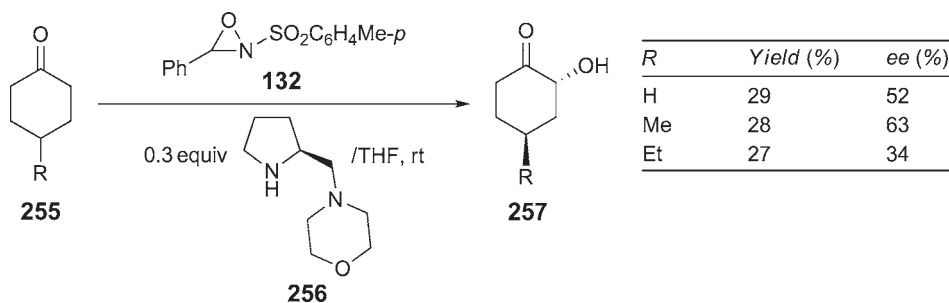
Table 20 (Continued)

Ketone/ester	Base	Product	Yield (%)	References
	KHMDS		86 <i>exo</i> / <i>endo</i> 5:1	1995JOC889
	NaHMDS		91	2002T4643
	KHMDS		72–82	1998TL1525, 2002T4879

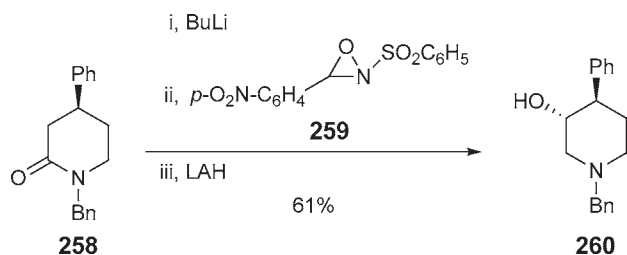
Treatment of α,β -unsaturated lactam **252** with lithium hexamethyldisilazide (LiHMDS) followed by oxidation of the resulted dienolate with *N*-sulfonyloxaziridine **33** gave rise to the α -hydroxylated product **253** in 38% yield <2001TL7879>. The γ -hydroxy product **254** was also isolated in 35% yield.



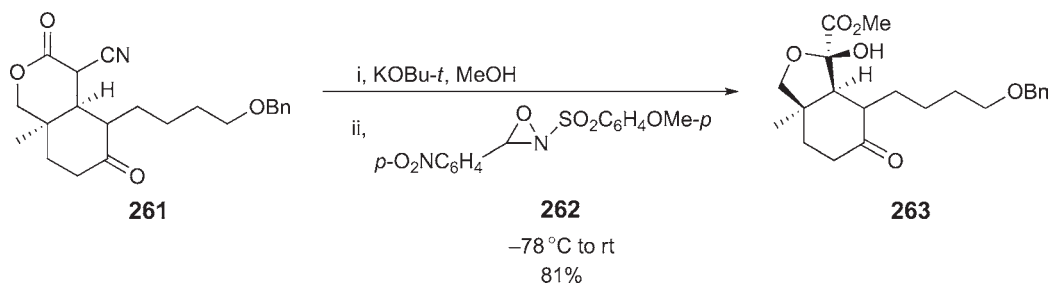
The organocatalytic asymmetric α -hydroxylation of ketones with *N*-sulfonyloxaziridines was studied by Engqvist *et al.* <2005TL2053>. For example, the direct diamine-catalyzed enantioselective α -hydroxylation of ketones **255** with *trans*-2-*p*-tolylsulfonyl-3-phenyloxaziridine **132** in the presence of chiral diamine **256** afforded the corresponding α -hydroxylated products **257** in moderate yields with up to 63% ee.



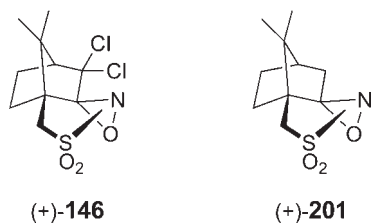
Treatment of lactam **258** with *t*-BuLi followed by reaction with *trans* 2-phenylsulfonyl-3-(*p*-nitrophenyl)oxaziridine **259** and lithium aluminium hydride (LAH) reduction gave the hydropiperidine **260** in 61% yield <2002JA11689>. Interestingly, the nitro group apparently does not interfere with the hydroxylation.



Reaction of **261** with potassium *tert*-butoxide in methanol followed by 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)oxaziridine **262** afforded **263** in 81% yield as a single isomer <1996J(P1)1517>. Other examples of enolate hydroxylations using these oxaziridines have appeared <1996J(P1)1523>.

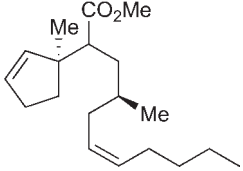
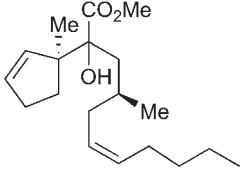
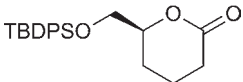
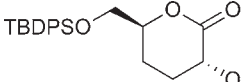
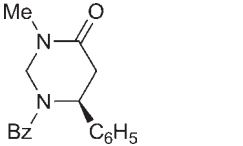
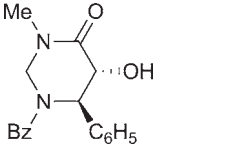
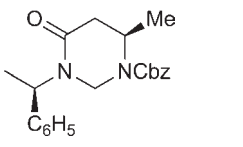
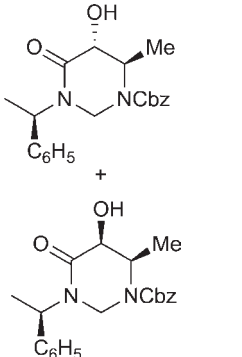
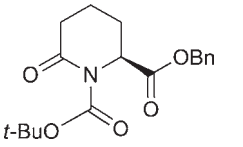
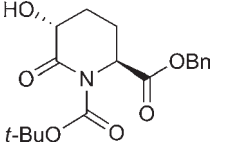


There are many examples of the asymmetric and diastereoselective hydroxylation of metal enolates using the enantiomerically pure camphor-derived *N*-sulfonyloxaziridines (+)-**146** and (+)-**202**, commercially available in both enantiomerically pure forms <2003OR1>. The enantiomeric purity of the α -hydroxy products is good to excellent and can be obtained in both enantiomeric forms, as the absolute configuration of the oxaziridine controls the stereoinduction. Examples are given in Table 21.



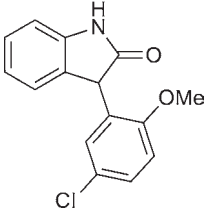
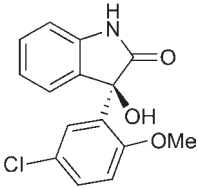
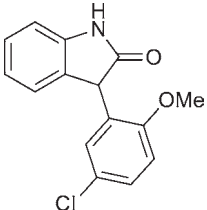
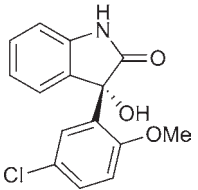
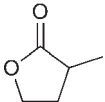
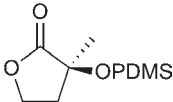
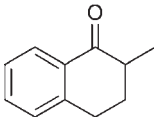
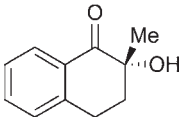
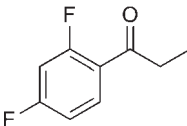
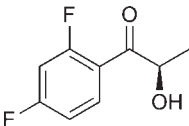
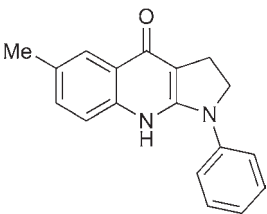
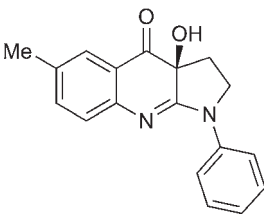
Hydroxylation of the lithium enolate of **264** with (+)-(camphorsulfonyl)oxaziridine **202** followed by trapping of the α -hydroxyl products with *t*-butyldiphenylsilyl chloride (TBDPSCl) gave mixtures of α -silyloxy products **265** and **266** in 84% yield in a ratio of 11:1 <2001JOC3338>. Use of (+)-(dichlorocamphorsulfonyl)oxaziridine **179** improved both the yield and diastereoselectivity.

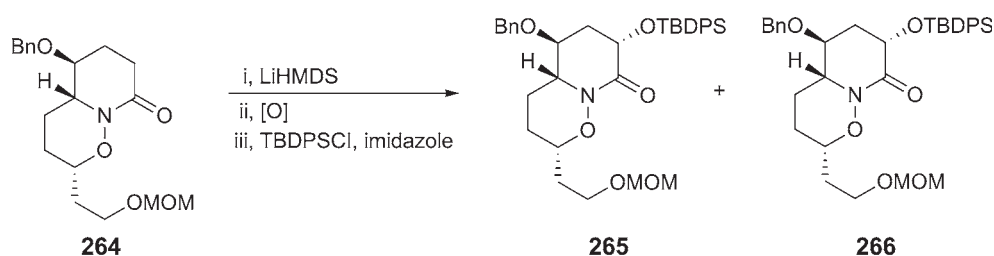
Table 21 Asymmetric and diastereoselective oxidation of metal enolates with camphorylsulfonyloxaziridines (+)-**146** and (+)-**202** at -78°C

<i>Ketone/ester/amide</i>	<i>Oxaziridine</i>	<i>Base</i>	<i>Product(s)</i>	<i>% ee (d.r.)</i>	<i>Yield (%)</i>	<i>Reference</i>
	(+)- 201	LDA		(1:1)	61	1997TL8785
		LDA TMEDA		(10:1)	61	1999OL451
		LDA		>98%	71	1995TL4397
	33 (-)- 201	LiHMDS NaHMDS LiHMDS NaHMDS		(47:53) (25:75) (78:22) (90:10)	41 77 66 27	1995T11831
		LiHMDS		(99:1)	88	2002JOC8440

(Continued)

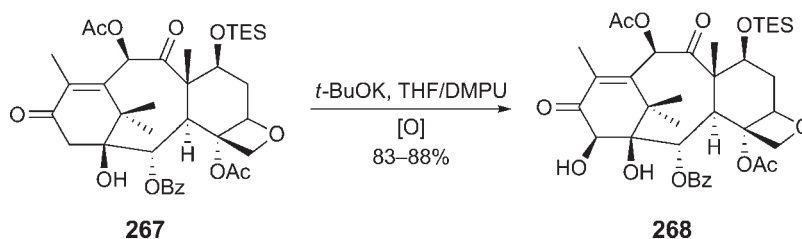
Table 21 (Continued)

<i>Ketone/ester/amide</i>	<i>Oxaziridine</i>	<i>Base</i>	<i>Product(s)</i>	<i>% ee (d.r.)</i>	<i>Yield (%)</i>	<i>Reference</i>
		KHMDS		>95	84	1997BML1255
	(-)- 202	KHMDS		>95	78	1997BML1255
	(+)- 146	i, NaHMDS ii, PDMSCl		78	74	1995JOC6148
		NaHMDS		80	83	2001TA2703
	(-)- 146	NaHMDS NaHMDS MgCl ₂		80 88	95 95	1997TA3047
	(-)- 146	NaHMDS		90	69	2005EJO1736

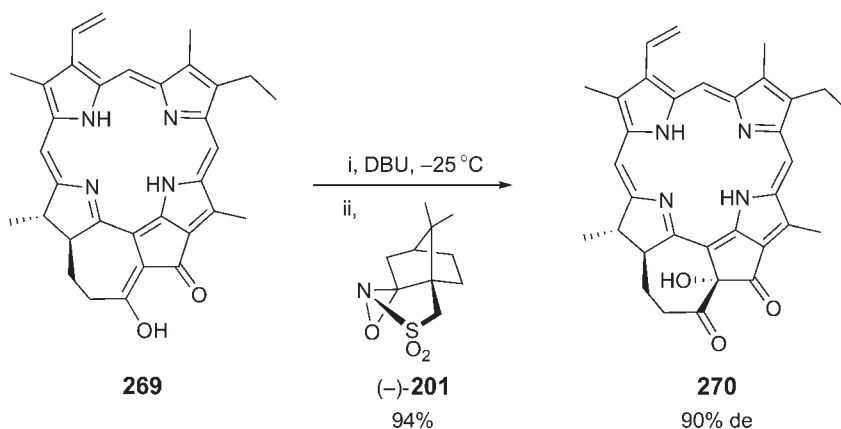


[O]	Yield (%)	Ratio 265/266
(+)- 201	84	11:1
(+)- 146	91	17:1

Hydroxylation of enolate generated from 7-TES-13-oxobaccatin III **267** with various *N*-sulfonyloxaziridines, **33**, (+)-**146**, and (+)-**202**, were studied by Baldelli *et al.* <2003JOC9773>. 7-TES-13-oxo-14 β OH-baccatin III **268** was obtained in 83–88% yield. The yield and diastereoselectivity of the hydroxylation were not affected by the choice of oxaziridine, indicating that the stereoselectivity was substrate controlled.

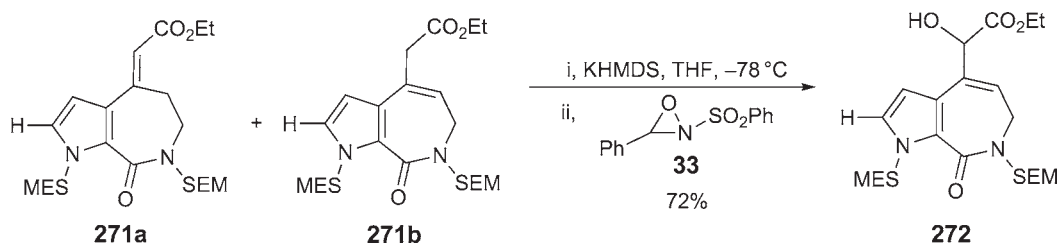


Treatment of cyclophenophorbide α -enol **269** with (–)-(camphorsulfonyl)oxaziridine **202** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave hydroxy chlorophyllone α -hydroxy diketone **270** in 94% yield and 90% de <1996JOC2501>. For hydroxylations of related β -diketones, see <1995TA313> and <2006T3412>.

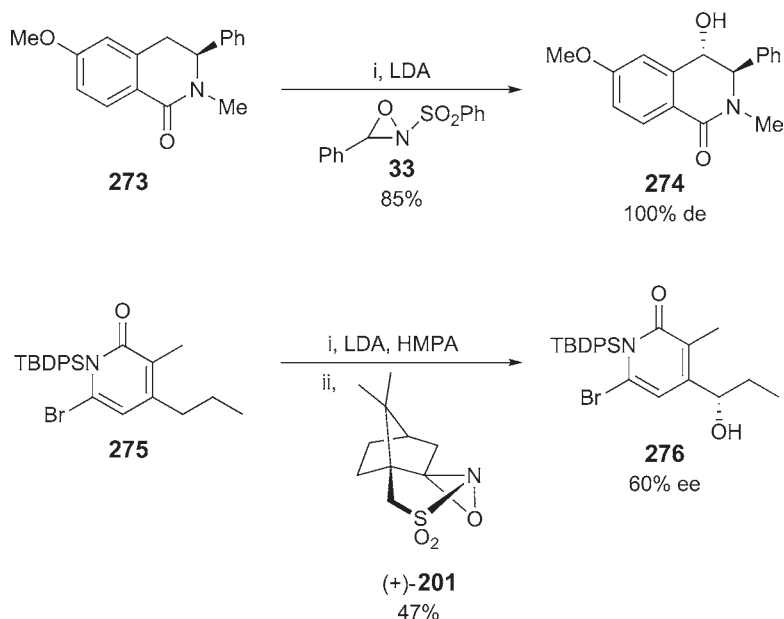


1.12.3.4.8(iv) Hydroxylation of vinylogous enolates

Reaction of a mixture of unsaturated esters **271a** and **271b** with KHMDS followed by addition of *N*-sulfonyloxaziridine **33** gave α -hydroxy ester **272** in 72% yield <1995TL413>. The bromo analogue was prepared similarly in 78% yield.

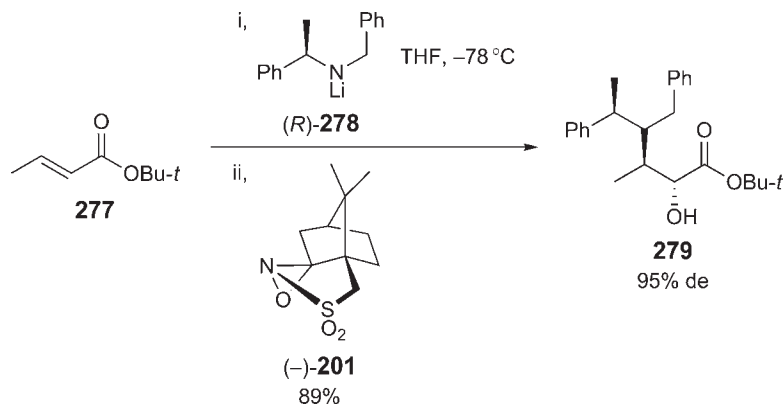


Treatment of the laterally lithiated amide generated from lactam **273** with LDA with *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** afforded hydroxyl product **274** in 85% yield as a single isomer <1999JOC8627>. Use of (+)-(camphorsulfonyl)oxaziridine **202** gave similar results. The *trans*-stereoselectivity is consistent with the earlier finding that the hydroxylation stereochemistry is controlled by nonbonded steric interactions in the transition state such that the oxygen of the oxaziridine is delivered from the sterically least hindered direction. Treatment of **275** with LDA followed by (+)-(camphorsulfonyl)oxaziridine **202** afforded hydroxyl product **276** in 47% yield and 60% ee <1997T8881>.



1.12.3.4.8(v) Tandem addition–hydroxylation

Diastereoselective conjugate addition of (*R*)-*N*-benzyl- α -methylbenzylamide **278** to α,β -unsaturated esters and subsequent enolate hydroxylation using (–)-(camphorsulfonyl)oxaziridine **202** affords α -hydroxy- β -amino esters in good to excellent yields and diastereoselectivities <2001SL1599, 2002TA1555>. For example, compound **279** was obtained in 89% yield and 95% de. The tandem addition–hydroxylation strategy was employed by Beevers *et al.* in the synthesis of potent inhibitors of hepatitis C virus NS3 proteinase <2002BML641>. Similar hydroxylation using *N*-phosphinoyloxaziridines have also been described <2003SL121>.



1.12.3.5 Cycloaddition Reactions of Oxaziridines

Kraiem *et al.* reported the cycloaddition reaction of 1-alkyl-3-aryloxaziridines **280** with chlorosulfonylisocyanate (CSI) **281** <2001TL9131>. The reaction gave rise to 2-alkyl-4-chlorosulfonyl-5-aryl-1,2,4-oxadiazolidin-3-ones **282** in 62–82% yields (Table 22). Hydrolysis of **282**, in the presence of triethylamine, afforded 2-alkyl-5-aryl-1,2,4-oxadiazolidin-3-ones **283** in 77–92% yields.

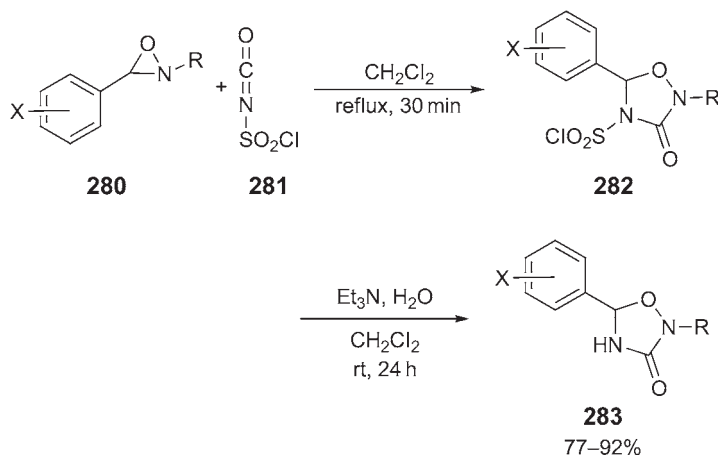
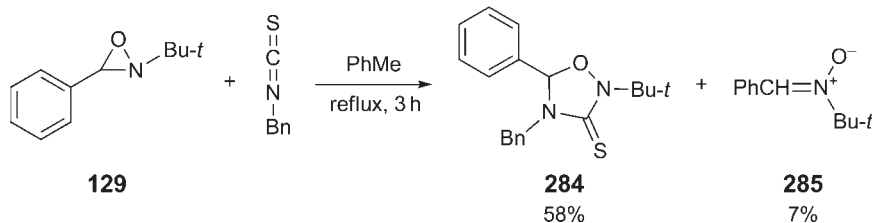


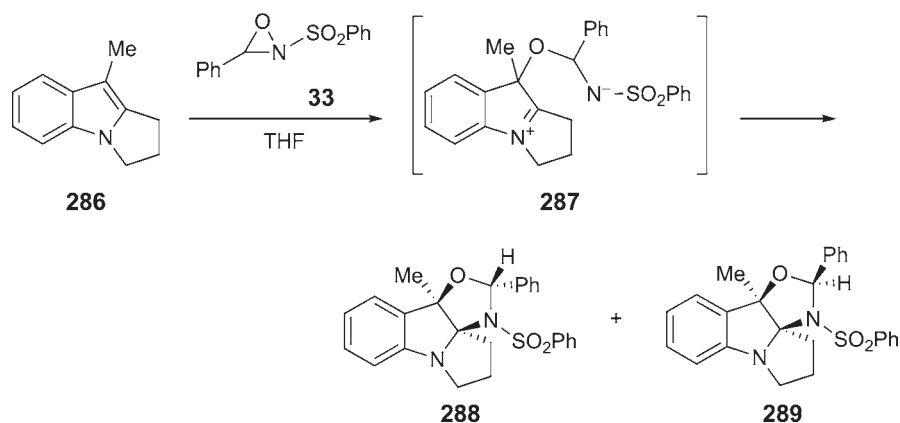
Table 22 Cycloaddition of 2-alkyl-3-aryloxaziridines **280** with CSI **281** <2001TL9131>

Entry	R	X	Yield (%)
1	Bu- <i>t</i>	H	75
2	Bu- <i>t</i>	Cl-4	67
3	Pr- <i>i</i>	H	69
4	Pr- <i>i</i>	Me-4	62
5	C ₆ H ₁₁ - <i>c</i>	H	82

Shimizu *et al.* reported that heating 2-*tert*-butyl-3-phenyloxaziridine **129** with alkyl isothiocyanates gave 4-alkyl-2-*tert*-butyl-3-phenyl-1,2,4-oxadiazolidine-5-thiones <1998H(48)1935>. For example, treating this oxaziridine with benzyl isothiocyanate in toluene under reflux for 3 h afforded **284** in 58% yield along with 7% of nitron **285**. Two reaction pathways were proposed for the formation of **284**. The first was the direct reaction of the oxaziridine with the isothiocyanate to give **284**. The second way involved thermal rearrangement of **129** to the nitron followed by a 1,3-dipolar cycloaddition with the isothiocyanate. The reaction was applied to the synthesis of glucosylaminoheterocycles.



Indole **286** reacts *N*-sulfonyloxaziridine **33** to gave a mixture of diastereomeric adducts **288** and **289** in a combined yield of 71% <1997JA1159>. A plausible mechanism for this transformation is that C-3 of the indole system acts as a nucleophile to yield a zwitterionic intermediate **287** which cyclizes to the products.



1.12.3.6 Miscellaneous Reactions of Oxaziridines

Reaction of lithiated sulfoxide **290** with various oxaziridines **291** was studied by Hajipour and Pyne (Equation 12) <1995JCM360>. It was interesting to note that the reaction took place at the oxaziridine carbon atom, affording β -hydroxyamino sulfoxides **292** and **293** as a mixture of diastereomers (Table 23).

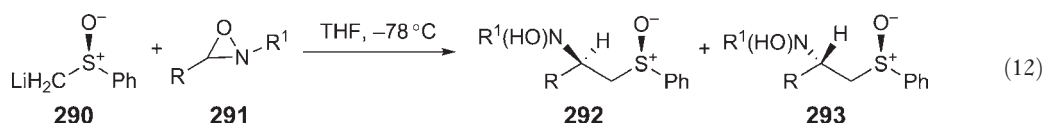
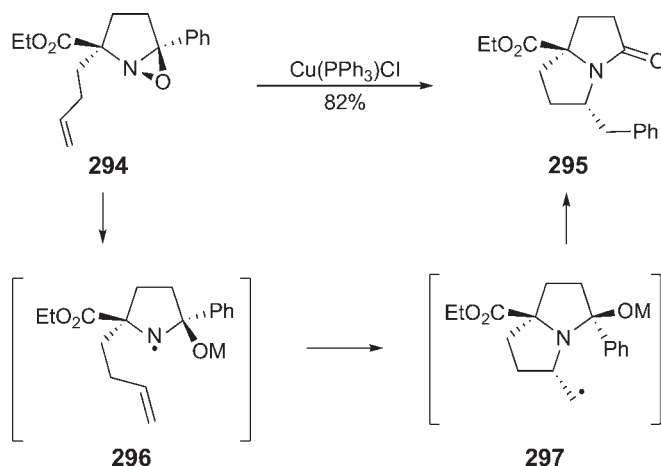


Table 23 Reaction of lithiated sulfoxide **290** with oxaziridines **291** <1995JCM360>

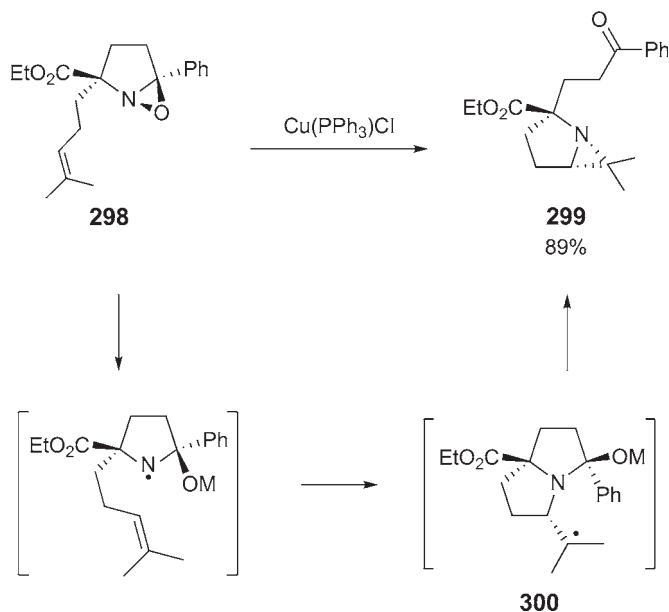
Entry	R	R ¹	Yield (292 + 293) (%)	291 : 293
1	Ph	Me	83	67:33
2	Ph	Bu- <i>t</i>	63	75:25
3			61	68:32

Treatment of oxaziridine **294** with copper(I) triphenylphosphine chloride afforded cleanly lactam **295** in 82% yield (Scheme 8) <1998TL5853, 2006S1981>. The lactam presumably results from the closure of an intermediate aminyl



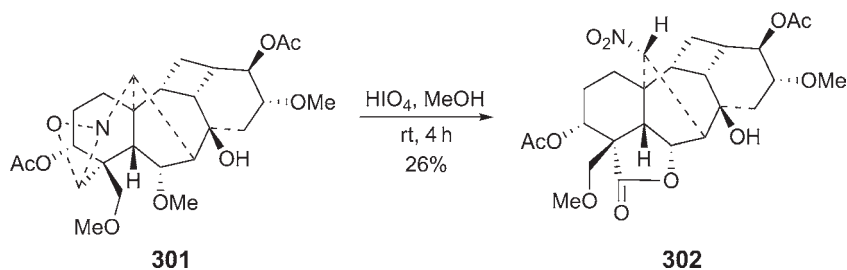
Scheme 8

radical **296** with the alkene to give a pyrrolidine ring with an exocyclic methylene radical **297**. Migration of a phenyl radical results in concomitant formation of the amide carbonyl group. On the other hand, treatment of oxaziridine **298** with copper(I) triphenylphosphine chloride gives aziridine **299** in 89% yield (**Scheme 9**). The aziridine presumably arises by attack of the intermediate tertiary alkyl radical **300** on nitrogen, in preference to the sterically more hindered migration of the phenyl radical that would give rise to the lactam.



Scheme 9

Treatment of oxaziridine **301** with HIO_4 in methanol at room temperature gave nitro compound **302**. This unusual product was obtained in 26% yield <2005T2149>.



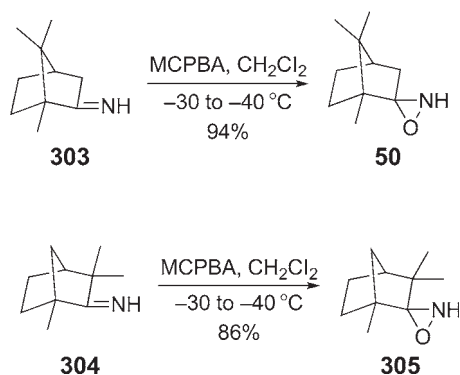
1.12.4 Synthesis of Oxaziridines

There are many reviews on oxaziridine chemistry, and all contain sections on their synthesis <1956JA6208, 1957CB2184, 1984CHEC(7)195, B-1985MI(42)283, 1989T5703, 1991S327, 1992CRV919, 1996CHEC-II(1A)365, 2003OR1>.

1.12.4.1 Oxidation of Imines

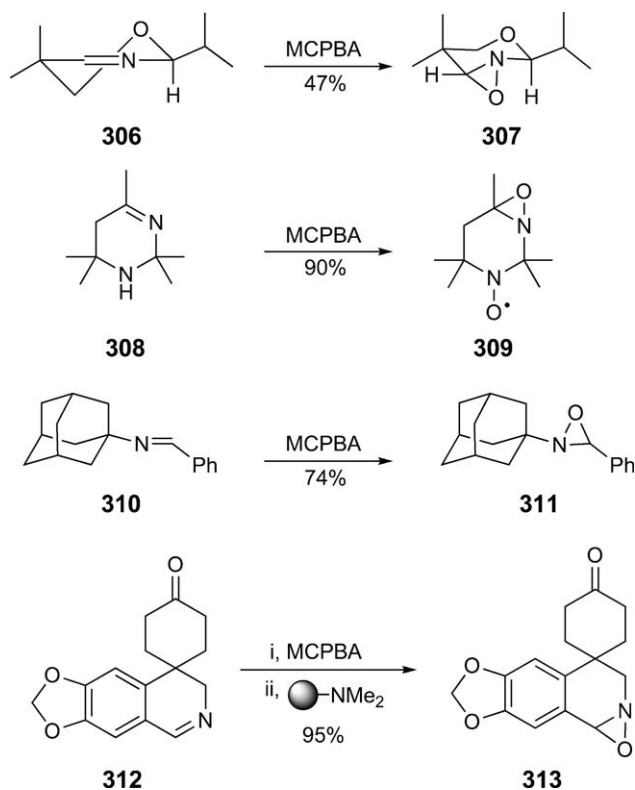
The oxidation of imines continues to be the most common method for the preparation of oxaziridines. Page *et al.* recently described the preparation of enantiomerically pure chiral NH-oxaziridines derived from camphor and fenchone <2000JOC4204>. Treatment of camphor imine **303** with 1 equiv of MCPBA at -30 to -40°C in dichloromethane gave NH-oxaziridine **50** in 94% yield. The fenchone-derived oxaziridine **305** was obtained similarly

in 86% yield from **304**. Both oxaziridines are remarkably stable in their pure form in comparison to their simpler analogues and can be kept at 5 °C for at least 6 months without decomposition.

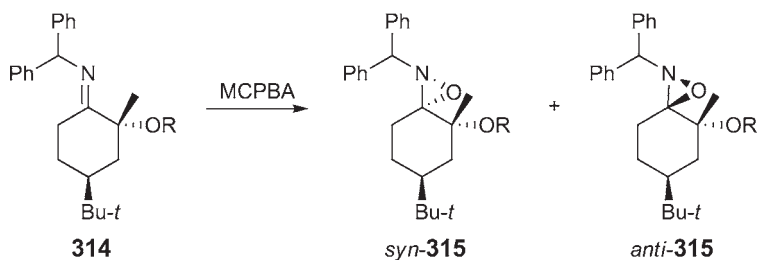


The reaction of 2-isopropyl-5,5-dimethyl-5,6-dihydro-2*H*-1,3-oxazine **306** with MCPBA leads to formation of the corresponding *N*-alkyl oxaziridine **307** as a single isomer <1995T139>. Due to the preferential conformation of imine **306**, the imine double bond is exclusively oxidized *anti* to the *i*-propyl moiety. Oxidation of imine **308** with MCPBA gave oxaziridine nitroxide **309** in 90% yield <2000TL8787> and similar oxidation of **310** gave oxaziridine **311** in 74% yield <2005S1496>.

Oxaziridine **313** was prepared by Ley and co-workers using solid-supported reagents and scavengers <2002T6285>. Reaction of imine **312** with MCPBA followed by treatment with a solid-supported amine afforded the oxaziridine in 95% yield.

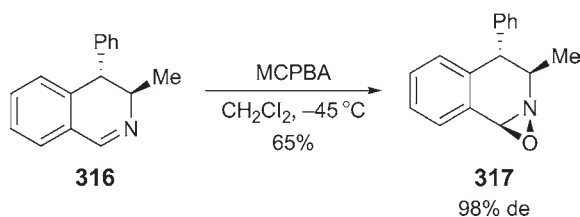


Oxidation of chiral imines **314** with MCPBA gave *syn*- and *anti*-oxaziridines **315** as a mixture of diastereomers in 49–63% yields <2000JOC5120>. It is interesting to note that the hydroxyl substituent favors *syn*-oxidation leading to *syn*-**315**, whereas the methoxy group directs oxidation *anti* to itself giving rise to the *anti*-product.



<i>R</i>	<i>syn:anti</i>	Yield (%)
H	>95:5	63
Me	<5:95	49

Imine **316** reacts with MCPBA in methylene chloride at -45°C to give oxaziridine **317** in 65% yield and 98% de [\(<1999T141>](#)). If the oxidation is carried out at room temperature, mixtures of products and lower de's result.

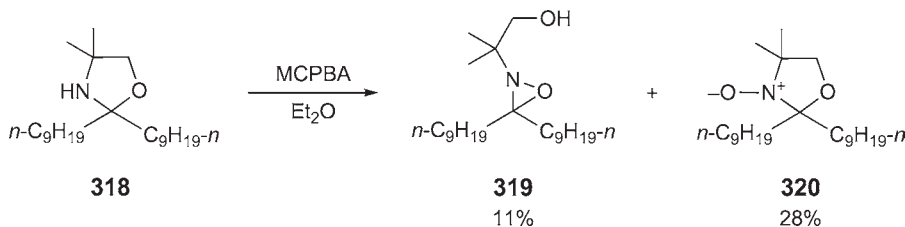


Several studies have described the MCPBA oxidation of substituted 1-pyrrolines, leading to mixtures of the *trans*- and *cis*-oxaziridines. The selectivity depends on the ring substituents ([Table 24](#)).

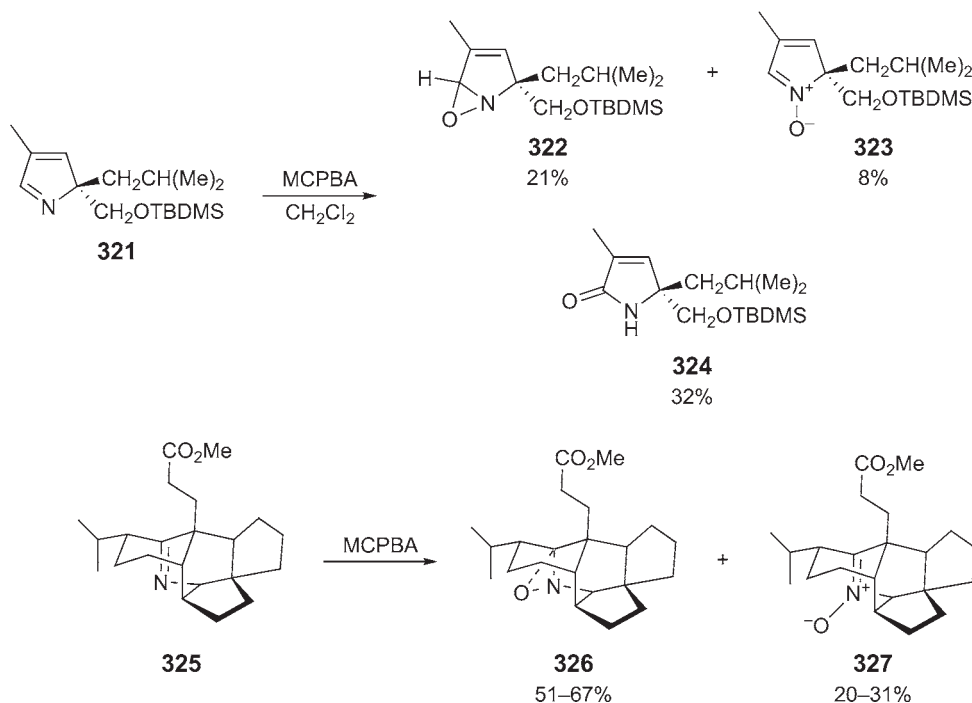
Table 24 Oxidation of substituted 1-pyrrolines with MCPBA

1-Pyrroline	Oxaziridines	<i>Trans:cis</i>	Yield (%)	Reference
		99:1	53	1995J(P1)491
	 + 	1:1		2002TA437
	 + 	3:1	72	2002TA437
			57	1999S2036

Oxidation of oxazolidine **318** with MCPBA in ether gave oxaziridine **319** and *N*-oxide **320** in 11% and 28%, respectively <1996T605>. The formation of this oxaziridine is presumably a result of oxidation of an imine intermediate that is in equilibrium with the starting oxazolidine.



Oxidation of imines **321** with MCPBA in methylene chloride resulted in the formation of the corresponding oxaziridine **322** along with lactam **323** and nitron **324** <2002TL2649>. Similar oxidation of imine **325** gave oxaziridine **326** in 51–67% yield along with 20–31% of isomeric nitron **327** as a by-product <1995JOC1131>.



Oxidation of cyclic imines **328** with magnesium monoprophthalate (MMPP) in methanol afforded oxaziridines **329** and **330** in good to excellent yields as a mixture of diastereomers (Table 25) <2003JME2397>. This oxidizing system has also been employed in the synthesis of other cyclic oxaziridines <1998TL5853>.

Treatment of imine **331** with KHSO₅ (Oxone) in the presence of NaHCO₃ afforded *N*-alkyl oxaziridines **332** in 67–85% yields (Table 26) <2005JOC301>. Optically active oxaziridines of this type could be obtained using phenyl ethylamine as the chiral directing group (Table 26, entries 3 and 4).

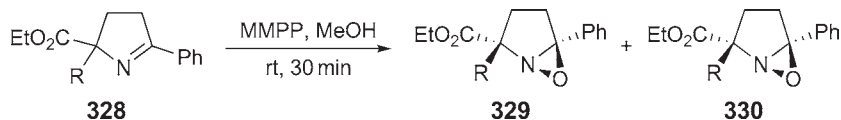
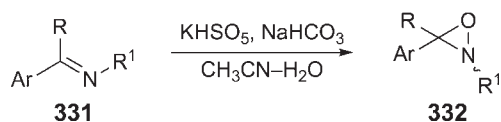


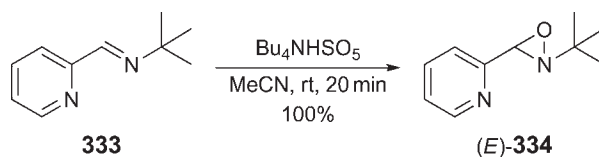
Table 25 Preparation of oxaziridines **329** and **330** <2003JME2397>

328 (<i>R</i> =)	<i>cis</i> - 329	<i>trans</i> - 330
Me	68	30
<i>n</i> -Bu	63	26
<i>n</i> -Pentyl	62	22
	50	18
	47	17
MeO ₂ C		

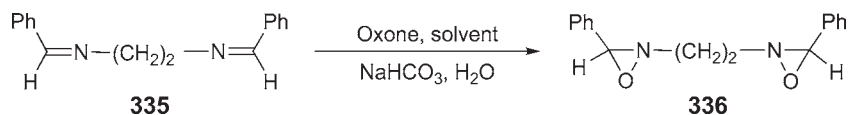
**Table 26** Preparation of *N*-alkyl oxaziridines **332**

Entry	Ar	R	R ¹	Yield (%)
1	Ph	H	Pr- <i>i</i>	67
2		H	Pr- <i>i</i>	85
3		H		88
4				87
5		H	Pr- <i>i</i>	85

Aldimines are oxidized to oxaziridines by tetrabutylammonium monoperoxysulfate (TBAO) and was investigated by Mohajer *et al.* <2004TL631>. The reaction gave the corresponding (*E*)- or a mixture of (*E*)- and (*Z*)-oxaziridines with high yields (>90%) and good to excellent selectivities (75–100%). The (*E*/*Z*)-ratio depends critically on the stereoelectronic nature of the imine substituents, the solvent, and the presence of Lewis acids and bases. For example, oxidation of imine **333** with TBAO afforded (*E*)-oxaziridine **334** in quantitative yield.



N,N'-Bisarylidenes are oxidized rapidly to give a diastereomeric mixture bisoxaziridines using buffered Oxone <2002PS(177)2309>. For example, **335** gives **336** in 96–98% yields. The oxidations were very efficient in both acetone and acetonitrile.



anti-Imines **337** were converted to oxaziridines **338** in good to excellent yields (60–90%) using a benzonitrile–hydrogen peroxide oxidizing system (Table 27) <2001SC263>. Commercial aqueous hydrogen peroxide (35%) can be used successfully in this reaction. Nonracemic oxaziridines were obtained when chiral imines were used.

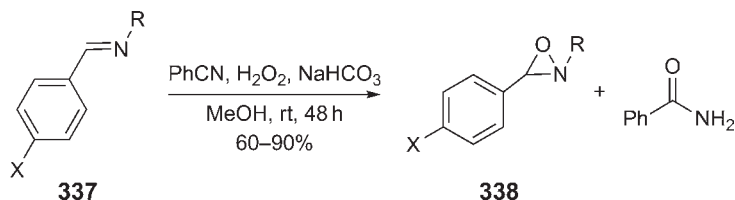


Table 27 Preparation of *N*-alkyloxaziridines **338** <2001SC263>

<i>X</i>	<i>R</i>	Yield (%)
H	Bu- <i>t</i>	67
NO ₂	Bu- <i>t</i>	85
H	Pr- <i>i</i>	88
NO ₂	Pr- <i>i</i>	87
H	C ₆ H ₁₁ - <i>ε</i>	85
NO ₂	C ₆ H ₁₁ - <i>ε</i>	85

Selective oxidation of *N*-alkyl imines to oxaziridines using the UHP/maleic anhydride system was recently described by Damavandi *et al.* (Equation 13) <2002SL933>. *N*-Alkyloxaziridines **349** were obtained in good to excellent yields (Table 28). Under similar conditions, the *N*-phenyl imine gave the corresponding nitron. A variety of *N*-alkyloxaziridines have also been prepared in good to excellent yields by oxidation of *N*-alkylimines using sodium tungstate–H₂O₂ (30%) in acetonitrile at room temperature <2005SL1176>.

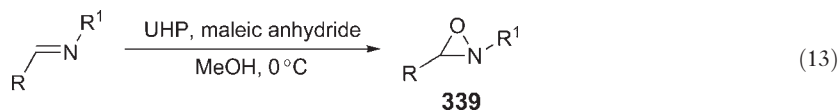
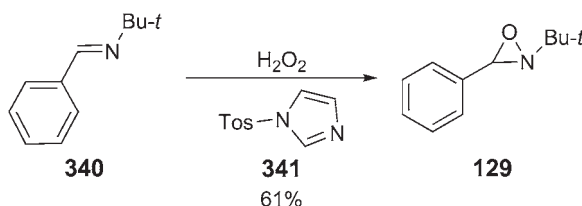


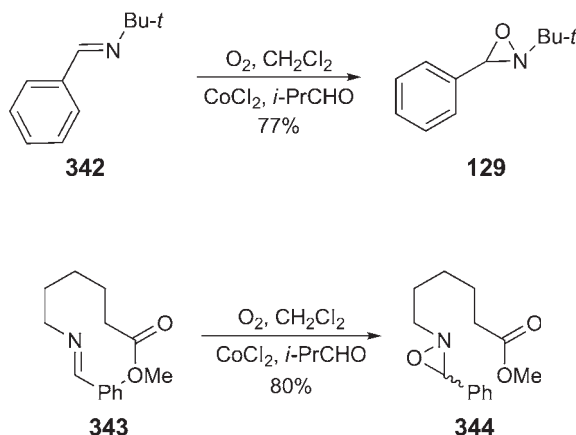
Table 28 Preparation of *N*-alkyloxaziridines **339** <2002SL933>

<i>R</i>	<i>R</i> ¹	Yield (%)
Ph	Bn	95
<i>p</i> -MeC ₆ H ₄	Bn	95
<i>p</i> -MeC ₆ H ₄	<i>n</i> -Bu	93
2-Furyl	<i>n</i> -Bu	90
<i>n</i> -Pr	<i>n</i> -Bu	80
<i>n</i> -Bu	<i>i</i> -Pr	80

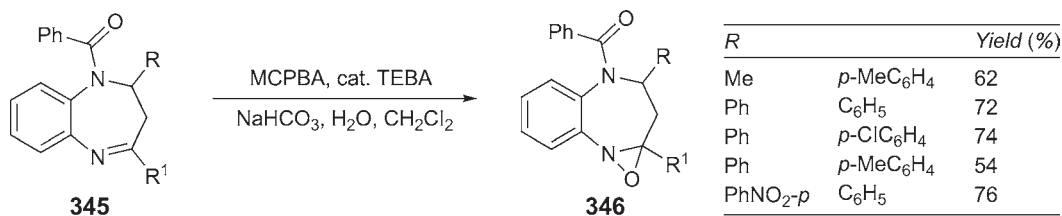
Oxidation of imine **340** with H₂O₂ in the presence of tosyl imidazole **341** gave oxaziridine **129** in 61% yield <1996T5773, 1997JOC188>. The oxidation takes place through the *in situ*-generated *p*-toluenesulfonic peracid.



Oxidation of imines to oxaziridines catalyzed by transition metal complexes using molecular oxygen as the terminal oxidant and aldehydes as co-reductants was investigated by Martiny and Jorgensen [<1995J\(P1\)699>](#). Different transition metal complexes were tested as catalysts and it was found that cobalt complexes could catalyze the selective oxidation of imines to oxaziridines. The cobalt-catalyzed oxidation of imines to oxaziridines is dependent on the aldehyde used as co-reductant. Aliphatic aldehydes led to smooth oxidation while the aromatic aldehydes were not effective. For example, oxidation of **342** with O_2 in the presence of CoCl_2 and 2,2-dimethylpropanal afforded oxaziridine **129** in 77% yield. Similarly, oxaziridine **344** was obtained in 80% yield from its corresponding imine **343** [<2001JOC8282>](#).

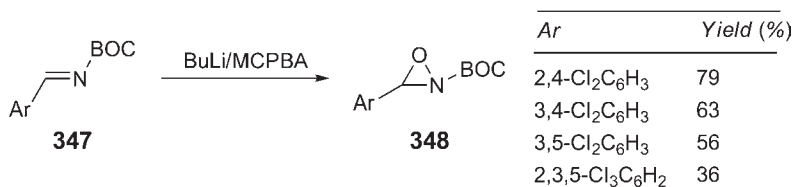


Polyfluoro *N*-aryl imines underwent oxidation with MCPBA to give polyfluoro *N*-aryloxaziridines [<1996JFC\(77\)175>](#). The MCPBA-mediated oxidation of 1,5-benzodiazepins **345** gave the corresponding oxaziridines **346** in good yields [<1999PS\(152\)1, 2000HAC158>](#).

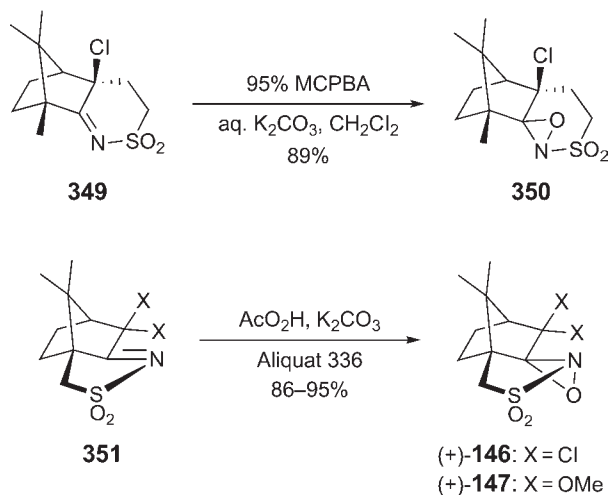


TEBA = benzytriethylammonium chloride

Treatment of *N*-BOC benzaldimines **347** with lithium *m*-chloroperoxybenzoate afforded the corresponding *N*-BOC oxaziridines **348** in 36–79% yields [<1995TL1439>](#). Use of MCPBA resulted in formation of *N*-BOC benzamides, and Oxone gave no reaction.



Oxidation of the camphor-derived *N*-sulfonylimine **349** with buffered MCPBA gave the *N*-sulfonyloxaziridine **350** in 89% yield <1997JOC3625>. Oxidation of (camphorsulfonyl)imines **351** with peracetic acid in the presence of K₂CO₃ and Aliquat 336 afforded the corresponding oxaziridines **146** and **147** in 86–90% and 90–95% yields, respectively <1998OS(9)212, 1996OS159>. Use of hydrogen peroxide for such oxidations has also been reported <1997JOC6093>.



Garcia Ruano *et al.* reported an important new procedure for the preparation of diverse *N*-sulfonyloxaziridines <2005OL5493>. This method involves the one-pot, two-step oxidation of readily available *N*-sulfinylimines **352** first with MCPBA followed by MCPBA/KOH to give the oxaziridines **353** in excellent yields (Table 29).

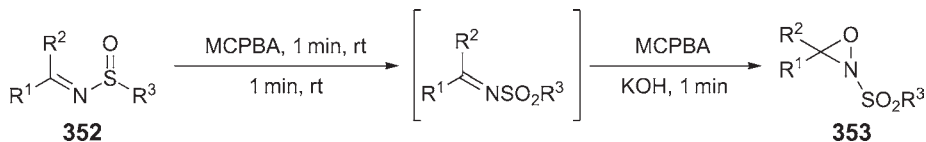


Table 29 Preparation of *N*-sulfonyloxaziridines **353** from *N*-sulfinylimines **352** <2005OL5493>

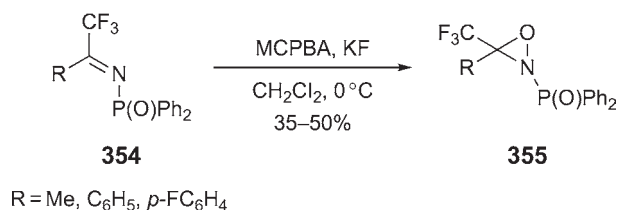
<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	Yield (%)
C ₆ H ₅	H	<i>p</i> -CH ₃ C ₆ H ₄	94
C ₆ H ₅ CH=CH ₂	H		99
4-NO ₂ C ₆ H ₅	H		97
Me	H		97
C ₆ H ₅	Me		89 ^a
<i>i</i> -C ₃ H ₇	Me		80 ^b
C ₆ H ₅	H	<i>t</i> -C ₄ H ₉	99
<i>i</i> -C ₃ H ₇	H		99
C ₆ H ₅	H	<i>i</i> -C ₃ H ₇	91
C ₆ H ₅	H	<i>o</i> -MeOC ₆ H ₄	99

^a3:1 mixture of diastereoisomers.

^b6:1 mixture of diastereoisomers.

The advantage that this procedure has over earlier methods is that *N*-sulfonyloxaziridines derived from aliphatic aldehydes and ketones can be prepared.

N-Phosphinoylimines **354** are oxidized with MCPBA in the presence of KF to give the corresponding *N*-phosphinoyloxaziridines **355** in 35–50% yields <2001TL101>. It is important that the reagents used in this reaction be thoroughly dried and that the oxidation be conducted under anhydrous conditions due to the sensitivity of **354** toward hydrolysis.



1.12.4.2 Derivatization of NH-Oxaziridines

As expected, *N*-substituted oxaziridines can be obtained by derivatization of NH-oxaziridines. Page *et al.* reported that a variety of camphor-derived *N*-substituted oxaziridines **356** can be prepared from NH-oxaziridine **50** (Table 30) <2000JOC4204>.

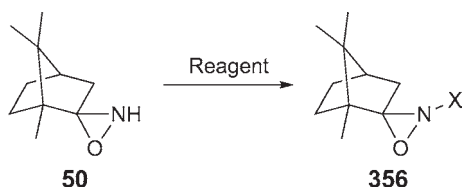


Table 30 Preparation of *N*-substituted oxaziridines **356** <2000JOC4204>

Reagent	Conditions	X	Yield (%)
<i>t</i> -BuOCl	Et ₂ O, -78 °C	Cl	85
PhSO ₂ Cl	DMAP, CH ₂ Cl ₂ , rt	PhSO ₂	62
MeOCOC	Pyridine, CH ₂ Cl ₂ , 0 °C to rt	CO ₂ Me	95
EtOCOC	Pyridine, CH ₂ Cl ₂ , 0 °C to rt	CO ₂ Et	89
C ₆ F ₅ SCl	Pyridine, CH ₂ Cl ₂ , rt	C ₆ F ₅ S	41

1.12.4.3 Isomerization of Nitrones

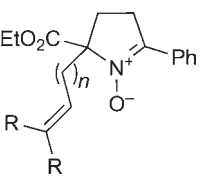
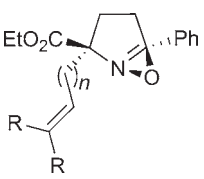
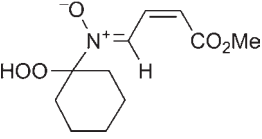
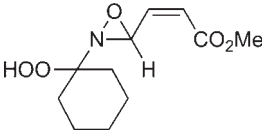
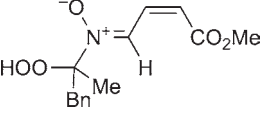
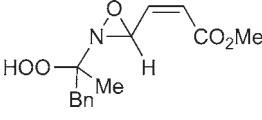
The photochemical rearrangement of nitrones to amides often involves initial formation of oxaziridine intermediates. These oxaziridines can be isolated in good to excellent yields (Table 31).

Table 31 Photochemical rearrangement of nitrones to oxaziridines

Nitron	Oxaziridine	Yield (%)	Reference
		45	2003JOC8065
		95	1997RJO705
		51–67	1995JOC1131

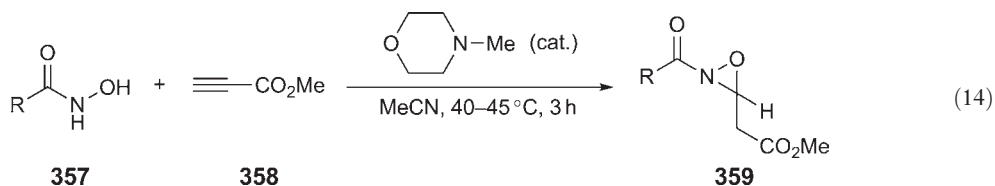
(Continued)

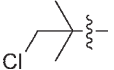
Table 31 (Continued)

Nitrone	Oxaziridine	Yield (%)	Reference
			1998TL5853
		85	1997S657
		87	1997S657

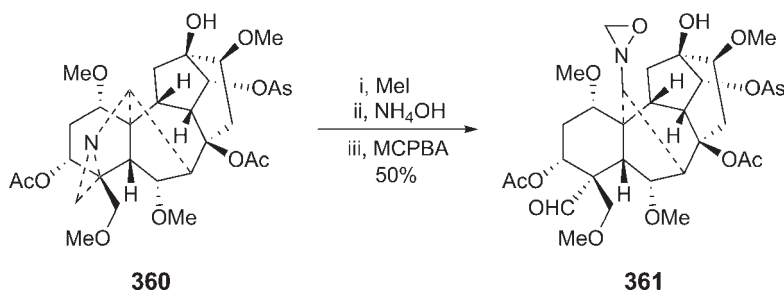
1.12.4.4 Miscellaneous Methods

Zong *et al.* reported a new method for preparing *N*-acyloxaziridines **359** via the tandem O,N-addition of hydroxamic acids **357** to methyl propiolate **358** (Equation 14) <1998TL6227>. The reaction was carried out in the presence of a catalytic amount of *N*-methyl morpholine. The desired *N*-acyl oxaziridines were obtained in good to excellent yields (Table 32).

**Table 32** Synthesis of *N*-acyloxaziridines **359** <1998TL6227>

R	Yield (%)
<i>n</i> -Pr	92
	91
	86
Ph	95
4-ClCH ₂ C ₆ H ₄	90
5-F-2,4-Cl ₂ C ₆ H ₂	89

When the norditerpenoid alkaloid imine **360** was subjected to reaction with MeI-NH₄OH and MCPBA, oxaziridine **361** was formed in 50% overall yield <2002H(57)2357>. Key steps in the proposed mechanism for the formation of **361** involve formation of a quaternary ammonium salt with MeI and peracid oxidation through a Baeyer–Villiger-type process.



1.12.5 Conclusions

This chapter reviews the literature from 1996 through early 2006 on the chemistry of oxaziridines. It reveals that most of the work in this area deals with oxaziridines' ability to function as amination and oxidation reagents. Stable oxaziridines with an *N*-carbonyl moiety act as aminating reagents and transfer a nitrogen atom to nitrogen, oxygen, sulfur, and carbon nucleophiles. The *N*-sulfonyloxaziridines are efficient oxidizing reagents and selectively oxidize many diverse nucleophilic substrates. A variety of *N*-sulfonyloxaziridines are available in both enantiomeric forms and their oxygen-transfer reactions afford predictable stereochemistry with high asymmetric induction. The most widely used application of the *N*-sulfonyloxaziridines is the hydroxylation of enolates to α -hydroxyl carbonyl compounds, a structural moiety common to biologically active compounds. The highly reactive perfluorooxaziridines, having an *N*-C₄F_{9-*n*} group, are among the few reagents able to hydroxylate an unactivated C–H. It seems reasonable to predict that future directions in oxaziridine chemistry will be focused on their ability to function as selective amination and oxidation reagents.

1.12.6 Further Developments

Enantiomeric purities ranging from 20 to 80% have been reported for the acid-promoted asymmetric oxidation of sulfides to sulfoxides by binaphthyl-derived oxaziridines has been described <2007T6232>. A novel amino hydroxylation of olefins has been developed using *trans*-2-phenylsulfonyl-3-phenyloxaziridine **33** <2007JA1866>. The reaction, which is catalyzed by copper(II) salts, affords good yields of the product. Oxidation of aldimines to oxaziridines using alumina-supported MoO₃ catalyst and anhydrous *t*-butyl hydroperoxide (TBHP) has been described. Yields are excellent.

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1.13

Thiaziridines and Thiazirenes

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1.13.1 Introduction

1.13.1.1 Historical Perspectives

The chemistry of heterocyclic compounds has played a considerable role in the development of modern organic chemistry. Small-ring compounds appear to envision a particular distinct category within this class of compounds, contributing uniquely – in their own right – to the understanding of the characteristics and chemistry associated with all carbons as well as heterocyclic three-membered rings. Indeed, small-ring compounds represent a fair portion of strained and, therefore, reactive organic systems in which the geometry of both sp^3 and sp^2 carbons has been distorted from the ideal tetrahedral configurations. Foremost among these reactive molecules are the small-ring heterocycles, such as thiaziridines and the thiazirenes <1996CHEC-II(1A)415>. Thus, small rings and the associated concepts of distorted hybridization and strain have fascinated organic and physical organic chemists for more than a century and this interest shows no sign of abatement – if anything, it is growing <1989CRV973, 1994JA9311>. Over the years, three-membered heterocycles, including those containing sulfur, have received great attention from both experimental and theoretical perspectives <B-1994MI389> in an attempt to bridge the gap between theoretical predictions and experimental tests <1996CHEC-II(1A)415, 1996CHEC-II(1B)1113>. Recently, however, theoretical methods have gained great importance; it is not surprising, therefore, that most of the papers related to thiaziridines and thiazirenes, in the last decade, focused on theoretical computational studies, the results of which suggest, in some cases, the isolability of some of the thus far rather elusive three-membered ring structures, e.g., thiaziridines **1** <2001JMT(535)247>.

The history of three-membered rings containing sulfur began in 1916 with the synthesis of the 2,2,3,3-tetraphenylthiirane (tetraphenylethylene sulfide) by Staudinger and Pfenninger <1916CB1941>. Following the preparation of the first pure aliphatic thiiranes (ethylene sulfide) by Delepine in 1920 <1920BSF740>, the importance of this group of compounds as reactive substances suitable for a variety of chemical transformations was recognized.

Furthermore, sulfur-containing saturated three-membered heterocycles have significant importance not only in organic synthesis but also for predictive theoretical and spectroscopic studies <1983HC(42)333, 1996CHEC-II(1A)173, B-1994MI389, 2001JOC3502, 2001AGE393, 2002CEJ217>. The chemistry of this class of compounds, that is, thiiranes, gained momentum when in 1934 Dachlauer and Jackel discovered a simple method for their synthesis from epoxides and alkali thiocyanates or thiourea <1936CA7122>. Yet, excluding a few isolated cases of earlier reported preparations of thiirane oxides, thiirane dioxides, and thiiranium salts, the first substituted unsaturated analogues – thiirene dioxides <1965JA5804> and thiirene oxides <1979JA390> – were synthesized and characterized almost two decades later by Carpino *et al.* The parent unsaturated thiirene oxide and dioxide, however, are not known to date <1996CHEC-II(1A)415>.

The presence of a heteroatom, coupled with the strain in the system, make the hetero-three-membered rings thermally unstable and highly (chemically) reactive. Consequently, electrophiles and nucleophiles, as well as thermally and photochemically induced reactions, are expected to result in a facile ring opening <1983HC(42)333, B-1994MI389>. In the presence of appropriate multiple-bond-containing trapping agents <1987MI113-01>, the unsaturated members of these series are expected to undergo facile cycloadditions and thus be trapped even if they prove to exist only as transient species. As a result, the weight of the ‘theoretical’ determinations of the structure, energy, reactivity and stability, spectra, bonding, charge distribution, and strain energy has been significantly increased (see Section 1.13.2). Ultimately, theoretical studies, together with the relevant and related experimental chemistry of small-ring heterocycles, have thus played a considerable role in the development of modern organic chemistry <1989CRV973, 1992JA4354, 1994JA9311, 1996CHEC-II(1A)415>.

This chapter, updating the one in CHEC-II(1996) <1996CHEC-II(1A)415>, is focused on the thiaziridine and thiazirene heterocycles (**1** and **2**, respectively, Figure 1), the three-membered ring systems containing two heteroatoms – sulfur and nitrogen – within their cyclic array. The synthesis of the thiaziridine system (i.e., **1**) was reported long ago <1896CB59> (see the Beilstein database), but has been recently shown not to have the originally assigned thiaziridine structure <2005JSF111>. On the other hand, the intermediacy of these saturated and unsaturated systems, that is, **1** and **2**, have been established, both theoretically–computationally and experimentally (see <1996CHEC-II(1A)415> and Sections 1.13.2–1.13.4).

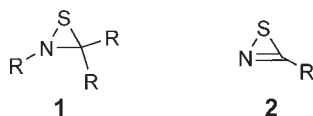


Figure 1

The preparation of several three-membered heterocycles incorporating two or three heteroatoms, for example, **3–7** preceded the synthesis of the thiadiazirine **7** <1973JA634>. The successful isolation and characterization of the labile thiaziridine *S*-dioxide system **8** (Figure 2) <1974AGE742> was reported later.

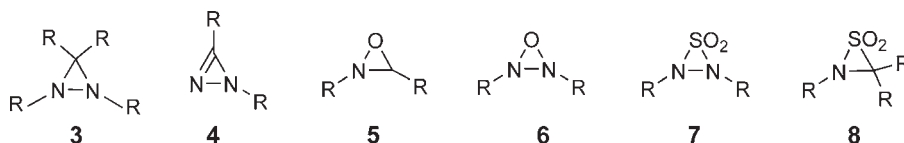


Figure 2

With the exception of the all-heteroatom, three-membered ring **9** <1975AG487>, the systems **10–13**, containing two or three heteroatoms within their cyclic skeleton, have been synthesized thus far. Most of them, however, have been proposed as reaction intermediates <1983HC(42)333>. Similarly, almost nothing is known about the unsaturated three-membered ring heterocycles **14–16**. However, the related two-sulfur atoms containing dithiirane ring systems **17** <1986T739, 1990SUL83> and **18** are known (Figure 3) <1993JA4914>. Recently some dithiiranes have been prepared, isolated, and characterized <2000AHC221, 2000BCJ729>.

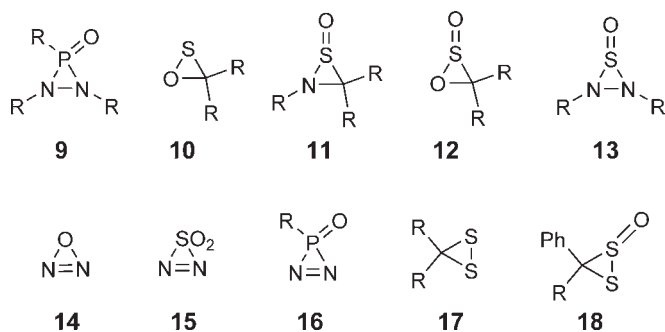
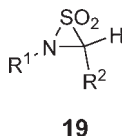


Figure 3

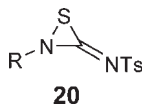
It is not surprising that in view of the well-documented stabilizing effect imparted to sensitive three-membered rings by bulky substituents [<1967JA362, 1967JA1030, 1969AGE449, 1969JOC2254, 1970JA6057>](#) all the successful syntheses and isolations of stable three-membered rings containing sulfur and additional heteroatoms, for example, **8**, as well as other isolable heteroatomic three-membered rings, for example, **9**, are those in which the ring carbon or nitrogen atom (or both) are substituted with very bulky *t*-butyl, 1,1,3,3-tetramethylbutyl, or adamantyl groups. It is to be expected that the same strategy with respect to substitution will be adopted in future attempts to synthesize the as yet elusive sulfur-containing three-membered thiazirenes and closely related systems.

Indeed, except for the bulky group-substituted thiaziridine 1,1-dioxides **19** (e.g., $R^1 = R^2 = \text{Bu}^t$), no other thiaziridines have been isolated thus far.



1.13.1.2 Scope and Limitations

Three-membered thiaziridinimines **20**, which have been proposed and demonstrated, experimentally [<1975JOC1728>](#), to be reactive intermediates, do not survive the reaction conditions on thermolysis. They can be effectively trapped [<1976JHC883>](#), however, so that their chemical properties can be inferred indirectly.



The unsaturated analogues of the thiaziridines, for example, the thiazirene systems (**21** and **22**), are unknown thus far but have been proposed as unstable intermediates, generated, mainly, photolytically and thermodynamically in certain chemical transformations ([Figure 4](#)) [<1975JA6197>](#). Significantly, the intermediacy of system **22** ($R = \text{Ph}$), the aza analogue of the corresponding thiirene dioxide, has been established in the base-induced successive dehydrohalogenations of α,α -dibromobenzylsulfonamide [<1974JOC1817>](#).

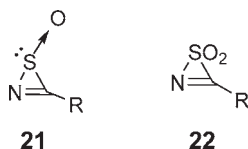


Figure 4

The thermal instability and high chemical reactivity of these three-membered ring heterocycles make them very intriguing and challenging for preparation and direct experimental testing of predictions, based on *ab initio* molecular calculations. Gas-phase ion-molecule investigations, however, have been demonstrated to be very useful for probing intrinsic reactivities of reactive small strained-ring intermediates <1994JA783>. Since these experimental results are directly comparable to *ab initio* molecular orbital (MO) calculations, they should be used in the study of the thiaziridine and thiazirene systems. In reality, however, the bulk of the studies reported in the last decade or so, in relation to these two systems, were theoretical (see Section 1.13.2.1).

From a theoretical point of view, the thiazirene systems **2** and **21** are unique: on the one hand, they may be considered as antiaromatic since they have a cyclic array of $4n\pi$ -electrons predicted by simple Hückel theory to be highly unstable <1973ACR393>. Indeed, this has been proved experimentally in the case of the analogous thiirenes <1978JOC2490>. On the other hand, based on a naïve analogy with cyclopropanones, some kind of ‘aromaticity’ can, in principle, be assigned to thiazirenes of type **21** and **22** <1974JOC1817, 1983HC(42)333>, assuming a possibility for d orbitals to allow transmission of electronic effects via π -conjugation <1978T2983, B-1994MI389>.

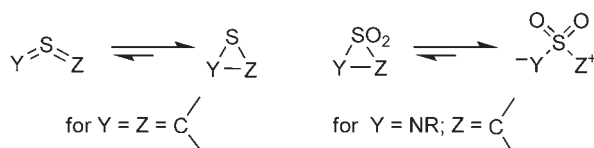
Although both thiaziridines and thiazirenes are rather chemically reactive species, three-membered rings containing a sulfur atom are generally more stable, thermodynamically, than other three-membered ring systems. This is probably due to a lower strain energy for the former, apparently associated with the capacity of the sulfur atom to better accommodate the extra strain of the small ring compared with either the carbon atom or other second row heteroatoms <1983HC(42)333>. Taking the above ‘aromaticity’ and accommodation of strain capacity of the sulfur atom into consideration may suggest that the as yet unknown thiazirene oxides (e.g., **21**) are more stable than their saturated analogues, the thiaziridine oxides (e.g., **19**), and, therefore, should be isolable.

In the following sections of this chapter, the reported studies of, and/or related to, both the thiaziridine and thiazirene systems in the last 10 years (1996–2005) are reviewed and discussed, in connection to, and continuation of, the corresponding review chapter in this series <1996CHEC-II(1A)415>.

1.13.2 Structure of Thiaziridines and Thiazirenes

1.13.2.1 Theoretical Methods

The only known thiaziridines are the substituted thiaziridine 1,1-dioxides **19**, R^1 and R^2 being the bulky Bu^1 or Ad groups <1974AGE742, 1981CB774>. A literature survey of sulfur-containing systems, which preceded the successful synthesis, isolation, and characterization of these thiaziridine systems, convinced those who prepared **19a** ($R^1 = R^2 = Bu^1$) that although analogous systems may, in principle, exist as three-membered rings, only the ring-closed 1,1-dioxides of thiaziridines (i.e., **19**), and thiadiaziridines can be expected to be more stable than their ring-opened isomers <1977CB1780>, as illustrated in Scheme 1.



Scheme 1

The parent thiaziridines were predicted to be less stable than their related readily accessible oxaziridines for the same reasons that thiiranes are less stable than their related oxiranes: while the ring strain energies of the sulfur-containing three-membered rings would be less than those of the corresponding oxygen compounds, this advantage would be more than offset by the weaker bonds of the sulfur compounds <1970CC707>. Indeed, thiaziridines are not known thus far except as reaction intermediates.

Previous relevant *ab initio* calculations with the $631G^*$ split valence basis set on the thiaziridine-related (*E*)- and (*Z*)-thiadiaziridine, (*E*)- and (*Z*)-diazene *N*-sulfide, and the transition structures connecting them gave the value of $113.7 \text{ kJ mol}^{-1}$ relative to the most stable structure, (*Z*)-diazene *N*-sulfide, for the lowest barrier between the open- and the less-stable closed-ring structures <1985PCI, 1996CHEC-II(1A)415>. This corresponds to a first-order half-life at 20°C of $\sim 350 \text{ h}$ for an Arrhenius *A*-factor of 10^{14} s^{-1} , but half-lives will be proportionately greater for the

smaller *A*-factors, more likely to apply in practice. These and related results <1985PC1> suggest that electronegative groups, as such, are not necessary for the relative thermal stability observed, for example, in the case of the bis(perfluoroethyl) thiadiaziridine <1983CC658>.

High-level quantum-chemistry calculations on the reactivity of thiocarbonyl *S*-imide pericyclic reactions, were performed by density functional theory (DFT), using gradient correlation functionals in conjunction with 6-31+G(d,p) and 6-31+G(3df,3dp) basis sets. For the sake of comparison, conventional *ab initio* quantum-chemistry calculations at correlated levels of theory (e.g., MP2 and G2(MP2)) were also performed; the result is that the 1,3-electrocyclic ring closure of the *S*-imides to form thiaziridines **1** is predicted to be an exothermic process by about 10 kcal mol⁻¹, with activation energies of about 30 kcal mol⁻¹ <1999PJC683>. This implies the relative thermodynamical stability of the thiaziridine ring structure on this pericyclic reaction coordinate.

Using *ab initio* Hartree–Fock (HF) MO and hybrid HF–density functional (B3LYP) methods, the molecular structure of the parent and several N-substituted thiaziridines, in their ground and planar-shaped transition state, corresponding to the nitrogen inversion process as well as to the energy enthalpy and free energy changes along with the activation barrier energy, were determined <2001JMT(535)247>. The bottom line is that the isolation of optical active thiaziridines that have their energy barrier to N-inversion $E_a \geq 97$ kJ mol⁻¹ (at rt), should be possible. This result – that the more electronegative the N-substituent is, the greater is the energy barrier to the ring nitrogen inversion – suggests that the isolation of an N-electronegative group-substituted thiaziridine is feasible.

The structure and stability of hypervalent *S*-difluorothiaziridine were theoretically investigated within a comprehensive study of the structures and stabilities of three-membered rings containing a hypervalent atom – Si, P, and S (Figure 5; i.e., **23**) <2001PCA10711>.

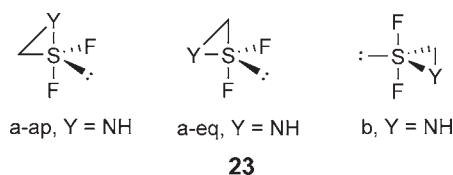


Figure 5

In applying an electron-pair bond model for the hypervalent molecules studied, the (apical, equatorial) and (equatorial, equatorial) isomers, namely **23-eq** and **23b**, respectively, are both local minima. This means that the tetracoordinated species are less strained than the pentacoordinated ones, due to less antibonding properties of the electron delocalization between the geminal ring bonds on the hypervalent sulfur atom. Yet, the more strained (eq, eq) isomers are, surprisingly, more stable than the (ap, eq) isomers in most of the hypervalent three-membered rings studied <2001PCA10711>.

An extensive quantum- (DFT B3LYP) mechanical study focused on the potential energy surfaces of the isomerization and dissociation of the CHNS system. The initiative for this study was the formation and Fourier transform infrared (FTIR) matrix spectroscopy-based isolation of the thiocyanic acid HSCN and isothiofulminic acid HSNC from the ultraviolet (UV) photolysis of the isothiocyanic acid HNCS <2001CPL(349)227>. The calculations were performed using DFT and correlated *ab initio* MP2 and CCSD(T) methods and employing a large aug-cc-pVTZ basis set. They revealed nine singlet and eight triplet local minima, three cyclic (**24a–c**) and one (**24d**) ‘thiazirines’ on the singlet and triplet potential energy surfaces, respectively (Figure 6) <2003PCA11209>.

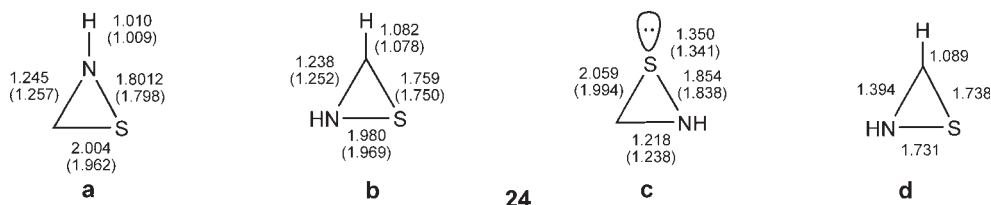


Figure 6

For singlet, the noncyclic isothiacyanic acid, HNCS, was found to be the most stable isomer and global minimum, whereas the cyclic thiaziridine, C(H)NS **24a–c**, the most stable isomer, was found to be 50.8 kcal mol^{−1} higher in energy, followed by thiazirines **24b** and **24c**, 59.3 and 76.4 kcal mol^{−1} higher, respectively. The cyclic triplet thiaziridine, CHNS, was found to have 90.0 kcal mol^{−1}, higher in energy than the referenced singlet HNCS and, therefore, the least stable cyclic isomer on the photolysis reaction coordinate <2003PCA11209>.

The activation energies for some isomerizations within the singlet CHNS system involving the cyclic thiaziridine systems **24a** (76.4/72.1 kcal mol^{−1}) and **24c** (54.3/54.2 kcal mol^{−1}) were calculated to be quite low – below 20 kcal mol^{−1}. The latter undergoes ring-opening process, thus calculated to be almost barrierless (0.2/0.1 and 3.7/3.8 kcal mol^{−1}), which strongly correlates with the experimentally established thermodynamic instability of thiaziridines.

Ab initio MO calculations at the HF/6-316(d,p) levels for the potential energy of the destabilized cation C₂H₄NS⁺ have been conducted with all structures being subjected to geometry optimization at both level of theory and have been characterized by harmonic frequencies calculations. At the HF/6-31(d,p) level, all the three cyclic structures **25a–c** of the C₂H₄NS⁺ ion are at minima <1997JMT(401)117>. The carbocation **25a** has the lowest energy and the cation **26** is the transition structure for the interconversion of the two equivalent isomers of this carbocation (Figure 7).

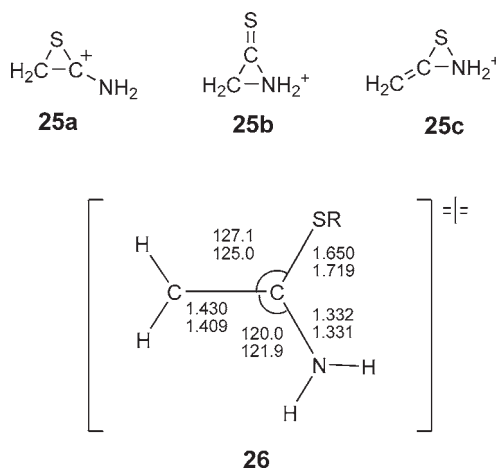


Figure 7

Ion **25b** lies in a shallow potential well at the HF level, with a barrier of only 3.1 kcal mol^{−1} to rearrangement to the corresponding α -amino-thioacetyl cation. The thiaziridinium ion **25c** (Figure 7) lies highest on the potential energy surface and has an additional strain resulted from the exocyclic carbon-carbon double bond. Yet its rearrangement to **25a** is protected by an energy barrier, calculated to be 37.2 kcal mol^{−1} <1997JMT(401)117>. The conclusion, therefore, is that this thiaziridine cation **25c** should be a long-lived species in the gas phase and is lower in energy than its dissociation products CS + H₂C=NH₂, and is only 39.3 kcal mol^{−1} above the global minimum. The question still remaining is: How can the ion **25c** be experimentally formed?

A closely related computational study – on the structure, isomerization, and dissociation of the [S₂, N, C, S]⁺ isomers – by means of MP2 and QCISD(T) (single-point) methods, focused on the relative, both kinetic and thermodynamic, stability of the linear and cyclic isomers <2002CPL(359)373>. The calculations on the MP2/6-311G(d) level of theory identified four linear isomers of the above cation to be kinetically stable and, therefore, should be experimentally observable; the known isomer SiNCS⁺ is the global minimum <2000CPL(316)243>. In contrast, no cyclic kinetically stable isomers (i.e., **27a–c**) were found, the isomers of thiaziridine having the relative highest potential energies –97.14 and 94.24 kcal mol^{−1} – for **27c** and **27b**, respectively (Figure 8) <2000CPL(316)243>.

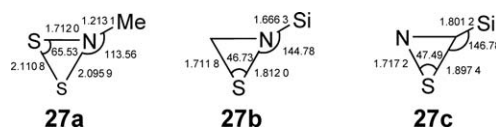


Figure 8

The kinetic stability of the linear isomers is easily explainable in terms of the smallest barriers to either their isomerization or their dissociation. Similarly, the high-lying cyclic thiaziridine isomers are kinetically unstable due to their smallest barriers to isomerization, namely 1.57 and 1.76 kcal mol⁻¹ for **27b** and **27c**, respectively. Significantly, the above theoretical results are in reasonable agreement with the results of mass spectroscopy experiments <2000PL316>.

A recent theoretical study on the potential energy surface of [HNCS₂]^{*}, using *ab initio* (G2 and G3) and DFT (B3LYP/6-31G(d,p)) calculations, have been conducted, to study the stability, heat of formation, geometries, and isomerization processes involved in the isomerization of this species <2005JST(722)217>. The potential energy minima obtained, via these calculations, were broadly classified into two types: chain-like and ring structures. Three of the latter having a three-membered thiaziridine/thiazirene backbone structure (i.e., **28a–c**) are included (based on the calculations performed) within the 26 most stable isomers of the singlet state. Significantly **28a** is planar and like its nonplanar isomer **28b** ‘belongs’ to the thiazirene class of as yet elusive compounds (i.e., **2**). It is not surprising that the thiaziridine system **28c** was found to be the most stable isomer (relative potential energy: 24.9 kcal mol⁻¹), compared with the thiazirene systems **28a** and **28b** (relative potential energy: 30.2 and 72.8 kcal mol⁻¹, respectively) (Figure 9).

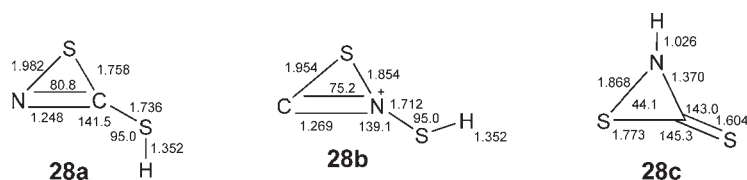


Figure 9

In summary, this study on the potential energy surface of [HNCS₂]^{*} suggests that this potential surface is rich in isomers; most of them – including the thiaziridines and thiazirenes – are quite stable with respect to dissociation or isomerization <2005JST(722)217>.

In an *ab initio* MO calculation study <1995JA2201>, it was found that the changes on rotating about the C–N bond of thiaformamide **29** are closer to those expected from the simple amide resonance picture than are those for formamide (i.e., **29a** ↔ **29b**), as shown in Figure 10.

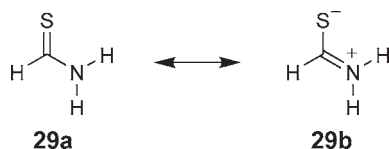


Figure 10

There is a considerable transfer of π -charge to the sulfur in the planar form, and the NH₂ resists out-of-plane bending distortions that would decrease the interaction in the dipolar canonical structure. Thus, the traditional picture of amide ‘resonance’ is more appropriate for thioamides than for amides.

If one visualizes the dipolar resonance structure **29b** as being somewhat similar to the isomeric open-ring structure of the parent thiazirene **2**, then the above results, together with those of the previously summarized computational studies, could suggest the isolability of thermodynamically stable thiazirenes.

1.13.2.2 Experimental Structural Methods

1.13.2.2.1 Thiaziridines

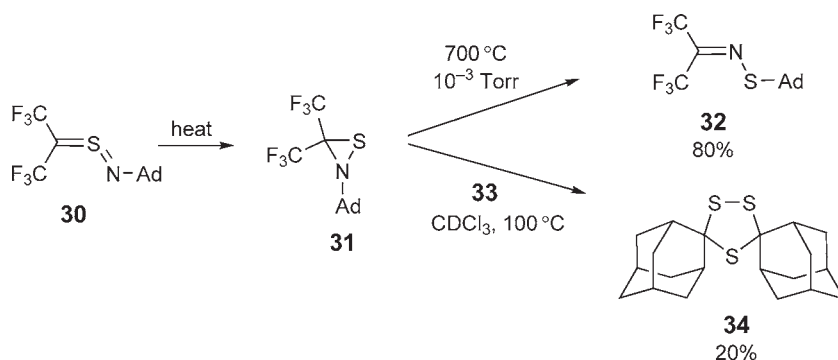
The three-membered rings **19a–d** (a: R¹ = R² = Bu^t; b: R¹ = Bu^t, R² = Ad; c: R¹ = Ad, R² = Bu^t; d: R¹ = R² = Ad) are the only thiaziridine (dioxide) systems isolated and characterized thus far. The recorded infrared (IR) and nuclear magnetic resonance (NMR) spectra of these four compounds are in full accordance with their assigned structure and are summarized in Table 1 <1981CB774, 1996CHEC-II(1A)415>.

Table 1 The IR and NMR spectra of the isolable substituted thiaziridines **19a–d**

Compound	Substituents		IR(SO ₂) (cm ⁻¹)		¹ H NMR (ppm)		
	R ¹	R ²	$\bar{\nu}_s$	$\bar{\nu}_{as}$	R ¹	R ²	3-H(s)
19a	Bu ^t	Bu ^t	1172	1320	1.33(Bu ^t)	1.13 (Bu ^t)	
19b	Bu ^t	Ad	1173	1322-1312	1.31 (Bu ^t)	1.73	2.00 (Ad)
19c	Ad	Bu ^t	1177	1307 (m)	1.68, 1.92	1.10 (Bu ^t)	
19d	Ad	Ad	1177	1323,1313 1305 (m)	2.13 (Ad) 1.72, 1.92		2.13 (Ad)

The IR spectrum of **19b** <1981CB774> is consistent with what is expected in cases of cyclic (or acyclic) sulfonamides. Further confirmation of the isolated thiaziridine dioxides was gained via the products of their thermolysis – the extruded sulfur dioxide and the remaining imines.

Reaction schemes describing the stepwise pathway from starting material(s) to intended, or unexpected, product(s) obtained have been extensively used to suggest the relevant mechanisms involved and to propose the structure of intermediate(s) along the reaction coordinate, both based on the actual reaction(s) results. Thus, in a study on the reaction of thiocarbonyl compounds with organic oxides, thiaziridines were proposed as key intermediates in the sulfur-transfer process leading to the *in situ* formation of thiocarbonyl *S*-sulfide, which further reacts to give 1,2,4-trithiolanes <1996PJC437>. Accordingly, the stable thiocarbonyl *S*-imide **30** was thermolized under flash vacuum pyrolysis (FVP) conditions expecting the formation of the thiaziridine **31** as the intermediate, which will rearrange into **32** in the gas phase. Under these experimental conditions, the only isolated product was compound **32**, as shown in Scheme 2 <1996PJC880>. In the presence of adamantanethione **33**, compound **30** afforded **34** (Scheme 2) <2002AXC231>.

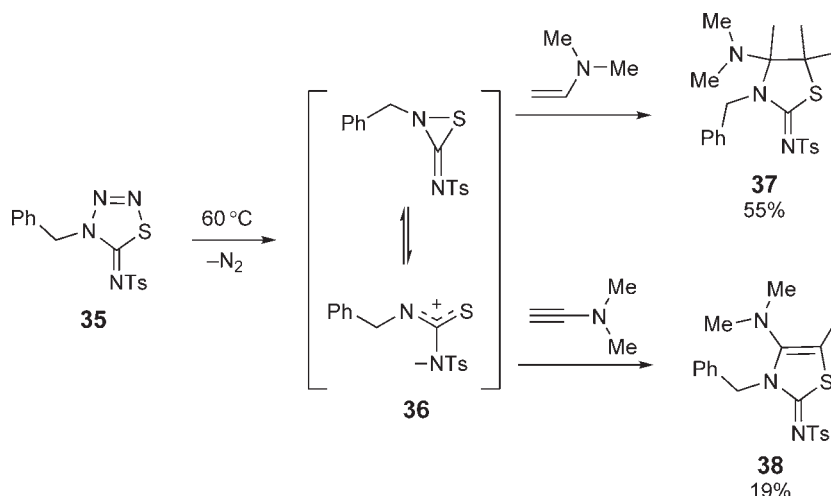
**Scheme 2**

By using ¹³C NMR spectroscopy and single crystal X-ray analysis, the previous claims for the isolation of thiaziridines <1896CB59> (see Beilstein database) were shown to be erroneous <2005JSF111>. However, although the intermediacy of thiaziridines cannot be excluded in these and similar sulfur-transfer reactions, the addition of sulfur to aldimines results in the formation of isolable thioamides as products, not thiaziridines <2005JSF111>.

1.13.2.2.2 Thiazirenes

UV spectroscopy and a polyvinyl chloride (PVC) film as matrix at 10–15 K were extensively used to detect, or to infer from the absorption spectra recorded, the intermediacy of thiazirenes **2** on thermolysis or photolysis <1978J(P1)746>.

Given the characteristic thermal instability of strained small-ring heterocycles and, consequently, their transient existence along chemical reaction coordinates, the trapping of thiazirenes appears to be the method of choice for obtaining experimental evidence (albeit indirect) concerning their structure. Such a case in point is the trapping of the thiaziridineimine **36** as shown in Scheme 3 <1974JA3973, 1975JOC1728>.



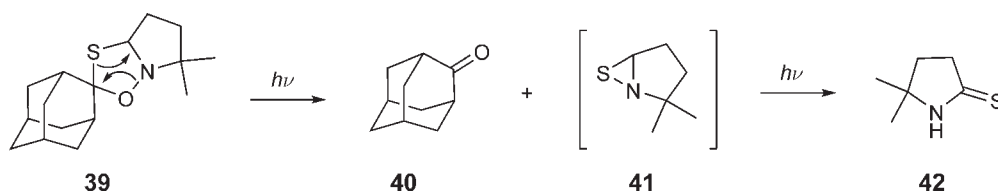
Scheme 3

The isolation and characterization of the final products **37** and **38** which contain the trapped intermediate moiety in this case and similar trappings followed by the isolation and characterization of the final products constitute very useful experimental structural methods for establishing the formation of unstable intermediates like thiaziridines and thiazirenes on various reaction coordinates.

1.13.3 Reactivity of Thiaziridines and Thiazirenes

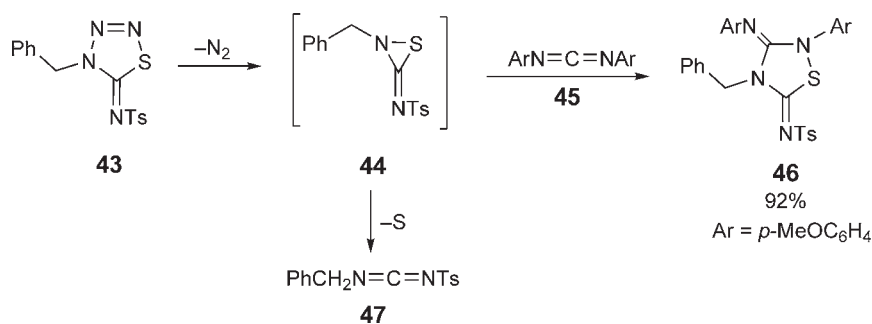
1.13.3.1 Thiaziridines as Intermediates

Up till now, the bulky groups substituted thiaziridine 1,1-dioxides **19a–d** were the only isolated compounds of this class. Yet, since the early 1970s, both thiaziridines **1** and thiaziridineimines **20** have been proposed as thermally unstable reaction intermediates based on the interpretation of the experimental results [<1970JHC415>](#). Thus, for example, photolysis of 1,4,2-oxathiazolidines (e.g., **39**) leading to thioamides (e.g., **42**) was proposed to involve the formation of a thiaziridine intermediate **41** by a concerted process, followed by photorearrangement of the thiaziridine formed to give the isolated thiolactam **42** (Scheme 4) [<1973AJC2491>](#).



Scheme 4

Thus, for example, the treatment of simple and fused oxaridines with sulfur-containing nucleophiles such as thiourea, potassium thiocyanate, potassium ethyl xanthate, potassium selenocyanate, and triphenylphosphine sulfide resulted in the formation of the related imines, most probably – in analogy to the results of the treatment of oxiranes with the same reagents – via the corresponding thiaziridine intermediate [<1973AJC2159>](#). Similarly, thermolysis of 3-benzyl-5-tosylimino-1,2,3,4-thiaziridine **43** in the presence of thione **45** furnished 1,2,4-dithiazolidine-5-imine **46** in an excellent yield. These results have been interpreted in terms of an unstable thiaziridineimine intermediate (**44**: $\text{R}^1 = \text{PhCH}_2$; $\text{R}^2 = \text{Ts}$) which is trapped by the $\text{C}=\text{S}$ compound in a regiospecific manner as depicted in Scheme 5 [<1976JHC883>](#). Thermolysis without the presence of thione **45** leads to the isolation of the sulfonyl carbodiimide **47**.

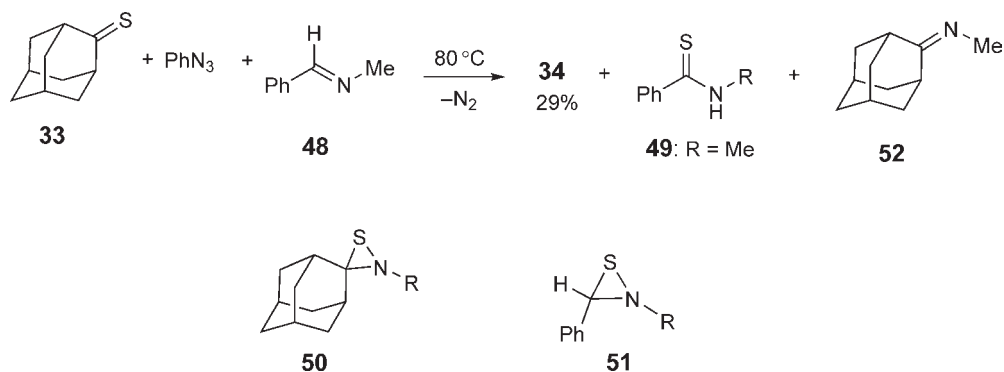


Scheme 5

It was previously shown that thiaziridines formed *in situ* as intermediates on thermolysis [<1975JOC1728>](#) or photolysis [<1983HC\(42\)333>](#) of ‘appropriately’ structured five-membered ring heterocycles can be trapped with a variety of cummulenes (e.g., ketenes, isocyanates, carbodiimides, and isothiocyanates) to give different five-membered ring heterocycles [<1975JOC1728>](#). The thiaziridines generated thermally can be easily and effectively trapped *in situ* with imines, nitriles, and thiones to provide the corresponding 1,2,4-thiadiazolidines and sulfonyl carbodiimides (e.g., **47**) in good yields.

Additional thermally induced rearrangements and/or reaction sequences leading to thiaziridine intermediates, being trapped to form isolable products, have been described and discussed in CHEC-II(1996) [<1996CHEC-II\(1A\)415>](#).

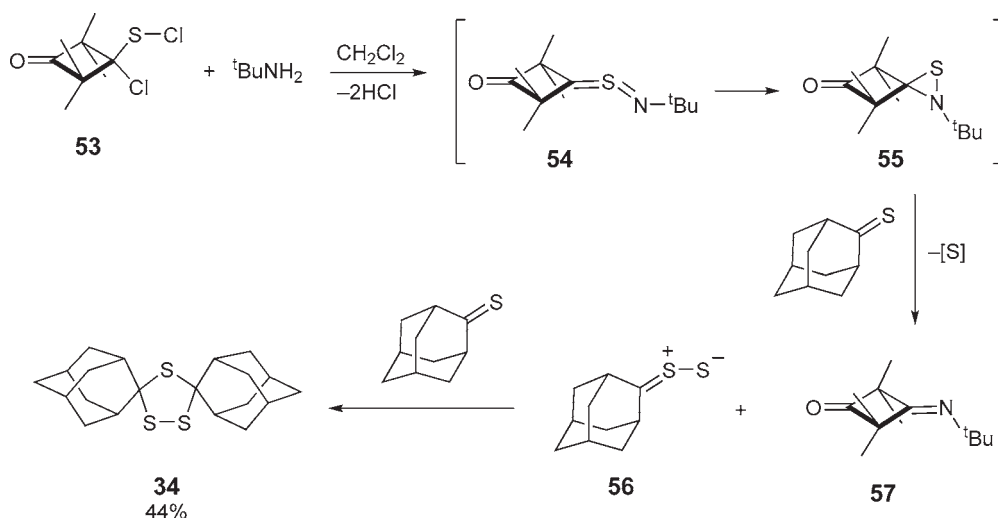
As was mentioned before, there exist only two reports in which the isolation of the corresponding thiaziridines **50** and **51** has been claimed (Beilstein database). Recently, the reaction of adamantanethione **33** with phenyl azide and the reactive sulfur acceptor, aldimine **48** (Scheme 6), was reported to afford the 1,2,4-trithiolane **34**, the thioamide **49**, and the imine **52** [<2005JSF111>](#).



Scheme 6

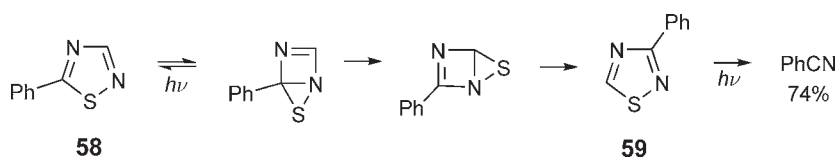
The formation of **49** is strong evidence that aldimine **48**, like other aldimines, is a reactive sulfur acceptor and that thiaziridine **51** is a likely intermediate in this reaction that undergoes an intramolecular stabilization via its ring opening accompanied by a hydrogen shift. The claimed intermediacy of thiaziridine **50** derived in this case, from ketimine **52**, cannot be denied since, if formed, it would have been subjected to a sulfur extrusion.

A closely related recent study [<2006HCA1042>](#) reported that the initially generated sulfinimide **54** from the reaction of α -chlorosulfonyl chloride **53** with *tert*-butylamine was trapped with adamantanethione, apparently via the intermediacy of the three-membered thiaziridine **55** (Scheme 7). This is analogous to, and in full agreement with, the interpretation of the results of the previous study – summarized in Scheme 7 – in terms of the intermediacy of the thiaziridines **50** and **51** [<2005JSF111>](#). Only compound **34** and decomposition products were ultimately obtained.



Scheme 7

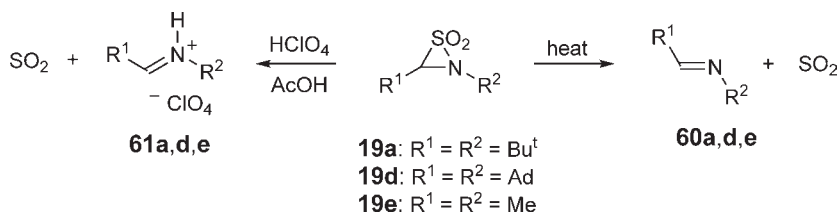
Finally, the formation of a 3-phenyl-1,2,4-thiadiazole **59** in the irradiation of 5-phenyl-1,2,4-thiadiazole **58** was proposed to undergo through the intermediacy of two consecutively formed bicyclic thiazirenes (**Scheme 8**) <2003JOC4855>.



Scheme 8

1.13.3.2 Thiaziridine 1,1-Dioxides

The only direct study of the chemical reactivity of the thiaziridine system was conducted on the thiaziridine 1,1-dioxide system **19**, the only thus far isolable compounds of the thiaziridine series. As could be predicted and in line with theoretical considerations, thermolysis of alkyl-substituted thiaziridine 1,1-dioxides **19a,d,e** afforded aldimines **60a,d,e** as a result of the cheletropic extrusion of the sulfur dioxide moiety (**Scheme 9**) <1981CB774>. Treatment of these thiaziridine 1,1-dioxides with perchloric acid has also resulted in the loss of sulfur dioxide with the concomitant formation of the corresponding ammonium perchlorate salts **61** <1981CB774>.



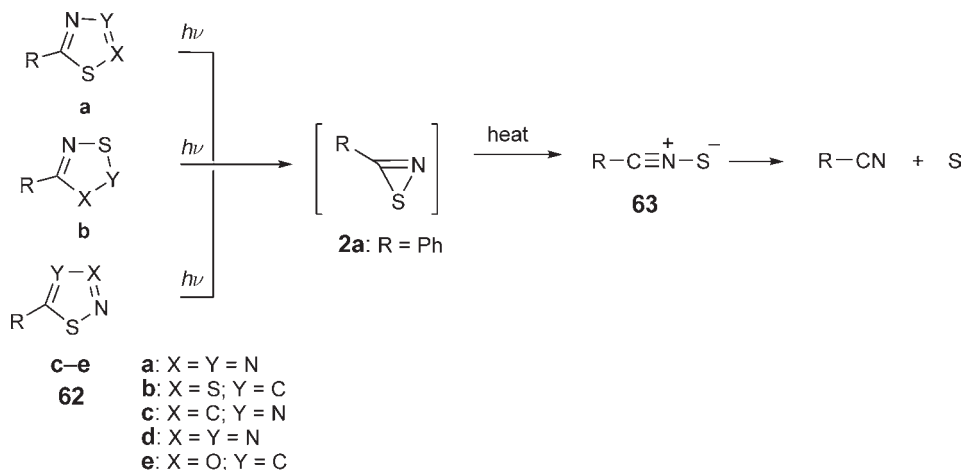
Scheme 9

In both cases, the driving force for the reactions to take place easily is the high initial energy content of the three-membered thiaziridine system. Similar results were obtained with the analogous thermodynamically more stable thiadiaziridine 1,1-dioxide system <1977CB1780>.

1.13.3.3 The Intermediacy of Thiazirenes

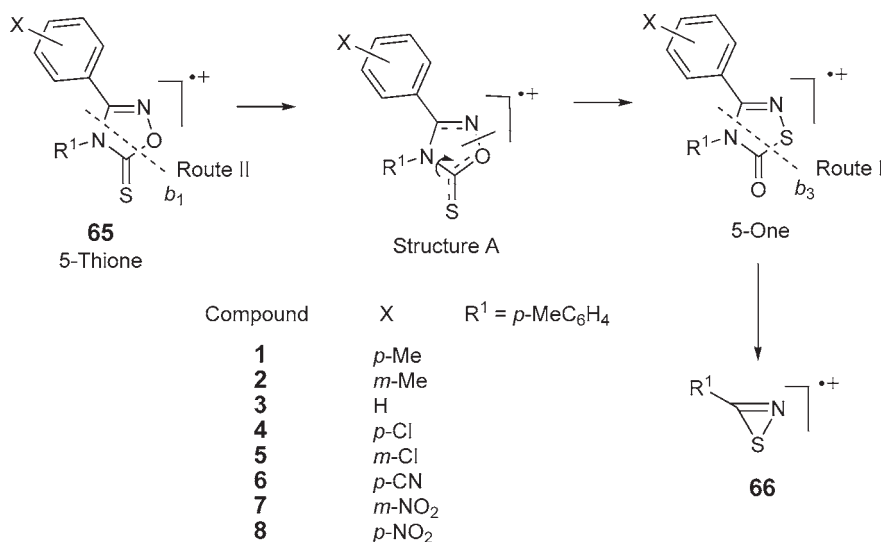
Thiazirenes are planar cyclic systems containing 4π -electrons in a cyclic array thus constituting antiaromatic compounds <1996CHEC-II(1A)415>. Consequently, their preparation and experimental detection should be possible only at very low temperatures.

In analogy with the matrix isolation and characterization of thiirene and selenirene <1977JA4842, 1978JOC2490>, a number of five-membered heterocyclic isomers of type **62a–e** were irradiated at 10–15 K to produce the thermally labile nitrile sulfides **63** (Scheme 10), most probably through the intermediacy of the three-membered ring thiazirenes **2** <1996CHEC-II(1A)415>.



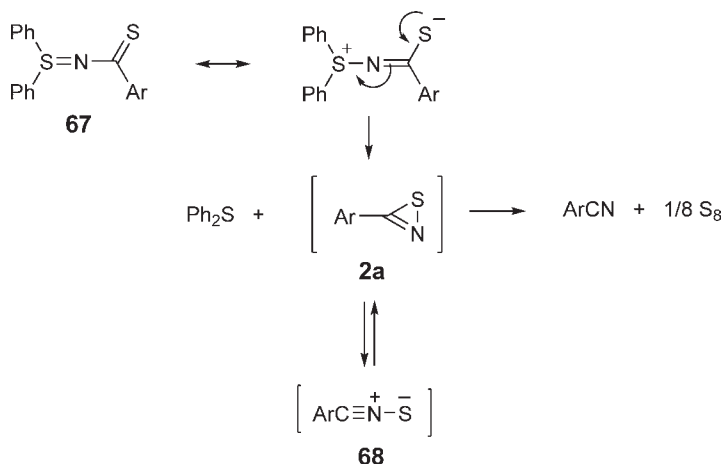
Scheme 10

Interestingly, the initially formed thiazirene (claimed to be stable at the irradiation/matrix temperature <1978J(P1)746>) rearranges above this temperature (10–15 K) to the corresponding nitrile sulfide (i.e., **2**; R = Ph, Scheme 10) and only then loses sulfur to give the benzonitrile. The cheletropic extrusion of sulfur from the postulated thiazirene formed, leading directly to the nitrile, was not observed. However, recent electron ionization mass spectral study of 1,2,4-oxadiazole-5(4*H*)-thiones **64** revealed a fragmentation pattern of the 3,4-disubstituted-5-thiones **65** in which the peak of the elusive thiazirenes **66** is clearly identified (Scheme 11) <2001JMP754>.



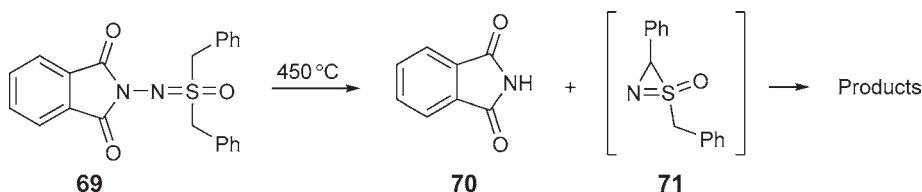
Scheme 11

The thermal decomposition of *N*-thiocarbonyl diphenylsulfimides **67** which results in the isolation of nitriles (or their derivatives) was suggested, on the basis of the kinetic experiments, to proceed via the intermediacy of the arylthiazirene **2a** and nitrile sulfide **68** (Scheme 12) <1996CHEC-II(1A)415>.



Scheme 12

Thermolysis of the dibenzylsulfoximide **69** resulted in an N–N bond cleavage and formation of phthalimide **70** as the only product identified. The resultant sulfur-containing products generated in this hydrogen-transfer process originated in the ring sulfoximide **71** (Scheme 13) <1972JCP(P1)1317>.



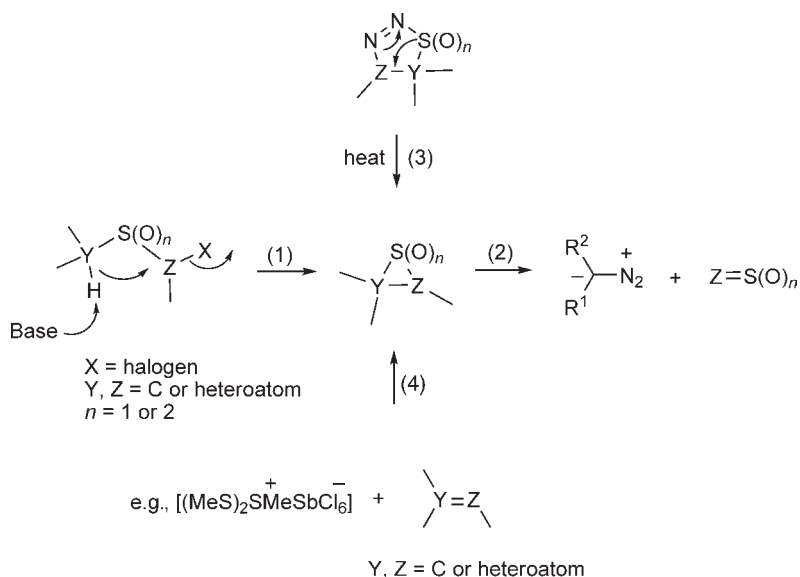
Scheme 13

1.13.4 Synthesis of Thiaziridines and Thiazirenes

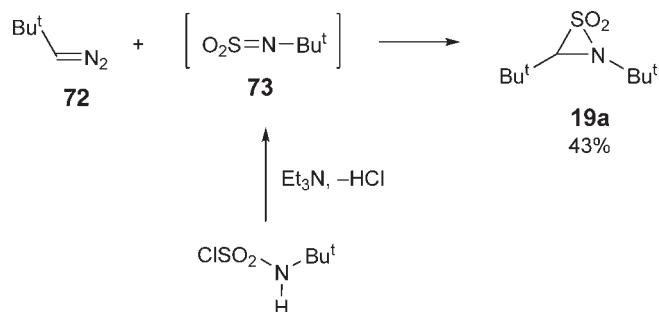
1.13.4.1 Synthesis of Thiaziridine 1,1-Dioxides

Just a score of ‘general’ methodologies are available for the preparation and isolation of three-membered ring heterocycles containing two heteroatoms; they are summarized in Scheme 14: (1) base-induced elimination of HX <1979JA390>; (2) the Staudinger approach for the preparation of aryl-substituted thiirene oxides, and dioxides, in which a diazo compound reacts with a sulfur double bond; (3) thermolysis of five-membered ring heterocycles containing both the expected three-membered ring moiety and two additional adjacent nitrogen atoms to be expelled as molecular nitrogen with concomitant formation of the targeted compound; and (4) the use of sulfur transfer agents which add sulfur to multiple bonds for which the successful synthesis of the three-membered thiirenium ions is a good example <1977TL911, 1996CHEC-II(1A)415>.

In fact, route (1) (Scheme 14) did not yield isolable thiaziridine 1,1-dioxides <1981CB774>. The only thiaziridine 1,1-dioxides **19a–d** known were synthesized by reacting diazoalkanes **72a** and **72b** with *N*-sulfonyl amines **73a** and **73b** generated *in situ* by hydrogen chloride elimination from the corresponding sulfamoyl chlorides with triethylamine at -78°C . If the workup temperature was kept below -30°C , the targeted thiaziridine dioxides **19a–d** were obtained in 32–47% yield <1974AGE742, 1981CB774>, as presented in Scheme 15 for the first prepared thiaziridine dioxide **19a** <1974AG816>.



Scheme 14



Scheme 15

The thiaziridine dioxide **19a**, which crystallizes as colorless needles from pentane at -78°C , is thermally unstable and easily decomposes quantitatively to sulfur dioxide and azomethine **74**.

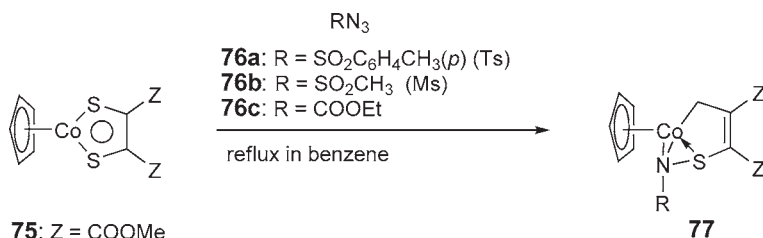
The IR and NMR spectra of **19b** correspond to the assigned structure (see [Table 1](#)).

A metalladithiolene ring is a very interesting conjugated 6π -electron system, which, in some cases, behaves as an aromatic ring, or undergoes additional reactions due to unsaturation [\[1999BCJ879, 1997CL807\]](#). Organic azides react with cobaltadithiolenes in the fashions, one of which is the bridging between Co and S by imide group. Thus, substituted imidobridged cobaltathiaziridines **77a–c** have been prepared in the reactions of disubstituted cobaltadithiolene **75** with various azides (**77a–c**; [Figure 11](#)) [\[2000JOM\(611\)376\]](#). Significantly, **77a–c** are isolable, stable organometallic thiaziridine compounds.

1.13.4.2 Attempted Synthesis of Thiazirene 1,1-Dioxides

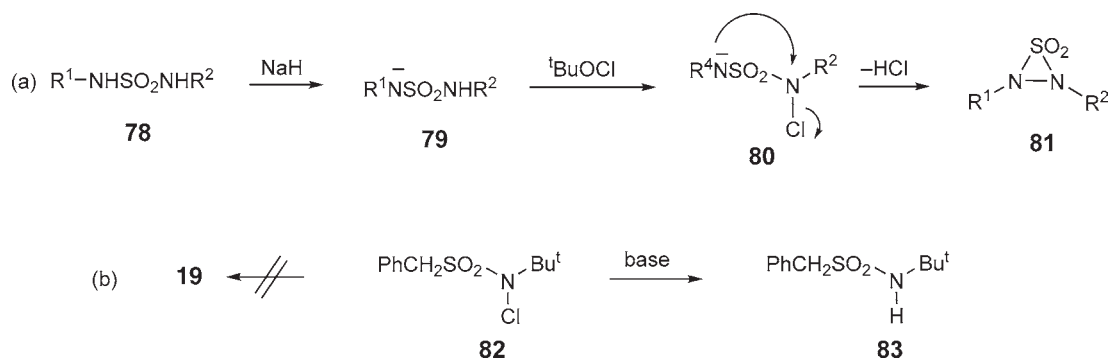
All known thiadiaziridine dioxides **81** have been prepared by essentially the same method as depicted in [Schemes 16\(a\) and 16\(b\)](#) [\[1973JA634, 1996CHEC-II\(1A\)415\]](#).

All attempts to apply the same methodology for the synthesis of the thiazirene 1,1-dioxide system failed [\[1974AGE742, 1974JOC1817, 1981CB774\]](#). Thus, for example, the treatment of the *N*-chloro compound **82** with triethylamine in methylene chloride, or with potassium *t*-butoxide in ether, afforded, after workup, only the reduction product **83**, not the expected thiazirene 1,1-dioxide ($\text{R}^1 = \text{Bu}^t$, $\text{R}^2 = \text{Ph}$; [Schemes 16\(a\) and 16\(b\)](#) [\[1974JOC1817, 1983HC\(42\)333\]](#).



Compound	Reaction time (h)	Yield (%)
77a: R = SO ₂ C ₆ H ₄ CH ₃ (<i>p</i>) (Ts)	2	78
77b: R = SO ₂ CH ₃ (Ms)	5	76
77c: R = COOEt	24	64

Figure 11



Scheme 16

Attempted synthesis of the elusive thiazirene 1,1-dioxide system **2** using this methodology was unsuccessful as far as the actual isolation of either the thiaziridine intermediate or the targeted thiazirene. However, the isolation of benzonitrile as the product of the reaction of α,α -dibromobenzylsulfonamide with triethylamine or potassium *t*-butoxide constitutes clear-cut evidence for the intermediacy of the thiazirene 1,1-dioxide along the reaction coordinate <1974JOC1817, 1996CHEC-II(1A)415>.

1.13.5 Conclusion

This chapter constitutes a walk on the trail of the fascinating and stimulating sulfur- and additional-heteroatom-containing, three-membered ring systems, which are the result of 35 years of efforts by the chemical community. Although much has been accomplished thus far, including the preparation, isolation, characterization, and studying representative prototypes of these labile species, a substantial amount of work remains to be done in this area. The challenge is there, since (1) many of these systems have been elusive and their existence has been inferred only indirectly or circumstantially; and (2) except for the recently synthesized cobaltathiaziridines, no new thermodynamically stable thiaziridines or thiazirenes have been prepared in the last decade.

In view of the recent success in synthesizing thermally and chemically sensitive compounds, and based on the accumulated data and experience gained, it is to be expected that hitherto-unknown three-membered rings containing sulfur and additional heteroatoms will be successfully synthesized, characterized, and thoroughly studied in the near future.

The significance of such studies is fourfold: (1) realization of the synthesis of hitherto-unknown, difficult-to-prepare novel heterocycles which are of particular theoretical and/or biological–medicinal importance; (2) contribution to the understanding of the factors which determine the structure, limits of bonding (including d orbital bonding

of sulfur), accessibility, and chemical properties – including acidity – of small-ring sulfur heterocycles; (3) development of novel and effective synthetic strategies and obtaining of data which will facilitate the correlation of theoretically based expectations with observable properties and thus enhance the understanding of heterocyclic chemistry in general and the chemistry of small-ring heterocycles in particular; and (4) gaining insight into anti-aromaticity and small-ring heterocycle carbanion chemistry, via fundamental basic research.

Relevant Website

<http://www.beilstein-institut.de> – Beilstein Database, Beilstein Institute.

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Biographical Sketch



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1.14

Three-membered Rings with Two Oxygen and/or Sulfur Atoms

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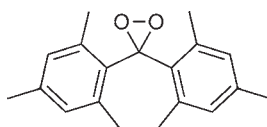
1.14.1 Introduction

Since CHEC(1984) and CHEC-II(1996) <1996CHEC-II(1A)429> have been published, important facts have been elucidated about all three title heterocyclic systems, namely dioxiranes **1**, oxathiiranes **2**, and dithiiranes **3**. In the last 10 years, papers published in the field of the title categories are largely dominated by the articles dealing with dioxirane chemistry.

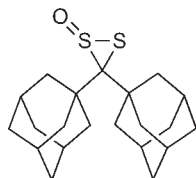
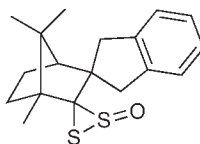
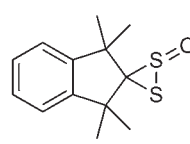
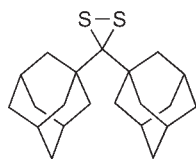
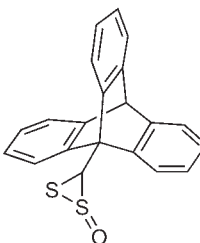
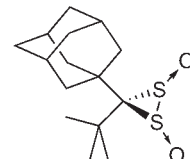
**1****2****3****a:** $R^1 = R^2 = H$ **b:** $R^1 = R^2 = CH_3$ **c:** $R^1 = CH_3; R^2 = CF_3$ **a:** $R^1 = R^2 = H$ **b:** $R^1 = CH_3; R^2 = H$ **c:** $R^1 = R^2 = CH_3$

The immense literature sources about the usage of dioxiranes as powerful and selective oxidants are focused in two main reactions: the epoxidation reaction, and carbon–hydrogen insertion reaction, thus reflecting general research interest. Particular progress has been made in the field of asymmetric variants of these reactions where excellent ee's have been achieved. Numerous chiral dioxiranes have been derived from parent chiral ketones as efficient intermediates in asymmetric epoxidations and C–H insertion reactions. Several reviews covering chiral ketone-catalyzed epoxidations reactions have appeared <1999SL847, 2000S1979, 2004ACR488, 2004ACR497>. A general review covering the chemistry of dioxiranes has also appeared <1999RCR253>.

Important progress in the structural elucidation of dioxiranes has been made by solving the very first crystal structure of the isolable and stable dioxirane **4** <1997JA7265>.

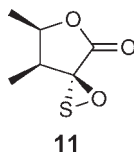
**4**

The chemistry of dithiiranes **3** has been centered on fundamental organosulfur chemistry, and new structures, **5** <1998TL3525>, **6** <1999CL695>, **7** and **8** <2003JOC1555>, **9** <2005T6693>, and **10** <2006OL91>, have been synthesized and confirmed by X-ray analysis.

**5****6****7****8****9****10**

A review by Nakayama and Ishii concerning the chemistry of small rings containing two sulfur atoms, one of the rings being dithiiranes, has been published <2000AHC221>.

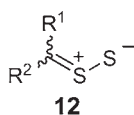
In the period covered by this edition, oxathiiranes are almost exclusively mentioned as possible intermediates <1996T1961, 1998T15027, 1998TL8983, 1998JA8914, 1999T10341, 2000OL2519, 2002JA8316, 2003EJO4012>. Only one paper reported infrared (IR) characterization of the intermediary oxathiirane **11** in an argon matrix at 10 K <2006EJO2918>.



1.14.2 Theoretical Methods

1.14.2.1 Dithiiranes

Conrotatory electrocyclic ring closure of thiosulfine **12a** to the energetically favored dithiirane has been investigated as a part of a theoretical study of a series of dicoordinated sulfur organic compounds, using post-Hartree–Fock (MP2, quadratic configuration interaction with single and double excitations (QCISD), and QCISD, and triple excitations added perturbatively (QCISD(T))) a6d multiconfiguration methods (complete active space self-consistent field (CASSCF), CASPT2) <1997JST(398)411>. Relative energies of the CH₂S₂ isomers, including the parent dithiirane **3a** and their radical cations, have been calculated at the B3LYP/6-31+G** level, providing support of experimental observations in the neutralization–reionization mass spectrometry experiment <1999PCA5123>. These calculations predicted that the parent dithiirane **3a** is less stable than corresponding dithioformic acid by 8.24 kcal mol^{−1}. A computational study (B3LYP/aug-cc-pVDZ and MP2/6-31+G*) on the effect of ring strain of small cyclic disulfides including **3a** in the reaction with HS[−] has been conducted to determine the reaction mechanism <2002JOC8983>. The ring-strain energy for parent dioxirane **3a** has been determined using the group-equivalent approach and is about 19 kcal mol^{−1}. Relative energies of methyldithiirane **3b**, dimethyldithiirane **3c**, methylthiosulfine **12b**, and dimethylthiosulfine **12c**, by using B3LYP hybrid functional with 6-31+G** basis set, have been calculated in order to explain the different behaviors of **12a** and **12c**. The authors have also calculated UV and IR spectra of studied compounds and compared them with the measured ones <2006EJO3721>.



a: R¹ = R² = H

b: R¹ = H; R² = CH₃

c: R¹ = R² = CH₃

Decomposition mode of dithiirane *trans*-1,2-dioxide **10** has been studied by density functional theory (DFT) calculations <2006OL91>.

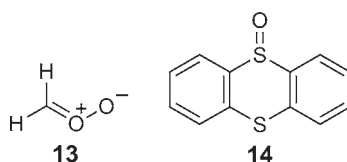
1.14.2.2 Oxathiiranes

O'Sullivan *et al.* reported FT-B3LYP/6-31G(d,p) geometry calculations of the different stereoisomers and conformers of the oxathiirane **11** as well as calculation of their IR spectra <2006EJO2918>. Different stereoisomers and conformers are possible depending on the position of the methyl groups (pseudoequatorial or pseudoaxial) and the position of the oxygen and sulfur atoms relative to the ring system. The calculated spectra for these different stereoisomers and conformers showed a strong absorption in the carbonyl region between 1897 and 1895 cm^{−1} and a slightly different pattern of bands in the region between 1200 cm^{−1} and 700 cm^{−1}.

1.14.2.3 Dioxiranes

1.14.2.3.1 General aspects

Lay and Bozzelli have calculated the value of enthalpy of formation $\Delta H^\circ_{f298} = -2.91 \pm 1.34 \text{ kcal mol}^{-1}$ of the parent dioxirane **1a** by using *ab initio* method at the G2 level of theory <1997CPL(268)175>. The strain energies for the dioxirane **1a**, as well as few substituted derivatives, namely dimethyldioxirane (DMDO) **1b**, difluorodioxirane, and methyl(trifluoromethyl)dioxirane (TFDO) **1c**, have been calculated by several *ab initio* orbital calculation methods using high-level computational schemes (G2, G2(MP2), complete basis set (CBS-Q)) <2002JOC3884>. In numerous publications, interesting aspects of carbonyl oxide chemistry such as cyclization to dioxiranes <1997JPO787, 2000JST(530)97, 2001JMM70, 2002CPH(285)221>, and the oxygen-donor potential <1999JST(492)165>, have been the focus of theoretical calculations. Performed calculations predicted that the parent dioxirane is 24–29 kcal mol⁻¹ more stable than the isomeric carbonyl oxide **13**, and that both forms can exist as distinct species divided by the activation energy as high as 18–24 kcal mol⁻¹ <1996JA4636>. Bach *et al.* have successfully used the B3LYP method to locate the *spiro* structures for oxygen-donation reactions <1997JPC6092>. Investigation of the relative stabilities of the zwitterionic forms derived from parent dioxirane have been carried out by high-level *ab initio* calculations using the Gaussian 94 program package <1998JST433217>. The peroxy acid–dioxirane equilibrium and base-promoted exchange of peroxy acid oxygens has been studied at the B3LYP/6-31G(d) level of theory, and the results suggested that under basic conditions an alkoxy dioxirane is in equilibrium with the peroxy acid <2000JA11272>. The ring opening of dioxirane has been studied with success by combination of DFT with multiconfiguration methods – CAS-DFT <2000CPL(316)569>. The density functional study has been carried out to understand the origin of the chemo- and stereoselectivity in the oxidation of thianthrene 5-oxide **14** by dioxirane <2001JOC2686>. The results of this study suggest that the probe **14** indicates that dioxiranes are more electrophilic in the reaction than they actually are. In the context of the theoretical electron density study of the peroxo function in transition metal complexes, the analysis of electron density in O–O single bond of 1,1-difluorodioxirane has been performed <2001PCA9231>.



1.14.2.3.2 The epoxidation reaction

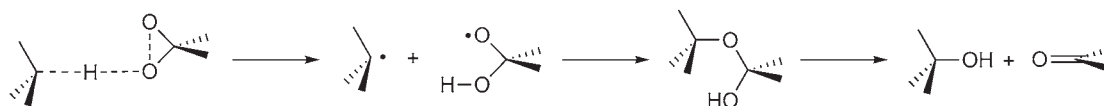
Detailed theoretical study at semi-empirical MO level with AM1 and PM3 hamiltonians on the epoxidation of ethylene by DMDO **1b** and TFDO **1c**, and *cis/trans*-1,2-dichloroethene and allene by DMDO, has revealed a spiro transition structure and that peroxide bond σ^* -level takes part at a very early stage in the reactions <1997JST(394)41>. Freccero *et al.* have located transition structures of the reactions of the parent dioxirane **1a** and DMDO **1b** with ethene, propene, *cis*- and *trans*-butene by B3LYP/6-31G* method <1998T6123>. Liu and Houk have used Hartree–Fock theory with the 3-21G* basis set to study epoxidation reactions of isobutene and α -methylstyrene by DMDO **1b** <1998JOC8565>. Computational results were found to be in a good agreement with experiment revealing a molecule-assisted homolysis pathway unlike for the reaction of alkenes with **1b**. Theoretical study of the transition state in alkene epoxidations suggests a marked stereoelectronic preference of fluorinated dioxiranes as electrophilic reagents <2000JA6297>. An intriguing theoretical study of C₆₀ epoxidation by DMDO **1b**, TFDO **1c**, and bis(trifluoromethyl)dioxirane has been performed by the AM1 method, revealing the expected spiro transition state <2000JOC1093>. In order to rationalize the activity of dioxiranes in alkene-epoxidation reactions, frontier orbital interaction approach has been applied, and the DFT method used to calculate barrier heights <2001JPO328>. Solvent effects have been found to reduce the activation energies calculated for alkene epoxidation by dioxiranes in the gas phase <2001EJO719>. A two-layered our own N-layered integrated molecular orbital and molecular mechanics (ONIOM) (B3LYP/6-31G*:AM1) approach has been used to predict the sidewall epoxidation of single-walled carbon nanotubes (SWNTs) with dioxiranes, and the method was found to be viable <2003OL3527>. Calculations have also been made to compare the calculated gas-phase activation barriers, $\Delta E^\ddagger$, for the epoxidations of ethene with DMDO **1b** and performic acid <2003JA924>. Dmitrenko and Bach have performed high-level *ab initio* and CASSCF calculations on the epoxidation of ethene with dioxirane and DMDO to distinguish between a symmetrical versus unsymmetrical spiro orientation of the dioxirane in the transition structure for oxygen atom transfer <2004PCA6886>.

1.14.2.3.3 The carbon–hydrogen insertion reaction

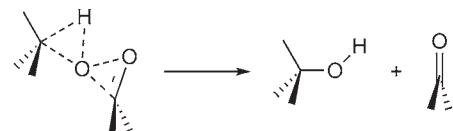
In the period covered by this edition, the hypothesis of a concerted process in the C–H insertion reaction has been challenged by a stepwise mechanism with groups both *pro* and *contra* (Scheme 1). A number of computational studies appeared applying different levels of theory on different model systems. A minireview covering selective alkane C–H bond functionalizations has also appeared <2004MI247>.



Minisci's radical pair formation mechanism:



Curci–Adam's concerted mechanism:



Scheme 1

Bach and co-workers reported a high-level *ab initio* study on the oxidations of methane, propane, and isobutane with dioxirane **1a**, DMDO **1b**, difluorodioxirane, and TFDO **1c** <1998JA10528>. The computational study provided a rationale for the formation of products resulting from free radical intermediates in the absence of dioxygen, and supports the generally accepted, highly exothermic, concerted oxygen-insertion mechanism for the oxidation of alkanes with dioxiranes. The barriers for the oxidation of alkanes were calculated using the B3LYP/6-311+G(3df,2p)//B3LYP/6-311+G(3df,2p) and CCSD-(T)/6-31G*//B3LYP/6-31G* levels of theory. It is interesting to note that at G2 level, C–H bond homolysis was found to be thermodynamically unfavorable in hydrogen-abstraction reactions of alkanes with dioxiranes. Further frontier molecular orbital (FMO) calculations and experimental results were done in the oxyfunctionalization of Binor **S 15** with dioxiranes **1b** and **1c** <2001JOC9063>. As a model of the oxidation of peptides, Shustov and Rauk <1998JOC5413> applied *ab initio* methods to study the mechanism of the oxidation of the C–H bonds in homo- and heterosubstituted alkanes by parent dioxirane. The results of this study suggest a new mechanism of the dioxirane oxidation of aliphatic C–H bonds that comprises bimolecular electrophilic interaction between C–H bond and the dioxirane. Much controversy comes with mechanisms proposed for the C–H bond-insertion reactions as there is evidence for both radical and nonradical pathways. The concerted mechanism prevails in most of the studies and is supported by the stereoselectivity <1997CEJ105>, high regioselectivity <1996AG(E)217>, kinetics <1996TL249>, and primary isotope effects <1997TL2373>. On the other hand, the radical mechanism is supported by the formation of some radical-derived products in these reactions <1995TL1697> whose formation was inhibited by the presence of oxygen or other radical traps <1995CC1573>. Minisci *et al.* <1998JOC254> proposed a ‘molecule-induced homolysis’ mechanism, where a radical pair intermediate is formed in one single step, without prior homolysis of the O–O bond. That mechanism has been further investigated on a set of propellanes both experimentally and computationally at the B3LYP/6-311+G**//B3LYP/6-31G* DFT level of theory <2001JA11248>. The oxygen insertion by parent dioxirane **1a** and cyanodioxirane into different alkanes (methane, ethane, propane, and isobutene) has been investigated using theoretical calculations (Becke3LYP hybrid DFT with the 6-31G* basis set), revealing the concerted electrophilic mechanism with a diradical character transition state <1998JOC6480>. Sarzi-Amadè and co-workers reported the study of oxygen insertion into the isobutene C–H bond by DMDO **1b** at the R(U)B3LYP level, supporting the radical pair formation in the reaction <2001TL2739>.

The same authors published a detailed report on the calculations of the oxygen insertion into unactivated C–H bonds by dioxiranes using DFT theory and on comparison of the transition structures for stepwise routes via radical pairs with the concerted pathway [<2003JOC811>](#). The articles dealing with the mechanism of OH formation from ozonolysis of isoprene and α - and β -pinene provide DFT and *ab initio* calculation results also for the dioxirane formation [<2001CPL\(358\)171, 2002JA2692, 2005JCP114308>](#).



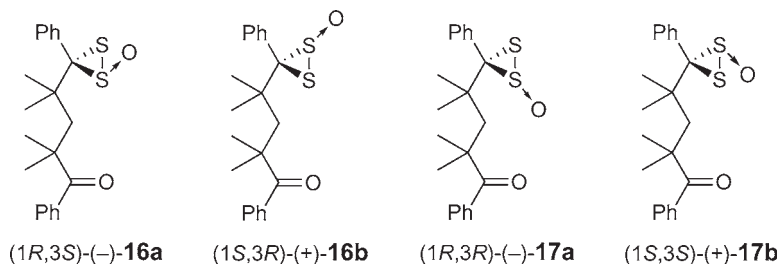
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1.14.3 Experimental Structural Methods

1.14.3.1 Dithiiranes

1.14.3.1.1 X-Ray diffraction

After CHEC-II(1996), more new stable dithiiranes **3** and dithiirane *S*-oxides have been characterized using X-ray single crystal structure analysis. This method has also been used to determine the absolute configuration of resolved enantiomers of **16**, previously known and characterized by X-ray only as a racemic mixture [<1997T12203>](#). (The assignment of the absolute configuration of enantiomers of **17** is discussed in [Section 1.14.4.1](#)).



The bond lengths and bond angles found in the enantiomers of **16** are comparable with those found in other dithiirane *S*-oxides. In the case of dithiirane **8**, the S–S bond length of 2.047(2) Å is shorter by 0.051 Å than that of the corresponding dithiirane 1-oxide **5** having 2.098(1) Å [<2003JOC1555>](#). Unusual bond angles were found in stereoisomeric dithiirane oxides **6** due to steric reasons. The X-ray analysis of an isomer of **6** revealed an S(1)–C(10)–S(2) bond angle of 70.4°, which is much smaller than those of the reported S–C–S bond angles of nonstrained cyclic dithioacetals [<1999CL695>](#). Also, in the case of the dithiirane 1-oxide **5**, the C(1)–C(2)–C(3) bond angle was found to be expanded to as large as 123.6° because of repulsion between two sterically demanding 1-adamantyl substituents connected to the three-membered dithiirane ring [<1998TL3525>](#). The crystals are triclinic for **16a** and **16b**, monoclinic for **5** [<1998TL3525>](#), **6** [<1999CL695>](#), **7** [<2003JOC1555>](#), **9** [<2005T6693>](#), and **10** [<2006OL91>](#), and orthorhombic for **8** [<2003JOC1555>](#).

1.14.3.1.2 Spectroscopic studies

1.14.3.1.2(i) NMR spectroscopy

^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic data for all indicated dithiiranes have been reported and important chemical shifts are collected in [Table 1](#). The configurations of the sulfinyl sulfur of **18** and **19** have been assigned by comparison of the chemical shifts of the geminal methyl groups with those of known *cis*- and *trans*-dithiirane *S*-oxides [<1995TL1867>](#).

In the case of **19c**, there is evidence of coupling between the dithiirane ring carbon and the *meta*-fluoro substituent on the phenyl ring (S–C–S, $^4J_{\text{C-F}} = 2$ Hz). ^1H NMR analysis was used for assignment of (*E*)- and (*Z*)-isomers of dithiirane *S*-oxides **5** and **20** based on the anisotropy of the S=O group [<1998TL3525>](#). This assignment has also been supported by aromatic solvent and Eu(fod)₃-induced shift studies (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadione). The anisotropic effect of the S=O group has also been used to distinguish *cis*-**9** from *trans*-**9** since the low-field shift in *trans*-**9** is due to the anisotropic effect being *cis* to the proton [<2005T6693>](#). It is interesting to note

Table 1 Spectroscopic data and melting points for dithiiranes

<i>Compound</i>	¹ <i>H</i> <i>NMR</i> δ (ppm)	¹³ <i>C NMR</i> <i>ring carbon</i> δ (ppm)	<i>UV</i> $\lambda_{\max}$ (nm)	<i>CD</i> $\lambda_{\max}$ (nm) (θ , (deg cm ² dmol ⁻¹) (c , mol dm ⁻³ , <i>solvent</i>)	<i>IR</i> $\bar{\nu}$ (cm ⁻¹)	<i>Melting</i> <i>point</i> <i>t</i> (°C)	<i>Specific optical</i> <i>rotatory power</i> [α] _D (10 ⁻¹ deg cm ² g ⁻¹) (γ , g cm ⁻³ , <i>solvent</i>)	<i>References</i>
18a		81.37 ^a			1664, 1222 ^b			1995TL1867
18b		80.72 ^a						1995TL1867
19a		85.59 ^a			1671, 1126 ^b			1995TL1867
19b		85.25 ^a			1673, 1126 ^c	93–94 (dec.)		1995TL1867
19c		85.12 ^a			1674, 1244, 1124 ^c			1995TL1867
39		85.8 ^d	453 ^c					1997TL1431
40b		88.7 ^d						1997TL1431
40a		88.7 ^d						1997TL1431
(±)-16						124–125 (dec.)		1997T12203
16a^f				307 (−4.5 × 10 ³), 270 (4.4 × 10 ³), −229 (7.2 × 10 ⁴) (1.1 × 10 ⁻⁴ , hexane/ethanol 98/2)		112–115 (dec.)	−210 (0.305, CHCl ₃)	1997T12203
16b^f				306 (3.7 × 10 ³), 270 (−4.6 × 10 ³), 229 (6.3 × 10 ⁴) (1.1 × 10 ⁻⁴ , hexane/ethanol 98/2)		112–113 (dec.)	+226 (0.305, CHCl ₃)	1997T12203
17						110–114 (dec.)		1997T12203
17a						104–106 (dec.)	Negative sign	1997T12203
17b						107–109 (dec.)	+98 (0.100, CHCl ₃)	1997T12203
<i>cis</i> - 5		86.2 ^a			1120 ^c	106–107 (dec.)		1998TL3525, 2000JOM(611)127
<i>trans</i> - 5		87.7 ^a			1123 ^c	99–100 (dec.)		1998TL3525, 2000JOM(611)127
20		87.4 ^a			1118 ^c	143–144 (dec.)		1998TL3525, 2000JOM(611)127
3a					2987(m), 1412(w), 1053 (m), 928(m), 581(s) ^g			2001AGE393

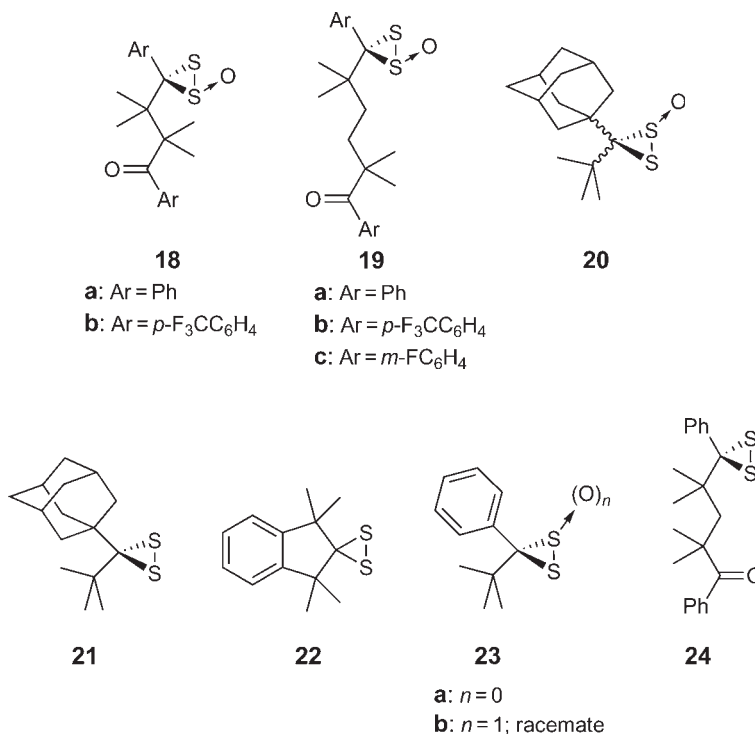
(Continued)

Table 1 (Continued)

<i>Compound</i>	¹ <i>H</i> <i>NMR</i> δ (ppm)	¹³ <i>C NMR</i> <i>ring carbon</i> δ (ppm)	<i>UV</i> λ_{max} (nm)	<i>CD</i> λ_{max} (nm) (θ , (deg cm ² dmol ⁻¹) (c , mol dm ⁻³ , <i>solvent</i>)	<i>IR</i> $\tilde{\nu}$ (cm ⁻¹)	<i>Melting</i> <i>point</i> t (°C)	<i>Specific optical</i> <i>rotatory power</i> [α] _D (10 ⁻¹ deg cm ² g ⁻¹) (γ , g cm ⁻³ , <i>solvent</i>)	<i>References</i>
23b		86.2 ^d			1118 ^c	62–64		2001AGE1924
179		90.0 ^d			1123 ^c	81–83		2001AGE1924
21		84.7 ^d	452			92–93		2003JOC1555
8		86.2 ^d	454		541	136–139 (dec.)		2003JOC1555
23		79.0 ^d	451					2003JOC1555
7		89.0 ^d			1098 ^c	103–104 (dec.)		2003JOC1555
22		88.4 ^d	455					2003JOC1555
<i>trans</i> - 9	5.49 ^d	66.9 ^d			1460, 1128 ^c	186–187 (dec.)		2005T6693
<i>cis</i> - 9	4.98 ^d	66.7 ^d			1462, 1130, 1122, 752 ^c			2005T6693
10		106.9 ^d			1064, 1084, 1114 ^c	95 (dec.)		2006OL91

^aSolvent not specified.^bNeat.^cKBr.^dCDCl₃.^eCH₂Cl₂.^fNeither chemically nor optically pure; see reference for details.^gArgon matrix, 10 K.

that the authors in the same article reported coupling constants ^1J ($^{13}\text{C}-^1\text{H}$) determined with gated decoupling, of 169 Hz for *cis*-**9** and 173 Hz for *trans*-**9**, values comparable to those of cyclopropane (161 Hz) and thiirane (171 Hz). In ^{13}C NMR spectra of **21**, **8**, and **22**, the dithiirane ring carbon resonates at around $\delta = 86$ ppm, and that of **23a** and **24** at a little higher field ($\delta = 79$ and 81 ppm, respectively), while the corresponding carbon of their 1-oxides appeared in a relatively narrow range ($\delta = 86$ –89 ppm) independent of the nature of substituents <2003JOC1555>.

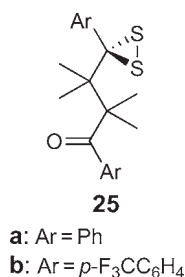


1.14.3.1.2(ii) IR spectra

Available IR data for indicated structures are gathered in Table 1. Maier and co-workers reported calculated (B3LYP/6-311+G(3df,3pd) and experimental (argon matrix, 10 K) IR bands of parent dithiirane **3a** to be in agreement, showing a very weak but clearly visible band at 581 cm⁻¹ <2001AGE393>. The S–O IR band of dithiirane *S*-oxide **23b** ($\tilde{\nu} = 1118$ cm⁻¹) has been reported <2001AGE1924>, and also of *trans*-**9** and *cis*-**9** ($\tilde{\nu} = 1128$ and 1122 cm⁻¹, respectively) <2005T6693>, for example.

1.14.3.1.2(iii) UV–Vis spectra

Ultraviolet–visible (UV–Vis) spectroscopy was used to monitor synthesis and decomposition of dithiiranes **25a** with an absorption maximum at 442 nm, and **25b** with an absorption maximum at 438 nm <1995TL1867>. The UV–Vis spectra of dithiiranes **21**, **8**, **23a**, and **22** reveal the absorption maximum in a range of 450–455 nm due to the S–S bond <2003JOC1555>. UV–Vis spectroscopic data for dithiiranes are collected in Table 1.



1.14.3.1.2(iv) CD spectra

Circular dichroism (CD) spectra were recorded for enantiomers of dithiirane 1-oxides **16a** and **16b** <1997T12203>. The (–)-enantiomer **16a** showed a negative Cotton effect at 307 nm, a positive second Cotton effect at 270 nm, and a negative third Cotton effect at 229 nm (Table 1). As expected, the (+)-enantiomer **16b** showed a mirror image CD curve.

1.14.3.1.2(v) Mass spectrometry

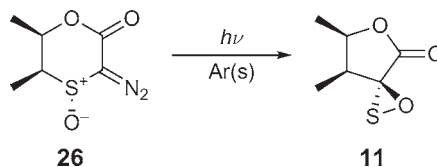
Tandem mass spectrometric experiments have been used to characterize both ionic and neutral parent dithiirane **3a** in the gas phase <1999PCA5123>. Collision activation experiments have established the connectivity of dithioformic acid, dimercaptocarbene, and dithiirane **3a** for the ion at m/z 78 generated by electron ionization of ethyl carbamoylmethane-dithioate, 5-amino-1,3,4-thiadiazole-2-thiol, rhodanine, and 1,2-dithiacyclopentane, respectively. Theoretical calculation of the CH_2S_2 isomers and their radical cations at B3LYP/6-31G** level have supported experimentally obtained data.

1.14.3.2 Oxathiiranes

1.14.3.2.1 Spectroscopic studies

1.14.3.2.1(i) IR spectra

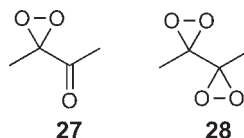
On irradiation of the α -diazo sulfoxide **26** at 308 nm in solid argon matrix at 10 K, the oxathiirane intermediate **11** was formed and its IR spectrum has been captured <2006EJO2918>. The experimental spectrum was compared to the spectra calculated for four conformers and stereoisomers of **11** (Scheme 2).



Scheme 2

1.14.3.3 Dioxiranes

The reader is referred to the article of Sander *et al.* <1997JA7265> dealing with a preparative-scale synthesis and structural analysis of the first crystalline dioxirane **4**. The article covers methods of structure elucidation described below. Another article dealing with quite stable dioxiranes **27** and **28** has also appeared <2006JOC5796>.



1.14.3.3.1 X-Ray diffraction

X-Ray single crystal structural analysis was used to unambiguously establish the structure of **4** which is in reasonable agreement with results of B3LYP/6-31G(d) theoretical calculations. The crystals are found to be orthorhombic. Compared to that in the parent dioxirane **1**, the O–O bond length in **4** (1.503 Å) is shortened by 0.013 Å while the CO bonds are found to be longer (1.414 Å, and 1.388 Å in **1a**).

1.14.3.3.2 Spectroscopic studies

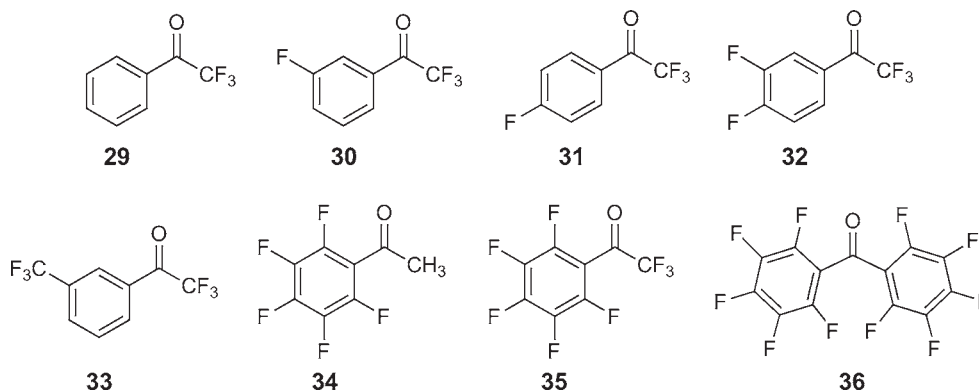
1.14.3.3.2(i) NMR spectroscopy

The ^1H NMR spectrum of **4** is characterized by three singlets: *o*- and *p*-methyl groups (δ = 2.19 and 2.24 ppm, respectively), and *meta* aromatic protons (δ = 6.82 ppm). The ^{13}C NMR spectrum of **4** exhibited seven signals, which were assigned by recording the distortionless enhancement by polarization transfer (DEPT) spectrum, by ^{13}C -labeling of the dioxirane ring, and by H–C long-range correlation. The dioxirane quaternary carbon atom resonates at

$\delta = 103$ ppm, which is in excellent agreement with the chemical shifts found earlier in other dioxiranes such as **1b**, **1c**, and **1d**. The experimental ^1H , ^{13}C , and ^{17}O NMR spectra are in good agreement with calculated (sum-over-states density-functional perturbation theory, SOS-DFPT) chemical shifts. The oxygen nuclei in **4** are somewhat more shielded in the ^{17}O NMR spectrum ($\delta = 321$ ppm) than those in DMDO **1b**.

Detailed NMR analysis of mono- and bis-dioxiranes **27** and **28**, respectively, has been reported <2006JOC5796>. The dioxirane carbon atom in mono-dioxirane **27** was found to resonate at 94.0 ppm, while the dioxirane carbon in bis-dioxirane **28** resonates at 113.7 ppm.

^{19}F NMR spectra of dioxiranes derived from fluorinated acetophenones **29–36** using Oxone have also been reported <2003OL2853>. The fluorine nuclei of CF_3 group bonded to dioxirane ring typically resonates at -85 ± 0.5 ppm.



1.14.3.3.2(ii) IR spectra

The IR spectrum of **4** is dominated by the mesityl groups. The absorption band at 1096 cm^{-1} is due to significant ^{18}O -isotopic shift caused by some contribution of the C–O vibration to this mode.

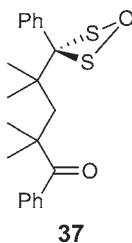
1.14.3.3.2(iii) UV–Vis spectra

The UV spectrum of **4** exhibits two strong absorption maximums at 206 and 274 nm.

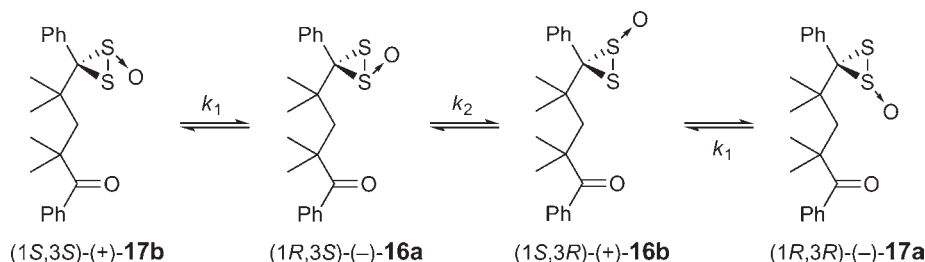
1.14.4 Thermodynamic Aspects

1.14.4.1 Dithiiranes

Melting points of isolated dithiirane and dithiirane 1-oxides are collected in Table 1. The majority of indicated compounds exhibited decomposition at the melting point. Ishii *et al.* achieved the optical resolution of dithiirane 1-oxides **16** and **17** by chiral high-performance liquid chromatography (HPLC) to give the corresponding enantiomers <1997T12203>. It is interesting to note that enantiomeric dithiirane 1-oxides **16a** and **16b** racemized to each other, which is not the case with **17a** and **17b**. The proposed racemization mechanism includes the formation of a 1,2,4-oxathietane intermediate **37**.



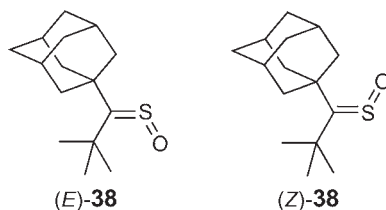
Racemization and isomerization (inversion at the sulfinyl sulfur) between **16** and **17** has been reported as indicated in Scheme 3 <1997T12203>. A retardation of the isomerization between **16** and **17** has been observed by adding a small amount of the radical scavenger, 1,1-diphenyl-2-picrylhydrazyl (DPPH), and the authors suggest that the isomerization is caused by a radical contaminant.



Scheme 3

In the case of **16a** and **16b**, it has been demonstrated that the rate constants k_2 are almost independent of concentration and solvent polarity, which indicates that the racemization is a unimolecular reaction and does not involve ionic species in the rate-controlling step. The value of k_2 is typically about $4.2 \times 10^{-6} \text{ s}^{-1}$ at 25°C . Activation parameters have been calculated from the rate constants measured in a temperature range from 20.4 to 39.8°C , revealing the values for $\Delta H^\ddagger = 24.3 \text{ kcal mol}^{-1}$, and $\Delta S^\ddagger = -2.0 \text{ cal K}^{-1}$. The same authors also reported thermal isomerization in solution between diastereomers of **20** accompanied by decomposition. Gradual isomerization in solution of *cis*-**9** into *trans*-**9** obeying the first-order kinetics ($k = 4.0 \times 10^{-7} \text{ s}^{-1}$, $r^2 = 0.966$) has also been reported [\[2005T6693\]](#). As in the case of **16** and **17**, the presence of DPPH resulted in substantial retardation of the isomerization ($k = 0.81 \times 10^{-7} \text{ s}^{-1}$, $r^2 = 0.913$).

trans-Dithiirane *S,S'*-dioxide **10** has been reported to be stable in the crystalline state and to gradually decompose in solution at room temperature to the corresponding (*E*)- and (*Z*)-sulfines **38**.



1.14.4.2 Oxathiiranes

No thermodynamic data are available for oxathiiranes.

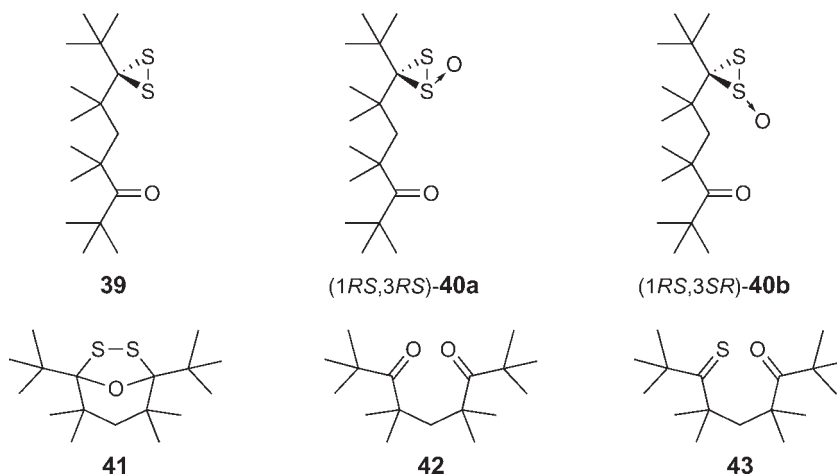
1.14.4.3 Dioxiranes

The first crystalline dioxirane **4** has been reported to melt at $62\text{--}64^\circ\text{C}$ [\[1997JA7265\]](#). The authors used HPLC analysis (reversed phase/methanol–water) for isolation of **4** from the reaction mixture. Bis-dioxirane **28** was found to be more stable than the corresponding mono-dioxirane **27** [\[2006JOC5796\]](#). It has been observed that **27** decomposes rapidly at 0°C , while at the same temperature **28** has been found to be stable for about 30 min. Zeller *et al.* used NMR experiments with different isotope-labeled acetones to demonstrate that DMDO **1b** and acetone are not in equilibrium [\[2005EJO5151\]](#).

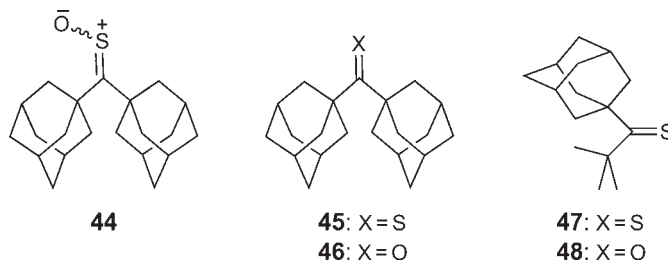
1.14.5 Reactivity of Three-Membered Rings with Two Oxygen and/or Sulfur Atoms

1.14.5.1 Dithiiranes

The dithiirane **39** is oxidized with *m*-chloroperbenzoic acid (MCPBA) at 0°C to give a diastereomeric mixture of dithiirane 1-oxides **40** in a 1:1 molar ratio. The stereochemistry of **40a** and **40b** has been determined by comparison of ^1H NMR spectra with those of known dithiirane 1-oxides **16a** and **17a** [\[1997TL1431\]](#). Upon heating the dithiirane **39** in refluxing 1,2-dichloroethane, chloroform, or benzene, a mixture of corresponding bicyclo compound **41** along with diketone **42** and thioketone **43** is obtained. Thermal isomerization of **39** into **41** is a common reaction of δ -oxodithiiranes and competes with desulfurization yielding thioketones.



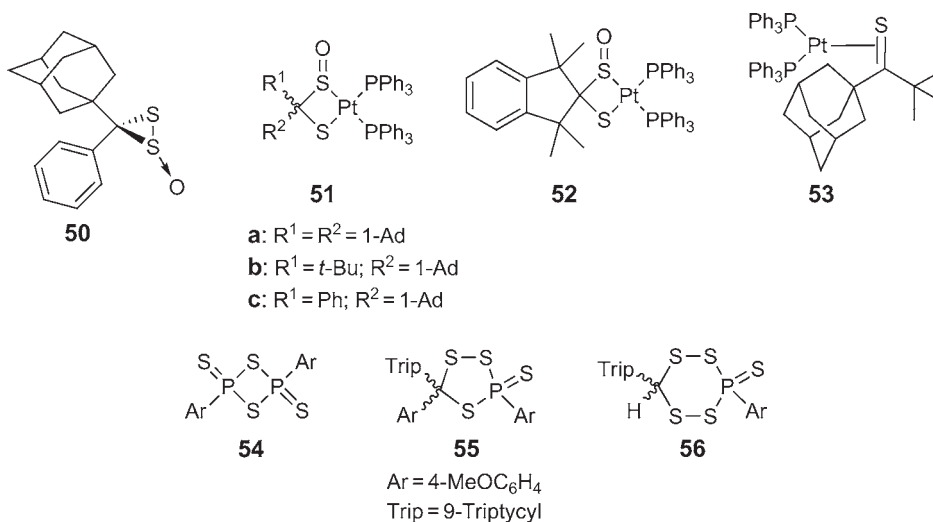
Analogously, dithiirane 1-oxides **5** and **20** are found to decompose at their melting points or in solutions to give sulfines **44** and **38**, thioketones **45** and **47**, together with corresponding ketones **46** and **48** <1998TL3525>.



Upon irradiation in the argon matrix at 10 K with light of wavelength $\lambda > 570$ nm, the parent dithiirane **3a** is transformed into dithioformic acids **49a** and **49b** <2001AGE393>. When secondary irradiation with monochromatic light ($\lambda = 500 \pm 10$ nm) is applied, the reaction starts along with partial reverse reaction of **3a** to **12a**. The final conversion into **49a** and **49b** is originated from the photoequilibrium **3a** $\leftrightarrow$ **12a**.



Treatment of dithiirane 1-oxides **5**, **7**, **20**, and **50** with platinum(0) complex $(\text{Ph}_3\text{P})_2\text{Pt}(\eta^2\text{-CH}_2=\text{CH}_2)$ results in the formation of the four-membered (sulfenato-thiolato) Pt^{II} complexes **51** and **52** <2002EJOC979>. These complexes are found to be thermally stable, but in solution they gradually decompose into complex mixtures dominated by triphenylphosphane sulfide. This is one of the few reactions of dithiirane derivatives to yield a stable product with retention of the two dithiirane ring sulfur atoms and it is found to be useful in trapping unstable dithiirane 1-oxides. On the other hand, $(\text{Ph}_3\text{P})_2\text{Pt}(\eta^2\text{-CH}_2=\text{CH}_2)$ dithiirane **21** gave the $(\eta^2\text{-thiocarbonyl})\text{platinum}$ complex **53**, which on reaction with **5** gives a mixture of **5**, **47**, **51a**, and **53** in the ratio of 14:21:27:37. In a review dealing with reactions of oligosulfides with $(\text{Ph}_3\text{P})_2\text{Pt}(\eta^2\text{-CH}_2=\text{CH}_2)$, there is a part also covering the synthesis and reaction of dithiiranes <2003CCR(245)167>. Dithiirane 1-oxides **5**, **7**, **20**, **23b**, and **50** have been subjected to reduction with Lawesson's reagent **54** giving corresponding dithiiranes <2003JOC1555>. Reaction of ^{34}S -labeled **5** with Lawesson's reagent gave the corresponding dithiirane **8** in which the ^{34}S atoms were quantitatively retained. In the case of 3-(9-tritycyl)dithiirane 1-oxide **9**, reaction with Lawesson's reagent **54** yielded not expected dithiirane but stereoisomers of 1,2,3,4-trithiaphospholanes **55** and 1,2,4,5,3-tetrathiaphosphorinanes **56** <2005T6693>.



Mlostoń and co-workers reported photo-rearrangement of methylthiirane **2b** in the argon matrix at 10 K, yielding corresponding dithioacetic acid [<2006EJO3721>](#).

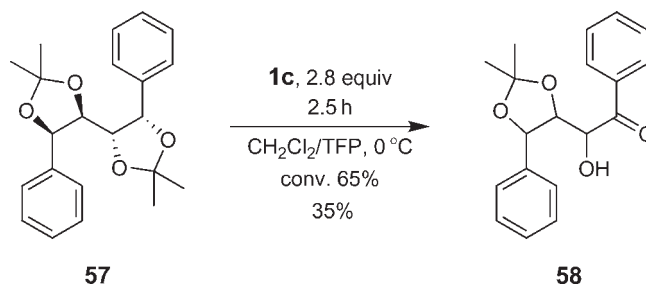
1.14.5.2 Oxathiiranes

Since no stable oxathiiranes are known to date, there are no papers dealing with oxathiirane reactivity.

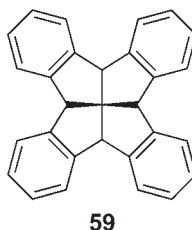
1.14.5.3 Dioxiranes

1.14.5.3.1 The carbon–hydrogen insertion reaction

Dioxiranes have the unique ability to yield O-atom insertions into alkane C–H bonds under extremely mild conditions. Although their reactivity exceeds that of peroxybenzoic acids by 2 orders of magnitude, the selectivity is not diminished, but even enhanced. When DMDO **1b** is employed, reaction times are typically a few hours, and with TFDO **1c**, a few minutes with unchanged selectivity [<1995PAC811>](#). Dioxiranes are useful reagents for the direct conversion of *O*-isopropylidene derivatives of vicinal diols into the corresponding 2-hydroxyketones. In the case of optically active acetonides, the preservation of configuration at the C–OH chiral center proximal to that transformed to C=O occurs. Furthermore, using an excess of TFDO **1c**, the diacetonide **57** could be selectively converted to compound **58** [<1996TL115>](#).

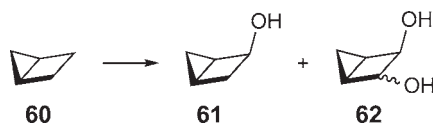


Curci and co-workers studied the dioxirane oxyfunctionalizations of a series of non-natural targets and found an interesting example of selective bridgehead dihydroxylation of fenestrindane **59** [<1996JOC8681>](#) and hydrocarbons bearing cyclopropyl moieties [<2003JOC7806>](#).

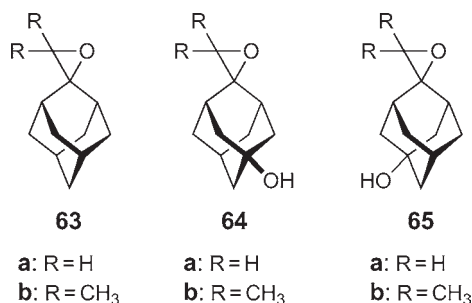


The dioxirane carbon–hydrogen insertion reaction was successfully employed for the direct regioselective oxygen-functionalization of brassinosteroids, a new class of plant phytohormones with antistress activity, at position C-25 <1996T10653> and/or C-14 <1999T8341>. A general approach to synthesis of deuterium-labeled brassinosteroids has also been developed <1998TL7525>. It has been demonstrated by Murray and Gu that for both C–H insertion and epoxidation reactions a rate acceleration is realized when intramolecular H-bonding stabilization of the activated complex takes place <1996JPO751>. Intramolecular C–H insertions and their selectivities were also the subject of investigations by Yang's group <2003JOC6321>.

DMDO **1b** regioselectively monooxidizes azidodiols, bromodiols, and triol derivatives into the corresponding ketols. The selectivity of reaction is determined by dipolar functionalities neighboring to the reaction center, which make the reactivity of polyols with DMDO **1b** highly predictable <1998T14301>. Interesting examples of regioselective intramolecular C–H insertion by dioxiranes generated *in situ* were given by Yang *et al.* <1998JA6611>. DMDO **1b** oxidation of 3-arylisochromans represents an easy route to corresponding 3-arylisocoumarins <1999T14719>. The selective and efficient aromatic ring hydroxylation of flavanones by DMDO **1b** has also been reported <2000TL1087>. The use of **1b** in highly regio- and stereospecific hydroxylation of the C-1 position of 2-deacetoxytaxinine leading to only the 1 β -hydroxy has been achieved <2000TL3907>. Apart from microbial hydroxylation, such high selectivity in the chemical oxidation of taxoids has been only reported using dioxirane **1b**. Measuring kinetic isotope effects in the oxidation of benzyl alcohols by DMDO **1b** supports a concerted, and not stepwise, mechanism for the title reaction <2001TL3753>. The concerted mechanism is also supported by observation that the oxidation of bicyclo[2.1.0]pentane **60** with DMDO **1b** or with TFDO **1c** gives only the corresponding *endo*-2-alcohol **61** (70–99% yield) and 2,3-diol **62** (0–30% yield) with no rearrangement products <2001TL7087>.



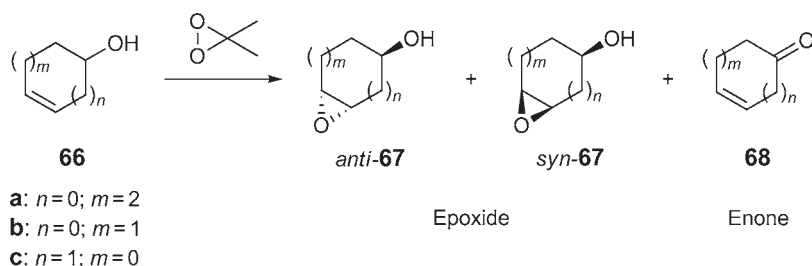
Methyleneadamantane oxide **63a** and isopropylideneadamantane oxide **63b** both react with TFDO **1c**, giving only the products of C–H insertion into H–C(5) (**64a**, **64b**) and H–C(7) (**65a**, **65b**) <2002TL4649>. In some C–H insertion reactions, for example in the oxidation of adamantane and 2,3-dimethylbutane with TFDO **1c**, chemiluminescence occurs. The species responsible for chemiluminescence has proposed to be excited trifluoropropanone, [CF₃COCH₃]^{*} <2001CC191>. A detailed account covering C–H insertions by Curci *et al.* has recently appeared <2006ACR1>.



1.14.5.3.2 The epoxidation reaction

1.14.5.3.2(i) General

Denmark *et al.* reported a general protocol for the catalytic epoxidation of alkenes by *in situ*-generated reactive dioxiranes capable of epoxidizing a variety of alkenes under biphasic conditions <1995JOC1391>. The epoxide diastereoselectivity (Scheme 4) showed pronounced dependence on the solvent used since the ratio of diastereomers, as well as the distribution between epoxide and enone products, is dependent on the solvent <1995TL2437, 1999TL8023>. Selected examples are given in Table 2.

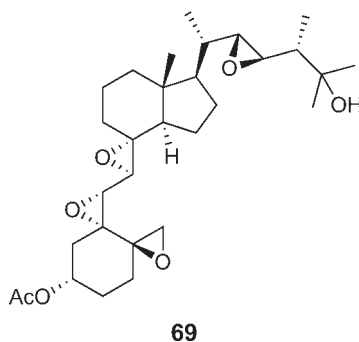


Scheme 4

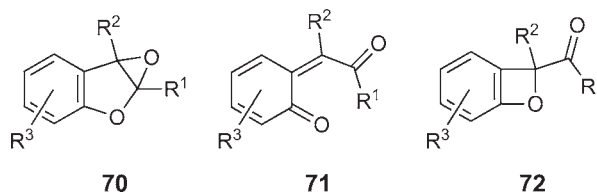
Table 2 Solvent effect on product distribution in DMDO epoxidation

Substrate	Solvent	Conversion γ (%)	Diastereoselectivity $n(\text{anti-67})/n(\text{syn-67})$	Epoxide/enone ratio $n(\text{epoxide})/n(\text{enone})$	Reference
66a	Me ₂ CO	94	54/46	46/54	1995TL2437
66a	Me ₂ CO/CH ₂ Cl ₂ 1/1	94	43/57	65/35	1995TL2437
66b	Me ₂ CO	92	47/53	70/30	1999TL8023
66b	Me ₂ CO/CH ₂ Cl ₂ 1/1	95	39/61	90/10	1999TL8023
66c	Me ₂ CO	96	46/54	100/0	1999TL8023
66c	Me ₂ CO/CH ₂ Cl ₂ 1/1	85	22/78	100/0	1999TL8023

Curci *et al.* have reported a nice example of a highly stereospecific dioxirane-mediated epoxidation of vitamin D₂ into the corresponding (all-*R*)-tetraepoxide **69** <1996JA11089>.



Sauter and Adam have applied DMDO **1b** for the epoxidation of benzofurans in their study of the DNA-damaging activity of benzofuran epoxides **70** and their valence-isomeric compounds **71** and **72** <1995ACR289>.

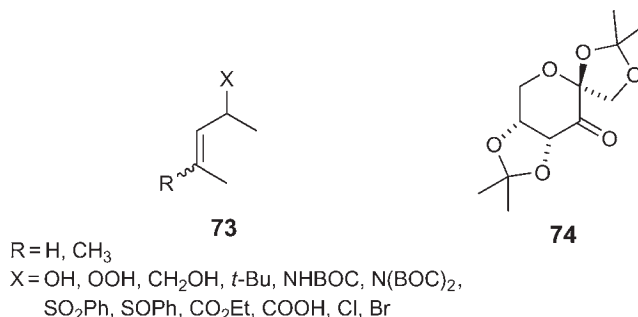


The benzofuran epoxides **70** are found to be the most reactive epoxides functioning as alkylative agents. Polyunsaturated free fatty acids, namely linoleic, arachidonic, and eicosatrienic acids, and also their methyl esters have been epoxidized using **1b** <2006HCA2243>. When the reaction is performed in water, it has been found that due to supramolecular organization of fatty acids into a micelle, the C=C bonds closest to the aqueous–micelle interface are most prone to epoxidation.

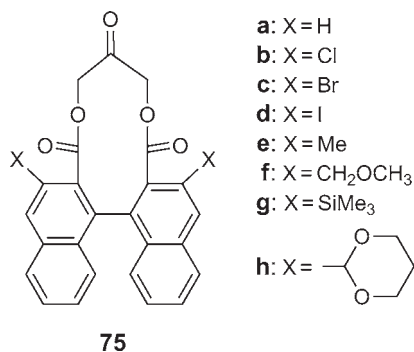
1.14.5.3.2(ii) Stereoselective epoxidations

Since CHEC-II(1996), the enantioselective variant of the epoxidation reaction of prochiral olefins by different chiral dioxiranes have been the center of interest of many research groups. The development of chiral dioxiranes for catalytic enantioselective epoxidation of alkenes has also appeared <1999SL847>. Porter and Skidmore published a critical review on the asymmetric epoxidations of electron-deficient olefins comprising the use of chiral metal hydroperoxides, polyamino acid catalysts, asymmetric phase-transfer methods, and the use of chiral dioxiranes <2000CC1215>. The reader is also referred to the detailed reviews by Frohn and Shi, which cover chiral ketone-catalyzed asymmetric epoxidation of olefins <2000S1979>, and by Yang, covering the same field with an emphasis on electronic effects in asymmetric catalysis <2004ACR497>. A study of structural effects of chiral ketones on the asymmetric epoxidation of prochiral olefins has also appeared <2005T6409>. The reaction has been generally performed using chiral dioxiranes generated *in situ* from the corresponding chiral ketones by potassium monoperoxosulfate (Oxone). Denmark *et al.* reported a detailed general protocol for the efficient and practical catalytic epoxidation of alkenes using Oxone <1995JOC1391>. Murray *et al.* have found a remarkable solvent effect on the diastereoselectivity in the epoxidation of cyclohex-2-en-1-ol, and in some cases a preferential *cis*-selectivity due to the effect of H-bonding <1995TL2437>. Adam *et al.* have studied diastereoselectivity in the epoxidation of heteroatom-substituted acyclic chiral olefins **70** by DMDO **1b** and TFDO **1c** <1996JA1899>.

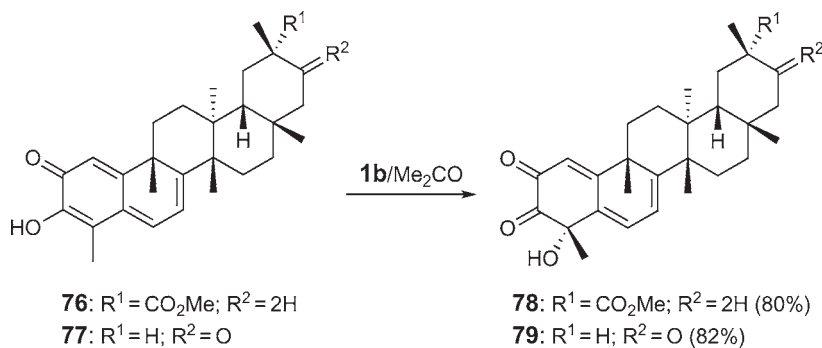
They found that the *erythro*/*threo*-selectivity is X-substituent dependent, acting through H-bonding, which was demonstrated by the TFDO **1c** epoxidation of **73**. An example of cyclohexene epoxidation by dioxiranes derived from various ketones grafted on solid supports has also appeared <1996MI273>. Shi and co-workers reported <1996JA9806> excellent ee's of asymmetric epoxidation of different *trans*-olefins by fructose-derived ketones **74**; before then, only low enantioselectivities (9–20%) have been reported on this type of reaction.



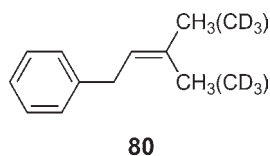
Yang *et al.* have applied *C*₂-symmetric chiral dioxiranes, generated *in situ* from corresponding chiral ketones **75** and Oxone, for asymmetric epoxidation of *trans*-olefins and trisubstituted olefins (33–87% ee) <1996JA491, 1996JA11311>.



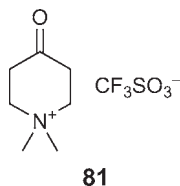
A very nice example of the oxidation by dioxirane **1b** where other oxidants failed is the regio- and stereoselective oxidation of C₃–C₄ enol double bond of quinine methide triterpenes pristimerin **76** and tingenone **77** <1996T10667>.



Using the olefin **80** and its deuterated analogue in the epoxidation by **1b**, the authors were able to measure the α - and β -secondary deuterium isotope effects elucidating the nature of the transition state of the oxygen transfer in these epoxidation processes <1996TL5991>.

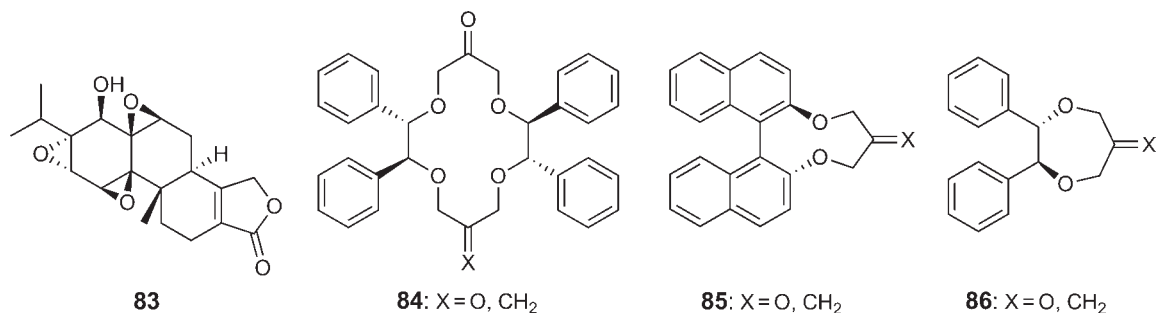


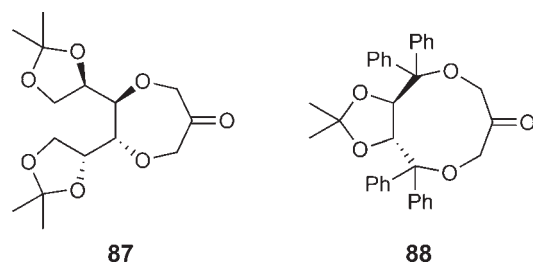
Denmark and Wu used ^{18}O -labeled ketone **81** in their studies of epoxidation of 1-phenylcyclohexene, yielding the conclusion that dioxiranes are the reactive oxidants in monophasic epoxidations with Oxone <1997JOC8964>.



Adam *et al.* have studied comparative diastereoselectivity in the catalytic epoxidation of chiral allylic alcohols, both in the heterogeneous mode with titanium-containing zeolites and the homogeneous mode with vanadium-catalyzed oxidant, as well as the stoichiometric process with MCPBA and DMD <1997JOC3631>. Several monocyclic epoxide analogues of triptolide **82** have been prepared using *in situ*-derived TFDO **1c** or isopropylpyruvate-derived dioxirane <1997TL6865>.

Song *et al.* have designed a series of structurally and electronically well-defined C_2 -symmetric chiral ketones **84–86** for use in the epoxidation of unfunctionalized olefins (max. 59% ee for *trans*-stilbene oxide) <1997TA2921>. Adam reported the synthesis and application of chiral C_2 -symmetric ketones **87** and **88**, derived from mannitol and TADDOL, respectively, in the epoxidation of prochiral olefins (ee's up to 80.5%) (TADDOL = (–)-*trans*-4,5-bis(diphenyl-hydroxymethyl)-2,2-dimethyl-1,3-dioxolane) <1997TA3995>.





Reactivity and selectivity in the epoxidation reaction of cyclohexene to cyclohexene oxide by different dioxiranes in the ketone/Oxone monophasic and biphasic system have been investigated [\[1998MI60\]](#). The rate of cyclohexene oxide formation increased proportionally to increasing ketone concentration, while the catalytic activity increased with the solubility of ketone in water. Electronic effects in catalytic asymmetric epoxidation by chiral dioxiranes derived from (*R*)-carvone have been studied by Yang *et al.* [\[1998JA7659\]](#). Significant effects of the nonconjugated remote C-8 substituent of chiral ketone **89** on enantioselectivity were demonstrated. The same group reported the design and synthesis of highly efficient chiral ketones **75** for the asymmetric epoxidation of unfunctionalized olefins (up to 95% ee for *trans*-stilbenes) and also provided evidence for a *spiro* transition state of the reaction (**Figure 1**) [\[1998JA5943\]](#).

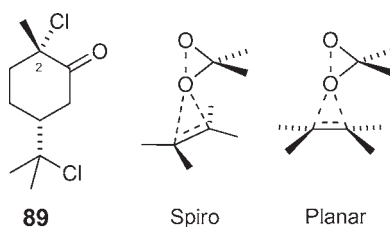
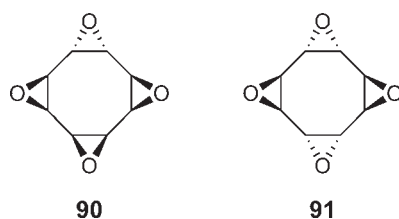
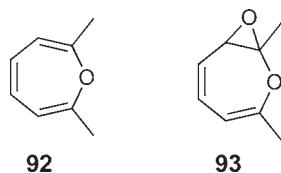


Figure 1

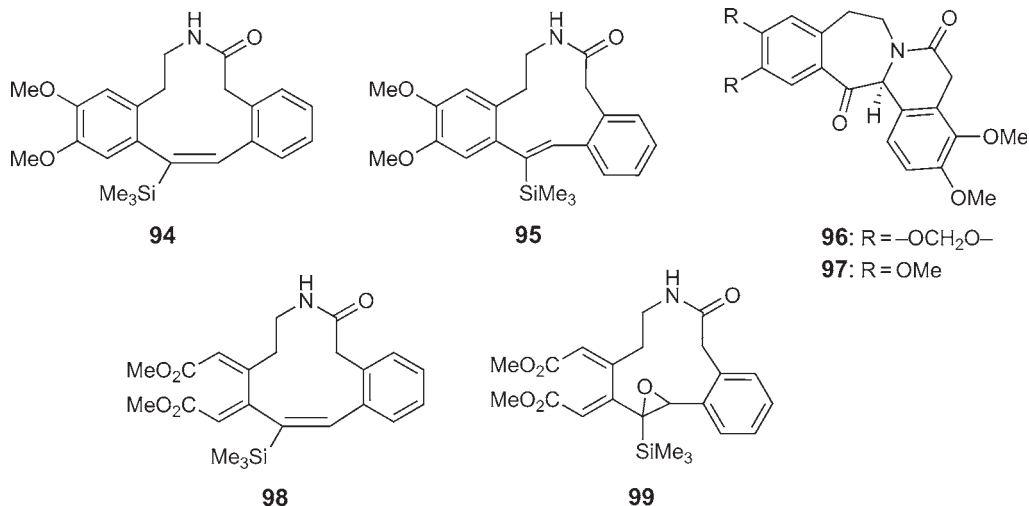
Moreover, in the same work, the ^{18}O -labeling experiment confirmed chiral dioxiranes to be the intermediates in chiral ketone-catalyzed epoxidation reactions. Murray *et al.* reported the synthesis and structural characterization of cyclooctatetraene tetraepoxides **90** and **91** through the oxidation of cyclooctatetraene with excess of DMDO **1b** [\[1998TL2899, 1999T4539\]](#).



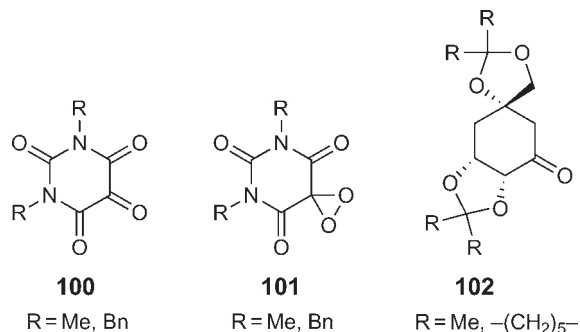
Steric and field effects in the diastereoselective epoxidation of substituted cyclohexenes by dioxiranes were investigated, revealing that the diastereoselectivity is determined by the steric and field effects of both dioxiranes and olefins [\[1999JOC1635\]](#). The reaction of 2,7-dimethyloxepin **92** with DMDO **1b** and TFDO **1c** has been reported together with detailed ^1H NMR study of the reaction and the possible evidence of intermediate 2,3-epoxyoxepin **93** [\[1998STC223\]](#).



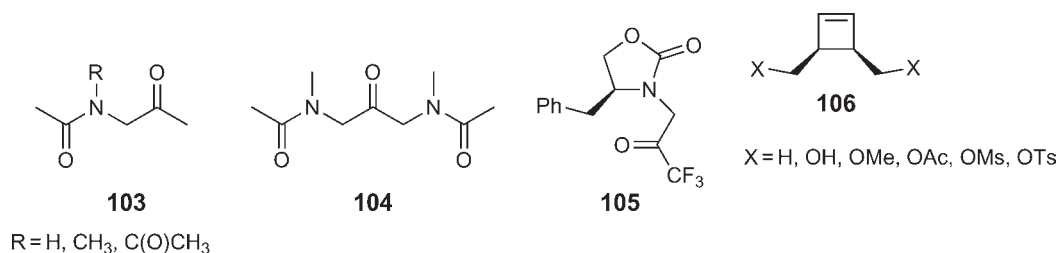
The oxidation of the sterically hindered stilbene double bond in the silylated 11-membered ring stilbene lactams **94** and **95**, intermediates in the synthesis of homoprotoberberins puntarenine **96** and saulatine **97**, with **1b** and **1c** resulted in the oxidative cleavage of their electron-rich aromatic rings. The oxidation of **94** with **1b** resulted in muconate **98**, whereas the epoxidation of **95** with **1c** gives epoxymuconate **99** <1999JOC4830>.



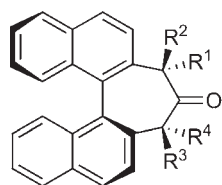
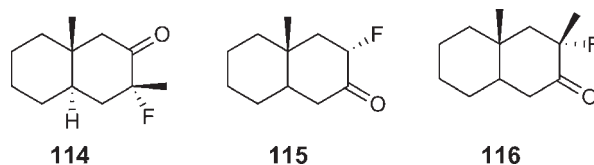
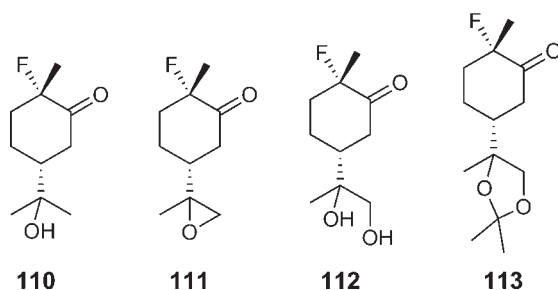
A range of di- and trisubstituted alkenes have been successfully epoxidized using *N,N*-dialkylalloxanes **100**, with assumption that the dioxirane **101** is the active oxygen-transfer species <1999TL8029>. Chiral ketones **102** derived from D-(–)-quinic acid have been applied in the asymmetric epoxidation of prochiral olefins, yielding the corresponding epoxides with ee up to 90% <1999TA2749>.



Armstrong and Hayter reported the synthesis of α -functionalized ketones **103** and **104**, but competing decomposition by the Baeyer–Villiger reaction prevented their use as promoters of alkene epoxidation by Oxone <1999T11119>. The authors reported only moderate enantioselectivity (up to 34% ee) observed with chiral oxazolidinone **105**. Freccero *et al.* reported the results of the stereoselective epoxidation of a series of *cis*-3,4-disubstituted cyclobutanes **106** bearing a CH_2X substituent (when X is an electron-withdrawing group) using DMDO **1a** and peroxy acids <1999T11309>. The authors offered an experimental and computational explanation for the *syn* facial selectivity, observed both in dioxirane- and peroxy acid-mediated epoxidations, on the basis of a deformation effect and of electrostatic interactions in the transition state.

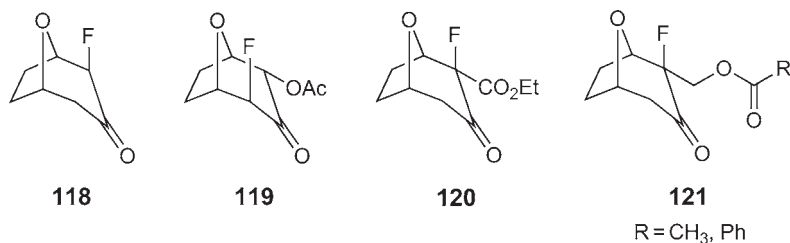


107 **108a** **108b** **109**
X = F, Cl

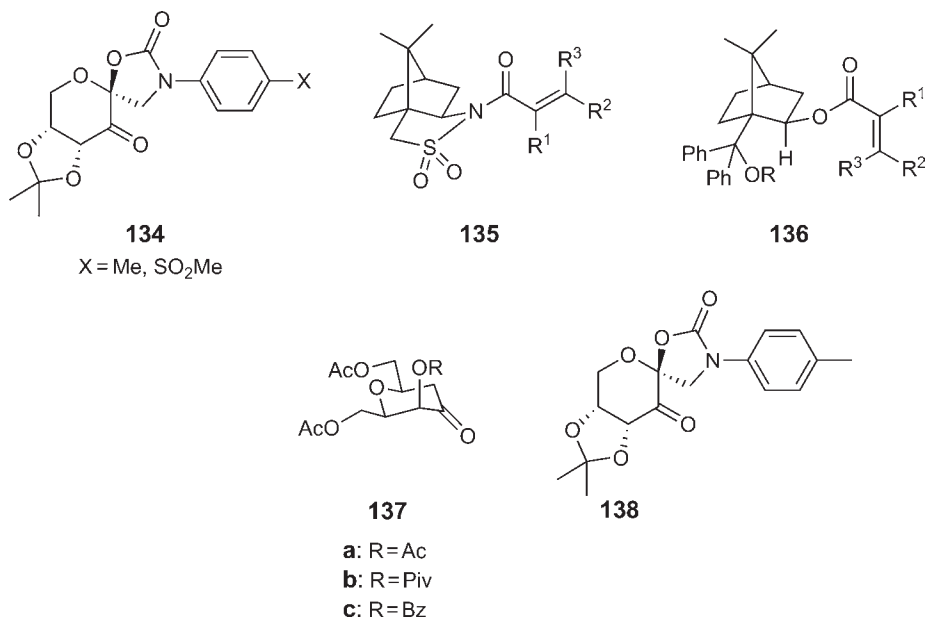


117

- a:** $R^1=R^2=R^3=R^4=H$
b: $R^1=R^3=R^4=H$; $R^2=F$
c: $R^1=R^3=H$; $R^2=R^4=F$
d: $R^1=R^2=R^3=F$; $R^4=H$
e: $R^1=R^2=R^3=R^4=F$



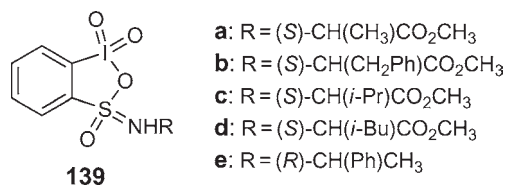
the ketone. Chiral auxiliaries, camphor-derived *N*- and *O*-enones **135** and **136**, have been epoxidized with **1c** in high diastereomeric ratio depending on their geometry <2004T6657>. Chiral tetrahydropyran-4-ones **137** having an axial α -substituent have been employed in the asymmetric epoxidation of various alkenes with moderate to high enantioselectivities (up to 83% ee) <2006T257>. The efficient synthesis of optically active 2-alkyl-2-arylcyclopentanones has been achieved by asymmetric epoxidation of tetrasubstituted benzylidenecyclobutanes using Shi's ketone **138**/Oxone in a catalytic system <2006TL5455>.



1.14.5.3.3 Oxidation of heteroatoms

1.14.5.3.3(i) Iodine

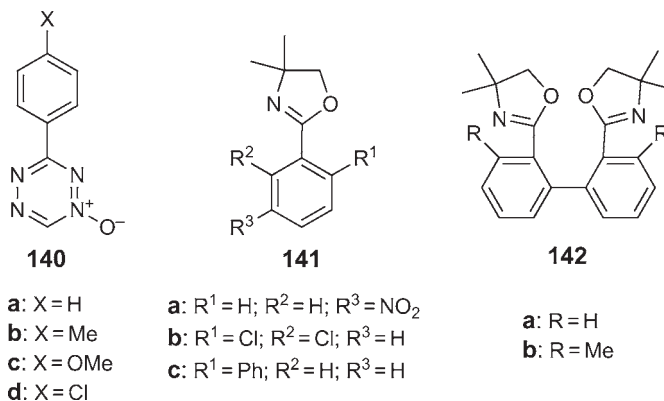
Zhdankin and co-workers reported <2004TL2719> the use of DMDO **1b** in the preparation of new pseudobenzo-doxole-based pentavalent iodine compounds **139**, amides of 2-iodoxybenzenesulfonic acid, which are potentially useful reagents for mild oxidation of alcohols.



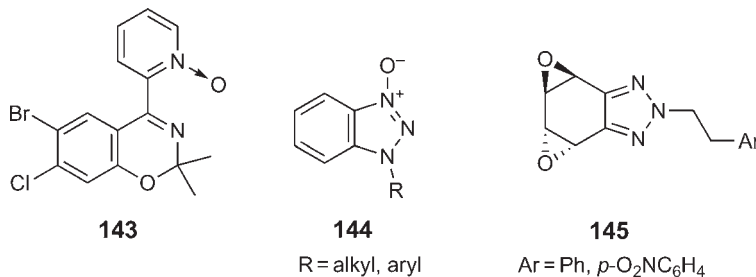
1.14.5.3.3(ii) Nitrogen

Adam *et al.* have successfully oxidized 3-aryl-1,2,4,5-tetrazines into the corresponding *N*-1-oxides **140**, directly by isolated TFDO **1c** <1996TL2377>. The reaction is highly regioselective at position N-1 because of steric repulsion between the *ortho*-hydrogen atoms of the phenyl and the *ortho*-electron pairs of the tetrazine ring. The authors proposed that the tetrazine N-oxidation proceeded by an S_N2 mechanism. Aryl oxazolines **141** and **142** were found to be readily cleaved by **1c** to the corresponding intermediate nitro-esters, which under basic hydrolysis yielded substituted benzoic acids <1997TL7083>. DMDO has also been used for oxidation of heterocyclic aromatic

amines, anilines, and tertiary amines <1997T15877>. The reaction gives the corresponding *N*-oxides in quantitative conversion yields. When the carbon–carbon double bond was present in the substrate, the oxidation was chemoselective.

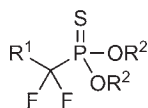
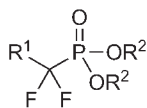


Curci and co-workers reported the high yield and highly selective oxidation of *N,N*-dimethylhydrazones into the corresponding nitriles by **1b** <1998TL2009>. When methyl(trifluoromethyl)dioxirane **1c** was used instead of **1b**, a decrease in nitrile yield and low substrate conversion occurred due to possible hydrazone-induced competitive decomposition of **1c**. The authors proposed that the oxidation involves electrophilic O-transfer from the dioxirane to the substrate through the labile intermediate. The persistence of dioxiranes **1b** and **1c** toward amine *N*-oxides and ammonium derivatives has been studied by the release of singlet oxygen <1998EJO2527>. The *N*-oxide may react with the dioxirane to yield mixtures of amine/*N*-oxide, depending on *N*-oxide nucleophilicity. Thus, more nucleophilic *N*-oxides derived from tertiary aliphatic amines react faster with dioxiranes to promote their deoxygenation and are more prone to release ¹O₂ than those of heteroatomic substrates. The reaction of **1b** and **1c** with aminoxyls has been studied by Curci and co-workers, providing new insights of the free radical mechanism that follows the initial attack by the aminoxyl at the dioxirane <1998EJO871>. An efficient procedure for the selective *N*-hydroxylation of *N*-BOC-protected primary amino acid esters with high ee using **1c** has been described (BOC = *t*-butoxycarbonyl) <2001TL755>. The oxidation of BOC-LeuOMe with **1c** occurs more rapidly than with **1b** but with different selectivity. The BOC- and acetyl-protected peptide methyl esters bearing alkyl side chains were oxidized by **1c** with chemoselectivity depending on the protecting group; that is, *N*-hydroxylation occurred with BOC protection and side-chain hydroxylation with acetyl-protected peptides <2007JOC525>. The well-known selectivity in dioxirane oxidations is again demonstrated in the *N*-oxidation of 2*H*-1,3-benzoxazine to yield potassium channel opener **143** in high yield <2001T7501>. Katritzky *et al.* reported the oxidation of a series of 1- and 2-alkylbenzotriazoles by DMDO **1b** <2001JOC5585>. Interestingly, **1b** has transformed 1-alkylbenzotriazoles into the corresponding *N*-oxides **144**, while 2-alkylbenzotriazoles have been converted into their 2-alkyl-*trans*-4,5,6,7-diepoxy-4,5,6,7-tetrahydrobenzotriazoles **145**.



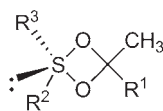
1.14.5.3.3(iii) Phosphorus

The efficient transformation of dialkyl 1,1-difluoromethylenephosphonothioates **146** into dialkyl 1,1-difluoromethylenephosphonates **147** using DMDO **1b** has been reported <1996TL4707>.

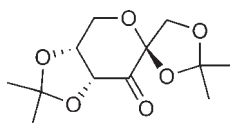
**146****147****a:** R¹ = Br; R² = C₂H₅**b:** R¹ = H; R² = Bn**c:** R¹ = C₁₂H₂₅; R² = C₂H₅**d:** R¹ = *o*-C₆H₁₁; R² = CH₃**e:** R¹ = C₉H₁₉(CH₃)CH; R² = C₂H₅**f:** R¹ = *p*-C₆H₅CH₂OC₆H₄CO; R² = C₂H₅

1.14.5.3.3(iv) Sulfur

Asensio *et al.* reported a detailed mechanistic study of the oxidation of simple sulfides by DMDO **1b** and TFDO **1c** <1996TL2299, 2002JA9154, 2004JOC9090>. In the reaction of **1b** with phenyl methyl sulfide in the presence of 1,1,1-trifluoropropanone-¹⁸O-hydrate (48% ¹⁸O-labeled), the ¹⁸O-labeled sulfoxide (23% ¹⁸O-atoms) and ¹⁸O-labeled sulfone (6.1% ¹⁸O-atoms) were formed. There is a clear evidence of involvement of a cyclic hypervalent sulfurane intermediate **148**. The thianthrene 5-oxide **14** was used as a probe for the oxidation with dioxiranes revealing these oxidants to be more electrophilic than they actually are <2001JOC2686>. *N*-(*p*-Tolylsulfonyl)sulfinilimines and *N*-(acetyl)sulfinilimines were easily oxidized into corresponding sulfoximines in high yield using **1b** <1997TL5559>.

**148**R¹ = CH₃, CF₃R² = R³ = alkyl, aryl

This method is particularly suitable for the synthesis of chiral sulfoximines with high optical purity since the reaction occurs with no loss of ee and with retention of the configuration. Thiophenes 2-substituted with electron-withdrawing groups, which are known to be difficult to oxidize, were efficiently transformed by **1b** to the corresponding 3-hydroxy-2,3-dihydrothiophene 1,1-dioxides <1998TL5049>. Enantioselective oxidation (ee's up to 26%) of prochiral sulfides to sulfoxides using dioxirane **149** generated from pyranose has also been reported <2006RJO12>.

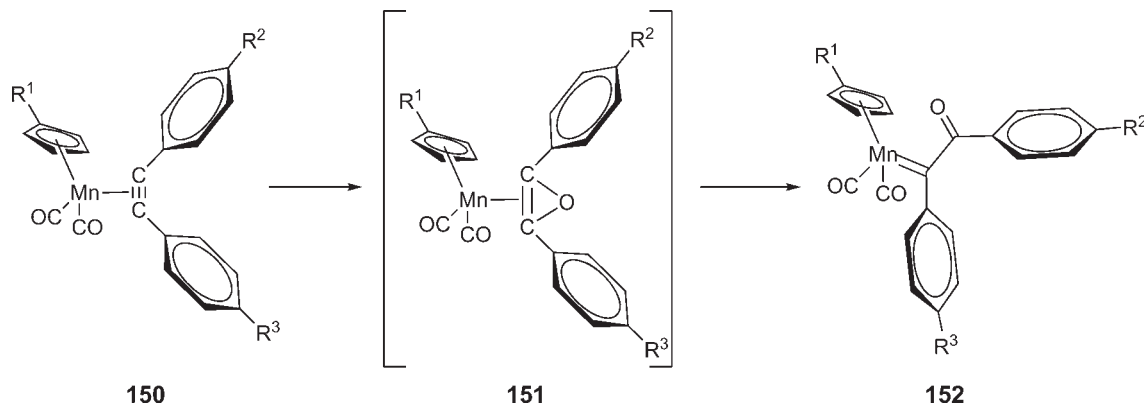
**149**

1.14.5.3.4 Oxidation of organometallic compounds

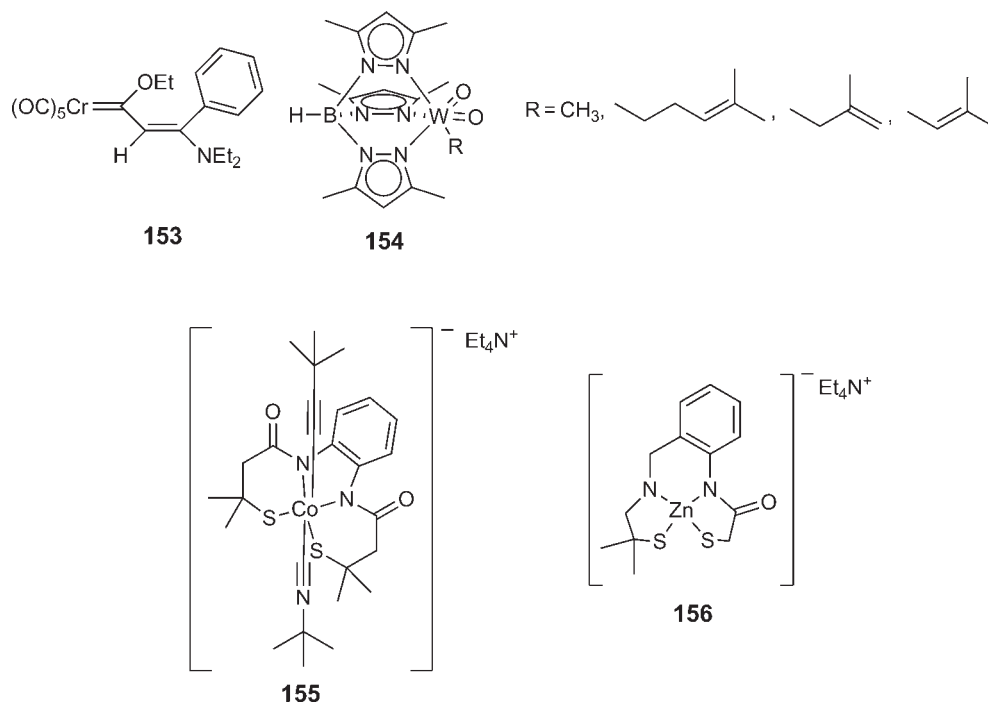
The oxidation of a coordinated alkyne ligand in diarylmanganese complex **150** by DMDO **1b** gives the corresponding α -keto carbene complex in 29–42% yield. The reaction involves the possible intermediate **151** containing a coordinated oxirene ligand <1995OM1545>. The oxirene ring as a 4 π -antiaromatic system is predicted by theoretical calculations <1994JA9311> to undergo facile ring opening to the α -ketocarbene, which then undergoes subsequent reactions <1996TL4707>.

It is known that DMDO **1b** promotes oxidative decomplexation of Fischer carbene complexes <1992TL3021>. This reaction has been further investigated on the Fischer carbene complex containing a conjugated enamino moiety (**152**), revealing the fact that the presence of an enamino group conjugated to the Fischer carbene moiety inverts the chemoselectivity previously observed <1996T3973>. Oxidative decomplexation of chromium Fischer carbene complexes induced by DMDO **1b** and dimesityldioxirane **4** has been studied <1999JOC1591>. Results obtained from this study suggested that the oxidative decomplexation of Fischer carbene complexes by dioxiranes involves an

initial attack of the dioxirane to the metal coordination sphere and subsequent oxidation of CO to CO₂, thus leaving an unstable chromium tetracarbonyl intermediate which will further react with O₂ to finally give ester and chromium(III) oxide.

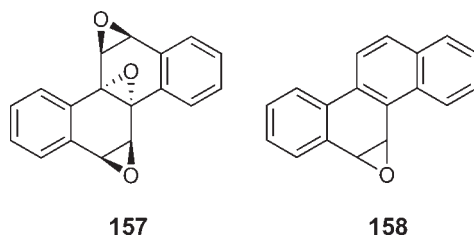


Adam *et al.* reported the epoxidation by **1b** and **1c** of olefinic side-chain units of series of tris(pyrazolyl)borato-substituted alkenyltungsten complexes **154** with selectivity controlled by electronic and steric factors of the organometallic fragment <1996OM4586>. The 6-coordinated Co complex **155** with ligated thiolates has been readily oxidized to the corresponding Co sulfonates with a stoichiometric amount of **1a** <2001JIB207>, whereas oxidation of a 4-coordinated Zn(N₂S₂) complex **156** with **1b** resulted in the formation of disulfonate species with loss of Zn, except in the case of bis(imine)/bis(sulfonate) species where Zn is retained <2005JIB690>.

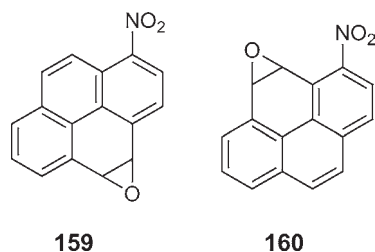


1.14.5.3.5 Oxidation of polycyclic aromatic hydrocarbons

In comparison with CHEC-II(1996), the period covered by the current edition is marked by decreased interest and consequently less publications on the title topic. It was found that DMDO reacts with chrysene to give the chrysene-5,6:4b,10b:11,12-trioxide **157**, accompanied by the monoxide **158** <1996TL8671>.

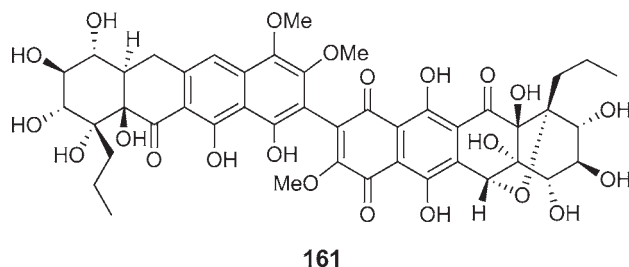


The single crystal X-ray crystallographic analysis of the trioxide **157** indicates that it is a nonplanar system. Murray and Singh reported the reaction of 1-nitropyrene, absorbed on silica gel, with DMDO **1b**, in which the formation of the two epoxides, namely 1-nitropyrene 4,5-oxide **159** and 1-nitropyrene 9,10-oxide **160**, took place <1998CRT449>. Although buckminsterfullerene C₆₀, a polycyclic aromatic compound, strictly speaking is not a hydrocarbon, it is logical to mention here its reaction with TFDO **1c**. The products of this stepwise oxyfunctionalization were, among others, C₆₀O, two regioisomeric C₆₀O₂ (isolated in good 40% overall yield), and mixtures of regioisomers of C₆₀O₃ <1999JOC8363>. In all products, the fullerene core remains intact and no rupture of the cage occurs during reaction.



1.14.5.3.6 Oxidation of enolates

α -Hydroxy ketones with predominantly *syn*-methyl orientation are available by the reaction of the trimethylsilyl enol ethers (derived from the conjugate addition of organocopper reagents to 3,4-dimethylcyclopentenone) with DMDO **1b** <1997TL4017>. An enantioselective variant of this method was achieved by replacing **1b** with an excess of the fructose-derived dioxirane **74** at pH = 8 <1998TA397>. Moderate to high enantioselectivities (ee values up to 82%) were obtained at short reaction times. The absolute configuration of the resulting α -hydroxyketones contributed to understanding mechanistic details on the 'spiro versus planar' transition states for the oxygen-transfer process. A DMDO **1b** oxidation for stereocontrolled introduction of hydroxyl groups was one of the key reactions in the synthesis of the AB/GH-ring systems of hibarimicinone **161**, a common aglycone of hibarimicins, a group of tyrosine kinase inhibitors <2002T4403>. Highly enantioselective (up to 90% ee) oxidation of enol silyl ethers derived from tetralones yielding the corresponding α -hydroxytetralones were reported both by Shi's and Solladié-Cavallo's groups, using fructose-derived dioxirane **71** and α -fluorocyclohexanones **96–113**, respectively <1998TL7819, 2003TL6523>.



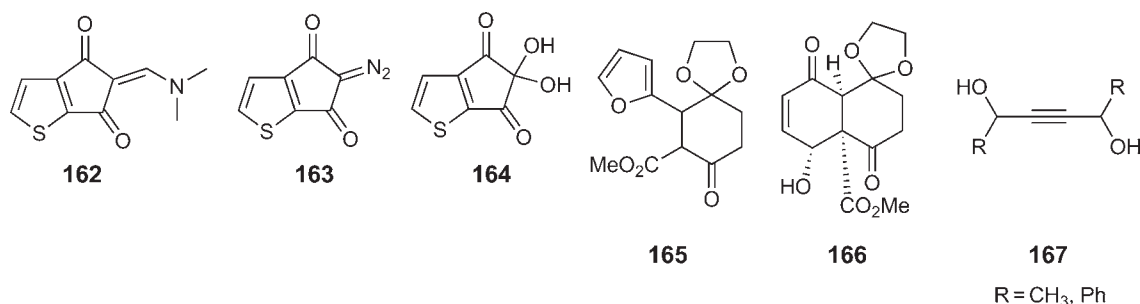
1.14.5.4 Decomposition and Rearrangement of Dioxiranes

The kinetics of decomposition of the DMDO **1b** have been studied in the reaction of adamantane oxidation both in the presence and in the absence of CCl₃Br <1996TL249>. The authors found that in the absence of CCl₃Br the

kinetics obey a second-order rate law, already found for the reaction of simple alkanes and cycloalkanes with dioxiranes. A more complex kinetic behavior was found when the reaction was run in the presence of CCl_3Br , and the products suggest that dioxirane radical decomposition may have occurred.

1.14.5.4.1 Miscellaneous reactions

Treatment of intermediary **162** or **163** with DMDO **1b** yielded a clean conversion to the thianthrin **157** <1997T4239>. The reaction of the furano-ketone **165** with **1b** gave the highly functionalized *cis*-decalin **166** via ring opening of the furan ring and cyclization <1999SL240>. DMDO **1b** and TFDO **1c** have been used to achieve selective and direct transformation of acetylenic 1,4-diols **167** into the corresponding diketones, leaving the acetylenic triple-bond moiety unreacted <2004TL8575>. A series of epoxy alcohols have been selectively oxidized into the corresponding epoxy ketones in high yield by **1b** and **1c** with no influence on configuration on the chiral centers of the epoxy functionality <2004JOC8510>.

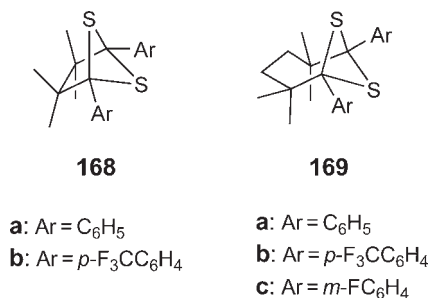


Oxidative nucleophilic substitution of the hydrogen in nitroarenes with the carbanion of isopropyl phenylacetate using **1b** gives corresponding isopropyl hydroxyaryl(phenyl)acetates, which is not the case with $\text{Bu}_4\text{N}^+\text{MnO}_4^-$ or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidants <2005T11952>.

1.14.6 Synthesis of Three-Membered Rings with Two Oxygen and/or Sulfur Atoms

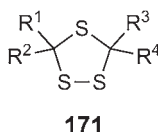
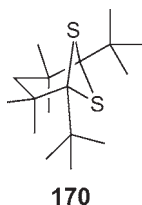
1.14.6.1 Dithiiranes

Ishii *et al.* prepared alkylaryldithiiranes **18**, **19**, and **25** by the reaction of 5,6-dithiabicyclo[2.1.1]hexanes **168** and 7,8-dithiabicyclo[4.1.1]octane **169** with Oxone in a two-phase water/dichloromethane system. These dithiiranes are stable in solution and their formation was proved by UV/Vis spectroscopy and chemical transformations, including the MCPBA oxidation to corresponding dithiirane *S*-oxides <1995TL1867>.

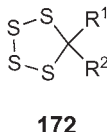


In similar way, starting from bicycloheptane **170**, the dialkyl dithiirane **39** and its stereoisomeric *S*-oxides **40** have been prepared and fully characterized <1997TL1431>. The parent dithiirane **3a** together with the thiosulfine **12a** was generated by flash vacuum pyrolysis of the unsubstituted 1,2,4-trithiolane **171a** in argon matrix. Depending on the wavelength, either a reversible interconversion between thiosulfine and dithiirane or the irreversible rearrangement into dithioformic acid can be achieved <2001AGE393>. Methyl dithiirane **3b** and dimethyl dithiirane **3c** have also been synthesized by flash vacuum pyrolysis of tetramethyltrithiolane **171c** and 3,5-dimethyl-1,2,4-trithiolane **171b** in an argon matrix <2006EJO3721>.

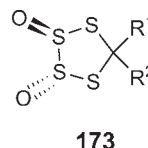
Dithiirane *S*-oxides are also synthetically available by oxidation of tetrathiolanes with DMDO **1b**. In such a way, di(1-adamantyl)dithiirane *S*-oxide **5**, as well as stereoisomers of 1-adamantyl-*tert*-butyldithiirane *S*-oxide **20**, were prepared from corresponding tetrathiolanes **172** <1998TL3525>. When oxidized with 4 molar amounts of **1b**, tetrathiolane **172** gives dioxide **173**, which was reported to decompose above -10°C in solution to yield corresponding diastereomeric dithiirane 1-oxides **20** (91%), the tetrathiolane **172** (8%), and elemental sulfur <1999JA7959, 2000JOM(611)127>.



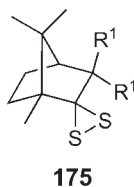
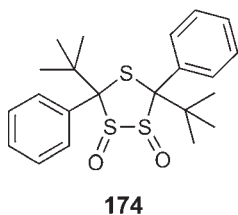
- a:** $\text{R}^1=\text{R}^2=\text{R}^3=\text{R}^4=\text{H}$
b: $\text{R}^1=\text{R}^3=\text{H}; \text{R}^2=\text{R}^4=\text{Me}$
c: $\text{R}^1=\text{R}^2=\text{R}^3=\text{R}^4=\text{Me}$



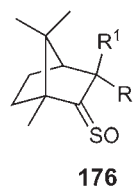
- a:** $\text{R}^1=\text{R}^2=1\text{-Ad}$
b: $\text{R}^1=t\text{-Bu}; \text{R}^2=1\text{-Ad}$



The synthesis of **23b** from the decomposition of 1,2-dioxide **174** has also been reported, but the reaction suffers from many side products and only 14% of dithiirane 1-oxide has been detected <2004JOC1695>. Sterically crowded spirodithiiranes **175** have been synthesized by treatment of thione *S*-oxides **176** derived from *d*-camphor with Lawesson's reagent **54** <1998TL3525>. Dithiiranes **175** have been characterized but not isolated because of their fragile nature during chromatography. The same article reports subsequent oxidation of **175** using MCPBA to give corresponding stable *S*-oxides **6** and **175a**.

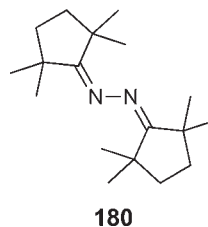
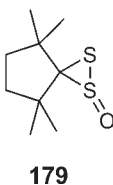
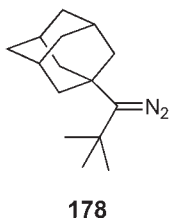
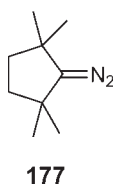


- a:** $\text{R}^1-\text{R}^2=(\text{CH}_2)_4$
b: $\text{R}^1-\text{R}^2=\text{CH}_2\text{-}o\text{-C}_6\text{H}_4\text{-CH}_2$

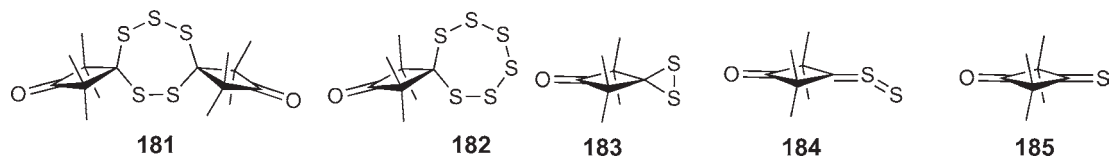


- a:** $\text{R}^1-\text{R}^2=(\text{CH}_2)_4$
b: $\text{R}^1-\text{R}^2=\text{CH}_2\text{-}o\text{-C}_6\text{H}_4\text{-CH}_2$

The reaction of diazocompounds with S_2O represents an alternative method for generation of dithiirane 1-oxides. Thus, diazocyclopentane **177** and 1-adamantyl-*tert*-butyldiazomethane **178** reacted with S_2O to give corresponding dithiirane 1-oxides **179** and **20** along with azine **180** and ketone **48**, respectively <2001AGE1924>. Also, (9-triptycyl)-diazomethane in the reaction with S_2O furnished dithiirane 1-oxide **9** (18%) <2005T6693>.

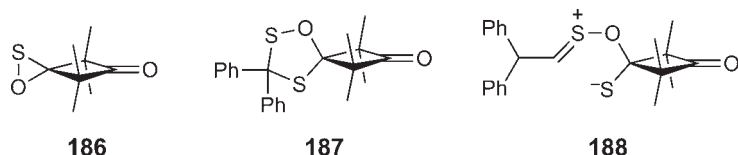


Młostoń *et al.* reported that the formation of seven-membered sulfur heterocycles **181** and **182** possibly appears to be the result of a domino reaction involving both the dithiirane **183** and its valence isomer, thiosulfine **184** <2002JOC5690>. Dithiirane **183** is presumed to exist in equilibrium with the thiosulfine **184** and is generated from the reaction of **185** with elemental sulfur in the presence of sodium benzenethiolate.

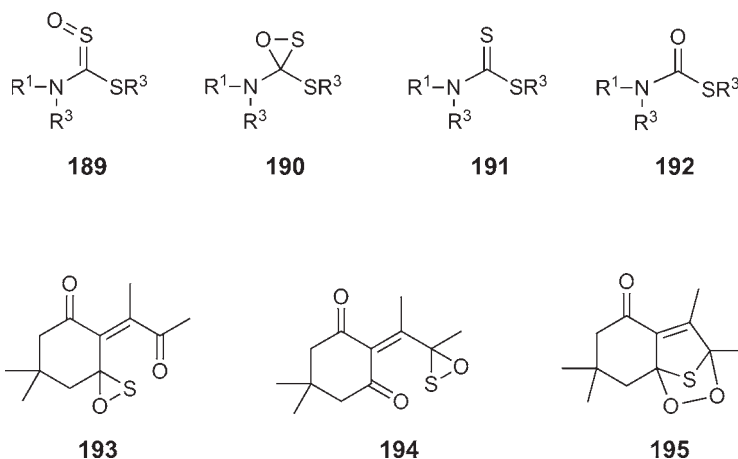


1.14.6.2 Oxathiiranes

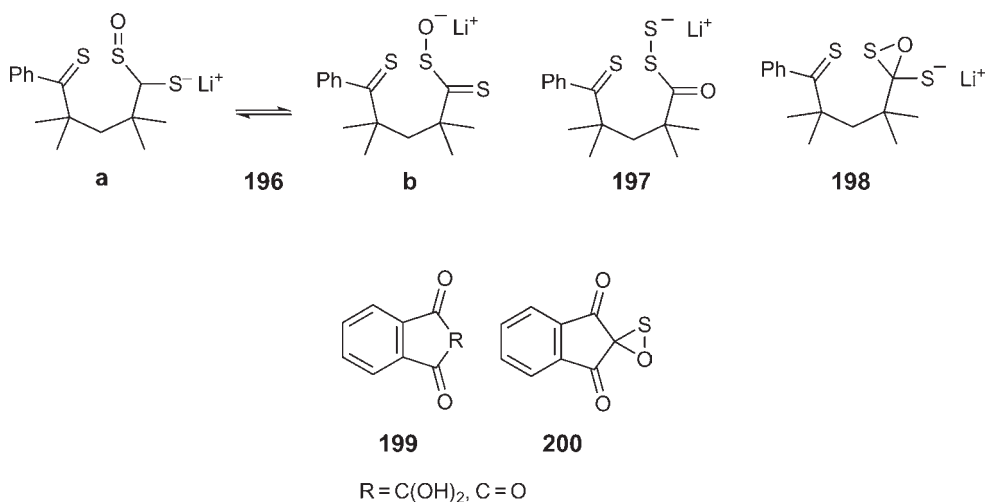
In the last 10 years, this extremely labile class of three-membered rings has been sporadically reported mostly as possible intermediates, and only one paper of Sander *et al.* deals with the characterization of the oxathiirane structure in argon matrix by IR spectroscopy <2006EJO2918>. The hypothetical reaction pathway toward oxathiirane **186** has been proposed and includes the oxadithiolane **187**, which equilibrates with the sulfonium thiolate zwitterion **188**, and finally yields oxathiirane **186** by intramolecular substitution <1997LA187>. These types of oxathiiranes are reported as the hypothetical intermediates in the conversion of thiocarbonyl *S*-oxides into corresponding carbonyl compounds.



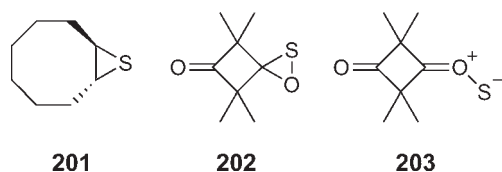
Electrocyclization of the (*E*)-sulfines **189** to the intermediate oxathiiranes **190** on the way to corresponding C=S or C=O compounds **191** and **192** has been suggested <1998TL8983>. Oxathiiranes **193** and **194** has been also postulated in the thermolysis of 2,5-dimethylthiophene endoperoxide **195** <1998JA8914>. The endoperoxide **195** has been prepared by photooxygenation of corresponding thiophene, and its derived oxathiiranes **193** and **194** have shown to efficiently transfer a sulfur atom to norbornene, cyclooctyne, and cyclooctene <2002JA8316>. The authors stipulate that the oxathiirane **193** is preferentially formed and acts as sulfur-transferring intermediate because of its extended conjugation in comparison to the cross-conjugation in **194**.



The rearrangement of **196** to **197** possibly proceeds via the oxathiirane intermediate **198** <1999T10341>. In the reaction of **199** with potassium thiosylate, an intermediary oxathiirane **200** is responsible for transfer of up to 18% of the available sulfur to the *trans*-cyclooctene <2000OL2519>.

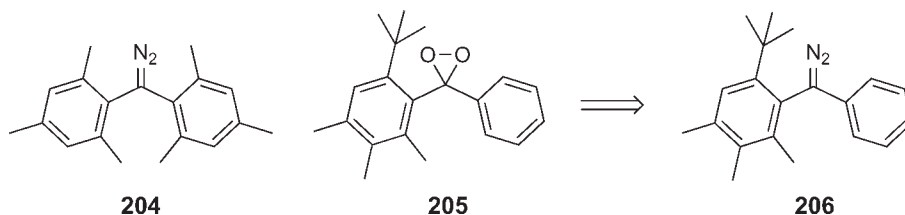


Adam *et al.* reported a direct sulfur transfer from the labile 1,2,4-oxadithiolane **187** to the *trans*-episulfide **201** in the presence of *trans*-cyclooctene [<2003EJO4012>](#). The authors proposed the transient oxathiirane **202** and carbonyl *O*-sulfide **203** as the active episulfidating agents. In the oxathiirane **202**, the sulfur atom is positively polarized, while in **203** it is negatively charged, making **202** more electrophilic and more likely to serve as a sulfur-donating species. In the study of photochemistry of the α -diazo sulfoxide **26**, the oxathiirane **11** has been observed as an intermediate in an argon matrix at 10 K and was already mentioned in [Section 1.14.3.2.1 <2006EJO2918>](#).



1.14.6.3 Dioxiranes

The synthesis of diverse dioxiranes using the Oxone system remains the most used method for their preparation. The variety of the structures of *in situ* dioxiranes generated from corresponding ketones is presented in [Section 1.14.5.2](#). Using this method, the synthesis and characterization of interesting mono- and bis-dioxiranes **27** and **28** from biacetyl has been reported [<2006JOC5796>](#). Apart from ketones, aldehyde-derived dioxiranes have also been used as catalysts for asymmetric epoxidations of unfunctionalized alkenes [<2003TL7403>](#). In the preparative-scale synthesis of dimesityldioxirane **4**, the precursor dimesityldiazomethane **204** was employed [<1997JA7265>](#). The authors used preliminary matrix isolation studies for the spectroscopic characterization of reactive intermediates with the aim to optimize the reaction. In the same fashion, the 6-*tert*-butyl-2,3,4-(trimethylphenyl)phenyldioxirane **205** has also been synthesized from corresponding diazo compound **206** and characterized by NMR spectroscopy [<2005EJO496>](#). Keto-derivatized cyclodextrins have been reported to catalyze peroxomonosulfate oxidation of different substrates, most probably by the formation of corresponding cyclodextrin dioxiranes [<1998CAR17, 1999CAR10>](#).



Sawaki and co-workers reported a direct observation of the cyclization of diarylcarbonyl oxide using trapping and laser flash spectroscopic experiments <2004TL5791>. They have shown that the reactivity of intermediate carbonyl oxides is controlled and tuned by the resonance-stabilizing donor substituent. Another approach to converting ketones into dioxiranes includes reaction of arenesulfonylimidazoles with hydrogen peroxide <1997JOC188>.

1.14.7 Important Compounds and Applications

Murray and Singh have reported an improved synthesis of DMDO **1b** <1997OS91>, while Curci and co-workers have reported an improved synthesis of TFDO **1c** <2003SC3009>. A growing interest in utilizing *in situ*-generated dioxiranes as oxidants for synthetic, bleaching, and decontamination applications is reflected by an increasing number of patents and application articles. Thus, *in situ*-generated dioxirane(s) are used for the neutralization of chemical and biological warfare (CBW) agents <2005USP20050085402>. Dioxiranes derived from bicyclic or tricyclic diketones are used for bleaching fabrics <1996USP5525121>. Cleaning compositions in dentistry including dioxirane in aqueous solution are also in use <2003USP20030118520>. A series of δ -substituted 5-unsaturated steroids, bearing different functional groups such as hydroxy, carbonyl, acetyl, or ketal groups as well as different side chains, have been converted to the corresponding synthetically and biologically interesting 5 β ,6 β -epoxides with excellent β -selectivities and high yields using dioxiranes <2005USP6841665>. A process for preparing dioxiranes from ketones and their use in the oxidation of substrates susceptible to nucleophilic oxidation have been described <1997USP5621118>. Catalytic asymmetric epoxidation of prochiral olefins using a chiral ketone has also been subjected to patent applications <1998USP5763623, 2002USP6348608, 2002USP20020133031, 2003USP20030055293>. A process for the oxidation of tertiary amines and nitrogen-containing aromatic heterocycles to amine oxides has been described <2003USP20030078424>. Delcomyn *et al.* have reported an analytical method for the determination of *in situ*-generated DMDO from an aqueous matrix using a selected ion-monitoring method <2005JCH(1089)211>. Dioxiranes generated *in situ* from pyruvates and Oxone have been found to be environmentally friendly oxidizing agents for disinfection <2006EST625>.

1.14.8 Conclusion

Dithiirane chemistry has provided a few untypical crystal structures as well as stereochemically and kinetically interesting reactions.

Still, little is known about oxathiiranes; they have been proposed as reaction intermediates and are reported to be unstable, but detectable in argon matrices.

In contrast, dioxirane chemistry has increasingly developed. Dioxiranes are approved as very powerful chemo- and stereoselective oxidative reagents. Remarkable progress has been made in developing dioxirane-catalyzed enantioselective oxidations.

1.14.9 Further Developments

There are a number of very recent publications dealing with the chemistry and application of dioxiranes. The use of dioxiranes in chemo- and stereoselective oxidations continue to be in the focus of interest. DMDO **1b** has been used in an efficient one-pot *trans*-dihydroxylation of 2*H*-pyrans used in the synthesis of some natural products <2007TL6275>. Oxidation of some cage hydrocarbons has been performed using **1b** and **1c** and experimental results compared with DFT calculations <2007OBC2302>. Polybutadienes and hydroxyl-terminated polybutadiene have been chemoselectively epoxidized using DMDO/MoO₃ complex and *in situ* generated DMDO **1b** <2007MI119, 2007MI67>. Chiral dioxiranes obtained from glucose-derived ketones and oxone have been used in highly chemo- and enantioselective epoxidation of conjugated *cis*-enynes <2007JOC4093>. Direct and highly stereoselective C–H insertion reaction at *tert*-CH of *cis,cis*-1,3,5-trimethylcyclohexane and of 1,3- and 1,4-dimethylcyclohexane has been achieved using TFDO **1c** <2007TL3575>. Trapping of triplet 1,3-diphenylpropynylidene, generated by photolysis ($\lambda > 571$ nm) of 1,3-diphenyldiazopropyne, with O₂ resulted in corresponding dioxirane among other trapping products <2007JA2308>. A simple protocol for the preparation of TFDO **1c** on a preparative scale has also been reported <2007SL47>. A method of producing a dioxirane-based multi-purpose bleaching

solution has been described <2007USP2007219108>. A process for preparation of diazacyclopentalene derivatives (building blocks for cysteinyl proteinase inhibitors) by TFDO **1c** mediated epoxidation of dihydropyrroles has also been subjected to patent application <2007WO2007017698>.

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1.15

Three-membered Rings with Two Heteroatoms including Selenium or Tellurium; Three-membered Rings with Three Heteroatoms

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1.15.1 Introduction

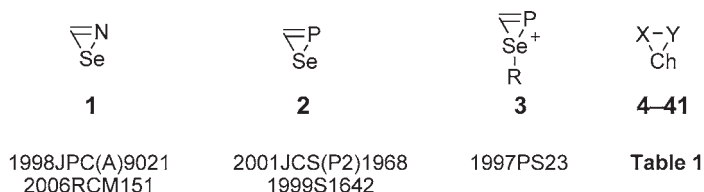
In the 'Outlook' of Chapter 1.15 written for CHEC-II(1996) [<1996CHEC-II\(1\)457>](#), the following prediction was made: "Since remarkable progress has been made in the chemistry of highly reactive multiple-bond species including heavier typical elements by taking advantage of kinetic stabilization, the synthesis of a number of new types of heteroatom-containing three-membered ring systems will be achieved starting from such unsaturated compounds." This prediction has indeed turned out to be correct, and additional results have appeared in the last 10 years on those ring systems containing two heavy atoms – mainly two group 15 elements and one Se or Te atom, these being obtained from the heavily substituted RE=ER (E: P, As, Sb) double-bonded compounds. Some further reports appeared, also on systems containing a heavy chalcogen and one carbon and a further heteroatom (Ge, P) and also the synthesis of a diselenasilirane and a diselenastannirane have been reported. Especially noteworthy, however, is the lack of data on three-membered rings containing nitrogen apart from the heavy chalcogen elements.

Information on unsaturated systems is scarce, and only a phenylated (at Se) selenaphosphirenium cation has been observed by nuclear magnetic resonance (NMR) spectroscopy in the presence of a noncoordinating counterion (CF_3SO_3^-), which was transformed to a selenaphosphene with halide counteranions [<1997PS23>](#). The assumed

presence of selenaphosphirene as a very reactive (and therefore unobservable) intermediate is also a reasonable assumption. This is supported by the formation of the final reaction product (1,2,4-selenadiphosphole) in the reaction of $\text{Bu}^t\text{C}\equiv\text{P}$ and selenium <1999S1642>.

The number of synthesized systems is small. This fact can be attributed to difficulties arising from the instability of the strained ring systems. Computational results are also scarce in spite of the likely interest in the antiaromaticity of the unsaturated three-membered rings containing a chalcogen element. Among the unsaturated compounds, only **1** <1998PCA9021, 2006RCM151> and **2** <2001J(P2)1968> have been computed, but their properties were not discussed.

We discuss the compounds presented in **Scheme 1** and **Table 1**, where it is also summarized what kind of information is available about the different rings. For the successful synthesis of these compounds, the use of bulky protecting groups is mandatory. In **Scheme 2**, we have collected these various groups with the abbreviations used in the chapter.



Scheme 1 Unsaturated and saturated ring systems discussed in the review with numbering.

1.15.2 Theoretical Methods

1.15.2.1 General Remarks, Saturated Rings

Three-membered rings are known to be destabilized by significant angle strain; however, this effect is compensated partly by σ -aromaticity, which was first suggested by Dewar, for cyclopropene <1984JA669>. Recently, it has been shown by Schleyer and co-workers <2005PCA3711> that all kinds of saturated homoatomic three-membered rings formed from main group elements ($(\text{SiH}_2)_3$, $(\text{GeH}_2)_3$, $(\text{NH})_3$, $(\text{PH})_3$, $(\text{AsH})_3$, O_3 , S_3 , and Se_3) exhibit σ -aromaticity. Inagaki and co-workers <2004CL934> have derived a single electron counting rule summing up the electrons of atomic p orbitals including σ (axial and tangential) and π (perpendicular) contributions. While the tangential orbital set is stabilized by Möbius aromaticity, the axial and perpendicular orbitals are subject to Hückel aromaticity requirements. The resulting conclusions are similar to the results of Schleyer and co-workers, for example, for Se_3 .

A further instructive statement has been formulated by Bachrach and Jiang <1998MI204945> pointing out the beneficial stabilizing effect of second- and third-row atoms in the three-membered rings. This stabilizing effect is attributed to the bonding angles, which tend to be much smaller than at carbon, thereby better accommodating the small angles of the ring. Also, the long bonds between the heavy atoms allow the angles to widen and therefore reduce the strain. Thus, it is understandable that three-membered rings containing heavy atoms, but not with nitrogen, are reported.

Structural data were computed for diphenyl- and dimethyl selenodiphosphirane (at the B3LYP/6-311G(2d,p) level) <2003JPO450>, and for dimesityltelluradistibirane and dimesityltelluradibismirane (B3LYP functional and effective core potentials of different quality) <2005AGE3717>. The bond distances are in reasonable agreement with X-ray structural parameters of more heavily substituted derivatives. This agreement between the different structures led the authors to conclude that the chalcogenodiphosphiranes and their heavier analogs can generally be described with single bonds, unlike their group 14 element-containing analogs selenadisiliranes and their heavier-element-containing congeners discussed in <1996CHEC-II(1)457>. The latter compounds can rather be described as a π -complex between the chalcogen and the double bond formed between the group 14 elements. Interestingly, no theoretical study seems to deal with an analysis of the different bonding mode in these related three-membered rings.

1.15.2.2 Theoretical Treatment of Fully Conjugated Rings

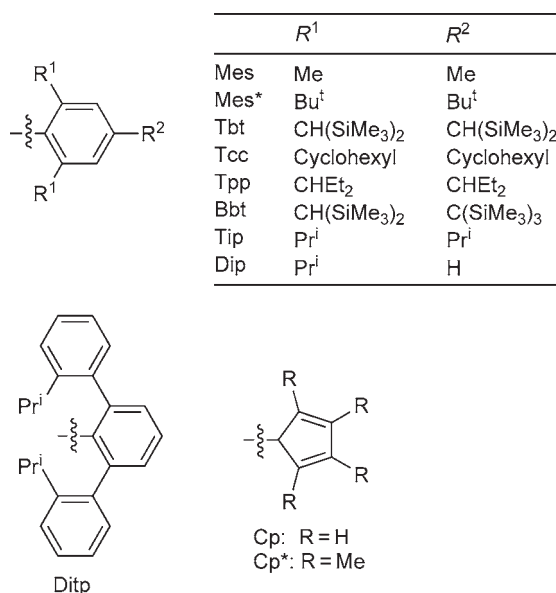
While the effect of σ -aromaticity is known to stabilize three-membered rings as discussed above, for the unsaturated systems containing one Se or Te atom, a destabilizing π -antiaromaticity is predicted by the Hückel rule. In spite of the possible interest regarding π -antiaromaticity of these rings, only three reports could be found in the literature dealing with calculations for the selenazirine **1** <1998PCA9021, 2006RCM151> and selenaphosphirene **2** ring systems <2001J(P2)1968>. However, as these works were aimed at different subjects, the computation studies of

Table 1 ChXY Saturated rings (**Scheme 1**) with numbering, references, and available spectroscopic information. X-ray means that an X-ray structure is available; DFT, density functional theory

No.	Ch	X	Y	References	Available data
4	Se	C	Si	1996CHEC-II(1)457	
5	Se	C	Ge	1997OM5127	
6	Se	C	Sn	1996CHEC-II(1)457	
7	Se	C	N	a	
8	Se	C	P	1996CHEC-II(1)457, 2000T6259, 2002JA9706, 2003BCJ471	X-ray, NMR
9	Se	C	As	a	
10	Se	C	Sb	a	
11	Se	C	Se	a	
12	Se	Si	Si	1996CHEC-II(1)457, 2002CL34	NMR
13	Se	Si	Se	2002CL34	NMR, UV-Vis
14	Se	Ge	Ge	1996CHEC-II(1)457	
15	Se	Sn	Sn	1996CHEC-II(1)457	
16	Se	Sn	Se	1997JA11124	X-ray, NMR
17	Se	N	N	a	
18	Se	P	P	1996CHEC-II(1)457, 1994CB997, 1995CB1207, 1995HAC33, 2003JPO450	X-ray, NMR, DFT
19	Se	As	As	a	
20	Se	Sb	Sb	1998CL725	X-ray, NMR
21	Se	Se	Se	1999PCA4078, 2004CL934	
22	Te	C	Si	a	
23	Te	C	Ge	1997OM5127, 1998CL811	X-ray, NMR
24	Te	C	Sn	a	
25	Te	C	N	a	
26	Te	C	P	a	
27	Te	C	As	a	
28	Te	C	Sb	a	
29	Te	C	Te	a	
30	Te	Si	Si	1996CHEC-II(1)457, 2002CEJ2730	X-ray, NMR
31	Te	Si	P	1996OM1845	NMR, MS
32	Te	Si	As	1996CHEC-II(1)457	
33	Te	Ge	Ge	1996CHEC-II(1)457, 2003OM5212	
34	Te	Sn	Sn	1996CHEC-II(1)457	
35	Te	Sn	Te	a	
36	Te	N	N	a	
37	Te	P	P	1993ZAAC1083	NMR, MS
38	Te	As	As	a	
39	Te	Sb	Sb	2005AGE3717	X-ray, DFT
40	Te	Bi	Bi	2005AGE3717	X-ray, DFT
41	Te	Te	Te	1999PCA4078	

^aNo literature found.

these three-membered rings were carried out primarily to have a more complete description of the system investigated. Thus, neither the bonding structure nor the likely π -antiaromaticity was discussed. Compound **1** was computed at the G2(MP2, SVP) level and was predicted to be less stable than selenocyanate HNCSe and nitrile selenide HCNSe by 145.4 and 24.2 kJ mol⁻¹, respectively <1998PCA9021>. Also, the corresponding radical cations were considered and the destabilization of the three-membered ring **1**⁺ is somewhat altered here (112.9 and 58.8 kJ mol⁻¹, with respect to the HNCSe⁺ and HSeCN⁺ radical cations, respectively). In contrast, selenaphosphirene **2** was reported (in a footnote) to be more stable than HC≡P=Se <2001JP21968>. This reversed stability ordering is in agreement with the stabilizing role of second- (and third-) row elements on three-membered rings <1998MI204945>. An indication that the antiaromatic selenaphosphirene ring is rather unstable can be concluded from the fact that selenaphosphirene + HCP was calculated to be less stable than 1,2,4-selenadiphosphole by as much as 301.9 kJ mol⁻¹ <2001JP21968>. Nevertheless, selenaphosphirene was a real minimum on the potential energy surface. This conclusion was obtained upon an attempted optimization of the 1,3-dipole P⁺=C(R)-Se⁻, previously suggested as a reaction intermediate <1999S1642>. The Se₃ and Te₃ rings were also computed and their relative energy was compared to the open-chain isomers <1999PCA4078>.



Scheme 2 Bulky protecting groups and their abbreviations used in this chapter.

1.15.3 Experimental Structural Methods

1.15.3.1 X-Ray Structures

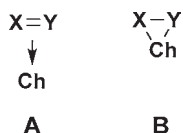
Table 2 shows the structural data of rings containing group 14 elements as well as Se or Te.

Table 2 Structural data of rings (C–X–Y) containing heavy group 14 elements (Si, Ge, Sn) and Te

No.	Ch	X and Y with substituent	ChX (Å)	ChY (Å)	XY (Å)	XChY (deg)	Reference
33	Te	X = Y: Ge(Tip) ₂	2.6107	2.6107	2.4694	56.45	2003OM5212
30	Te	X = Y: Si(Ph, SiBu ^t) ₃	2.536	2.532	2.343	55.1	2002CEJ2730
23a	Te	X: Ge(Mes, Tbt), Y: C=R ^a	2.597	2.11	1.88	45.8	1997OM5127

^aR: fluorenyl.

It has previously been discussed <1996CHEC-II(1)457> that the structure of three-membered rings containing heavy group 14 elements can be described as a π -complex, formed between a group 14 element double bond and the chalcogen (A, **Scheme 3**).



Scheme 3 Models to describe the bonding in saturated three-membered rings.

The telluradigermirane and the telluradisilirane structures covered in the present report have somewhat different substituents at the group 14 elements than those reported before <1996CHEC-II(1)457>, but this variation results only in slight structural differences (bond lengths differ by less than 0.02 Å). In the case of the telluradisilirane ring **30**, the ring silicon atoms have exocyclic silyl substituents, allowing for a direct comparison of the exocyclic (2.405(7)–2.455(7) Å) and endocyclic (2.34 Å) SiSi distances. The shortening of the endocyclic SiSi bonds indicate at least a partial double bond character. Also, in agreement with the previous structural findings, the silicon and germanium

environment is nearly planar (excluding tellurium). All of these geometrical parameters also hold for the telluragermylene **23a** ring, suggesting that the bonding in the three-membered ring with at least one heavy group 14 element can be described as a π -complex between the chalcogen element and the double bond (A, [Scheme 3](#)).

For the group 15 elements, however, the bonding situation seems to be somewhat different. The bulky substituent groups at the group 15 atoms are in a *trans*-arrangement and form a plane together with the two group 15 element atoms. This feature alone could be a characteristic of a π -complex, but it can also be attributed to the pyramidally arranged phosphorus (arsenic, antimony, or bismuth) atoms. The distance between the group 15 elements falls in the normal single bond range. These structural features were also reproduced by density functional theory (DFT) computations, where smaller substituent groups were used [\[2003JPO450, 2005AGE3717\]](#). Thus, it seems that the structure of the three-membered rings with two group 15 elements can properly be described using the usual single bond model (B, [Scheme 3](#)). Although these structural differences have been pointed out, (see [Table 3](#)) no theoretical work has been carried out to analyze these phenomena.

Table 3 Structural data of rings containing two heavy group 15 elements as well as Se or Te

No.	Ch	X with substituent	ChX (Å)	ChX (Å)	XX (Å)	XChX (deg)	Reference
18	Se	PCp ⁺	2.268(2)	2.266(3)	2.202(3)	58.1(1)	1994CB997
18	Se	PBbt ^a	2.250(3)	2.250(3)	2.250(3)	59.70(8)	2003JPO450
			2.270(3)	2.270(3)	2.239(4)	59.46(10)	
20	Se	SbBbt	2.565(1)	2.562(2)	2.852(2)	67.60(5)	1998CL725
39	Te	SbBbt	2.7607(7)	2.7719(6)	2.8833(6)	62.817(16)	2005AG(E)3717
40	Te	BiBbt	2.8546(4)	2.8648(4)	3.02388(3)	64.190(9)	2005AG(E)3717

^aTwo molecules were found with one hexane in the unit cell.

The structure of the diselenastannirane ring **16** (with Tbt and Ditp substituents on tin) is a nearly equilateral triangle [\[1997JA11124\]](#). The Se–Se distance (2.524(4) Å) is significantly longer (by about 0.2 Å) than the typical Se–Se single bond length, while the Sn–Se distance (2.528(2) and 2.532(3) Å) is typical of a Sn–Se single bond. For the three-membered ring Se₃, bond lengths of about 2.40 Å have been computed with reasonably large basis sets [\[1999PCA4078\]](#). Unfortunately, for the related diselenasilirane [\[2002CL34\]](#), no X-ray structure data have been obtained, and consequently it is not clear if the long Se–Se bond is a characteristic typical of three-membered rings with two selenium atoms.

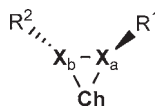
The selenaphosphirane structure is of particular interest, since it contains an unprecedented pentavalent phosphorus. The phosphorus atom is in the center of a highly distorted trigonal bipyramid; the selenium and the carbon ring atoms are in the apical and equatorial positions, respectively. The P–Se distance is 2.4540(10) Å, and the C–Se and C–P bond lengths are 1.998(2) and 1.767(2) Å, respectively. While the C–Se distance is in the typical range for a single bond, the P–Se distance shows a considerable lengthening with respect to the sum of the covalent bond radii (2.27 Å). Although some lengthening is typical for the axial bonds, it is worth mentioning that in the NMR spectrum, no ¹J_{PSe} coupling has been observed (see below) [\[2002JA9706\]](#).

1.15.3.2 NMR Data

The only unsaturated compound observed by NMR spectroscopy is **3** (R = Ph), as a reaction intermediate with the noncoordinating CF₃SO₃[−] counteranion. Analysis of the reaction mixture by ³¹P NMR spectroscopy has shown that it contains a single resonance signal at 350 ppm (¹J_{SeP} 315 Hz) [\[1997PS23\]](#) consistent with the chemical shift observed for the phosphirenylium cation (309.7 ppm).

Most of the saturated heteroselenirane and heterotellurirane rings investigated by NMR spectroscopy contain group 15 elements, having the general formula shown in [Scheme 4](#). The most relevant NMR properties are summarized in [Table 4](#). Unfortunately, no signal was observed in the ¹²⁵Te NMR spectrum of **40** probably due to considerable peak broadening caused by the adjacent two bismuth atoms having nuclear spins of 9/2. The high field Te and P shift was noted to be characteristic of the small diphosphatellurirane ring **37** [\[1993ZFA1083\]](#).

The difference of the chemical shifts between the aryl and the *O*-aryl-substituted phosphorus atoms, as well as the Se–P coupling constants, has been attributed to an increase in sp² character of that phosphorus which bears the oxygen substituent [\[1995HAC33\]](#). Unfortunately, there is no X-ray structure available for these compounds,



Scheme 4 Substituted dipnictogen-seleniranes.

Table 4 The most important NMR data of substituted dipnictogen-seleniranes and -telluriranes shown in [Scheme 4](#)

No.	Ch	X	R ¹	R ²	δ_{Ch} (ppm)	δ_{Ea} (ppm)	δ_{Eb} (ppm)	$^1J_{ChEa}$ (Hz)	$^1J_{ChEb}$ (Hz)	Reference
18	Se	P	Cp [*]	Cp [*]	379.1	88.9	88.9	124.7	124.7	1994CB997
18	Se	P	Mes [*]	OMes [*]	27.6	−65.2	76.6	103.0	236.2	1995HAC33
18	Se	P	R ₁	R ₁	152.2	−3.7	−3.7	90.0	90.0	1995CB1207
18	Se	P	Bbt	Bbt	14.6	−55.3	−55.3	126	126	2003JPO450
20	Se	Sb	Bbt	Bbt	95.0	a	a	a	a	1998CL725
37	Te	P	Bu ^t	Bu ^t	−696	−70	−70	229	229	1993ZAAC1083
39	Te	Sb	Bbt	Bbt	−622.3	a	a	a	a	2005AG(E)3717
40	Te	Bi	Bbt	Bbt	a	a	a	a	a	2005AG(E)3717

R¹: $-\text{C}(\text{SiMe}_3)=\text{PPh}_3$.

^aNo data available.

although it would be interesting to see whether the increased s character of phosphorus was also structurally noticeable. Such a change in the hybridization is likely to influence the bonding angles about phosphorus; furthermore, it might affect the π -complex character (A, [Scheme 3](#)) of the three-membered ring.

The $^1J_{\text{SeP}}$ coupling constant has been noted to be unusually small; however, it was considered to be characteristic of the three-membered rings [<1995CB1207>](#). The dynamic behavior of the Cp^{*} ligands could clearly be seen by ^1H NMR spectroscopy. At room temperature, three broad signals could be detected at $\delta = 1.93$, 1.78, and 0.78 ppm at -15°C , five singlets were observed as a result of the diastereotropy of the methyl groups [<1994CB997>](#).

The selenaphosphirane **8a** has been characterized by multinuclear NMR spectroscopy; however, no ^{77}Se chemical shift data were reported. The $\delta = -41.1$ ppm chemical shift for phosphorus and the $^1J_{\text{PSe}}$ coupling constant of 125 Hz ([Table 5](#)) are close to the values observed for the aryl-substituted diphosphaseleniranes ([Table 4](#)), and are in good agreement with its proposed structure. The configuration of the Se atom has been determined on the basis of the J_{PC} coupling constants [<2000T6259>](#).

Table 5 NMR spectroscopic data for **8a** and **8b** observed in different solvents

No.	Solvent	δ_{Se} (ppm)	δ_{P} (ppm)	$^1J_{\text{PSe}}$ (Hz)	Reference
8a	C ₆ D ₆	a	−41.1	125	2000T6259
8b	Solid state	a	−26.1	b	2002JA9706
8b	C ₆ D ₆	147.5	−26.6	b	2002JA9706
8b	CD ₃ CN	144.3	−20.2	b	2002JA9706
8b	CD ₂ Cl ₂	138.3	−19.3	b	2002JA9706
8b	CDCl ₃	129.9	−13.6	b	2002JA9706

^aNo data available.

^bNo coupling was observed.

The 1,2 σ^5 -selenaphosphirane **8b** [<2002JA9706>](#) has different NMR characteristics from the known 1,2 σ^3 -selenaphosphiranes (e.g., **8a**). The $\delta_{\text{P}} = -26.1$ ppm chemical shift [Table 5](#) in the solid-state ^{31}P NMR spectrum ($\delta_{\text{P}} = -26.6$ ppm in C₆D₆) is typical of a pentacoordinate phosphorus. In the ^{77}Se NMR spectrum (C₆D₆ solvent), a singlet was observed at $\delta_{\text{Se}} = 147.5$ ppm. In contrast to the 1,2 σ^3 -selenaphosphiranes, no coupling has been observed between the selenium and phosphorus nuclei. The spectrum exhibits a strong solvent dependence, as it is summarized in [Table 5](#). With the increasing acceptor number of the solvent, the ^{31}P NMR and ^{77}Se chemical shifts change toward the higher and lower fields, respectively. The ^{31}P NMR signal, however, is still at the high field region, and

thus it was argued [<2002JA9706>](#) that the pentacoordinate state of phosphorus is retained in all solvents used for the investigation. Not only do the phosphorus and selenium signals show solvent dependence, the α -proton of the aryl ring attached to phosphorus is also sensitive to the solvent, exhibiting a shift toward lower fields as the acceptor number of the solvent becomes larger. All these observations were attributed to an increasing Se–P charge separation (particularly an increasing negative charge at selenium) with the increasing solvent acceptor number. Together with the long Se–P distance and the highly distorted nature of the phosphorus trigonal bipyramid (concluded from the X-ray data of **8b**, as discussed above), it seems that this unusual bonding and thus **8b** itself is rather vulnerable.

The structure of **31** ((Tip)₂SiTePSiPr₃) has been characterized by multinuclear NMR spectroscopy ($\delta_P = -267.6$, $\delta_{Si} = -66.5$, and $\delta_{Te} = -1124$ ppm, $^1J_{PTe} = 483$ Hz) [<1996OM1845>](#). Although the ^{31}P NMR values differ considerably from those observed in diphosphatelluriranes (**Table 4**), the different substituent pattern might account for this observation. The NMR characteristics of **30** (Te(SiPh, SiBu^t)₂) are similar to those of compound **31** ($\delta_{Si} = -81.09$, $\delta_{Te} = -1285.4$ ppm, $^1J_{SiTe} = 173.9/179.4$ Hz; the splitting of the signals was attributed to hindered rotation) [<2002CEJ2730>](#).

The NMR spectroscopic data of the available stanna- [<1997JA11124>](#) and siladiselenirane [<2002CL34>](#) are collected in **Table 6**. The high field signals of the stannadiselenirane both in the ^{119}Sn and in the ^{77}Se NMR spectra were noted to be characteristic of the three membered rings, and are in good agreement with the NMR characteristics of the previously published selenadistanniranes (see 1996CHEC-II(1)457).

Table 6 NMR spectroscopic data for the known sila **13**- and stannadiselenirane **16**

No.	Group 14 element (X) with substituents	δ_{Se} (ppm)	δ_X (ppm)	Reference
13	Si(Tbt, Dip)	–174	–44	2002CL34
16	Sn(Tbt, Dip)	–193	–406	1997JA11124

1.15.3.3 Miscellaneous Spectroscopic Data

In the mass spectrometric investigations, the peak corresponding to the molecular ion has been observed for all the compounds. Due to the heavy substitution, the fragmentation pattern is more characteristic for the substituents than for the three-membered ring, and will not be discussed here in detail.

Most of the three-membered rings are reported to be colored, and this information – if available – is presented for the synthesis of the compounds. UV/Vis spectroscopic data, however, are rarely reported. In the case of the diselenasilirane, a low-lying absorption maximum at 509 nm has been reported in tetrahydrofuran (THF). This band was attributed to an $n \rightarrow \sigma^*$ absorption of the Se–Se moiety, specifically noting the significantly red-shifted band position in comparison with the usual Se–Se absorptions (e.g., 329 nm in PhSeSePh). This considerable bathochromic shift was attributed to the highly strained diselenasilirane skeleton [<2002CL34>](#). Further UV–Vis absorption data have been reported for telluradistibirane (458, 390, and 346 nm) and telluradibismirane (521, 450, and 338 nm). Apparently, the presence of three heavy atoms in the ring results in a low excitation energy. It is noteworthy that the telluradistibirane did not undergo decomposition when irradiated with a 100 W high-pressure mercury lamp, despite the low-energy excited states.

1.15.4 Thermodynamic Aspects

Most of the three-membered rings discussed in this chapter are rather stable, their decomposition temperature usually being at 150–200 °C with simultaneous melting. This can partly be attributed to the presence of the bulky protecting groups, but it seems that the presence of more than one heavy element in the three-membered ring is also a stabilizing factor.

1.15.5 Reactivity of Fully Conjugated Rings

None of the fully conjugated rings could have been isolated; however, it is apparent that some seleno- and telluraphosphirenes are reaction intermediates, as concluded from the final reaction products, which could unambiguously be characterized (see [Section 1.15.7](#)). The cationic selenaphosphirene intermediate **3** (R = Ph), which was observed by

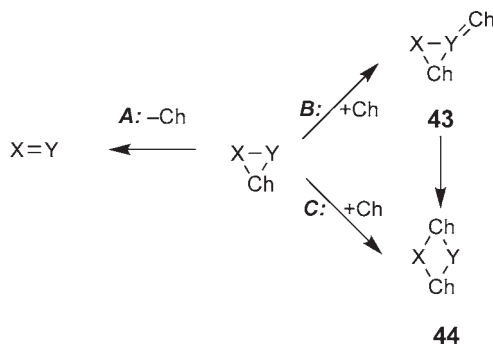
NMR spectroscopy with the noncoordinating counterion (CF_3SO_3^-), forms C-halogenated phosphalkenes as major isomers (88–98%) with counterions Cl^- or Br^- <1997PS23>, while the P halogenated regioisomers are minor reaction products. This indicates that, unexpectedly, selenium is the more electrophilic part of the cationic intermediate.

The formation of the five-membered 1,2,4-selenadiphosphole **42** <1999S1642> indicates that the 1,2-selenaphosphirene intermediate (unobservedly assumed <1999S1642>) reacts very rapidly with the $\text{Bu}^t\text{C}\equiv\text{P}$ reactant. Although this assumption seems very likely, no supporting experimental evidence was obtained. Nevertheless, in view of the computed large (301.9 kJ mol^{-1}) energy difference between that intermediate ($+\text{Bu}^t\text{C}\equiv\text{P}$) and the reaction product <2001J(P2)1968>, and by invoking the Hammond principle it would seem that a rapid reaction takes place with the unstable selenaphosphirene. The Te analog of **42** has also been obtained by a similar procedure, indicating the possible formation of the telluraphosphirene intermediate as well <1999S1642>.

1.15.6 Reactivity of Nonconjugated Rings

1.15.6.1 Introduction

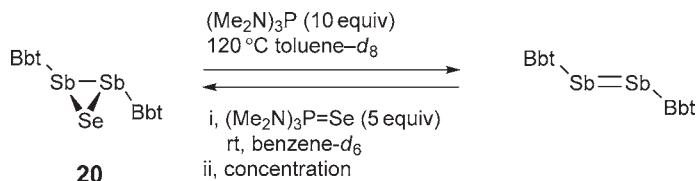
An important reaction of the three-membered rings is their decomposition with the loss of the chalcogen (reaction *A* in Scheme 5). This reaction is, in many cases, the reverse of the synthesis. In order to facilitate the decomposition, a chalcogen acceptor is needed and, in many cases, $(\text{Me}_2\text{N})_3\text{P}$ or a trialkyl-phosphine is used for this purpose. A further reaction possibility is again related to the synthesis of the three-membered ring, and is one where a chalcogen source is usually required. When the chalcogen is in excess, the well-known oxidative chalcogenation reaction of group 15 elements (P, As) can be anticipated (reaction *B* in Scheme 5) resulting in **43**. The formation of a four-membered ring with two chalcogens **44** (reaction *C* in Scheme 5) had already been reported in <1996CHEC-II(1)457> for the group 14 element containing three-membered rings. The possibility for interconversion of **43** to **44** also exists. Interestingly, not all of these reactions were observed for all of the rings. Apparently, the reactions are influenced not only by the nature of the heteroatoms, but also by the presence of the bulky protecting groups.



Scheme 5 Chalcogenation and dechalcogenation reaction possibilities of the heteroseleniranes and heterotelluriranes.

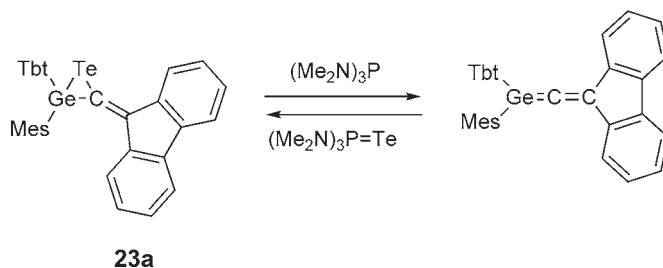
1.15.6.2 Dechalcogenation Reactions (Reaction A in Scheme 5)

The deselenation of the selenadistibirane **20** ring results in the formation of the corresponding distibene in a reversible and nearly quantitative reaction as is shown in Scheme 6 <1998CL725>.



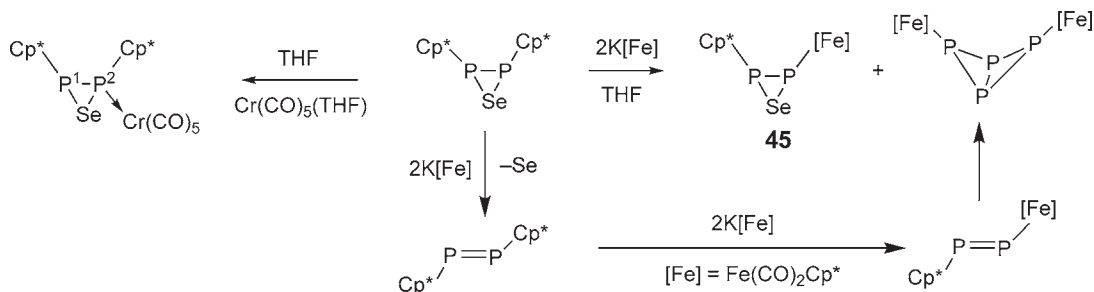
Scheme 6 The (reversible) deselenation reaction of selenadistibirane.

Another reversible reaction is the detelluration of the telluragermylene **23a** described by Tokitoh and coworkers <1997OM5127> to give the first stable germaallene <1998CL811> by using $(\text{Me}_2\text{N})_3\text{P}$ (Scheme 7).



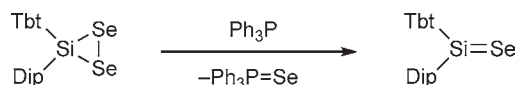
Scheme 7 The reversible detelluration reaction of the telluragermylene **23a**.

Diphosphaseleniranes could also be deselenated by using $\text{KFe}(\text{CO})_2\text{Cp}^*$ ($\text{K}[\text{Fe}]$). The resulting diphosphene (Scheme 8) has been detected by NMR spectroscopy as an intermediate, producing the bicyclic phosphane complex (Scheme 8). The deselenation, however, is a side reaction (20%), the main product being the substituted diphosphaselenirane **45** (Scheme 8). It should be mentioned here that the Cp^* -substituted diphosphaseleniranes can also be complexed with chromium pentacarbonyl, as shown in Scheme 8. Interestingly, this is the only example of metal complexation of heteroseleniranes or heterotelluriranes <1994CB997>.



Scheme 8 Deselenation and complexation reactions of the pentamethylcyclopentadienyl-substituted diphosphaselenirane **18**.

The deselenation of the diselenasilirane **13** is known to yield the corresponding silaneselone (Scheme 9). Although the selenation of the silaselenone is a possible synthetic method to produce the diselenasilirane ring, there is no information dealing with the reversibility of the reaction <2002CL34>. It should be noted that no direct deselenation of the analogous diselenastannirane has been reported <1997JA11124>. Since, diselenastannirane and stannaselone were formed from the same precursor depending on the amount of the deselenating agent $(\text{Me}_2\text{N})_3\text{P}$ used <1997JA11124>, it is likely that the stannaselone, as well as its silicon analog, are formed from diselenastannirane.



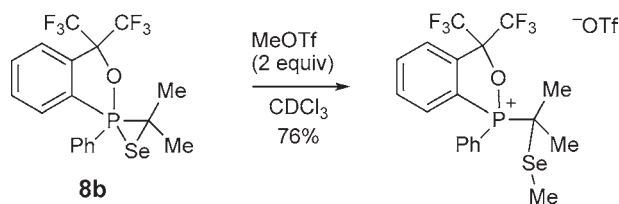
Scheme 9 Deselenation of the diselenasilirane ring resulting in silaneselone.

1.15.6.3 Chalcogenation and Ring-Opening Reactions

While reaction **B** (Scheme 5) is commonly observed for phosphines, in the case of the heterophosphiranes, this reaction seems to be more a hindered process. While the sulfur analog of **8a** adds an excess amount of sulfur to the

phosphorus forming a pentavalent selenaphosphirane-sulfide, no such reaction has been mentioned to occur between Se and **8a** <2000T6259>. Also, 2,3-di-*tert*-butyl-1-telluradiphosphirane **37** does not form P(V) compounds using an excess of Te <1993ZFA1083>. Similarly, the expected 1,3-dichalcogen-2,4-phosphasilacyclobutane (reaction C) was not observed from selenasilaphosphirane **31** when treated with an excess of elemental tellurium or sulfur <1996OM1845>. The telluradisilirane **30** (with Ph and SiBu^t₃ substituents at silicon) did not react with excess Te when it was synthesized from the corresponding disilene and tellurium. In contrast, the same disilene provided four-membered rings of type **44** (only), when sulfur or selenium were the reaction partners <2002CEJ2730>. It seems that the heavier chalcogens are less prone to react with the three-membered rings, and also that the group 15 element containing seleniranes and telluriranes are less reactive toward chalcogens than their group 14 element-containing analog as discussed in <1996CHEC-II(1)457>.

The reactivity of **8b** deserves specific attention. When treated with 2 equiv of methyl triflate (in CDCl₃), the *R*-(methylseleno)alkyl phosphonium triflate was obtained as a highly air-sensitive material in 76% yield (Scheme 10) <2002JA9706>. It is reasonable to assume that methyl triflate undergoes an electrophilic attack on the negatively charged selenium center of **8b**, and this is followed by dissociation of the polarized Se–P bond (see Section 1.15.3).



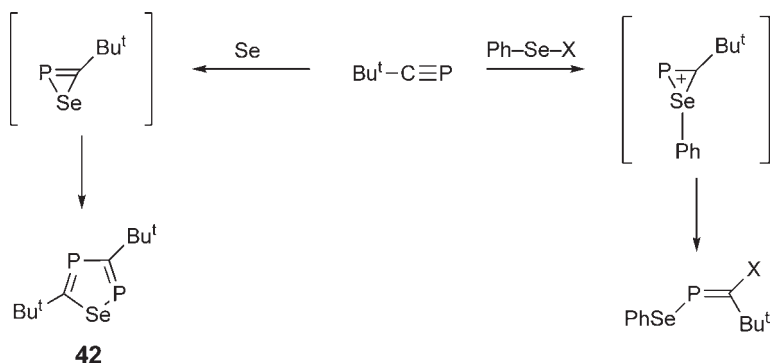
Scheme 10 The reaction of the selenaphosphirane **8b** with methyl triflate.

1.15.7 Ring Synthesis from Acyclic Compounds

The usual synthetic method is addition of the chalcogen to a multiple bond, but excess of the reactant or forced conditions lead to further reactions (see Section 1.15.6)

1.15.7.1 Unsaturated Systems

The unsaturated (presumably antiaromatic) rings seem to be very reactive, and such systems could not be isolated. As discussed in Section 1.15.2, incorporation of a second-row element (e.g. phosphorus) is beneficial for stability, and accordingly we have information only on selenaphosphirenes. To obtain this compound, Bu^tC≡P is a good precursor, and an investigation of its reactivity indicates that selenaphosphirenes are likely reaction intermediates. The available information is summarized in Scheme 11.



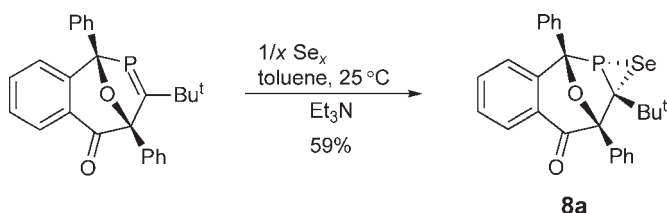
Scheme 11 Selenaphosphirene intermediates observed or assumed in reactions with Bu^tC≡P.

Reacting $\text{Bu}^t\text{C}\equiv\text{P}$ and PhSeX ($\text{X: SO}_3\text{CF}_3$) at -78°C in dichloromethane followed by warming up to ambient temperature resulted in a golden yellow solution, which exhibits a single ^{31}P resonance at 350 ppm ($^1J_{\text{PSe}}$ 315 Hz) attributable to the formation of the cyclic cation **3** (R: Ph) <1997PS23> (Scheme 11). The reaction of $\text{Bu}^t\text{C}\equiv\text{P}$ with Se at 70°C (with Te at 120°C) in toluene resulted in the 1,2,4-selena(tellura)diphosphole (Scheme 11). The reaction was assumed to proceed via the unstable selena(tellura)phosphirene intermediate <1999S1642>, which could not be detected, due to its instability (as indicated by the computational results) <2001JP21968> (see Sections 1.15.2 and 1.15.6).

1.15.7.2 Saturated Systems by Chalcogen Addition

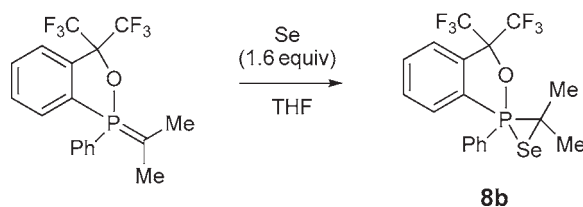
When the phosphorus–carbon double bond is reacted with selenium, the saturated product could be isolated. These systems seem to be more stable than their unsaturated counterparts. This behavior can be explained by the fact that more protecting groups are placed about the three-membered ring by saturation; also, the antiaromaticity destabilizes the unsaturated systems.

When selenium is used in an equivalent amount, it adds to the $\text{P}=\text{C}$ bond (Scheme 12) forming selenaphosphirane **8a** in 59% yield <2000T6259>. The presence of triethylamine catalyst is essential so as to avoid long reaction times. The reaction is stereospecific, and on the basis of the $^2J_{\text{CP}}$ coupling constants it has been suggested that the position of the Se is opposite to the oxygen bridge.



Scheme 12 Formation of selenaphosphirane **8a**.

Also, the colorless selena- λ^5 -phosphinidene **8b** has been obtained by addition of selenium to a phosphorus ylide (Scheme 13) in THF at room temperature <2002JA9706, 2003BCJ471>.

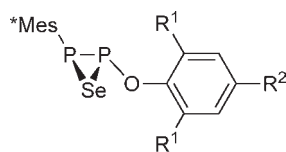


Scheme 13 Formation of **8b** from phosphorus ylide by addition of selenium.

The oxidation of $\text{Tip}_2\text{Si}=\text{P}-\text{SiPr}_3^i$ with elemental tellurium in toluene at room temperature has furnished the yellow three-membered heterocycle **31** in quantitative yield as has been reported by Driess *et al.* <1996OM1845>. Similarly, the disilene $\text{Ph}(\text{SiBu}^t_3)\text{Si}=\text{Si}(\text{SiBu}^t_3)\text{Ph}$ provided the corresponding light green telluradisilirane with tellurium (Te_n) in C_6D_6 within several hours <2002CEJ2730>, while with selenium (and sulfur) the four-membered ring 1,3-diselena-2,4-disilacyclobutane was formed, presumably via the selenadisilirane (thiadisilirane).

The synthesis of diphosphaseleniranes **18** by treating diphosphenes with selenium has already been discussed in <1996CHEC-II(1457>. The method has been extended to asymmetric compounds <1995HAC33>, as shown in Scheme 14. The reaction proceeds at 60°C in benzene when pyridine is used as a catalyst. The compound **18a** was isolated by column chromatography as a stable colorless crystalline solid in 37% yield, although **18b** and **18c** were not stable enough to permit isolation by the method which was employed for **18a**.

Tbt- and Bbt-substituted diphosphenes were reacted with gray selenium in a sealed tube in C_6D_6 at 120°C for 120 h, and this resulted in a mixture of the appropriately substituted orange diphosphaselenirane in 57% yield and



18a: $R^1 = R^2 = \text{Bu}^t$

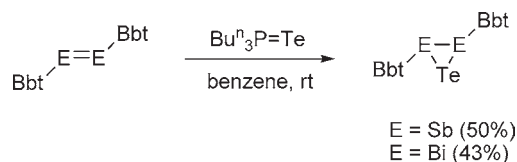
18b: $R^1 = \text{Bu}^t$; $R^2 = \text{Me}$

18c: $R^1 = \text{Bu}^t$; $R^2 = \text{H}$

Scheme 14 Asymmetrically substituted diphosphaseleniranes **18a–c** synthesized from diphosphenes by addition of selenium.

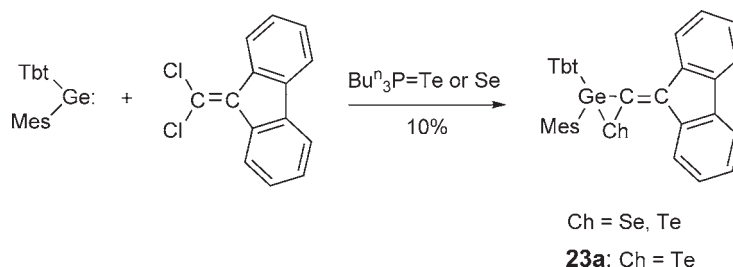
diselenoxophosphorane as a by-product <2003JPO450>. Interestingly, with the extremely bulky Tbt and Bbt substituents on phosphorus, the reaction proceeded without NEt_3 as the catalyst, while in case of $\text{Mes}^*\text{P} = \text{PMes}^*$ the analogous reaction occurred with NEt_3 as a catalyst (albeit at 70°C and over a 2 h reaction period). It is also worthy to note that the Bbt-substituted diphosphene did not react with tellurium in C_6D_6 at 120°C over 40 h, and even at 150°C for an additional week.

The analogous Bbt-substituted antimony and bismuth heterotelluriranes, however, were reported to be formed. The kinetically stabilized (by the bulky Bbt group) telluradibismirane was obtained as brown crystals (after purification by column chromatography) by reacting the corresponding dibismuthene with the soluble Te source $(\text{Me}_2\text{N})_3\text{P}=\text{Te}$ in benzene at room temperature as shown in **Scheme 15**. The reaction of the dibismuthene with elemental tellurium did not proceed at low temperature. At 110°C , however, no three-membered ring was formed, but instead the Bbt-substituted ditelluride was obtained, presumably due to the demanding reaction conditions, which were needed to dissolve the tellurium. The reaction of $(\text{Me}_2\text{N})_3\text{P}=\text{Te}$ with distibene provided the three-membered ring in the form of orange crystals <2005AGE3717>.

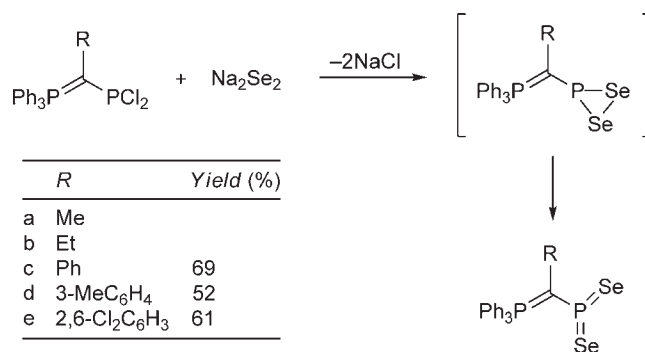


Scheme 15 Addition of tellurium on distibene and dibismuthene.

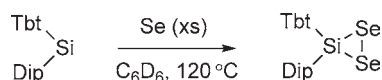
In an analogous (reversible) reaction, $(\text{Me}_2\text{N})_3\text{P}=\text{Te}$ was treated with the germaallene and this resulted in the formation of telluragermyrane **23a** (**Scheme 7**) <1998CL811>. The germaallene itself was synthesized from the telluragermirane **23a**, which was obtained according to **Scheme 16** <1997OM5127>. The success of this synthesis is somewhat surprising since the *exo*-methylene group at the three-membered ring is expected to increase the strain energy. Nevertheless, the orange compound is rather robust and **23a** only decomposes at $209\text{--}217^\circ\text{C}$ while melting (the selenium analog consists of a pale orange crystalline solid; m.p. $263\text{--}269^\circ\text{C}$ dec.) <1997OM5127>.



Scheme 16 Synthesis of **23a** using germylene and the soluble tellurium source $\text{Bu}^n_3\text{P}=\text{Te}$.



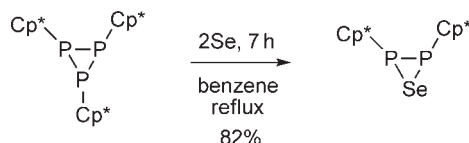
Scheme 20 Formation of diselenoxophosphorane, via the assumed diselenaphosphirane intermediate.



Scheme 21 Formation of diselenasilirane.

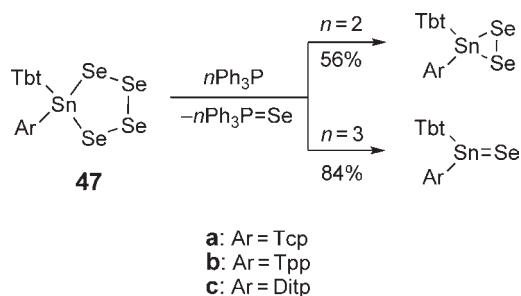
1.15.8 Ring Synthesis by Transformations of Another Ring

Cyclotriphosphane (Cp^{*}P)₃ forms the pale yellow selenadiphosphirane when treated with Se in boiling benzene. The yield and formation of the possible by-product (1-selena-2,3,4-triphosphetane) depends on the amount of selenium and the reaction time used <1994CB997>. Using an excess of selenium and 7 h reaction time resulted in a yield as high as 82% (**Scheme 22**).



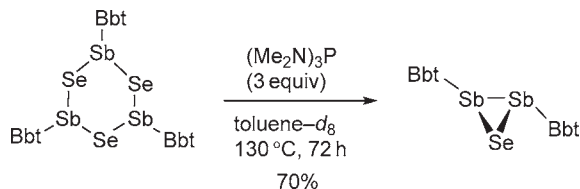
Scheme 22 Formation of selenadiphosphirane from triphosphirane.

The reaction of the five-membered ring **47** with a twofold excess of the deselenating agent triphenylphosphine furnished the orange-red diselenastannirane **16** ring in 56% yield. Using a larger amount of triphenylphosphine (3 mol) gave stannaneselone in 84% isolated yield <1997JA11124> (**Scheme 23**). A similar reaction had been reported previously for the Ge analog of **47** – see <1996CHEC-II(1)457>.



Scheme 23 Synthesis of diselenastannirane.

The air-stable orange-colored selenadistibirane was also obtained by using a deselenating ring transformation and taking advantage of steric protection of the Bbt groups, as shown in **Scheme 24** <1998CL725>. It was also obtained from the corresponding distibene in a reversible reaction with $\text{Se}=\text{P}(\text{NMe}_2)_3$ (see Section 1.15.6).



Scheme 24 Synthesis of selenadistibirane.

1.15.9 Outlook

The diheteroseleniranes and diheterotelluriranes with group 14 or group 15 element heteroatoms and bulky protecting groups reported in recent years show reasonable stability in spite of the apparent angle strain present in the three-membered ring. This stability, and also the reported examples which contain only one heavy atom (apart from the heavy chalcogen elements), indicates that more three-membered rings of this type will appear in the future. Computations, which were rarely reported for these compounds, are likely to be carried out in the future, providing new insight into the bonding and the relative stability with respect to possible isomers, and should therefore be instructive for finding new synthetic targets. Computational studies on the unsaturated systems might help to predict what kind of stabilizing substituents and conditions should be used to obtain these apparently elusive species. Although there seems to be no information about the practical use of these compounds, this can change with the increasing number of new substances.

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Biographical Sketch



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1.16

Three-membered Rings with Two Heteroatoms including Phosphorus to Bismuth

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1.16.1 Introduction

The scope of three-membered rings with two heteroatoms of heavier group 15 elements includes essentially heterocyclopropanes and heterocyclopropenes with two phosphorus atoms. This chapter also covers bicyclic and polycyclic molecules containing the structural motif of the rings under discussion. Such species frequently result from transformations of phosphalkenes or oligomers. Monocyclic diphosphirane and diphosphirene derivatives are synthesized from acyclic precursors with a P–C–P linkage or alternatively via [2+1] cycloadditions. A few examples

of phosphasiranes and diarsiranes are described in the literature, whereas the corresponding antimony and bismuth analogues are still elusive.

An early review on three-membered rings containing phosphorus atoms by Mathey dates back to 1990 <1990CRV997>. Koenig and Etemad-Moghadam gave an account on cyclopropanes and cyclopropenes with two heteroatoms of the heavier group 15 elements in CHEC-II(1996) <1996CHEC-II(1)469>, and in 2001 a more updated review <2001MI1-57>. An excellent review by Bertrand and Bourissou covers the chemistry of unsaturated diphosphorus-containing three-membered ring systems <2002TCC1>.

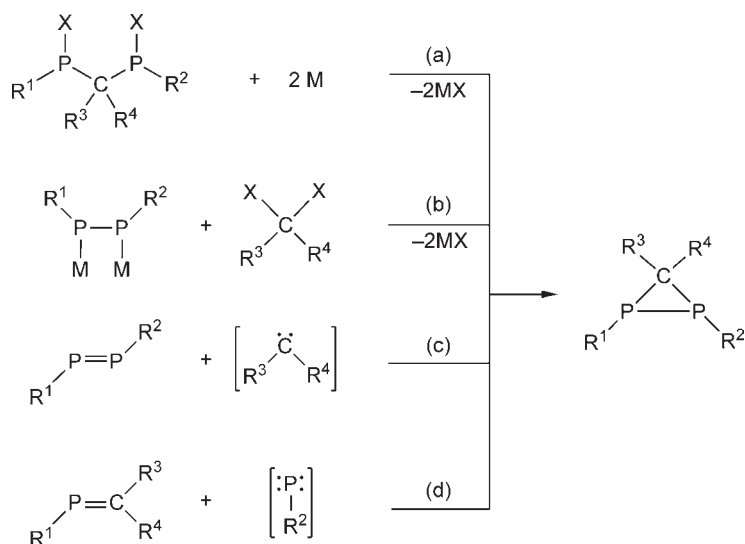
This chapter is concerned with advances of three-membered diphospha-cyclopropanes and -cyclopropenes, and from a formal point of view following on from Koenig's contribution <1996CHEC-II(1)469>.

In sharp contrast to the prolific chemistry of phosphorus-containing three-membered rings reports on related arsenic- and antimony-containing species are scarce. In addition to *P*-2,4,6-tri-*tert*-butyl-phenyl-As-pentamethylcyclopentadienylphosphasirane <1992ZFAC75> and 1,2-Bis(2,4,6-tri-*tert*-butylphenyl)diarsirane <1989CB1809> mentioned in CHEC-II(1996) only three new phosphasiranes and two phosphastibiranes have been described in the meantime.

1.16.2 Synthesis

1.16.2.1 Diphosphiranes

The synthesis of diphosphiranes has been effected by a number of different approaches (Scheme 1).



Scheme 1

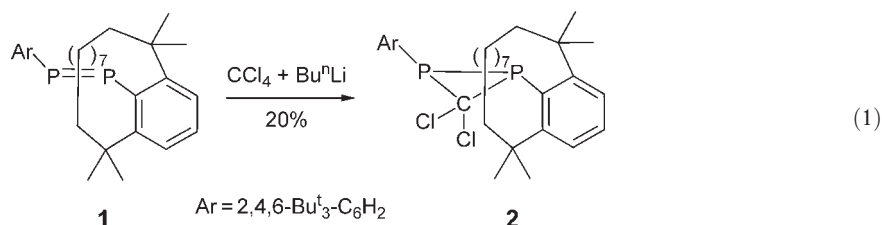
The dehalogenation of 1,3-dihalogeno-1,3-diphosphopropane derivatives by group I and II metals results in a ring closure to diphosphiranes provided that R^1 and R^2 at the phosphorus atoms are sufficiently bulky substituents (path (a)) <1979ZOB471, 1980ZOB689, 1984ZC345>. Another approach (path (b)) makes use of the cyclocondensation of diphosphides with gem-dihalogeno derivatives. This type of synthesis was performed with a number of gem-dihalogenoalkanes or -alkenes, or isocyanide dichlorides or a 2,2-dichloro-1-phosphaethene. Restrictions are encountered with the only limited number of salt-like diphosphides or 1,2-bis(trialkylsilyl)-1,2-diphosphanes <1983AGE632>.

Path (c) describes the formal [2+1] cycloaddition between diphosphenes and carbenes, which may be liberated from diazoalkanes, sulfur ylides or, as given in the case of mono- or dihalogenocarbenes from haloforms or carbon tetrahalides in the presence of strong bases such as potassium hydroxide, potassium *tert*-butoxide, or alkyllithiums <1986TL1145, 1987PS425, 1987T1793, 1989CC593, 1989TL177, 1988OM978>. Moreover, some particularly

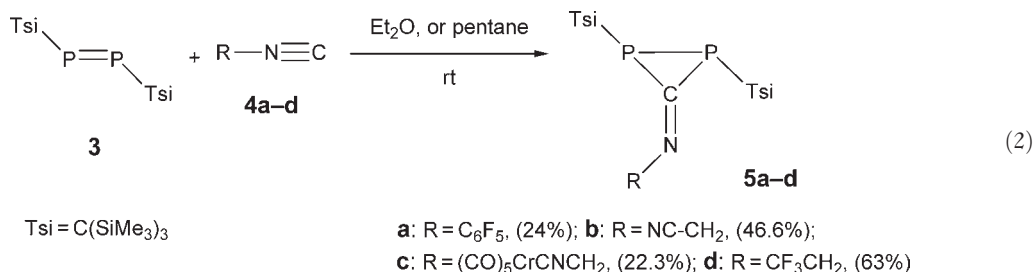
electrophilic isocyanides undergo [2+1] cycloadditions with diphosphenes to afford 3-imino-1,2-diphosphiranes <1994OM4406>. In a few cases the construction of the diphosphirane skeleton was possible by the [2+1] cycloaddition of *in situ* generated phosphinidenes to the P=C double bond of phosphalkenes (path (d)). Clearly, this approach suffers from the rarity of suitable precursors from which phosphinidenes may be generated under mild conditions <1983PS35, 1990CB1245>. The scope of this synthetic principle is widened markedly by the employment of *in situ* formed [W(CO)₅] phosphinidene complexes which, of course, furnishes diphosphirane metal complexes instead of the free rings <1993S763>.

In 1996 a collection of preparative procedures on phosphorus compounds including diphosphiranes appeared in volume III of *Synthetic Methods of Organometallic and Inorganic Chemistry* <1996MI-B128>.

Following the pathway to diphosphiranes via the [2+1] cycloaddition between diphosphenes and dihalogenocarbenes Yoshifuji reacted diphosphene (*E*)-**1** with a mixture of carbon tetrachloride and *n*-butyllithium. (*E*)-Diphosphirane **2** was obtained in 20% yield, while 64% of precursor (*E*)-**1** were recovered <2002CC3012> (Equation 1).



In a project on electron-deficient isocyanides, Lentz studied the reactivity of pentafluorophenyl isocyanide **4a**, isocyanoacetonitrile **4b**, pentacarbonylchromium diisocyanomethane **4c**, and 2,2,2-trifluoroethylisocyanide **4d** toward bis[tris(trimethylsilyl)methyl] diphosphene **3**. Combination of the reactants in pentane or diethyl ether at ambient temperature led to the formation of the expected diphosphirane imines **5a–5d** as yellow crystals in moderate yields (Equation 2). For the success of this process very bulky substituents at the P=P unit and electron-withdrawing groups at the nitrogen atom are required, which is evident by the decrease of thermostability in the series **5c** ≈ **5a** > **5b** > **5d** <1998JFC73, 1999ZFA1934>.

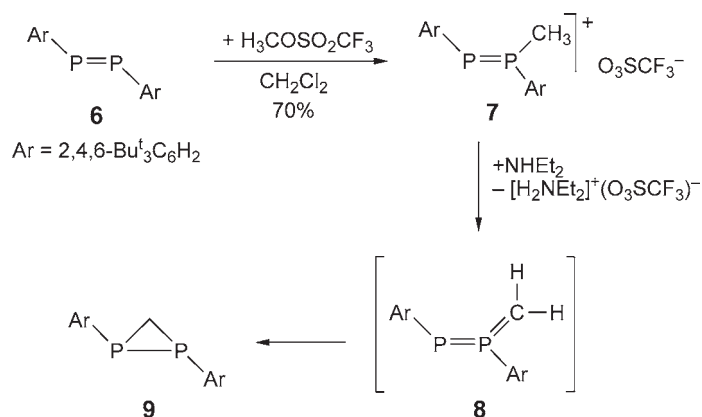


The conversion of bis(2,4,6-tri-*tert*-butylphenyl)diphosphene **6** into diphosphirane **9** was accomplished by methylation with a large excess of methyl triflate in a concentrated dichloromethane solution to give the isolable phosphanylphosphonium salt **7** (70%) and its subsequent deprotonation by diethylamine as a base. It was assumed that methylene(phosphinidene)phosphorane **8** was first formed and then underwent an electrocyclic rearrangement to **9** (Scheme 2).

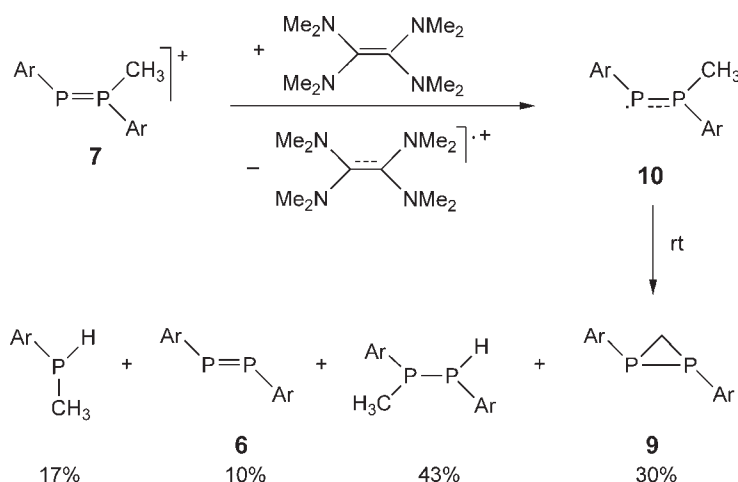
By the use of methyl lithium as a base diphosphane, Ar(Me)PP(Me)Ar was formed as a mixture of isomers instead of diphosphirane **9** <1999AGE3329>.

Salt **7** was smoothly reduced by tetrakis(dimethylamino)ethene in acetonitrile to the intense green radical **10**. Crystals of **10** as well as its hexane solution decompose at ambient temperature. Thereby diphosphirane **9** was generated in ca. 30% yield in addition to diphosphane Ar(Me)PP(H)Ar (43%), diphosphene **6** (ca. 10%) and phosphane ArP(Me)(H) (ca. 17%). The formation of diphosphirane **9** and Ar(Me)PP(H)Ar was explained by the disproportionation of radical **10** (Scheme 3) <2001AGE723>.

Deprotonation of ferrocenyl phosphane **11** with 2 M equiv of *n*-butyllithium in dimethoxyethane (DME) at –78 °C and subsequent combination of the dilithiated species with bis(trimethylsilyl)dichloromethane at 0 °C afforded



Scheme 2



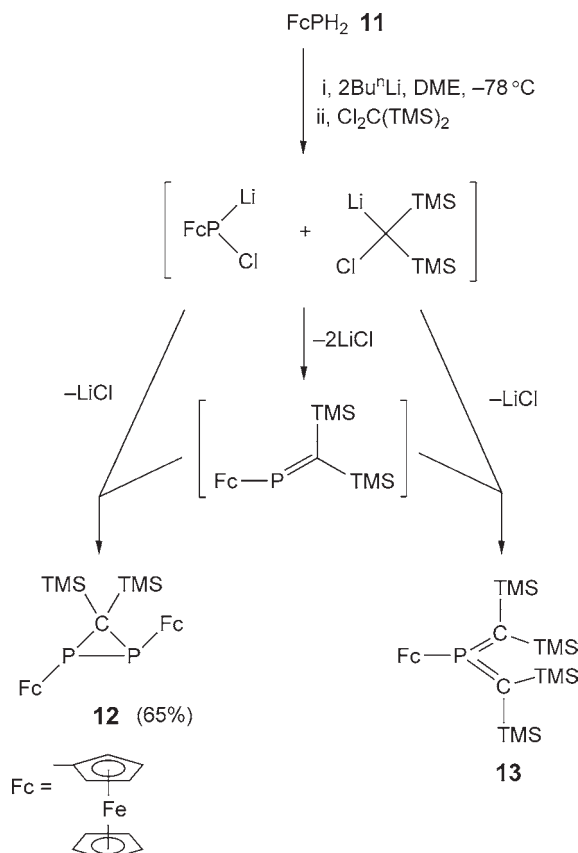
Scheme 3

diphosphirane **12** in 65% yield with small amounts of bis(methylene)phosphorane **13** as a by-product. The formation of these products may be rationalized by invoking an initial lithium chloride exchange. The resulting phosphenoid and carbenoid which are unstable under these conditions immediately dimerize under elimination of LiCl. Further reaction with either the phosphenoid or the carbenoid leads to **12** or **13** (Scheme 4) <1997JOM237>.

1.16.2.2 Polycyclic Diphosphiranes

Cage compounds featuring the structural motif of a diphosphirane are almost always produced by oligomerization, cycloadditions, or ene-reactions starting from phosphalkynes. These processes may be metal-assisted or may take place in the absence of metal compounds. Monocyclic oligomerization products of phosphalkynes such as di- and triphospholes or 1,3,5-triphosphinines may also be precursors for polycyclic diphosphiranes. The following section is organized by an increasing number of rings fused together, and not by the nature of the starting material or the particular type of reaction which leads to the target molecule.

Treatment of chloromethylene phosphane $\text{ClP}=\text{C}(\text{TMS})_2$ with 2 equiv of lithium bis(trimethylsilyl) phosphanide in DME afforded the lithium salt of 1,2-diphosphapropenide **14** (Scheme 5).



Scheme 4

By combination with a second molecule of $\text{ClP}=\text{C}(\text{TMS})_2$, compound **14** was converted into lithium 2,3,4-triphosphapentadienide **15**. When a solution of this salt was heated in moist DME at 100°C for 2 h transient 1,2,3-triphosphabutadiene **16** was generated, which immediately underwent an electrocyclization reaction to the yellow oily 1,2,3-triphosphabicyclo[1.1.0]butane **17** (Scheme 5) <1996AGE313>.

The 1,2,4-triphosphole $\text{P}_3\text{C}_2\text{Bu}^\text{t}\text{CH}(\text{TMS})_2$ **18** readily underwent a slow electrocyclization reaction when irradiated by a tungsten lamp (100 W) to afford the isomeric 1,3,5-triphosphabicyclo[2.1.0]pent-2-ene **19**. After 1 week the conversion was about 60% complete. An interesting feature of bicyclic **19** was the fast [1,3]-sigmatropic rearrangement whereby atoms P_A and P_B became magnetically equivalent. The facile cleavage of the weak P–P bond is favorable for this migration (Scheme 6) <1998CC1537>.

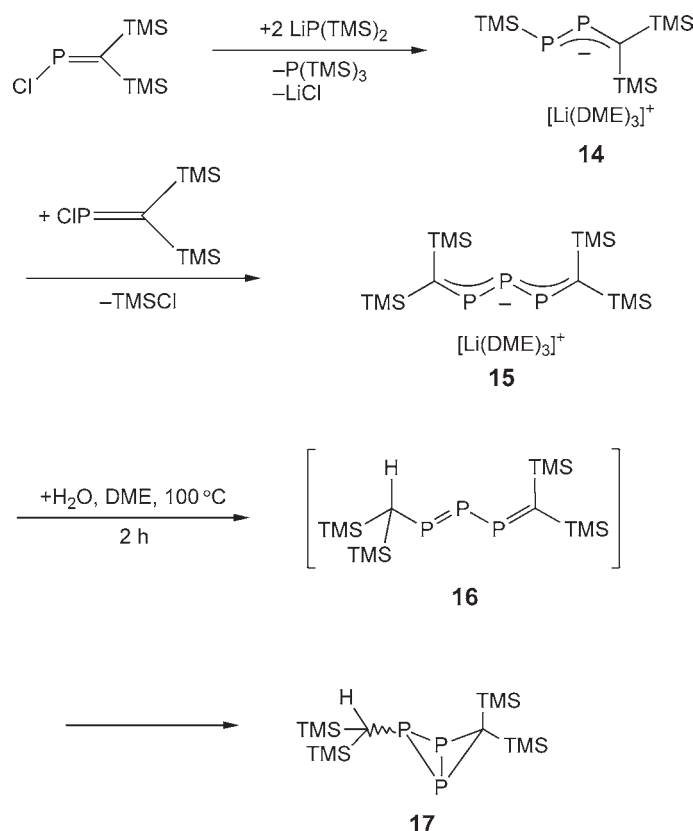
Condensation of the chloromethylene phosphanes $\text{ClP}=\text{C}(\text{R})(\text{TMS})$ ($\text{R} = \text{TMS}, \text{Ph}$) with dihydrophosphasilete **20** proceeded quantitatively with the formation of phosphalkenes **21a** and **21b** as yellow oils. When heated to 180°C for 2 h they underwent isomerization to the bicyclic diphosphiranes **22a** and **22b** (Scheme 7) <1999CEJ1581>.

Reaction of the amino-substituted phosphalkyne $\text{Pr}_2^\text{i}\text{N}-\text{C}\equiv\text{P}$ with diazoalkanes **23a–23c** as 1,3-dipolar reagents took place in toluene solution at ambient temperature with evolution of N_2 and elimination of diisopropyl cyanamide. After 3–5 h bicyclic diphosphiranes **24a–24c** were isolated. While solutions of **24a** and **24c** were stable, the mixture of diastereoisomers **24b** decomposed in toluene (Scheme 8).

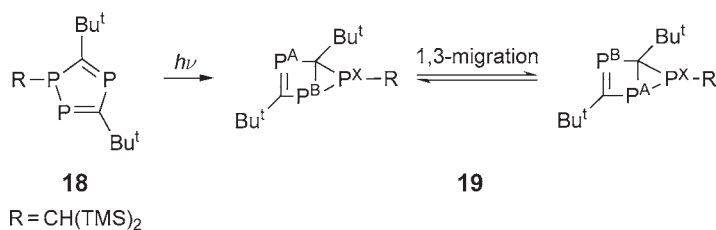
An analogous reaction of $\text{Pr}_2^\text{i}\text{N}-\text{C}\equiv\text{P}$ with diazocyclopentadiene **23d** occurred on heating of the mixture at 85°C for 18 h and led to the formation of the 1,2-diphosphole derivative **25** in 10% yield. Subsequent addition of 9-diazafluorene yielded the expected bicyclic diphosphirane **24d** (Scheme 9) <1996CB1271>.

This result contrasts with the behavior of $\text{Bu}^\text{t}\text{C}\equiv\text{P}$ toward diazo compounds, where [3+2] cycloadditions usually gave rise to the formation of 1,2,4-diazaphospholes.

η^8 -Cyclooctatetraene complexes of hafnium have proved to be excellent templates for the cyclotrimerization of $\text{Bu}^\text{t}\text{C}\equiv\text{P}$, whereby according to the particular reaction conditions complexes of different cyclotrimers were constructed.



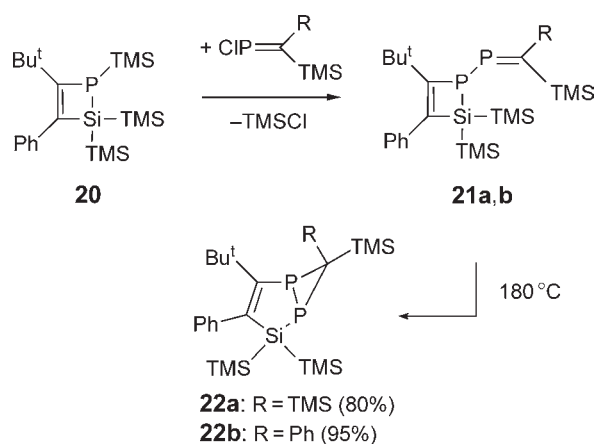
Scheme 5



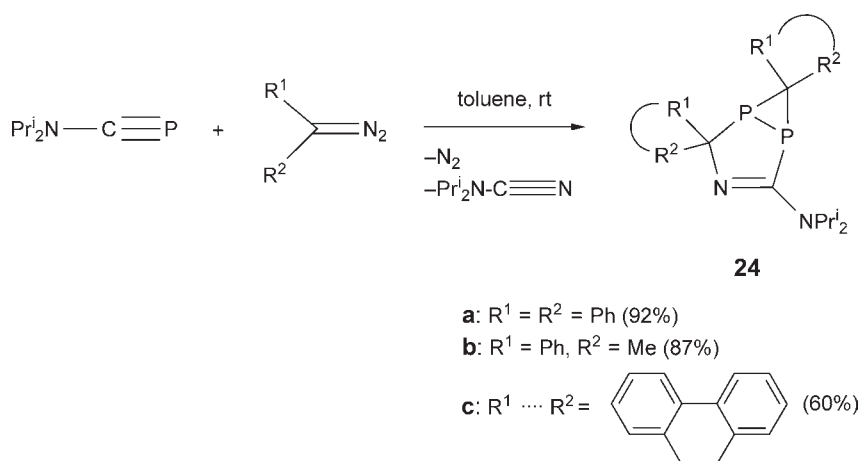
Scheme 6

A 1,3,5-triphosphinine was liberated from the coordination compound **25** by oxidation with hexachloroethane in toluene. If, however, the chlorination of complex **25** was conducted in pentane complex **26** was obtained in 44% yield. The hafnium complex **26** was hydrolyzed by an excess of water to the bicyclic diphosphirane **27** in 53% yield together with 10% of the 1,3,5-triphosphinine. Under milder and more controlled conditions, for example, the treatment of **26** with silica gel containing 2% H_2O or with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$, the addition of the second equivalent of water was suppressed and the two heterocycles **28** and **29** were formed in equal amounts (Scheme 10) <1999EJ1763>.

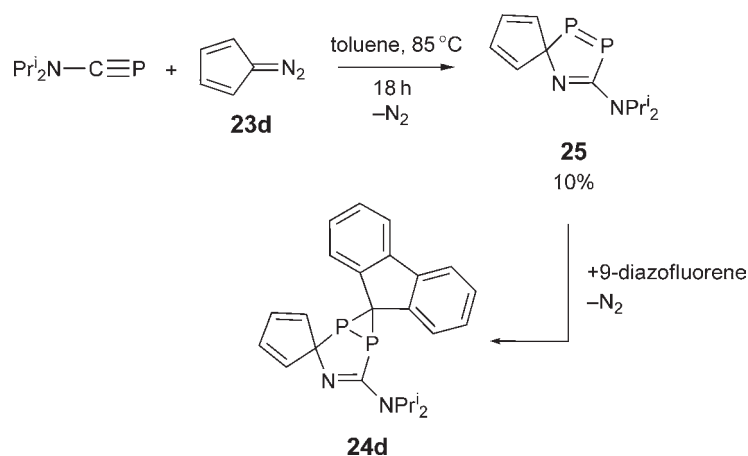
The reduction of the triphosphinine 1,3,5- $\text{P}_3\text{C}_3\text{Bu}^t_3$ with LiAlH_4 in diethyl ether led to the triphosphabicyclo[3.1.0]hexanediyl complexes **30**, which upon quenching with aqueous hydrochloric acid gave an 80:20 mixture of *exo*- and *endo*-isomers of triphospha-bicyclo[3.1.0]hexane **31** (Scheme 11). From the mixture isomer **31a** was isolated as colorless crystals in 34% yield.



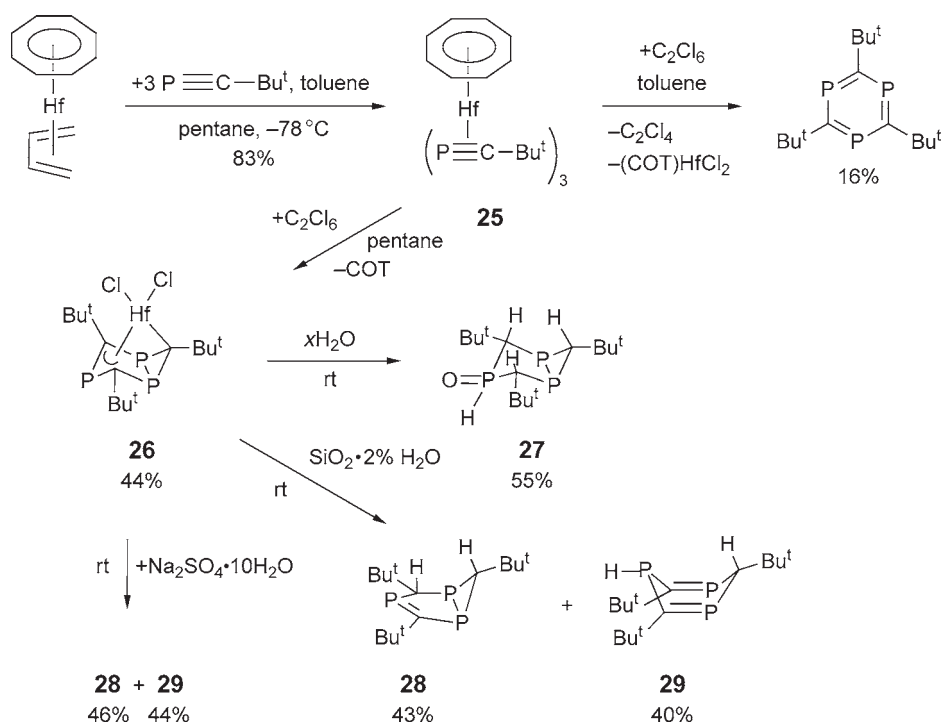
Scheme 7



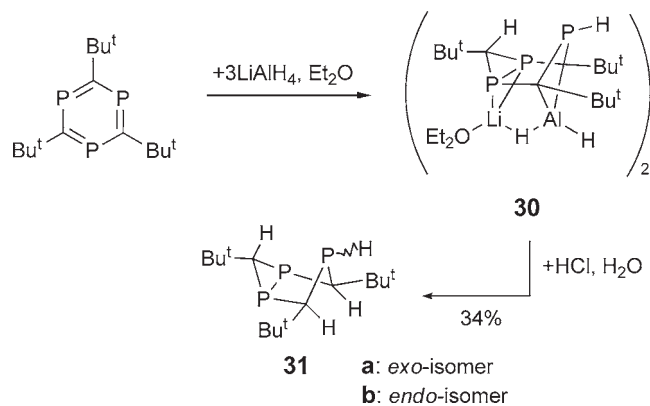
Scheme 8



Scheme 9



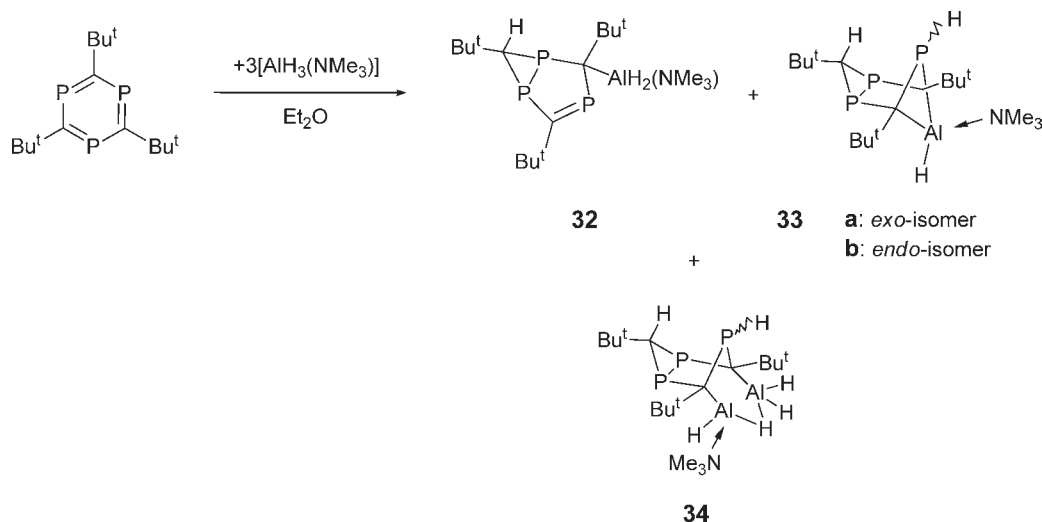
Scheme 10



Scheme 11

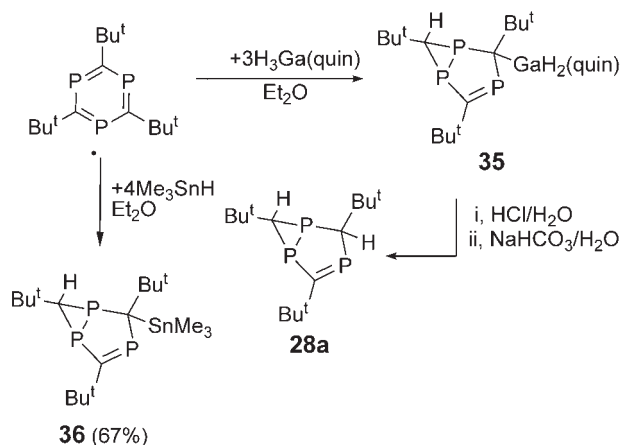
Jones also tested the reactivity of neutral group 13 trihydride reagents toward the 1,3,5-tripospha-1,3,5-triene. The reaction of 3 equiv $[\text{AlH}_3(\text{NMe}_2)]$ with the heterocycle in diethyl ether afforded a mixture of the crystalline compounds **32**, **33**, and **34**. They could not be separated on a preparative scale but crystals of pure **33b** and **34** could be selected and characterized by X-ray analyses (Scheme 12).

In contrast to this, reduction of $\text{P}_3\text{C}_3\text{Bu}^t_3$ with 3 equiv of $\text{GaH}_3(\text{quin})$ (quin = quinuclidine) in diethyl ether cleanly gave the triphosphabicyclo[3.1.0]hexane complex **35** in low yield. Acid quenching followed by basic workup led to the free bicyclic diphosphirane **28a** which is an isomer of the bicyclic diphosphirane **28** previously liberated from a hafnium complex <1999EJI763>.



Scheme 12

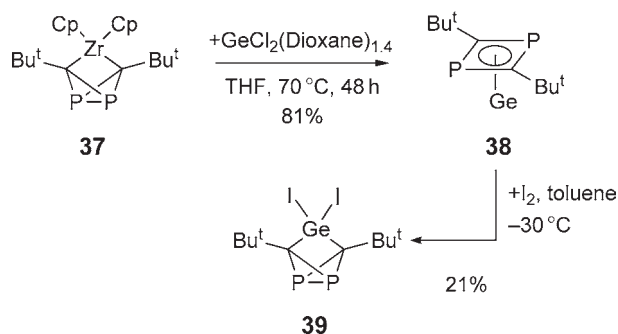
Similarly, treatment of the triphosphinine with 4 equiv of Me_3SnH in diethyl ether gave colorless oily **36** in 67% yield (Scheme 13) <2004JCD1971>.



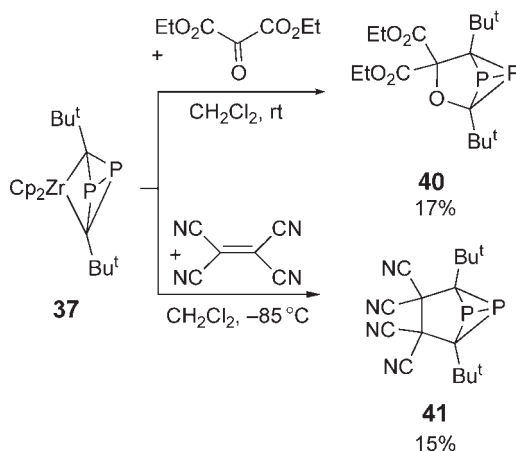
Scheme 13

The yellow crystalline half-sandwich **38** was prepared in 81% yield from the tricyclic zirconium species **37** upon treatment with the dioxane complex of germanium dichloride in tetrahydrofuran (THF) at 70°C for 48 h. Iodination of **38** in toluene at -30°C led to the immediate disappearance of the purple color. After stirring for 18 h at 25°C the tricyclic cage compound **39** was formed quantitatively according to nuclear magnetic resonance (NMR) spectra. Due to its excellent solubility the isolated yield dropped to only 21% (Scheme 14) <2003OM2891>.

Mesoxalic acid esters tend to undergo cycloaddition reactions at their central carbonyl function. Treatment of complex **37** with an excess of diethyl mesoxalate furnished the oxadiphosphatetricyclo[3.1.0.0^{2,6}]hexane **40** as a colorless oil in 17% yield after chromatography (Scheme 15). When a threefold excess of tetracyanoethene was added to a solution of **37** in dichloromethane at -85°C the color of the reaction mixture changed spontaneously from red to black, and 1,6-diphosphatetricyclo[3.1.0.0^{2,6}]hexane **41** was isolated in 15% yield (Scheme 15) <1999S639>.

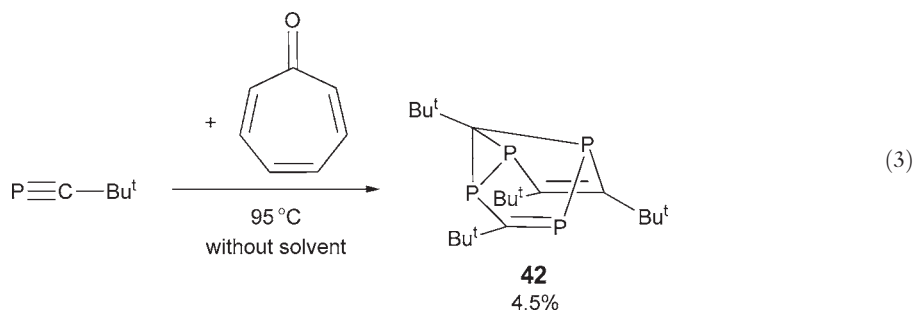


Scheme 14



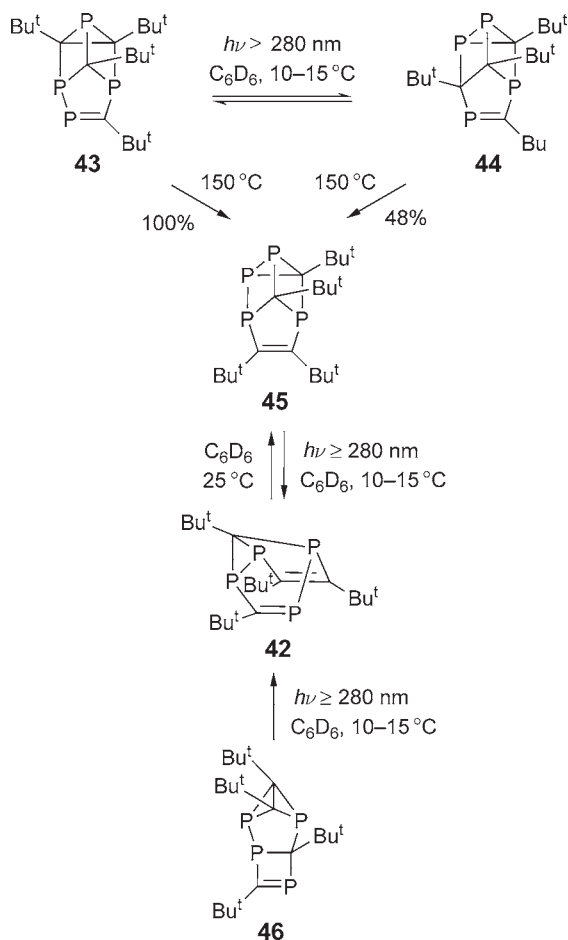
Scheme 15

Tetraphosphasemibullvalene derivative **42** was obtained on a number of different routes. First evidence for the formation of the tricyclic compound in 4.5% yield came from the thermolysis of phosphalkyne Bu^tC≡P in the presence of neat tropone at 95 °C (Equation 3).

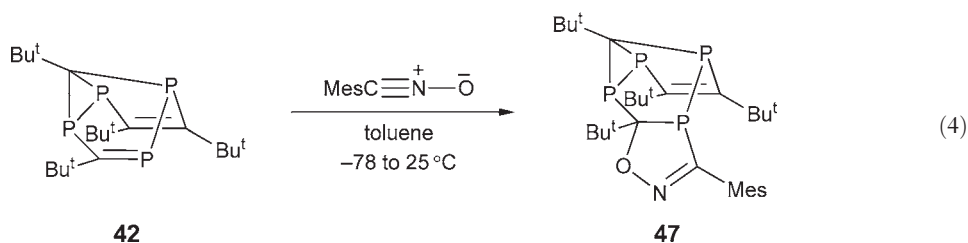


The tetraphosphasemibullvalene **42** was also accessible by various valence isomerizations of the polycyclic compounds **43–46**. Compounds **43** and **44** equilibrate when irradiated in C₆D₆ with UV light. Heating both isomers in the absence of solvent at 150 °C was accompanied by rearrangement to yield **45** (100 and 48%). Photolysis of **45** led to its valence isomer **42** in 75% yield. Finally, compound **46** was completely photolyzed to furnish an 80:20 mixture of **42** and **45** (Scheme 16).

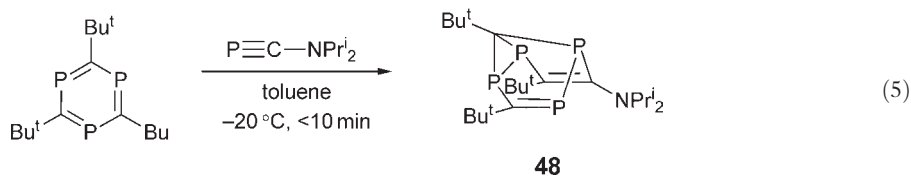
Combination of equimolar amounts of **42** and mesitylnitroxide in toluene gave rise to the generation of the [3+2] cycloadduct **47** (Equation 4) <1997AGE1337>.



Scheme 16

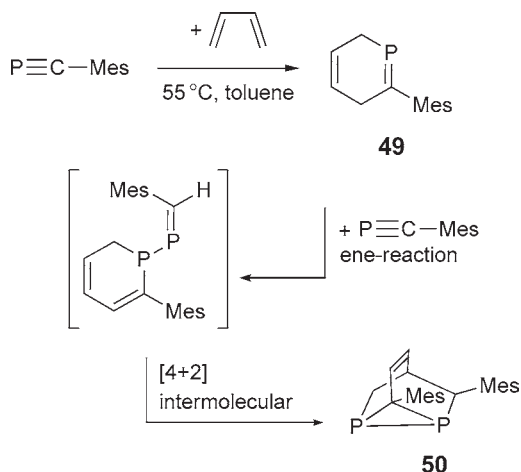


Reaction of the triphosphinine $\text{P}_3\text{C}_3\text{Bu}^t_3$ with di(isopropyl)aminophosphaethyne in toluene at -20°C quantitatively furnished the orange crystalline tetraphosphasemibullvalene **48** (Equation 5) <1998EJI2071>.



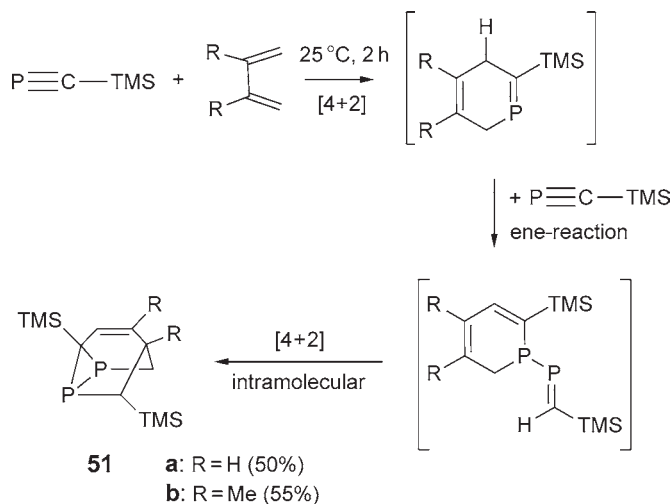
From a formal point of view the reaction of kinetically stabilized phosphalkynes with 1,3-dienes should furnish 1-phosphacyclohexa-1,4-dienes. However, at 90°C with alkyl-substituted phosphalkynes the primarily formed Diels–Alder adducts have not been detected, because the initial $[4+2]$ cycloaddition was followed by an ene-reaction and a final intramolecular $[4+2]$ cycloaddition to give diphosphatricyclooctenes.

However, the analogous reaction of mesitylphosphaethyne with the diene in toluene as a solvent at 55 °C led to the isolable phosphalkene **49**. Even though the ene/[4+2] cycloaddition sequence with a second equivalent of phosphalkyne was slow, product **50** was isolated after 1 week as an orange oil (**Scheme 17**) <1998S1305>.



Scheme 17

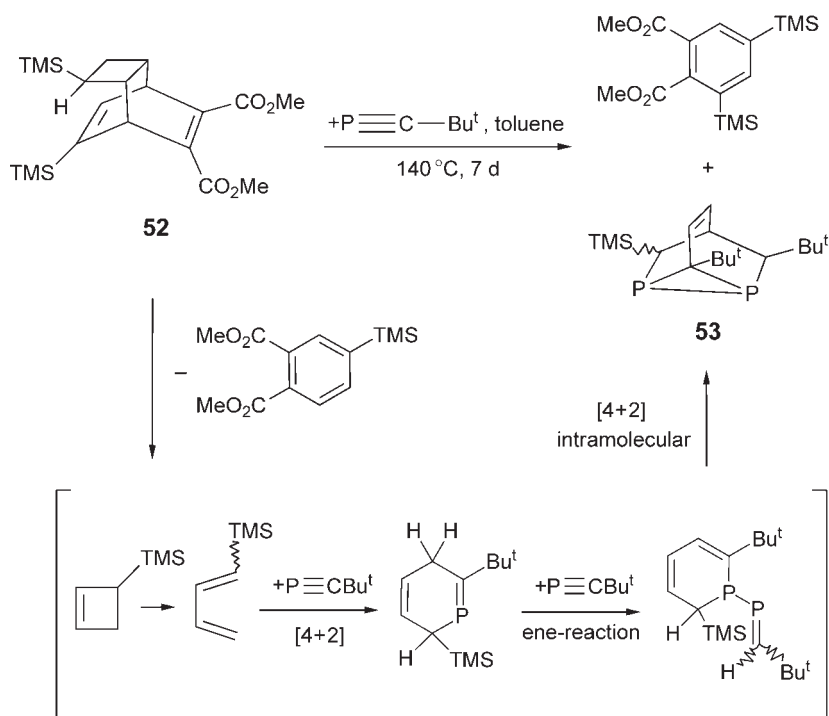
The increased reactivity of trimethylsilylphosphaethyne allows the cycloaddition sequence with dienes, discussed before, even at room temperature, whereby diphosphatricyclooctenes **51a** and **51b** were obtained in 50% or 55% yield, respectively (**Scheme 18**) <1999EJO363>.



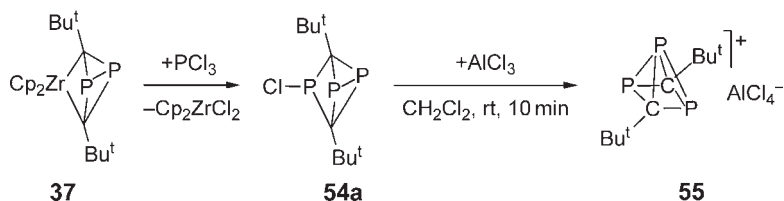
Scheme 18

Another diphosphatricyclooctene **53** resulted from the reaction of the tricyclic compound **52** with $\text{P}\equiv\text{C}\text{Bu}^t$ in toluene at 140 °C for 7 days (**Scheme 19**). The key step of this reaction was the cycloreversion of the precursor to produce a 1-TMS-butadiene which entered the tandem sequence of Diels–Alder reaction, ene-reaction, and intramolecular [2+4] cycloaddition (**Scheme 19**) <1999EJO1041>.

Reaction of tricyclic compound **54a**, previously obtained from **37** and PCl_3 <1991AGE207> with a stoichiometric amount of AlCl_3 in CH_2Cl_2 at 20 °C, produced a colorless solution from which a small amount of white crystalline **55** separated (**Scheme 20**). The square-based pyramidal cation, which is isoelectronic with $[\text{C}_5\text{R}_5]^+$ features four diphosphirane units. The cation may also be considered as a nido-cluster according to Wade's rules <2003AGE2778>.



Scheme 19



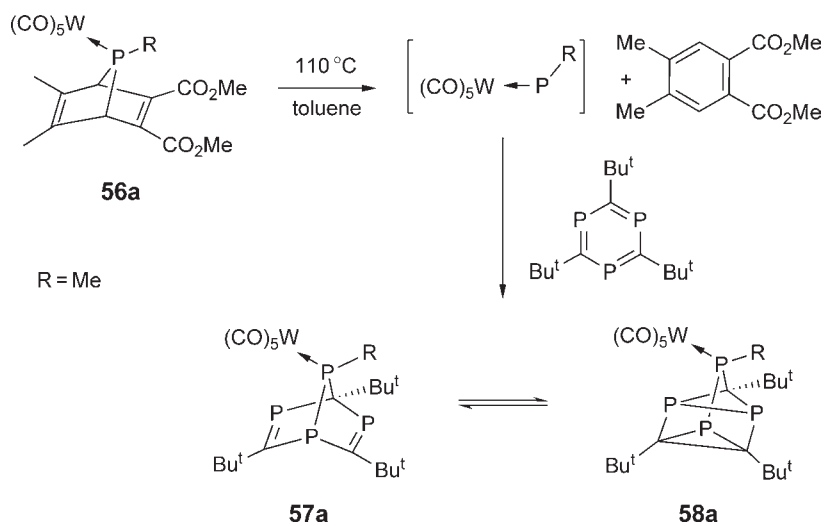
Scheme 20

The thermolysis of 7-phosphanorbornadiene complex **56a** ($\text{R} = \text{Me}$) in toluene at 110°C in the presence of 1,3,5-triposphinine $\text{P}_3\text{C}_3\text{Bu}^t_3$ led to a 1:8 equilibrium mixture of the tetraphosphanorbornadiene complex **57a** and the tetraphosphaquadricyclane derivative **58a**. Fractional crystallization from a hexane–dichloromethane solution furnished yellow crystalline **58a** (49% yield) and orange crystalline **57a** (6% yield) (Scheme 21).

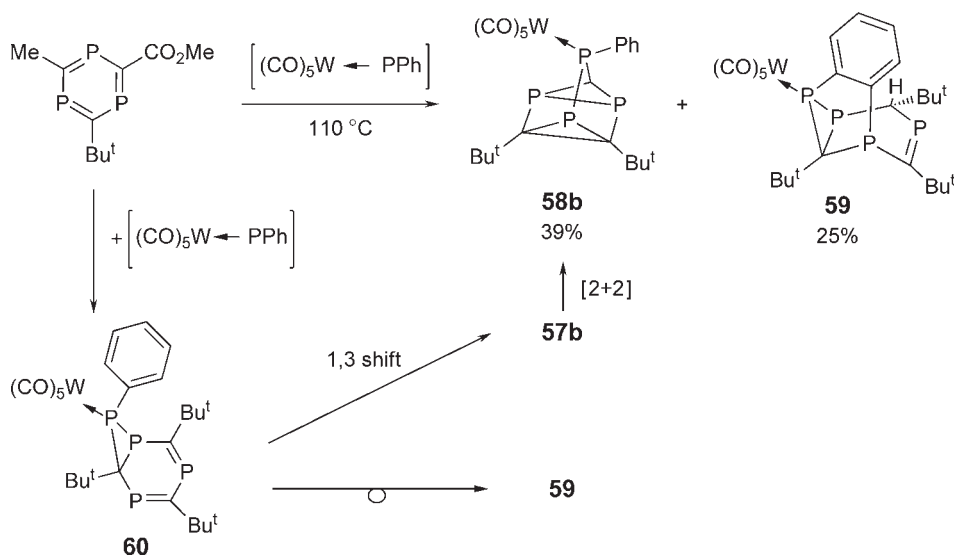
This process involves the *in situ* formation of reactive electrophilic phosphinidene complex $[(\text{CO})_5\text{W} \leftarrow \text{PMe}]$ and its interception by the heterocycle. Interestingly and in contrast to the pure hydrocarbon analogues here, the tetraphosphaquadricyclane isomer is by $6.6 \text{ kcal mol}^{-1}$ more stable than the respective tetraphosphanorbornadiene <2001AGE4412>.

Treatment of $\text{P}_3\text{C}_3\text{Bu}^t_3$ with $[(\text{CO})_5\text{W} \leftarrow \text{PMe}]$, generated *in situ* by thermal decomposition of **56b** ($\text{R} = \text{Ph}$) at 110°C , furnished a 2:1 mixture of quadricyclane **58b** and the tricyclic compound **59**, which were separated by fractional crystallization as colorless or yellow crystals in 39% and 25% yield, respectively. The presence of a three-membered ring in **59** agrees with an initial attack of the phosphinidene complex at a $\text{P}=\text{C}$ bond of the triphosphinine to give transient **60**. An intramolecular electrophilic aromatic substitution furnished product **59**, whereas rearrangement of **60** to tetraphosphanorbornadiene **57a** and its intramolecular [2+2] cycloaddition would rationalize the formation of **58b** (Scheme 22) <2001CEJ3545>.

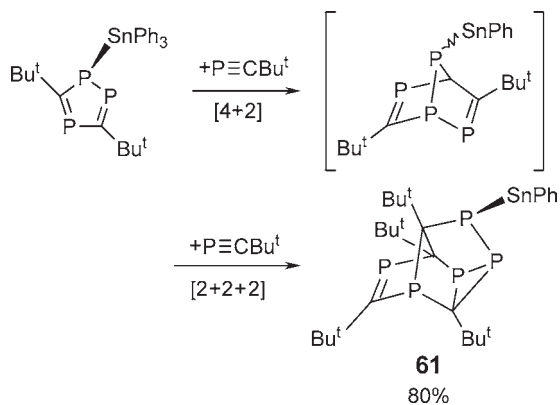
The intermediacy of a tetraphosphanorbornadiene was also invoked for the reaction between 1-triphenyl-3,5-di-tert-butyl-1,2,4-triphosphole and phosphalkyne $\text{Bu}^t\text{C}\equiv\text{P}$ in hexane at 70°C which led to the formation of yellow crystalline **61** in 80% yield. The product is asymmetric and contains seven stereogenic centers. Surprisingly, there was only one pair of enantiomers obtained (Scheme 23) <1999CEJ3143>.



Scheme 21



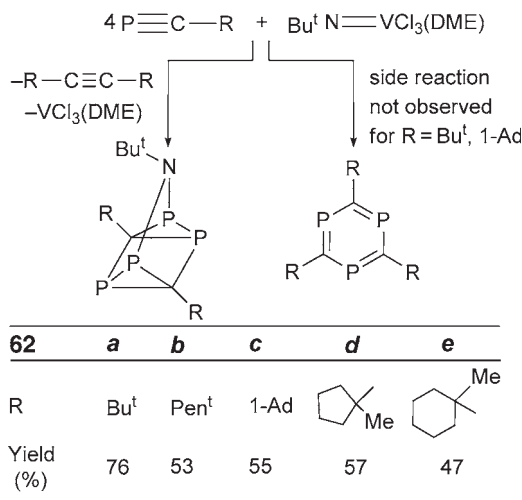
Scheme 22



Scheme 23

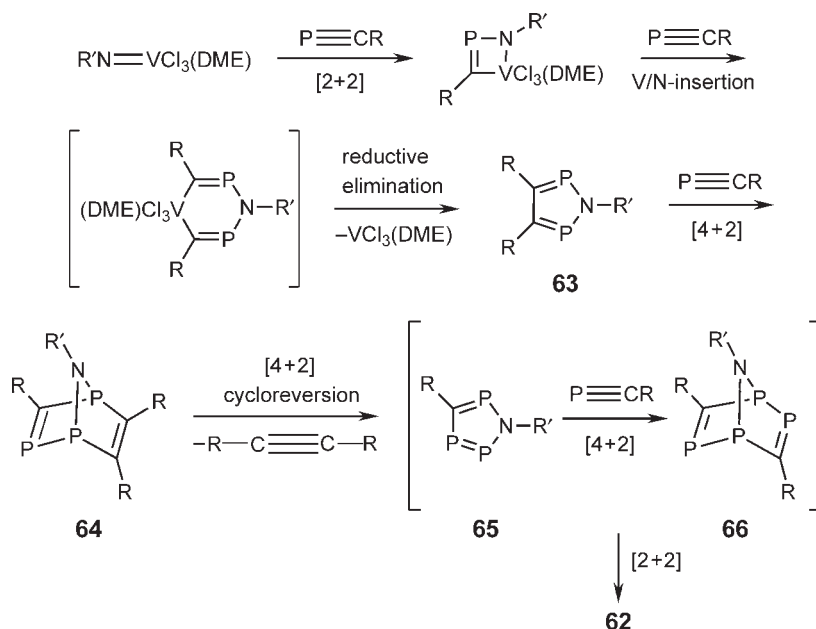
The reaction of a series of kinetically stabilized phosphalkynes $\text{RC}\equiv\text{P}$ with complex $\text{Bu}^t\text{N}=\text{VCl}_3(\text{DME})$ in the molar ratio 4:1 rather selectively afforded yellow azatetraphosphaquadricyclanes **62a–62e**, in yields of 47–76%. Small amounts of the corresponding 1,3,5-triphosphinines (1–3%) were formed as by-products only with $\text{R}=\text{Pen}^t$, 1-methylcyclopentyl, and 1-methylcyclohexyl.

Product **62a** was also selectively formed from the reaction of 4 equiv of $\text{Bu}^t\text{C}\equiv\text{P}$ with $\text{Bu}^t\text{N}=\text{VX}_2(\text{DME})$ ($\text{X}=\text{Cl}, \text{Br}$). Variation of the substituent at nitrogen in the imidovanadium (V) complex also enabled the substitution pattern of the tetracyclic product to be changed as evident from the reaction of 4 equiv of $\text{Bu}^t\text{C}\equiv\text{P}$ with 1- $\text{AdN}=\text{VCl}_3(\text{DME})$ under comparable conditions (Scheme 24).



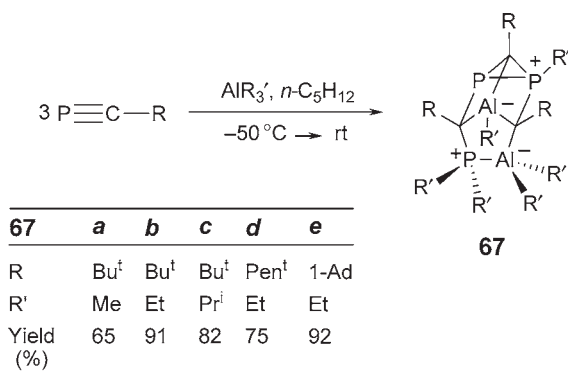
Scheme 24

The formation of the 3-aza-1,2,4,6-tetraphosphaquadricyclanes **62a–62e** was rationalized by a sequence of [2+2] cycloadditions, insertion reactions, reductive eliminations, [4+2] cycloaddition, and cycloreversion processes (Scheme 25) <1998AGE1233, 2001ZN951, 2000CEJ4558>.



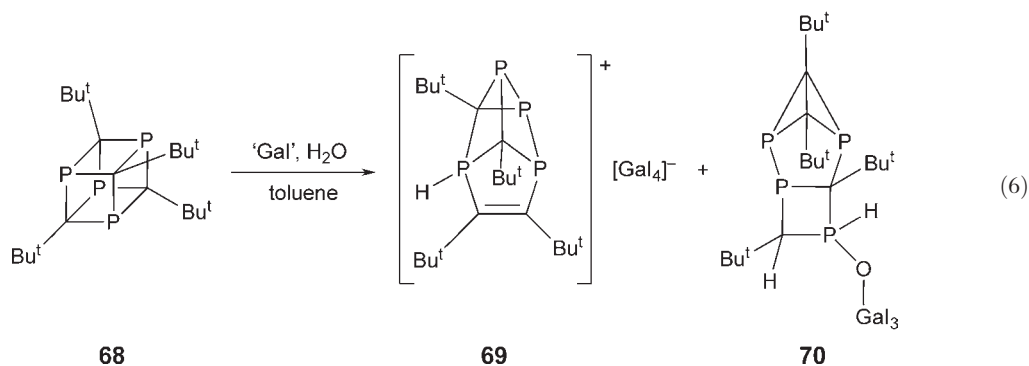
Scheme 25

When mixtures of the kinetically stabilized phosphalkyne $P\equiv C-R$ ($R = Bu^t$, Pen^t , 1-Ad) and the triorganoaluminum compounds AlR_3' ($R' = Me$, Et , Pr) in pentane are allowed to warm from $-50^\circ C$ to ambient temperature, quantitative cyclotrimerization of the phosphalkyne with incorporation of 2 equiv of the Lewis acid occurred to afford polycyclic **67** featuring the structural motif of a diphosphirane. With exception of colorless crystalline **67b** all other products are nondistillable oils (**Scheme 26**) <1997CB255>.



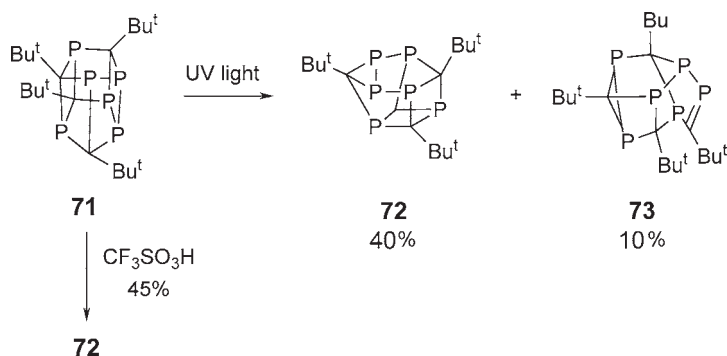
Scheme 26

Tetraphosphacubane **68** was not effected by gallium monoiodide in dry toluene. After the addition of a few drops of water and stirring the slurry overnight, crystalline compounds **69** and **70** were isolated in yields less than 5%. Their identity was confirmed by X-ray diffraction analysis (**Equation 6**) <2003AXC339>.



UV irradiation of a solution of hexaphosphapentaprismane **71** in toluene gave yellow **72** and orange **73**, which could be separated by fractional crystallization in 40% and 10% yield, respectively.

Surprisingly, the cage compound **72** was obtained as the only product by treatment of hexaphosphapentaprismane **73** with CF_3SO_3H at ambient temperature (45% yield) (**Scheme 27**) <2003ICA103>.

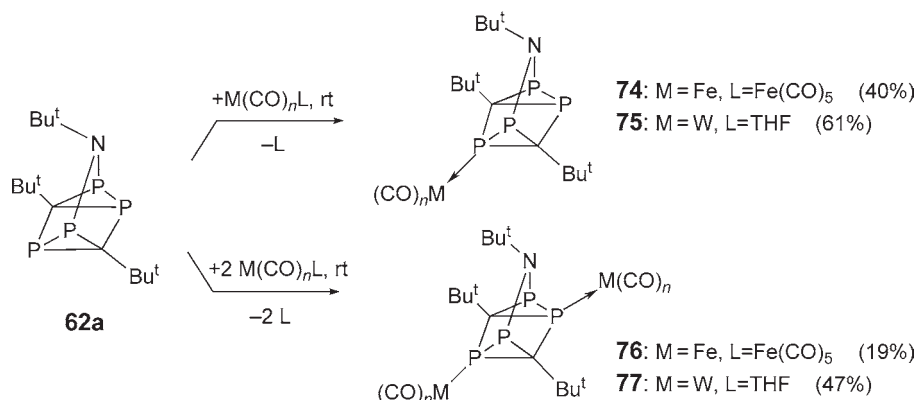


Scheme 27

1.16.2.3 Complexes of Diphosphiranes

Generally, transition-metal complexes of diphosphiranes are accessible on two essentially different routes. The first route involves the substitution of a labile ligand from a suitable complex by the preformed diphosphirane. Alternatively, the diphosphirane complex may be synthesized from a phosphorus-containing precursor that is already ligated to a metal, and thus the complex under discussion is generated in the coordination sphere of a metal.

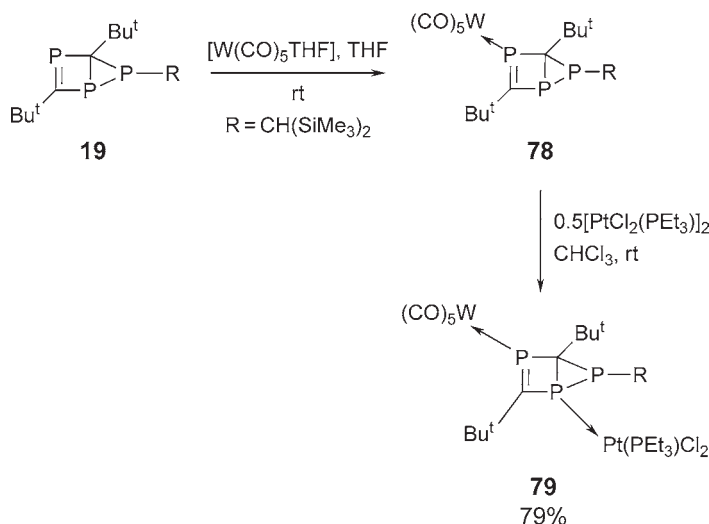
In keeping with the first pathway the reaction of the azatetraphosphaquadricyclane **62a** with diironenneacarbonyl in toluene or with $[\text{W}(\text{CO})_5\text{THF}]$ (in a molar ratio of 1:1) in tetrahydrofuran afforded the complexes **74** and **75**, which were isolated by chromatographic workup and subsequent crystallization as yellow crystals in 40% or 61% yield, respectively (Scheme 28).



Scheme 28

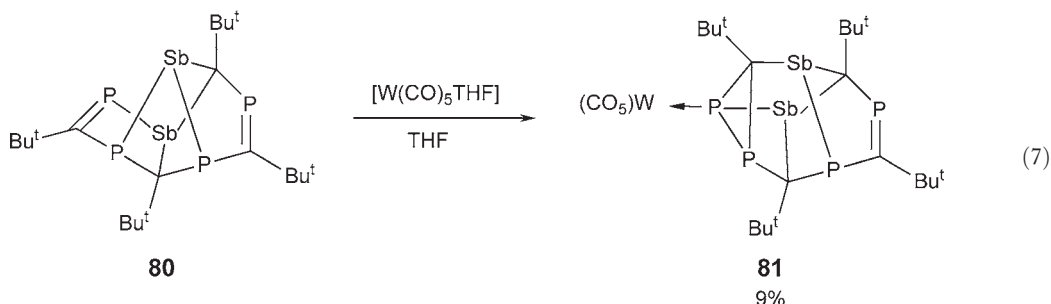
When **60a** was allowed to react with diironenneacarbonyl or, respectively, $[\text{W}(\text{CO})_5\text{THF}]$ in a molar ratio of 1:2, the yellow dinuclear complexes **76** and **77** were formed in 19% or 47% yield, respectively (Scheme 27) <2001ZN951>.

Complex $[\text{W}(\text{CO})_5\text{THF}]$ readily reacts with the bicyclic compound **19** in THF at room temperature to afford the red η^1 -complex **78**, whereby the 1,3-migration process discussed in Scheme 6 is completely stopped. When treated with $[\text{PtCl}_2(\text{PEt}_3)_2]$ compound **78** was cleanly converted into the yellow bimetallic complex **79** in 79% yield (Scheme 29) <1998CC1537>.

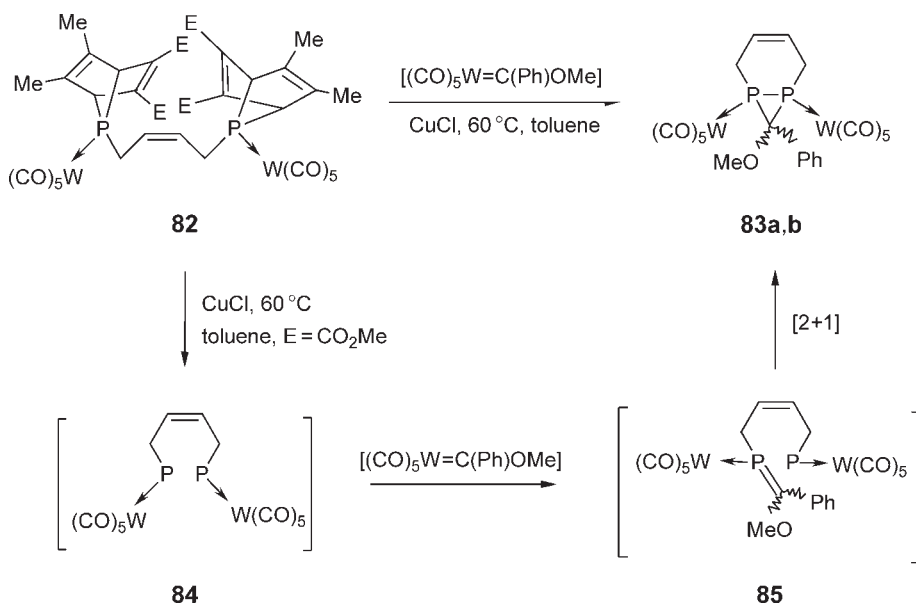


Scheme 29

Treatment of the cage compound **80** with an excess of $[\text{W}(\text{CO})_5\text{THF}]$ did not lead to a simple adduct at one of the various donor positions, but instead gave complex **81** in 9% yield after column chromatography. The formation of **81** may be initiated by coordination of **80** to a $[\text{W}(\text{CO})_5]$ fragment through the two-coordinated phosphorus atom adjacent to the antimony and the formation of a diphosphirane ring at the expense of a four-membered P_2SbC ring (Equation 7) <1997JCD4321>.

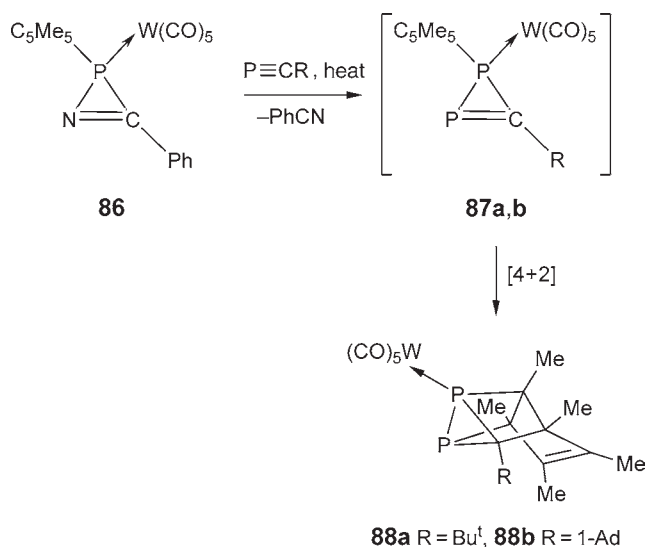


From a formal point of view the addition of phosphinidene complexes to $\text{P}=\text{C}$ double bonds should yield diphosphirane complexes. In keeping with this the reactive complex $[(\text{CO})_5\text{W} \leftarrow \text{PPh}]$ adds to the triphosphinine $\text{P}_3\text{C}_3\text{Bu}^t_3$ in toluene to give compound **59** as described in Scheme 22 <2001CEJ3545>. Co-thermolysis of the dinuclear carbonyl tungsten complex **82** in the presence of a fivefold excess of carbene complex $[(\text{CO})_5\text{W}=\text{C}(\text{Ph})\text{OMe}]$ in toluene under the catalysis of CuCl furnished the diphosphirane complex **83** as a mixture of isomers in 32% yield. This result is explained by initial formation of the transient bisphosphinidene complex **84**, which is trapped by the carbene complex to give the elusive intermediate **85**. Compound **85** undergoes a [2+1] cycloaddition of the remaining phosphinidene unit onto the $\text{P}=\text{C}$ bond to the final product (Scheme 30) <1999JOM53>.



Scheme 30

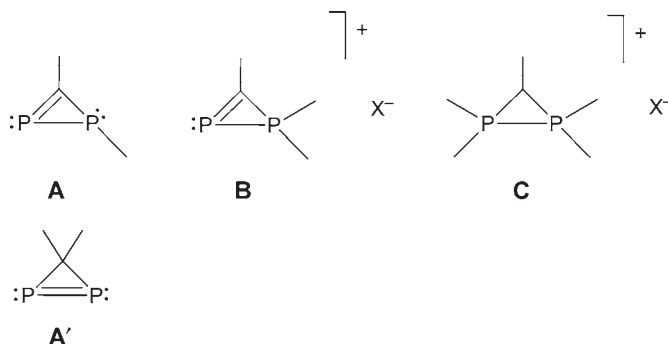
Co-thermolysis of a *P*-pentamethylcyclopentadienyl-substituted 2*H*-azaphosphirene complex **86** with alkyl-phosphaalkynes furnished cage compound **88a** and **88b** featuring the structural motif of a diphosphirane complex. The key step of this reaction was the formation of transient diphosphirene complexes **87a** and **87b** which underwent a spontaneous intramolecular Diels–Alder reaction to the final product (Scheme 31) <1997PS545>.



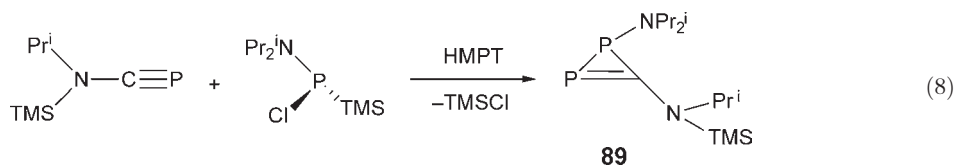
Scheme 31

1.16.2.4 Diphosphirenes and Diphosphirenium Salts

In this section synthetic aspects of free 1*H*-diphosphirenes **A**, diphosphirenium salts **B**, and of salts **C** containing two σ^4 phosphorus atoms are discussed.

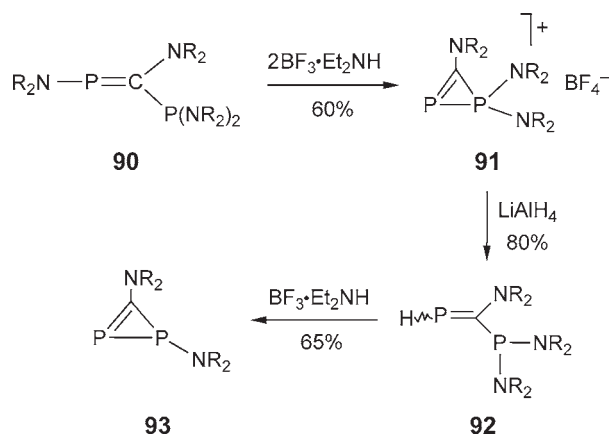


The tautomeric 3*H*-diphosphirenes **A'** are still unknown, however, postulated as intermediates in the generation of a trans-1,2,4,5-tetraphosphatricyclo[3.1.0.0]hexane <1991AGE90>. The first stable 1*H*-diphosphirene **89** was prepared from a functionalized aminophosphane <1990CB1245> by reaction with an amino-substituted phosphalkyne (Equation 8) <1989AGE1673>.



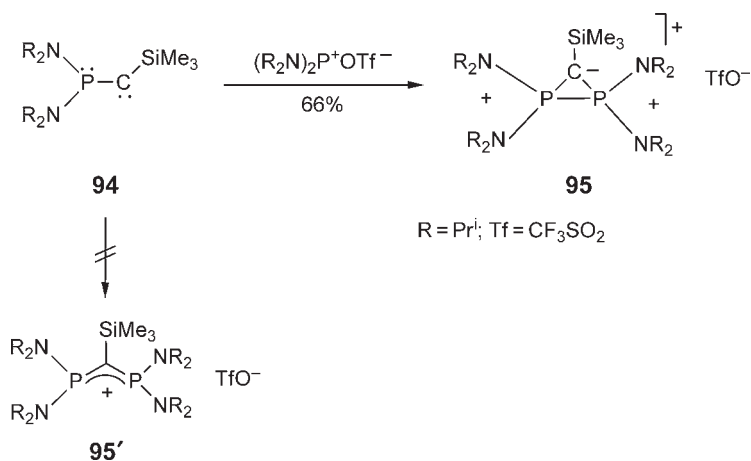
From a formal point of view this process may be regarded as the [2+1] cycloaddition of a transient phosphinidene to the PC triple bond of the electron-rich phosphalkyne. A little later a different approach to diphosphirenes was devised by Bertrand. When a toluene solution of phosphalkene $Pr^iNP=C(NPr_2^i)P(NPr_2^i)_2$ **90** was treated with 2 equiv of boron trifluoride–diethylamine complex at room temperature, a clean reaction took place to afford the pale yellow crystalline diphosphirenium salt **91** (60% yield) <1991JA8160> <1994JA6146>.

The reduction of **91** with $LiAlH_4$ afforded the phosphalkene $E/Z H \sim P=C(NPr_2^i)P(NPr_2^i)_2$ **92**, which upon treatment with boron trifluoride–diethylether complex was converted to the 1*H*-diphosphirene **93** (Scheme 32) <1997CC2399> <1999EJI1479>.



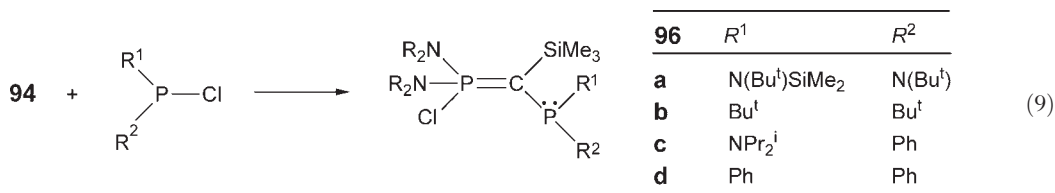
Scheme 32

When the stable acyclic carbene $(Pr^i)_2P-C-SiMe_3$ **94** was allowed to react with bis(diisopropylamino)phosphonium triflate in a CH_2Cl_2 /pentane mixture at $0^\circ C$, the 1,2-bisphosphoniacyclopropanide **95** was formed as colorless crystals in 66% yield. From a formal point of view this cation is the cyclic version of a bisphosphinocarbenium ion **95**, which was not observed here. In contrast to the acyclic bisaminocarbenium ions (amidinium ions), the carbon center in **95** is carbanionic in character (Scheme 33) <2000SCI75, 2002JA2506>.

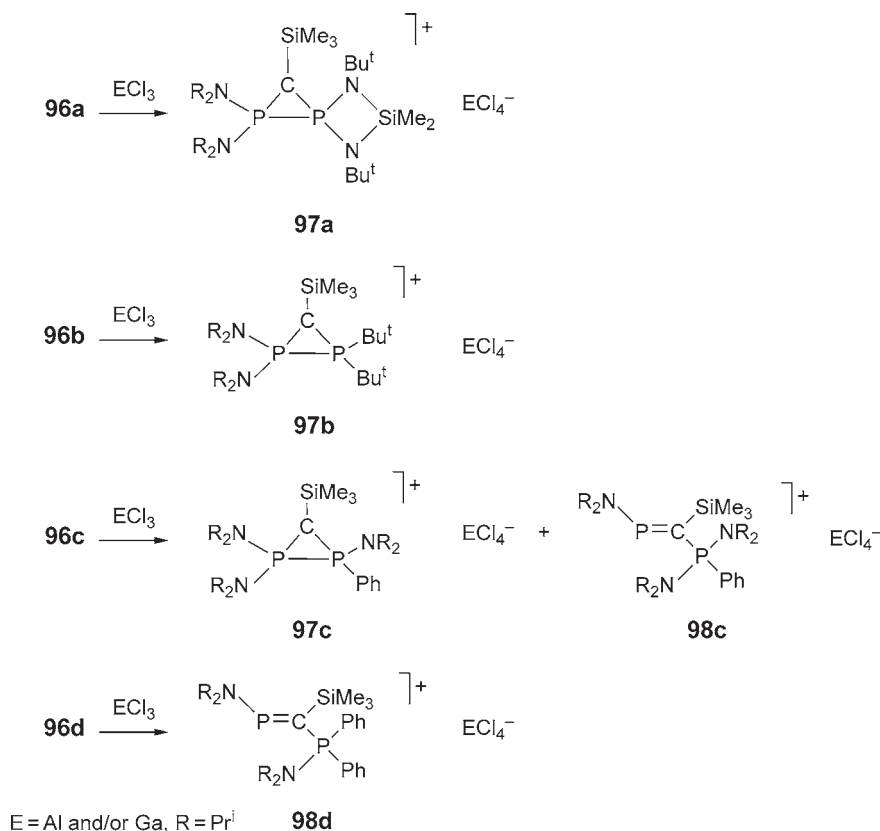


Scheme 33

Another pathway to such salts is based on chloride abstraction from *C*-phosphino-*P*-chloro phosphorus ylides **96** which are accessible by the combination of carbene **94** with an appropriate chlorophosphane in a pentane solution (Equation 9).



Addition of aluminium and gallium trichloride to phosphorus ylides **96a–96c** leads to the formation of the heterocyclic salts **97a–97c** (Scheme 34).



Scheme 34

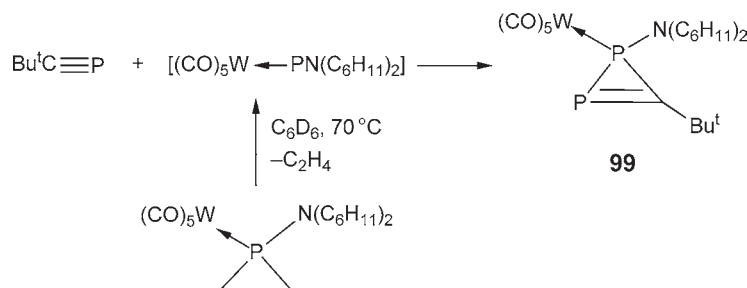
It is interesting to note that in the case of the bulky C-phosphino ylides **96a** and **96b** treatment with the Lewis acid cleanly gave the heterocycles **97a** and **97b**, whereas decreased steric requirement as given in **96c** led to a 1:4 mixture of ring and ylide **98c**. Last, in the case of the diphenylphosphino derivative **96d** ylide **98c** has been isolated in 55% yield as colorless crystals with no trace of the isomeric heterocycle detected [2002JA2506]. As will be discussed in Section 1.16.4 in more detail calculation of the parent compound has shown a significant stabilization of the ylide $[\text{H}_2\text{NP}=\text{C}(\text{SiH}_3)\text{PH}_3]^+$ when compared with the cyclic isomer. Thus, the existence of **95**, **97a**, **97b**, and **97c** is due to the steric congestion of the substituents at the phosphorus atoms.

1.16.2.5 Diphosphirene, Diphosphirenium, and Diphosphirenium Complexes

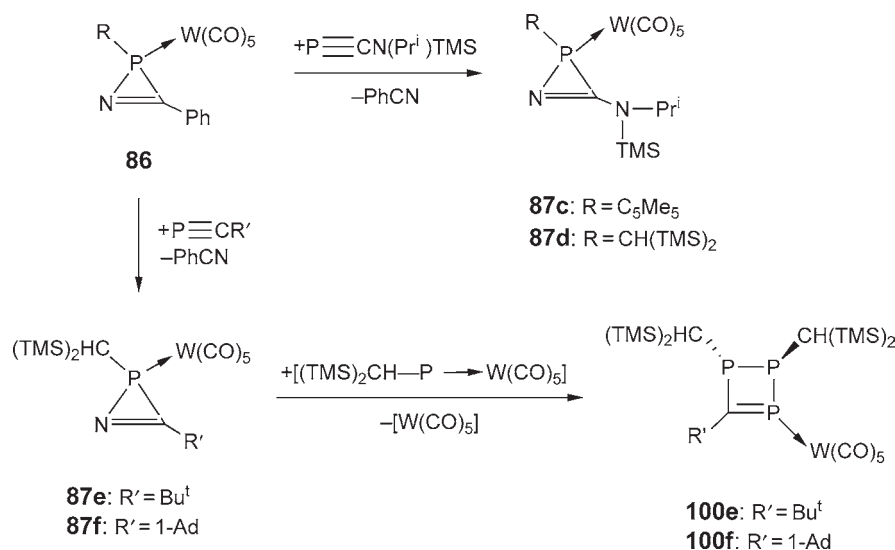
This section covers only transition-metal complexes which are directly formed during the synthesis of the heterocycles, or such which result from ligand displacement reactions with suitable metal complexes. Chemical transformations at the metal-bound three-membered ring with metal complexes whereby the structural integrity of the diphosphirene moiety is destroyed is considered in Section 1.16.5.2 in more detail.

The first 1*H*-diphosphirene complex **99** resulted from the [2+1]cycloaddition of an *in situ* generated phosphinidene complex to $\text{P}\equiv\text{C}-\text{Bu}^t$ (Scheme 35) [1991CC1305].

As briefly indicated in Scheme 31, 3*H*-azaphosphirene complexes also serve as sources for reactive $\text{W}(\text{CO})_5$ -phosphinidene complexes under mild conditions, and may be intercepted by phosphalkynes. Isolable diphosphirene complexes **87c** and **87d** were formed when the thermolysis of the precursors **86** [$\text{R} = \text{C}_5\text{Me}_5$, $\text{CH}(\text{TMS})_2$] was performed in the presence of $\text{P}\equiv\text{CN}(\text{Pr}^i)\text{TMS}$ (Scheme 36) [1995CC2113, 1997PS545].



Scheme 35



Scheme 36

In the case of **87e** and **87f** insertion of a second equivalent of phosphinidene complex $[(\text{CO})_5\text{W}-\text{PCH}(\text{TMS})_2]$ into a P–C or P–P bond of the three-membered ring has led to 1,2-dihydro-1,2,3-triphosphete complexes **100e** and **100f**. The reactions of aluminium trihalides and gallium trichloride with 3 equiv of kinetically stabilized phosphalkynes $\text{P}\equiv\text{CR}$ proceed according to an unusual spirocyclotrimerization to provide the complexes **103a–103f** exhibiting structural features of a zwitterionic diphosphirenium alkanide complex (Scheme 37).

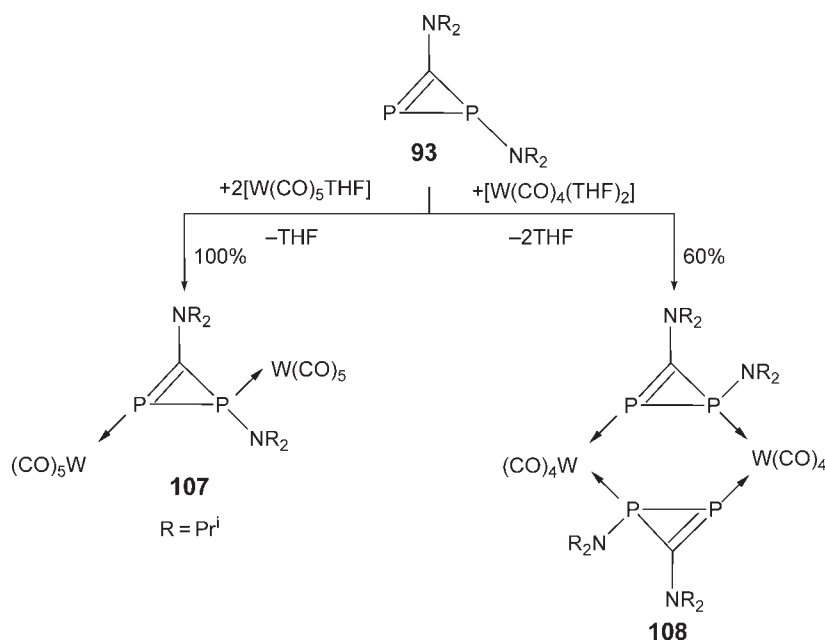
The initial step of the reaction is an attack of the Lewis acid at the phosphalkyne carbon atom. The resulting cation **101** participates in a regioselective [2+2] cycloaddition to form the dimer complex **102**. In a formal [2+1] cycloaddition step the third phosphalkyne adds to one of the phosphorus atoms in **102** in a highly diastereoselective way to afford products **103a–103f** in high yields. At this point it should be mentioned that the precursors for phosphalkynes, the phosphalkenes $\text{Me}_3\text{SiP}=\text{C}(\text{R})\text{OSiMe}_3$ ($\text{R} = \text{Bu}^t$, CMe_2Et), when treated with 2 equiv of aluminium chloride, are also cleanly converted into the spirocyclotrimerization products **103a** and **103b** <1996CB489>.

Diphosphirene **93** as well as the diphosphirenium salt **91** were converted into their respective pentacarbonyl tungsten complexes **104** and **105** by $[\text{W}(\text{CO})_5\text{THF}]$ in THF solution <1999EJI1479>. The η^1 -iron tetracarbonyl complex **106** was readily obtained in 85% yield by reaction of **93** with 1 equiv of $[\text{Fe}_2(\text{CO})_9]$ <1999CC1535> (Scheme 38).

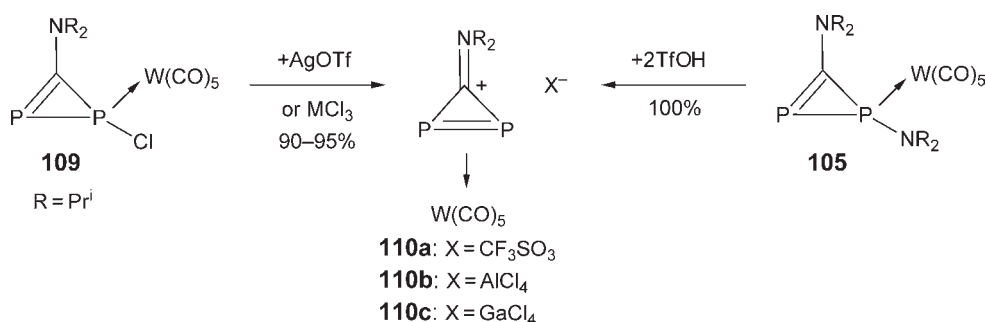
The dinuclear complex **107** was isolated as yellow crystals in near quantitative yield, when a twofold excess of $[\text{W}(\text{CO})_5\text{THF}]$ was employed in the reaction with **93**. The free 1*H*-diphosphirene **93** and 1 equiv of $[\text{W}(\text{CO})_4(\text{THF})_2]$ underwent reaction to give the dinuclear complex **108**, which was obtained in 60% yield as yellow crystals <1999EJI1479> (Scheme 39).



The first η^2 -diphosphirenylium complexes **110a–110c** were synthesized from the reaction of diphosphirene complex **109** in CH_2Cl_2 solution at -78°C with either silver trifluoromethanesulfonate or aluminium or gallium trichloride. The products were isolated as highly air- and moisture-sensitive brown oils in 90–95% yield. Alternatively, the heterolytic cleavage of the PN bond of **105** with 2 equiv of trifluoromethanesulfonic acid directly afforded complex **110a** in near quantitative yield (Scheme 40) [<1997JA9923, 1999EJI1479>](#).



Scheme 39



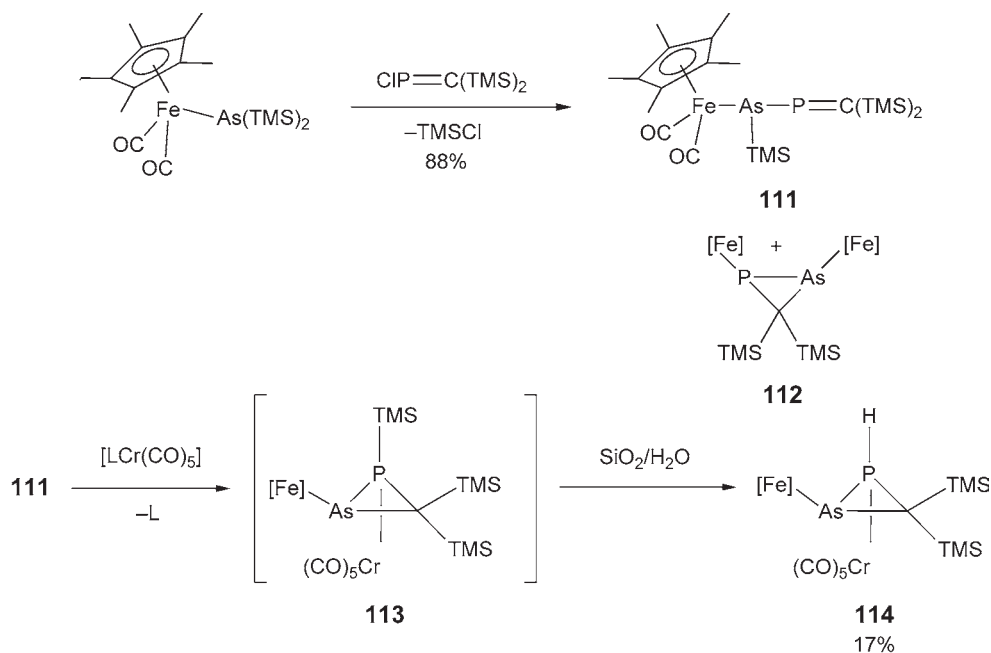
Scheme 40

1.16.2.6 Phosphaarsiranes

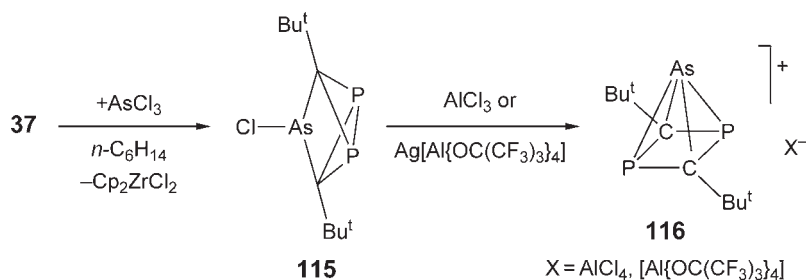
Treatment of metalloarsane $[(\eta^5-C_5Me_5)(CO)_2FeAs(SiMe_3)_2]$ with 1 equiv of $ClP=C(SiMe_3)_2$ in THF led to the formation of metallo-1-arsa-2-phosphapropene **111**, which was isolated by crystallization in 88% yield as red needles. From the oily liquor a few red crystals of dimetallophosphaarsirane **112** were isolated. Compound **111** and an excess of $[(Z)-(cyclooctene)Cr(CO)_5]$ were combined in *n*-pentane at ambient temperature after 2d orange crystalline phosphaarsirane **114** was isolated by column chromatography on Florisil in 17% yield. The primary product **113** obviously suffered from hydrolysis during chromatography. The genesis of **113** from precursor **111** may be rationalized by a 1,2-silyl shift from $[(\eta^5-C_5Me_5)(CO)_2Fe-As\{Cr(CO)_5\}(TMS)-P=C(TMS)_2]$ to give a λ^5, σ^3 -arsanediy-l-methenediy-l-phosphorane complex which spontaneously cyclized (Scheme 41) <1996CB219>.

Analogous to the reaction described in Scheme 20 treatment of the tricyclic zirconocene derivative **37** with $AsCl_3$ afforded compound **115**. The cationic cage **116** was readily formed by removal of the chloride anion from **115** through use of $AlCl_3$ or by replacement of the chloride anion with the noncoordinating anion $[Al\{OC(CF_3)_3\}_4]^-$ (Scheme 42).

As in its phosphorus analogue **55** the arsenic atom is occupying the apical site of the square-based pyramidal cation. From a formal point of view the nido-cluster is constructed from four phosphaarsirane moieties <2006CC1375>.



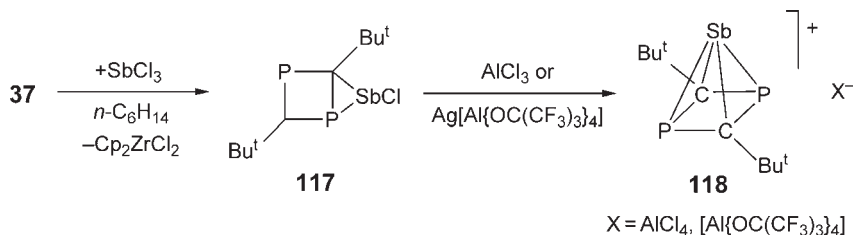
Scheme 41



Scheme 42

1.16.2.7 Phosphastibiranes

Treatment of **37** with 1 equiv of SbCl_3 furnished the bicyclic compound **117** featuring the structural motif of a phosphastibirane. Removal of the chloride anion by a Lewis acid (e.g., AlCl_3) or exchange of chloride by reaction with $\text{Ag}[\text{Al}\{\text{OC}(\text{CF}_3)_3\}_4]$ yielded the cage compound **118** with the antimony atom located in the apex of the square-based pyramidal structure (Scheme 43) <2006CC1375>.



Scheme 43

1.16.3 Physicochemical and Structural Aspects of Diphosphiranes and Diphosphirenes

1.16.3.1 Stability

As pointed out earlier by Koenig and Etemad-Moghadam, the stability of diphosphiranes is highly dependent on the steric requirements of the substituents <1996CHEC-II(1)469, 2001MI1-57>.

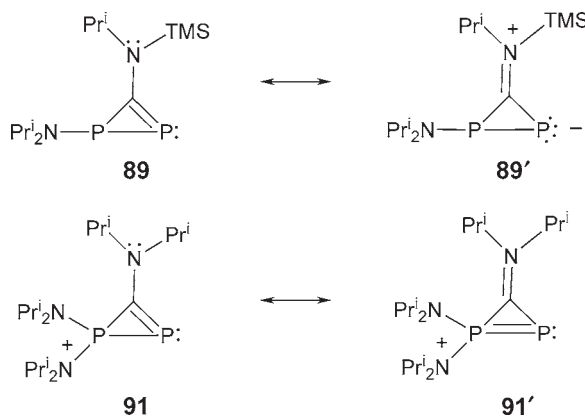
Whereas the diphosphirane containing two 2,4,6-tri-*tert*-butylphenyl substituents **9** is perfectly stable at 25 °C, the corresponding di-*tert*-butyl derivative at 25 °C undergoes dimerization to a 1,2,4,5-tetra-*tert*-butyl-tetraphosphacyclohexane.

The incorporation of the diphosphirane unit into a polycycle does not necessarily lead to an increase in thermal stability as demonstrated by the thermal isomerization of tetraphosphasemibullvalene **42** into cage compound **45** (Scheme 16) <1997AGE1337>. The same is true for tetraphosphasemibullvalene **48**, which decomposes at 20 °C.

In contrast to this 3-aza-1,2,4,6-tetraphosphaquadricyclanes **62a–62e** are markedly more stable. The crystalline *tert*-butyl derivative melts at 76 °C, and the solid adamantyl derivative **62c** was purified by bulb-to-bulb distillation at 140 °C and 10^{−5} bar <1998AGE1233, 2001ZN951>.

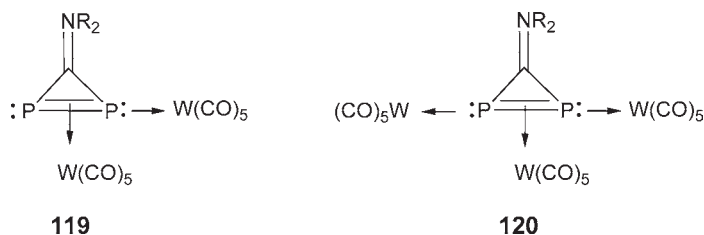
Steric bulk is a crucial requirement for the successful synthesis of the bisphosphonia cyclopropanides **97** by chloride abstraction from the *P*-chloro-ylide precursors (R₂P)₂ClP=C(SiMe₃)(PR¹R²) **96** with GaCl₃ or AlCl₃. Whereas the formation of the rings cleanly proceeded with **96a** [R¹–R² = N(Bu^t)SiMe₂(Bu^t)] or **96b** (R¹ = R² = Bu^t) reaction of **96c** (R¹ = NPr₂ⁱ, R² = Ph) with GaCl₃ to afford a 1:4 mixture of ring compound **97c** and phosphonium salt **98c**. Precursor **96d** (R¹ = R² = Ph) under the same conditions was cleanly converted to the open chain compound [R₂NP=C(SiMe₃)P(NR₂)Ph₂]⁺(GaCl₄)[−] **98d** <2002JA2506>. Electron delocalization also seems to enhance the thermal stability of diphosphirenes and diphosphirenium salts markedly, which may be expressed by zwitterionic canonical formulas.

Based on spectroscopic and X-ray structural evidence, diphosphirenes such as **89** show the features of a phosphalkene with an inverse distribution of π -electrons. Similarly, for diphosphirenium salts, structure **91'** underlines the characteristics of a phosphinidene phosphorane <1989AGE1673, 1991JA8160, 2001AGE2471>.



In many cases the stability of organophosphorus species increases by coordination to transition-metal complex fragments. This coordination imparts electronic changes onto the ligand by blocking lone pairs of electrons, and second an increased steric bulk is created which may protect the ligand for kinetical reasons. As evident from compound **19**, a 1,3-migration of atom P_x from P_A onto P_B causes the reversible opening and closing of the diphosphirane ring. This process was completely stopped by coordination of a [W(CO)₅] group onto the dicoordinate phosphorus atom of the four-membered ring (Scheme 29) <1998CC1537>.

A very impressive stabilization effect by one or more [W(CO)₅] units was observed during the preparation of diphosphirenium salts **110**, **119**, and **120** (Schemes 40 and 52) <1997JA9923, 1999EJI1479>.



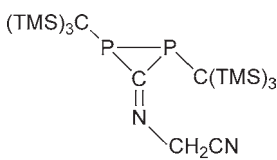
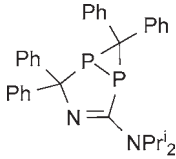
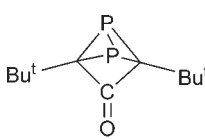
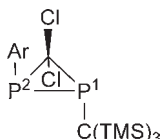
1.16.3.2 Spectroscopic Data

1.16.3.2.1 NMR studies

Table 1 lists ^1H , ^{13}C , and ^{31}P NMR data for a few selected and representative diphosphiranes. The main spectroscopic features associated with the uncomplexed diphosphirane are as follows.

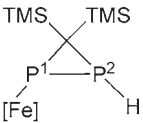
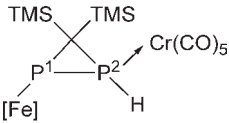
1. High-field shifts of the ^{31}P resonances in the range from 0 to -200 ppm, the phosphorus atoms in the bridgehead position of bicyclodiphosphabutanes experience an even higher shielding [$\delta^{31} = -346.6$ s for **121**]. Of course, ^{31}P chemical shifts are also dependent on the nature of the P-substituents as well as the substituents at the endocyclic carbon atom (see **122**) <1989CC593>. Usually, electronegative atoms or groups are causing significant low-field shifts.
2. ^{13}C -chemical shifts of the endocyclic carbon atom cover an extremely large range (e.g., $\delta^{13}\text{C} = 6$ ppm for $(\text{Bu}^t\text{P})_2\text{CH}_2$ <1978ZNB1208> and 199.5 ppm for **5b** <1999ZFA1934>. The $^1J_{\text{PP}}$ coupling constants have a negative sign and their absolute values vary considerably. Small values are typical for three-membered rings with exocyclic double bonds (e.g., -38 Hz in $(\text{Bu}^t\text{P})_2\text{C}=\text{N}-2,4\text{-Bu}^t\text{C}_6\text{H}_3$ <1987CB421> to -62 Hz in **5b**). In ferriodiphosphirane **123** a $^1J_{\text{PP}}$ coupling of 212 Hz was measured. The endocyclic $^1J_{\text{PC}}$ coupling constants also have a negative sign and their values range from -15.1 Hz in **124** <1988AGE837> to -103 Hz in **5b** <1999ZFA1934>. The proton directly linked with an endocyclic phosphorus atom gives rise to a very low $^1J_{\text{PH}}$ coupling constant [$^1J_{\text{PH}} = 153$ Hz for $\text{HP}-\text{P}(\text{NPr}^i)_2-\text{C}(\text{SiMe}_3)_2$ <1993CB645>]. Coordination of a $[\text{Cr}(\text{CO})_5]$ moiety onto P(2) in the diphosphirane to give **124** leads to a marked deshielding of the coordinated phosphorus atom ($\Delta\delta = 113.3$ ppm) and a very low coordination shift for the uncoordinated one ($\Delta\delta = 1.8$ ppm). The $^1J_{\text{PP}}$ coupling constant increases by 64 Hz upon complexation and for the $^1J_{\text{PH}}$ coupling in **124** 304 Hz were found <1992CB1553>.

Table 1 Selected NMR data for some diphosphiranes

Diphosphirane	$^{31}\text{P}^a$	$^1J_{\text{PP}}^a$	$^{13}\text{C}^a$	$^1J_{\text{PC}}^a$
 5b^b	-94.4 d -120.4 d	-62	199.5 dd	-68 , -103
 24a^c	-112.7 } -119.1 } AB	-201.0	no	no
 121^d	-346.4 s	—	187.52 t	-15.1
 122^e	-29.4 d (P1) -77.8 d (P2)	-144	no	no

(Continued)

Table 1 (Continued)

Diphosphirane	$^{31}\text{P}^a$	$^1J_{\text{PP}}^a$	$^{13}\text{C}^a$	$^1J_{\text{PC}}^a$
 123^f	−26.6 d (P1) −227.2 (P2)	−212	no	no
 124^f	−28.8 d (P1) −115.9 dd (P2) ^g	−276	no	no

^a δ (ppm) from TMS or external 85% H_3PO_4 , couplings to ^{31}P in Hz.

^b<1999ZFA1934>.

^c<1996CB1271>.

^d<1988AGE837>.

^e<1989CC593>.

^f<1992CB1553>.

^g $^1J_{\text{PH}} = 304$ Hz; no not observed.

In **Tables 2** and **3** selected NMR data of diphosphirenes, diphosphirene complexes, diphosphirenium salts, and other derivatives are compiled. In their ^{31}P NMR spectra the free diphosphirenes **89** and **93** show the expected doublets at high field ($\delta = 14.9$ to -23.7 ppm for the σ^2 -phosphorus atom and $\delta = -116.3$ to -121.7 ppm for the σ^3 -phosphorus nuclei with coupling constants $^1J_{\text{PP}}$ ranging from -104.8 to -121 Hz. The ring carbon atoms give rise to double doublets in the region typical for $\text{P}=\text{C}$ units in phosphalkenes ($\delta = 191.2$ – 202.6 ppm) with coupling constants $^1J_{\text{CP}}$ of -82.2 to -87.2 Hz to the dicoordinate phosphorus, which are slightly larger than those to the tricoordinate P atoms (77.9 – 80.7 Hz) <1989AGE1673, 1999EJI1479>.

Upon coordination of ring **93** to $[\text{W}(\text{CO})_5]$ unit via its σ^3 phosphorus center to yield complex **105**, the doublet of the σ^2 -P-atom is deshielded by $\Delta\delta = 38.7$ ppm, whereas the σ^3 -P-atom is slightly high-field-shifted ($\Delta\delta = -1.3$ ppm). The coupling constant $^1J_{\text{PP}}$ increases by 43 Hz upon complexation. The ring carbon atom is slightly deshielded $\Delta\delta = 4.7$ ppm on going from **93** to **105** whereby the coupling constants $^1J_{\text{PC}}$ decrease by 2.8 and 31.2 Hz.

More dramatic coordination shifts were observed with tetracarbonyliron complex **106** [$\delta = 52.6$ d (σ^2 -P), -53.0 d (σ^4 -P); $^1J_{\text{PP}} = 195$ Hz] in comparison to free **93**. Depending on the nature of the substituent at the σ^4 -phosphorus center in **128** (R = F), **109** (R = Cl), **127** (R = OH), **126** (R = Ph), the ^{31}P NMR shift of dicoordinate phosphorus ranges from $\delta = +43.2$ (R = F) to $\delta = -60.0$ ppm (R = Ph), whereas resonances for the W-bound P-atom varies from $\delta = -12.1$ (R = F) to -177.5 ppm (R = Ph). $^1J_{\text{PP}}$ coupling constants are observed between -148 Hz (R = Ph) and -238 Hz (R = F), some reflecting the electronegativity of the contact atom of the P-substituent.

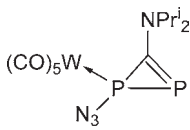
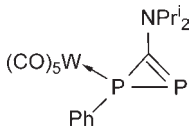
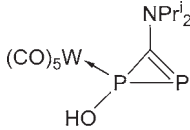
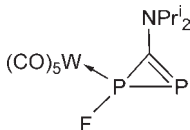
The ^{31}P NMR spectrum of the diphosphirenium salt **91** is characterized by a doublet at δ 58.5 ppm for the dicoordinate P-atom and a doublet of quintets at -46.6 ppm for the phosphonium unit with coupling constants $^1J_{\text{PP}} = -247.4$ Hz and $^3J_{\text{PH}} = 19.8$ Hz <91JA8160>. The respective resonances in the diphosphirenium complex **104** are markedly deshielded and observed at $\delta = 39.9$ (d, $^1J_{\text{PP}} = -130$ Hz, σ^3 -P) and $\delta = -33.9$ (dq, $^1J_{\text{PP}} = -130$, $^3J_{\text{PH}} = 20$ Hz, σ^4 -P) <1999EJI1479>. Singlets for the phosphorus nuclei in the diphosphirenium complex **110a** and the dimer **129** appear in the typical high-field region at $\delta = -157.4$ and -164.5 ppm. The ^{13}C resonances of the ring carbon atoms in **110a** and **129** give rise to triplets at $\delta = 205.1$ ($^1J_{\text{PC}} = 90.9$ Hz) and $\delta = 162.2$ ($J_{\text{PC}} = 83$ Hz), respectively <1998SCI2080, 1999EJI1479>. The ^{31}P NMR spectra of the diphosphonia-cyclopropanide ions **95**, **97a**, **97b**, and **97c** show resonances for the bisamino-substituted phosphorus centers in the narrow range of $\delta = 6.9$ – 10.4 ppm, whereas the second phosphorus atom appears at $\delta = 7.3$ to -68.0 in dependence of the substituents. Coupling constants $^1J_{\text{PP}}$ range from -136.0 to -254.5 Hz. The negative charge located at the ring carbon atom in **95** and **97** is

Table 2 Selected NMR data for some diphosphirenes and diphosphirene complexes

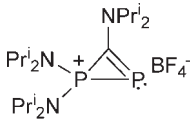
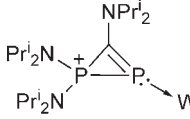
<i>Diphosphirenes</i>	$\delta^{31}\text{P}^{\text{a}}$			$\delta^{13}\text{C}^{\text{a}}$	
	$\sigma^2\text{-P}$	$\sigma^3\text{-P}$	$^1J_{\text{PP}}$	<i>PCP</i>	$^1J_{\text{PC}}$
 89^b	14.9 d ^c 4.6 d ^d	−118.7 d ^c −116.3 d ^d	−104.8 ^c −108.8 ^d	196.8 dd ^c 202.6 dd ^d	−79.6, −83.4 ^c −80.7, −87.7 ^d
 93^e	−23.7 d	−121.7 d	−121	191.2 dd	−77.9, −82.2
<i>Diphosphirene complexes</i>					
 87^d	−28.2 d	−159.2	−115.1	204.8 dd	−44.5, −78.1
 130^g	−31.6 d	−150.6 d	−127.5	193.3 dd	−33.3, −79.1
 105^g	15.0 d	−123.0 d	−164	195.9 dd	−48.4, −80.6
 107^h	−6.3 d	−86.9 d	−111	188.3 dd	−37.5, −46.4
 106ⁱ	52.6 d	−53.0 d	−195	195.4 dd	−34.0, −83.6
 109^h	34.6 d	−78.5 d	−218	189.0 dd	−34.7, −88.6

(Continued)

Table 2 (Continued)

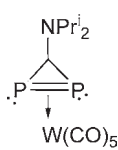
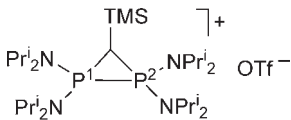
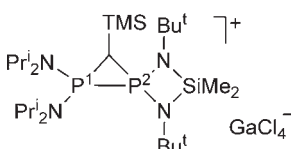
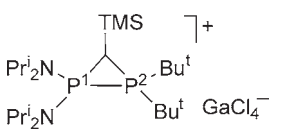
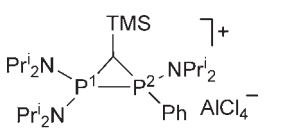
<i>Diphosphirenes</i>	$\delta^{31}\text{P}^{\text{a}}$			$\delta^{13}\text{C}^{\text{a}}$	
	$\sigma^2\text{-P}$	$\sigma^3\text{-P}$	$^1J_{\text{PP}}$	<i>PCP</i>	$^1J_{\text{PC}}$
 125^h	−5.0 d	−96.6 d	−210	no	no
 126^h	−60.0 d	−177.5 d	−148	no	no
 127^h	33.7 d	−67.4 d	−199	nd	nd
 128^h	43.2 d	−12.1 d	−238	nd	nd

^a δ (ppm) from TMS or external 85% H_3PO_4 , couplings to ^{31}P in Hz.^b<1989AGE1673>.^cmajor isomer.^dminor isomer.^e<1997CC2399>.^f<1995CC2113>.^g<2001AGE2471>.^h<1999EJI1479>.ⁱ<1999CC1535>.**Table 3** Selected NMR data for some diphosphirenium, diphosphirenylium, and diphosphoniacyclopropanide derivatives

<i>Diphosphirenium and diphosphirenylium salts</i>	$\delta^{31}\text{P}^{\text{a}}$			$\delta^{13}\text{C}^{\text{a}}$	
	$\sigma^2\text{-P}$	$\sigma^4\text{-P}$	$^1J_{\text{PP}}$	<i>PCP</i>	$^1J_{\text{PC}}$
 91^b	58.5 d	−46.6 dq ^c	−247.4	185.9 d	−81.2
 104^d	33.9 d	−33.9 dq ^c	−130	nd	nd

(Continued)

Table 3 (Continued)

	$\delta^{31}\text{P}^{\text{a}}$			$\delta^{13}\text{C}^{\text{a}}$	
	$\sigma^2\text{-P}$	$\sigma^4\text{-P}$	$^1J_{\text{PP}}$	PCP	$^1J_{\text{PC}}$
 110a^d	−157.4			205.1 t	−90.9
	$\delta^{31}\text{P}$			$\delta^{13}\text{C}^{\text{a}}$	
	P(1)	P(2)	$^1J_{\text{PP}}$	PCP	$^1J_{\text{PC}}$
 95^e	7.3 s	7.3 s		49.6 t	−7.3
 97a^e	8.0 (AB)	6.9 (AB)	−164	67.7 dd	−5.2, −7.1
 97b^e	10.4 d	−21.5	−136.0	nd	nd
 97c^e	8.5 d	−68.0	−245.5	nd	nd

^a δ (ppm) from TMS or external 85% H_3PO_4 , couplings to ^{31}P in Hz.

^b<1991JA8160>.

^{c3} $J_{\text{PH}} = 19.8$ Hz.

^{d3} $J_{\text{PH}} = 20$ Hz; ^d<1999EJ1479>.

^e<2002JA2506>; nd not determined.

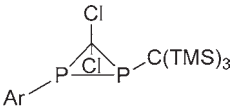
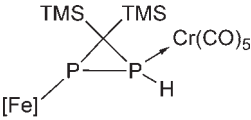
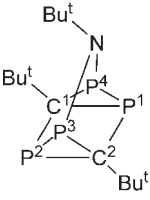
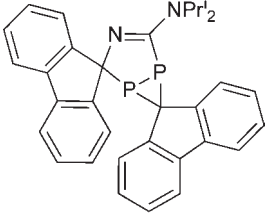
responsible for resonances at comparatively high field ($\delta = 49.6$, t, $^1J_{\text{PC}} = 7.3$ Hz and 67.7 dd, $^1J_{\text{PC}} = 5.2$, 7.1 Hz) <2002JA2506>. In the phosphaaarsirane species **113** and **114** signals at $\delta^{31}\text{P} = 33.5$ (s) and -100.8 ppm (d, $^1J_{\text{PH}} = 303$ Hz) are observed.

1.16.3.3 Structural Data

About 20 structural studies on diphosphiranes have been reviewed in Koenig's recent accounts on three-membered ring compounds published in CHEC-II(1996) <1996CHEC-II(1)469> and in *Phosphorus Carbon Heterocyclic Chemistry: the*

Rise of a New Domain <2001MI1-57>. Since then, numerous diphosphiranes and complexes thereof have been published, but no new original features have been brought to light. The molecular structures of diphosphirane rings in the crystal confirm the *trans*-configuration of the substituents at the heteroatoms. The P–P bond lengths within the heterocycle vary between 2.117(3) Å for **122** and 2.280(2) Å for **5e** (Table 4). In most of the diphosphiranes, however, P–P distances are found between 2.17 and 2.21 Å, and thus very close to the P–P bond lengths of acyclic diphosphanes, despite the considerable strain within these rings. According to calculations and photoelectron spectra, this is probably due to a significant mixing of the phosphorus lone pairs and the Walsh orbitals. The long P–P bond in **5e** is not unusual for diphosphiranes with exocyclic C=C or C=N double bonds. The very short P–P bond in **122** which is amidst a P=P double bond in diphosphenes (2.02 Å) <1992CRV1839> and a P–P single bond in diphosphanes (2.22 Å), and the quasi-planar CPPC skeleton (torsion angle 177.0°) which is orthogonal to the three-membered ring are explained by a ‘ π -complex’ like bonding situation between the π -bond of a diphosphene and a carbene.

Table 4 Structural data of selected diphosphiranes

Compound	Bond lengths (Å)			Bond angles (°)	
	P–P	P–C	P–R	P–C–P	C–P–P
 122 <1996JOM(514)37>	2.117(3)	1.808(6) 1.835(6)	1.783(6) 1.798(6)	71.0(2)	53.9(2) 55.1(2)
 124 <1992CB1553>	2.163(3)	1.865(8) 1.933(9)	2.286(3) (Fe) 1.211(74) (H) 2.381(3) (Cr)	69.4(3)	53.8(2) 56.8(3)
 62a <1998AGE1233>	2.172(10) (P2–P3) 2.2185(11) (P1–P4)	1.894(2) (P1–C1) 1.842(2) (P4–C1) 1.865(2) (P3–C2) 1.896(2) (P2–C2)	1.716(2) (P4–N) 1.716(2) (P3–N) 1.880(2) (P1–C2) 1.881(2) (P2–C1)	72.83(8) (P4–C1–P1) 70.79(8) (P2–C2–P3)	55.50(6) (C1–P1–P4) 54.67 (C1–P4–P1) 55.27(7) (C2–P3–P2) 53.94(6) (C2–P2–P3)
 24c <1996CB1271>	2.185(2)	1.874(5) 1.884(5)	1.903(5) 1.866(6)	71.1(2)	54.6(2) 54.2(2)

(Continued)

Table 4 (Continued)

Compound	Bond lengths (Å)			Bond angles (°)	
	P–P	P–C	P–R	P–C–P	C–P–P
 48 <1998EJI2071>	2.274(1)	1.858(2) 1.865(2)	1.809(2) 1.796(2)	75.3(1)	52.5(1) 52.2(1)
 5e <1999ZFA1934>	2.280(2)	1.806(7) 1.851(6)		77.1(3)	50.6(2) 52.3(2)

The endocyclic P–C bond lengths cover the wide range between 1.808(6) Å in **122** and 1.933(9) Å in **124**. The standard value for a P–C single bond amounts to 1.85 Å. The endocyclic bond angles at the carbon atom range from 69.4(3)° in compound **124** to 77.1(3)° in **5e**, thereby correlating with the P–P distances. Endocyclic CPP angles are measured between 50.6(2)° in **5e** and 56.8(3)° in **124**.

The P–P bond length in free diphosphirene **89** of 2.218(1) Å (**Table 5**) matches well with the PP single bonds encountered in may diphosphiranes and diphosphanes. The tricoordinate phosphorus atom is pyramidal, whereas the nitrogen atom at the carbon atom is planar whereby its lone pair is in conjugation with the P=C π -system. Evidence for this is given by a short CN bond [1.350(4) Å] and a slightly elongated P=C double bond. The endocyclic angles at the dicoordinate (52.3°) and the tricoordinate P-atom (48.9°) are slightly more acute than in the diphosphirane structures discussed before. Coordination of one [W(CO)₅] unit at the σ^3 -P atom of **130** or of two [W(CO)₅] fragments at both phosphorus centers in **108** is accompanied by a marked shortening of the PP separation [2.176(1) or 2.130(5) Å, respectively].

Table 5 Structural data of selected diphosphirenes, diphosphirenium, and diphosphoniacyclopropanide salts

Compound	Bond lengths (Å)			Bond angles (°)	
	P–P	P–C	P–R/C–X	P–C–P	C–P–P
 89 <1989AGE1673>	2.218(1)	1.702(4) (P1–C1) 1.787(4) (P1–C2)	1.702(3) (P–N) 1.350(4) (C–N)		48.9(1) (P1–P2–C1)
 130 <2001AGE2471>	2.176(1)	1.696(3) (P1–C1) 1.788(3) (P2–C1)	1.832(3) (P–C) 2.520(1) (P–W) 1.327(4) (C–N)	77.22(13)	53.28(10) (C1–P1–P2) 49.49(10) (P1–P2–C1)

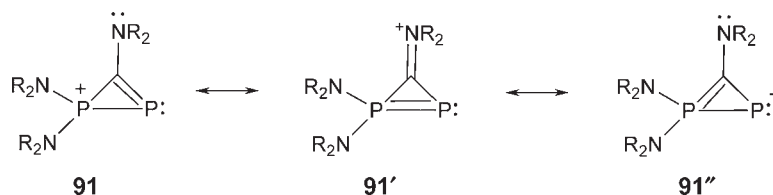
(Continued)

Table 5 (Continued)

Compound	Bond lengths (Å)			Bond angles (°)	
	P–P	P–C	P–R/C–X	P–C–P	C–P–P
108 <1999EJI1479>	2.130(5)	1.798(15) (P1–C1) 1.686(15) (P2–C1)	1.680(11) (P–N) 2.529(4) (P1–W) 2.508(3) (P2–W) 1.327(18) (C–N)	75.3(8)	49.9(5) (C1–P1–P2) 54.7(5) (C–P2–P1)
91 <1991JA8160>	2.095(1)	1.747(4) (P1–C1) 1.737(4) (P2–C1)	1.643(3) (P–N) 1.637(3) (P–N) 1.322(4) (C–N)	73.9(1)	52.8(1) (C1–P1–P2) 53.3(1) (C1–P2–P1)
95 <2000SCI754>	2.1195(11)	1.731(3) (C1–P1) 1.710(3) (C1–P2)	1.651(3) (P1–N1) 1.659(3) (P1–N2) 1.651(2) (P2–N3) 1.642(2) (P2–N4) 1.859(3) (C–Si) $\Sigma \angle C = 360^\circ$	76.04(13)	51.51(10) (C1–P1–P2) 52.42(10) (C1–P2–P1)
97a <2002JA2506>	2.1209(12)	1.737(3) (P1–C1) 1.706(3) (P2–C1)	1.664(3) (P1–N1) 1.661(3) (P1–N2) 1.671(3) (P2–N3) 1.669(3) (P2–N4) 1.872(3) (C–Si) $\Sigma \angle C = 360^\circ$	76.05(14)	51.30(11) (C1–P1–P2) 52.65(12) (C1–P2–P1)
129 <1998SCI2080>	2.205(3) (P1–P2) 2.634(3) (P1–P2a)	1.743(6) (P1–C1) 1.738(6) (P2–C1)	1.336(7) (C–N)	78.6(3)	50.6(2) (C1–P1–P2) 50.8(2) (C1–P2–P1)

The PC double bonds in **108** and **130** compare well with that in the free diphosphirene **89**, and the same is true for the P–C single bonds in all three compounds [1.787(4)–1.798(15) Å]. Short CN separations of 1.327(4) Å agree with multiple bonding. The endocyclic angles in **130** and **108** are 77.22(13)° and 75.3(6)°.

The quaternization of one phosphorus atom in the cation of **91** causes a further shortening of the P–P bond to 2.095(1) Å accompanied by an equalizing of both PC contacts to 1.737(4) and 1.747(4) Å. Again a short CN bond [1.322(4) Å] points to an extensive π -delocalization as expressed by the canonical formulas **91**–**91''**. Thus, the cations also show the structural features of a phosphinyldene σ^4 -phosphorane **91'** or a phosphorus ylide **91''**.



The P–P distances in cations **95** and **97a** are between PP single and double bonds [2.1195(11) and 2.1209(12) Å] and the PC bonds of 1.710(3) and 1.731(3) Å agree with slightly widened PC double bonds. Obviously, the negative charge on the ring carbon atom is stabilized by negative hyperconjugation with both phosphonium centers in addition to some stabilization by the silicon atom. From a formal point of view, compound **129** may be envisaged as two 3*H*-diphosphirenyl radicals which are kept together by two long PP-one electron single bonds [2.634(3) Å] in an *anti*-orientation of the three-membered rings containing normal P–P bond of 2.205(3) Å. The CN distance [1.336(7) Å] as well as the endocyclic PC separations 1.738(6) and 1.743(6) Å mirror multiple bonding. The endocyclic bond As–P in phospharsirane complex **114** [2.285(1) Å] is slightly shorter than the calculated value of an As–P single bond of 2.31 Å but clearly exceeds the value for an As=P bond [e.g., 2.124(2) Å] in ArP=AsCHTMS₂ <1983CC881>. The As–C bond [2.076(3) Å] is longer than the sum of the covalent radii of As and C (1.98 Å), whereas the corresponding endocyclic PC bond of 1.833(8) Å agrees with the standard value of a single bond (ca. 1.85 Å). The endocyclic angle As–C–P [71.23(12)°] is significantly widened relative to the angles AsPC (59.34°) and PAsC [49.34(9)°] <96CB219>.

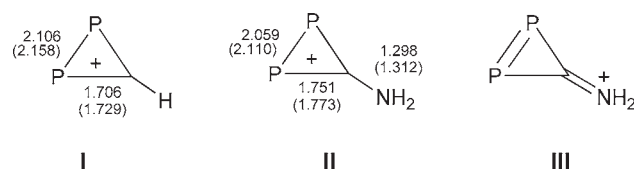
In square pyramidal **55**, PP bond lengths of 2.367(7) and 2.2517(8) Å were measured. The PC bonds to the apical P atom [1.999(2) Å (av.)] clearly exceed those in the base of the pyramid [1.802(2) Å (av.)] <2003AGE2778>. In the related cage compounds **116** and **118** featuring an As or an Sb atom in the apex PC bonds of comparable lengths [1.803(3) Å (av.) or 1.804(2) (av.) Å], respectively, were encountered. In **118** SbP and SbC distances of 2.5447(7) and 2.346(3) Å (av.) are found <2006CC1375>.

1.16.4 Theoretical Calculations

In previous reviews the results of quantum chemical calculations on diphosphiranes have been reported, and for more information these accounts are recommended. In this section preference is given to theoretical interpretations and predictions on the bonding situation and reactivity of unsaturated three-membered ring systems containing two phosphorus atoms.

The structural and NMR spectroscopic features of diphosphirene **89** are those of a cyclic C-aminophosphaalkene with an inverse electron distribution at the P=C double bond. Recent quantum-chemical calculations on the acyclic C-amino-substituted phosphoalkene HP=CH(NH₂) (B3LYP/6-31g* level) predict a strong polarization of the π -bond provided that π -delocalization of the lone pair of a planar amino group with the P=C double bond is given. In line with this, the phosphorus atom carries approximately –0.285 charge, whereas the carbon and nitrogen atoms in HP=CH(NH)₂ bear +0.013 and +0.272 charge, respectively. Experimental consequences are the shortening of the CN bond, a widening of the P=C bond and a high-field shift of the ³¹P NMR signal of the dicoordinate phosphorus atom <2000EJI2425>.

According to calculations <1999EJI1479> the PP and PC bond distances in the parent diphosphirenylium salt **I** are halfway between those of single and double bonds, but the positive charge is essentially distributed over the two phosphorus atoms (Table 6).

**Table 6** Calculated bond lengths and atomic charges for the diphosphirenylium salts I and II at the RHF/DZP level

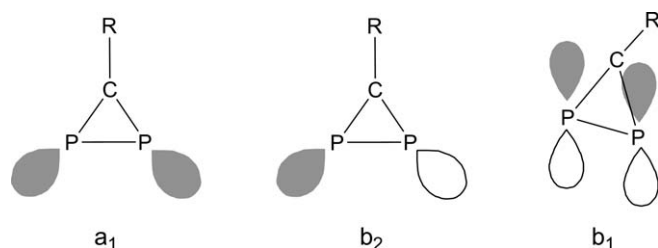
		Mullikan charges	' π ' charges
I	q_P	0.50 (0.50)	0.38 (0.38)
	q_C	0 (0)	0.24 (0.24)
II	q_P	0.38 (0.37)	0.20 (0.20)
	q_C	0.03 (~0.08)	0.24 (0.15)
	q_N	0.21 (0.34)	0.36 (0.45)

Data in paratheses have been obtained at the B3LYP/DZP level. Resonance form **III** is the best representation of the C-amino derivative **II**.

Obviously the electronic delocalization seems to be less important with increasing phosphorus substitution in the ring, when compared with a phosphirenylium ion which still possesses 70% of the electron delocalization of the cyclopropenium ion <1999ACR561, 1999EJI1479, 2002FCF(220)1>. Comparatively weak P(3p)–C(2p) and P(3p)–P(3p) interactions (π -bond strengths; C=C 70 kcal mol^{–1}; P=C 48 kcal mol^{–1}, P=P 34 kcal mol^{–1}) give an explanation for this. In the parent system **I** the HOMO and HOMO-1 refer to symmetric and asymmetric combinations of the two phosphorus lone pairs (a_1 : –17.0 eV; b_2 : –17.8 eV) while the HOMO-2 corresponds to a π_{PP} -orbital (b_1) (Table 7).

Table 7 Frontier orbital energies (eV) of **I** and **II** (from RHF)

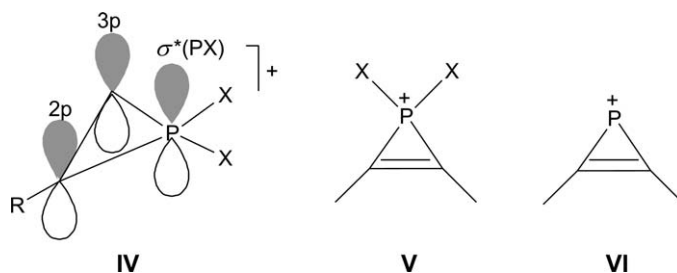
	HOMO-2	HOMO-1	HOMO
I	–18.4 (b_1)	–17.8 (b_2)	–17.0 (a_1)
II	–16.7 (b_2)	–16.6 (a_1)	–15.7 (b_1)



The situation is completely different for the amino-substituted derivative **II**, where the HOMO refers to the π_{PP} -orbital (b_1), whereas the HOMO-1 and HOMO-2 correspond to a_1 and b_2 orbitals. This result has relevance for the coordination behavior of the C-amino-functionalized diphosphirenylium ion **II** toward the [W(CO)₅] moiety. According to calculations at the B3LYP/DZ(P) level the η^2 -complex is by 3.8 kcal mol^{–1} more stable than the isomeric η^1 -complex. Fixation of cation **II** to the metal carbonyl fragment in the η^2 -mode leads to an elongation of the P–P bond from 2.11 to 2.31 Å. In the complexed ligand CN and PC separations of 1.32 and 1.80 Å are calculated <1999EJI1479>.

Structural data available from experimental <1991JA8160> as well as theoretical <1993MI2-1> studies make obvious that diphosphirenylium ions **IV** also benefit from a limited amount of electron delocalization. However, the

resonance energy of σ^4 -P-containing rings is smaller. Previously, the electron delocalization in phosphirenium ions **V** has been calculated to be only half that of the corresponding phosphirenylium ions **VI** <1996JOC5840>.



This difference between the σ^2 - and σ^4 -P-containing rings may be rationalized by the nature of the orbitals involved in π -delocalization. In diphosphirenylium ions **I** with dicoordinate phosphorus atoms, these are one 2p(C) and two 3p(P) orbitals. In ions of type **IV** one 2p(C), one 3p(P), and one $\sigma^*(PX)$ orbital have to be considered for the cyclic delocalization of two π -electrons. It is obvious that the Hückel-type three-orbital two-electron interaction typical for the cyclopropenium cation is more favored in diphosphirenylium ions **I** than in the related diphosphirenium systems **IV**.

As discussed before reaction of phosphino-silyl carbene ($\text{Pr}^i_2\text{N})_2\text{PC}(\text{SiMe}_3)$ **94** with phosphonium salt $[(\text{Pr}^i_2\text{N})_2\text{P}]^+\text{SO}_3\text{CF}_3^-$ afforded salt **95** featuring a cyclic cation with two σ^4 -phosphorus centers and consequently a negatively charged ring carbon atom. This species is the cyclic isomer of a still unknown bis(phosphino)carbenium ion $(\text{R}_2\text{P})_2\text{CR}^+$, the nitrogen analogues of which are the well-known amidinium salts. According to quantum chemical calculations at the B3LYP/6-31g* level with additional zero-point vibrational correction, the cyclic 2π -electron three-membered valence isomer is predicted to be $129.4 \text{ kcal mol}^{-1}$ higher in energy than the familiar planar amidinium system. To elucidate the bonding situation and electronic structure of the cyclic diphosphorus species, *ab initio* calculations of the model compound **VII** were performed (Figure 1). The calculated bond lengths (P–P, 2.102 Å; C–P, 1.726 and 1.727 Å) compare well with those for the sterically congested **95** as determined by an X-ray diffraction analysis <2000SCI754>. The calculation reveals that each of the diaminophosphenium units in **VII** carries a charge of approximately +1, whereas the carbon center bears a charge of –1.6 [–1.2 in the σ -space and –0.4 in the (formal) p-orbital]. If one subtracts a charge of –0.5 which is provided by the silyl group, a charge of –1.1 remains at carbon. This observation was rationalized by the angular compression exerted on the C-atom which renders it extremely electronegative and withdraws a significant amount of electron density from the neighboring atoms.

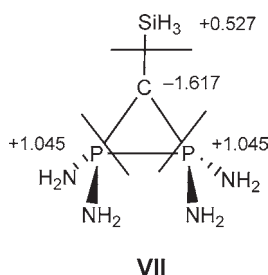


Figure 1 Charges of fragments for **VII**.

Further investigations on **VII** via analysis of the Laplacian of the electron density and the electron localization function (ELF) reveals a strong ‘banana’ P–P bond with large p-character (the bond ellipticity is 0.45) in the plane of the ring, and partial double bond character (Wiberg bond indices = 1.2) for the PC bonds <2000SCI754, 2002JA2506>. The cyclic structure of **VII**, however, is not a minimum on the potential energy surface, nor is this the open planar form (C_{2v} symmetry) analogous to that of amidinium ions. A minimum should, however, exist in an acyclic isomer with one planar P-atom, while the other is pyramidal. With small substituents at phosphorus, derivatives of this type rearrange by a 1,3 shift of a phosphorus substituent to the second P-center to yield

C-phosphinio-phosphaalkenes **XII**. Ring closure to cations of type **VII** is due to bulky substituents at both σ^4 -P-atoms. Another quantum chemical study on the system $[\text{P}_2\text{CH}(\text{NH}_2)_4]^+$ at the MP2/6-31G(d,p) level has shown that the ion **XI** at the highest energy is not a local minimum but a transition state and rearranges to cation **X** (Figure 2). The model **IX**, which corresponds to cation **95**, is not particularly energy rich and only the diposphiranium ion **VIII** is stabilized by $2.2 \text{ kcal mol}^{-1}$ in the family **VIII**, **IX**, and **X** with respect to **IX**. In accordance with experimental findings the C-phosphinio-phosphaalkene **XII** is the most stable ion in this series <2003JCD85>.

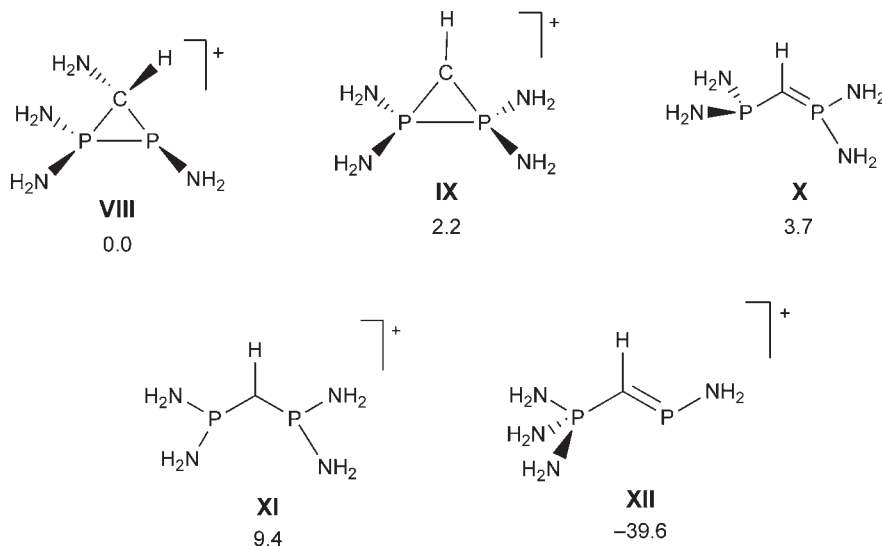


Figure 2 Structures of **VIII–XII** on the $[\text{P}_2\text{C}(\text{NH}_2)_4\text{H}]^+$ potential energy surface. ΔE_{rel} is given under each formula. Structure **XI** is not a minimum but a transition state.

Bonding in dimer **125** of a diphosphirenyl radical was analyzed by *ab initio* calculations for the parent system **XIII**. For the monomeric radical the calculations predicted a a^2A_2 ground state as illustrated by the canonical structures **XIV** and **XIV'** (Figure 3).

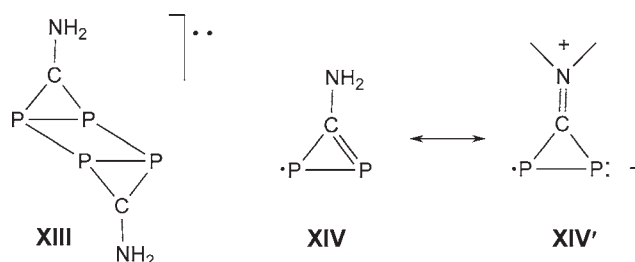


Figure 3

The spin density is equally distributed over the two P atoms and the single occupied molecular orbital is the π^* -orbital of the $\text{P}=\text{P}$ double bond. Because of the higher strength of the $\text{N}-\text{C}$ π -bond (64 kcal mol^{-1}) compared with that of the $\text{P}-\text{C}$ π -bond (44 kcal mol^{-1}), the radical is best described by the zwitterionic structure **XIV'**. The dimerization of the diphosphirenyl radical is exothermic ($-39 \text{ kcal mol}^{-1}$) and occurs via a $\pi^*-\pi^*$ interaction giving rise to the formation of **XIII** (Figure 4). A four-center bonding system with 6π -electrons best describes the P_4 -frame work; each $\text{P}-\text{P}$ bond is formally a one-electron bond which is reflected in the very long $\text{P}-\text{P}$ bond in **129** <1998SCI2080>.

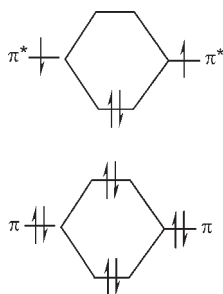


Figure 4 Orbital diagram for the dimerization of the diphosphenyl radical **XIV** into the $\pi^*-\pi^*$ dimer **XIII** (SOMO–SOMO interaction).

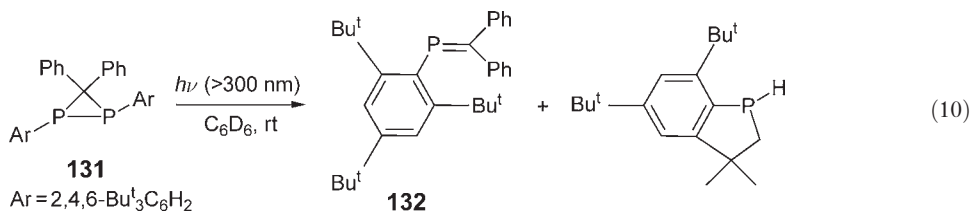
1.16.5 Chemical Properties

1.16.5.1 Diphosphiranes

The versatile chemistry of diphosphirane has been reviewed recently by Koenig and Etemad-Moghadam <1996CHEC-II(1)469, 2001MI1-57>. Thus ring-opening reactions with preferential P–P-bond cleavage occur under photochemical, thermal, anionic, or cationic reaction conditions. Due to the presence of bulky substituents on the phosphorus atoms, the products of such processes are in most cases stable and readily characterized. Thus, the diphosphiranes have to be considered as useful and versatile precursors of phosphalkenes, 1,3-diphosphapropenes, 1,3-diphosphaallenes, but also 1,3-diphosphaallyl anion or cation, or radical intermediates. In contrast to the many results given in the previous accounts, the further development of diphosphirane chemistry has stagnated to some extent.

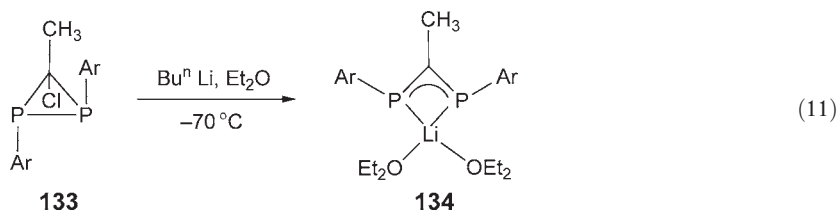
1.16.5.1.1 Photochemical reactions

Irradiation of the diphosphirane **131** ($\lambda > 300$ nm) gave phosphalkene **132** and a phosphindene (Equation 10) <1998HAC607>.



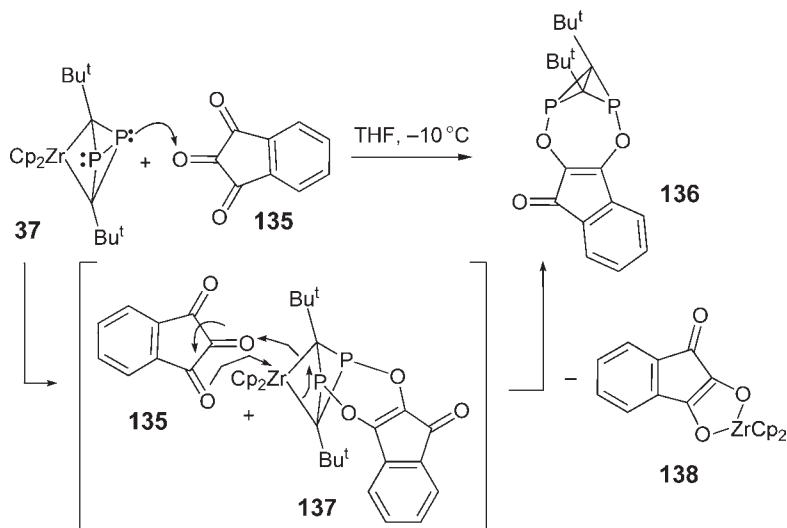
1.16.5.1.2 Reactions with nucleophiles (anionic ring opening)

Red crystals of compound **134** were isolated from the lithiation of diphosphirane **133** with *n*-butyllithium in diethyl ether at -70°C . The formation of the 1,3-diphosphaallyl anion results from a P–P bond cleavage. In the product the exo–exo position of the aryl groups confirms the theoretically predicted conrotatory anionic ring opening. A σ -allyl character agrees with the P–Li coupling constants (Equation 11) <1996JOM(514)37>.



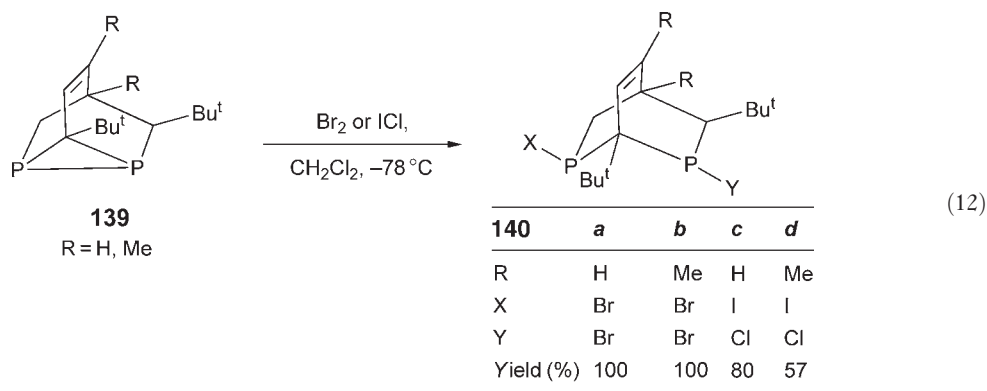
1.16.5.1.3 Oxidation reactions

The reaction of a threefold excess of indantrione **135** with complex **37** in THF at -10°C affords compound **136** as orange crystals in 26% yield. The formation of **136** was rationalized by a multistep cycloaddition between **37** and **135** to give **137** under scission of the P–P bond. The zirconocene unit is cleaved by a second molecule of **135** to furnish final product **136** (after C–C connection) besides complex **138** (Scheme 44) <1999S639>.

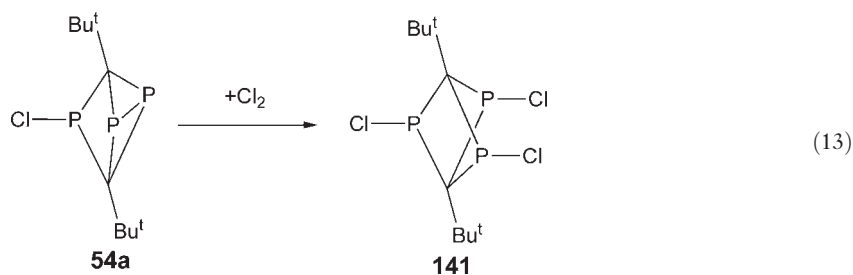


Scheme 44

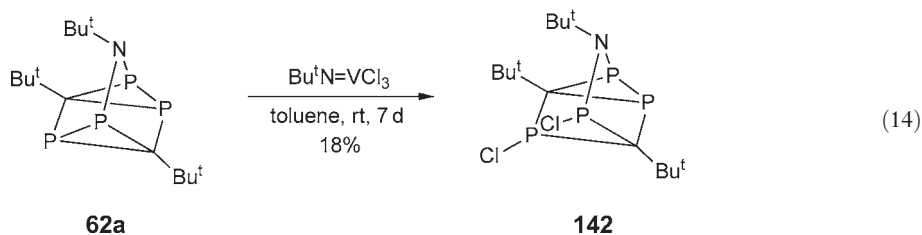
When solutions of bromine or iodine chloride were added dropwise to the diphosphatricyclooctens **139** at -78°C , spontaneous fading of the halogen solutions was observed. From the reaction mixture diphosphabicyclooctenes **140** were isolated in yields of 57–100% (Equation 12) <1998S427>.



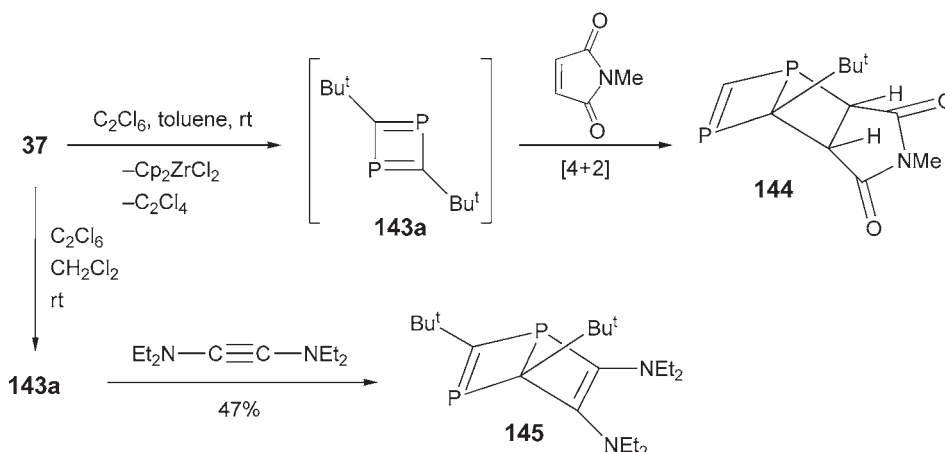
Chlorination of **54a** by elemental chlorine led to the trichloro compound **141** (Equation 13) <2005OM5789>.



Oxidative cleavage of a P–P bond in the quadricyclane **62a** was achieved by treatment with $\text{Bu}^t\text{N}=\text{VCl}_3$ in toluene within 1 week to afford tricyclic compound **142** as a colorless powder in 18% yield. Excessive $\text{Bu}^t\text{N}=\text{VCl}_3$ did not lead to an oxidative cleavage of the remaining P–P bond in **142** (Equation 14) <2001ZN951>.



Previously, it was reported that the chlorination of zirconocene derivative **37** by means of hexachloroethane produced a tetraphosphacubane via a transient 1,3-diphosphete **143a** <1992AGE758, 1994S1337, 1995AGE484, 1997CB823>. Reaction of **37** with C_2Cl_6 in the presence of *N*-methyl-maleimide furnished tricycle **144** as the formal result of a [4+2] cycloaddition of the olefine with transient **143a** (6%). The interception of **143a** with an ynediamine selectively afforded 1,3-diphospha Dewar benzene derivative **145** (47%) (Scheme 45).



Scheme 45

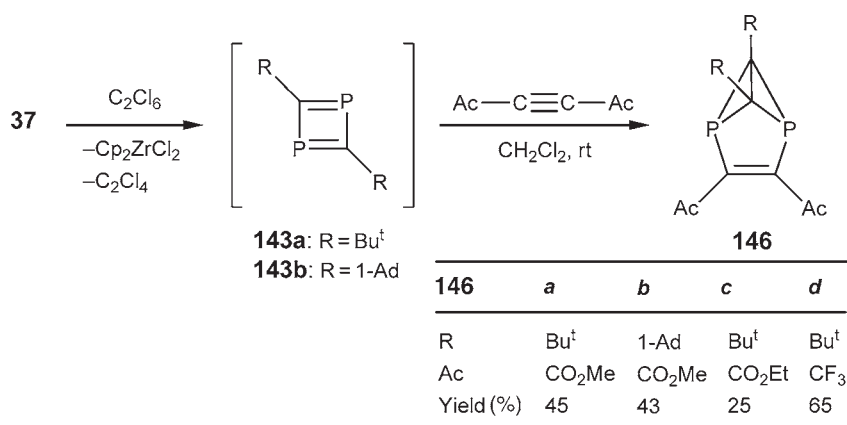
The presence of various bis(acceptor) functionalized alkynes during the liberation of the 1,3-diphosphetes **143** did not lead to diphospha Dewar benzenes. Instead, diphospha benzvalenes **146** were isolated in yields of up to 65% by column chromatography (Scheme 46).

Phosphaalkyne $\text{P}\equiv\text{CBu}^t$ also underwent a highly selective addition to the liberated 1,3-diphosphete **143a**. The initially formed Dewar benzene, however, reacted spontaneously with a second molecule of phosphaalkyne to the tetraphosphabishomoprismene **43** isolated as final product in 82% yield (Scheme 47) <2002JOM409>.

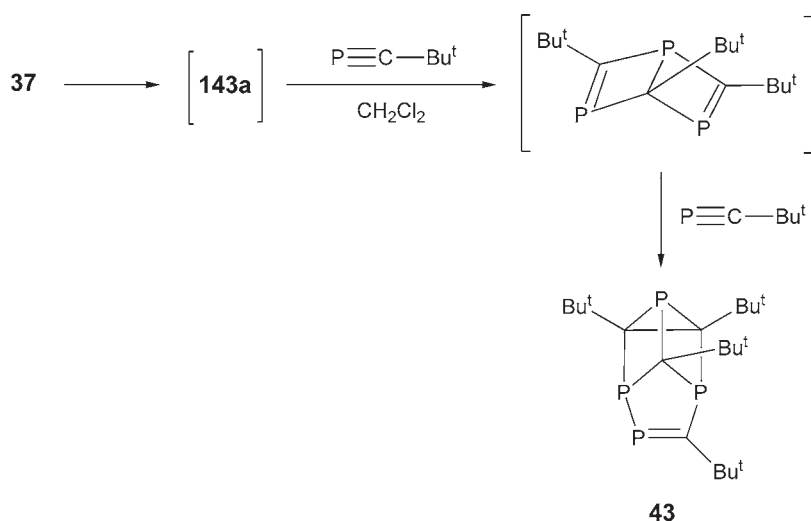
From a formal point of view, the removal of the zirconocene fragment from complex **37** may be achieved with the group 14 dihalides $\text{GeCl}_2 \cdot 1.4$ dioxane, SnCl_2 and PbI_2 . In these cases the unstable 1,3-diphosphete is stabilized as an η^4 -ligand at the metal center in complexes **38** and **147a** and **147b** (Equation 15) <2002CC86, 2003OM2891>.

However, according to a Mössbauer spectrum of **147a** and ^{119}Sn and ^{207}Pb NMR spectra, these compounds are better regarded as divalent group 14 species in which the organophosphorus ligand is existing as a six-electron dianion.

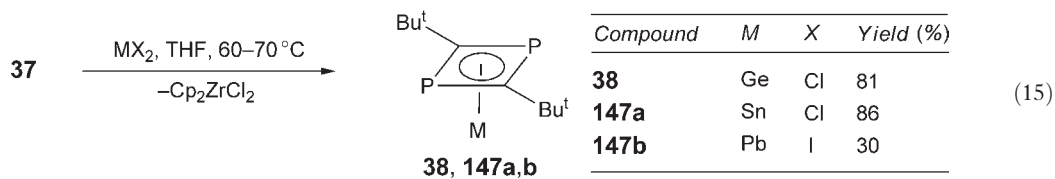
It has been depicted before in Scheme 29 that complex **78** may add the 14-electron fragment $[\text{Pt}(\text{PET}_3)_2\text{Cl}_2]$ to give complex **79** whereby the structural integrity of the bicyclic ligand was retained.



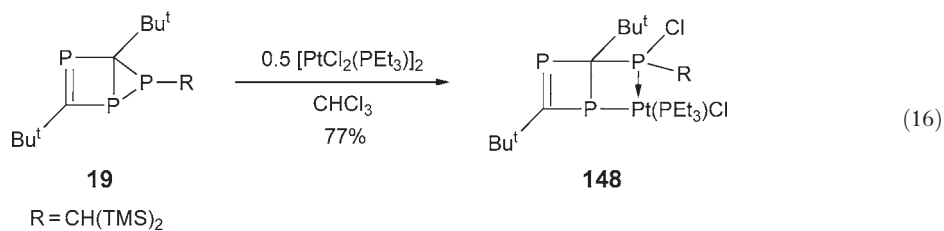
Scheme 46



Scheme 47

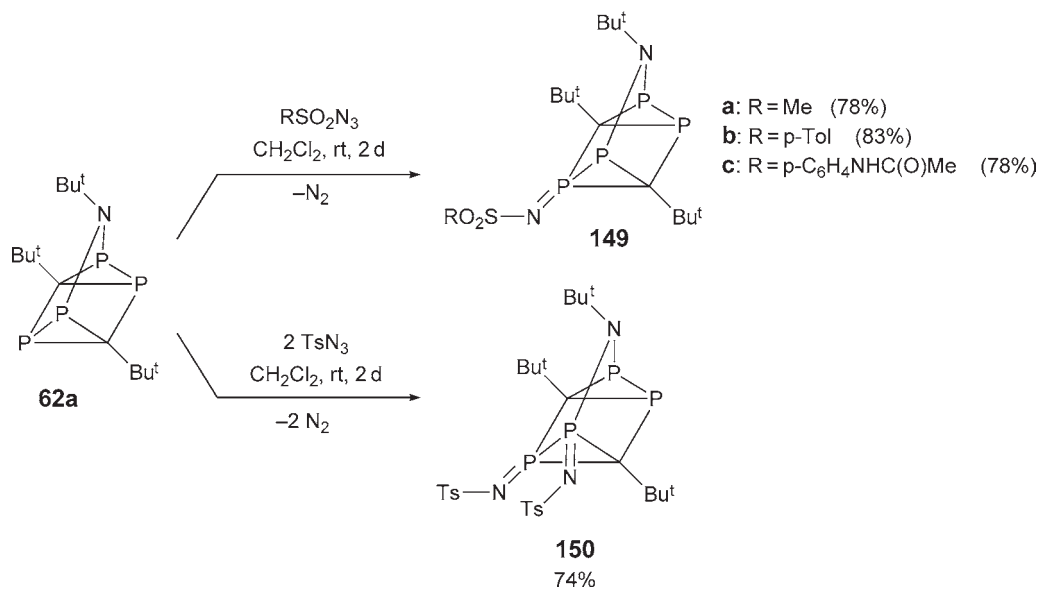


A different situation was encountered in the reaction of the free bicyclic ligand **19** with [PtCl₂(PEt₃)₂] which led to compound **148** (Equation 16).



Here obviously, insertion of the platinum atom into the reactive P–P bond of the three-membered ring and the subsequent migration of a chlorine atom from platinum onto phosphorus occurred [<1998CC1537>](#).

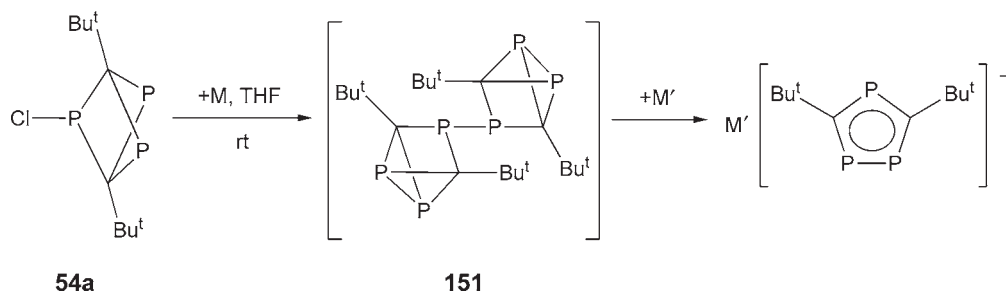
Reaction of **62a** with an equimolar amount of the sulfonylazides RSO_2N_3 [$\text{R} = \text{Me}$, *p*-Tol, *p*- $\text{C}_6\text{H}_4\text{NHC}(\text{O})\text{Me}$] resulted in the selective formation of the Staudinger products **149a–149c** as colorless solids (78–83% yield). With less electrophilic azides such as alkyl or aryl azides precursor **62a** did not show any tendency to form the corresponding phosphane imines even under drastic reaction conditions. When the reaction between **62a** and tosyl azide was performed in a 1:2 molar ratio, the doubly functionalized azaquadricyclane **150** was obtained as a pale yellow powder in 74% yield ([Scheme 48](#)) [<2001ZN951>](#). During this oxidation process, the diphosphirane structure remains intact.



Scheme 48

1.16.5.1.4 Reductions

Alkali metals and magnesium react with **54a** at room temperature in THF to form, selectively and in quantitative yield, the 1,3,4-triphospholides $\text{M}[3,5\text{-Bu}^t\text{-}1,2,4\text{-C}_2\text{P}_3]$ **152** ($\text{M} = \text{Li}$, Na , K or $\text{Mg}_2(\mu\text{-Cl})_3(\text{THF})_6$). The intermediacy of the symmetric dimer $\text{P}_6(\text{CBu}^t)_4$ **151** in this process was evidenced by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy in $d_8\text{-THF}$. In keeping with this, reduction of **54a** with the lanthanides Sm or Eu afforded **151**, the structure of which, however, has not been unequivocally assigned ([Scheme 49](#)) [<2005OM5789>](#).

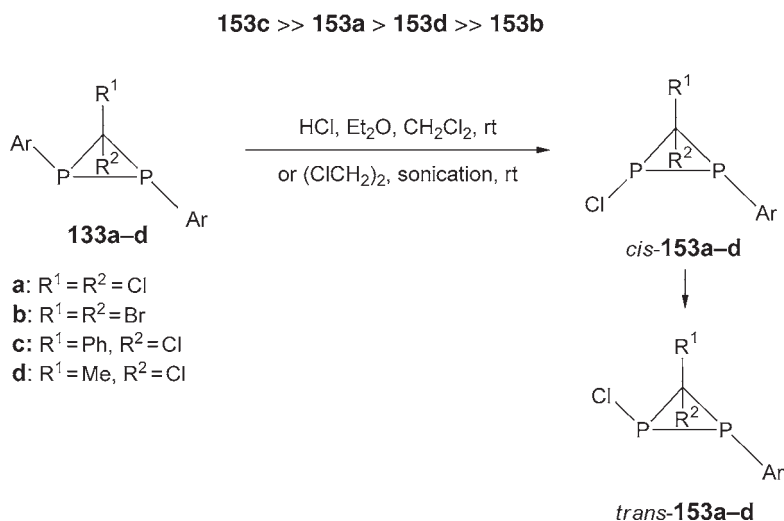


Scheme 49

1.16.5.1.5 Substitution reactions

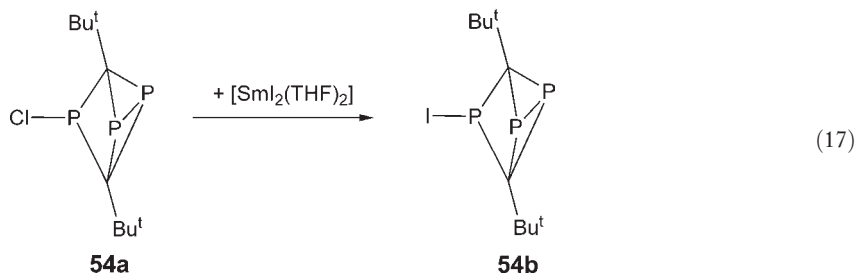
As pointed out in the previous sections ring-opening reactions with preferential endocyclic P–P scission is a most typical feature in the reactivity of diphosphiranes. However, the substitution of one aryl group in diphosphiranes **133–133d** by a chlorine atom leading to the trans *P*-chlorodiphosphiranes **153** via the *cis*-isomer intermediate has

been realized in CH_2Cl_2 by ethereal hydrogen chloride or alternatively by sonication in 1,2-dichloroethane. Only in the case of *trans*-**153** an analytically pure sample could be isolated in 50% yield. From NMR spectra a decreasing order of stability of the *p*-chlorodiphosphiranes can be established (Scheme 50) <1997MGC37>:



Scheme 50

Treatment of compound **54a** with $[\text{SmI}_2(\text{THF})_2]$ cleanly afforded the iodo analogue **54b** by a halide-exchange process. The molecular structure of **54b** was authenticated by X-ray diffraction analysis (Equation 17) <2006AGE3628>.

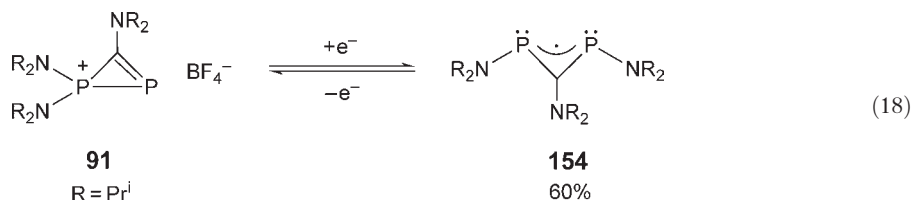


1.16.5.2 Diphosphirenes, Diphosphirenium, and Diphosphirenium Salts

The chemical properties of diphosphirenes, diphosphirenium, and diphosphirenium salts were investigated in the last decade by Bertrand.

1.16.5.2.1 Reductions

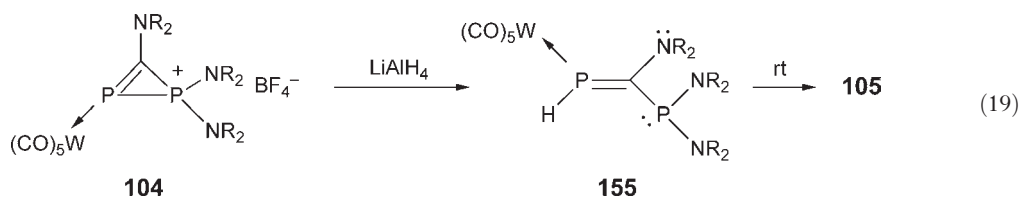
Electrochemical reduction of diphosphirenium salt **91** in dichloromethane at -1.6 V passed 1 equiv of charge yielding a deep red, highly oxygen-sensitive solution from which radical **154** has been isolated as red crystals in 60% yield. The reduction of **91** was also effected by lithium metal in THF. The symmetric structure of the 1,3-diphosphaallylic radical was substantiated by an electron spin resonance (ESR) signal from a THF solution ($g = 2.0048$), with a 1:3:4:3:1 splitting pattern caused by 2 equiv phosphorus nuclei and one nitrogen atom with hyperfine coupling constants $a_{\text{P}} = 9.4\text{ G}$ (2P), $a_{\text{N}} = 9.9\text{ G}$ (1N) and $a_{\text{N}} = 1.56\text{ G}$ (2N). Preparative oxidation of radical **154** via electrolysis in CH_2Cl_2 regenerated the diphosphirenium salt **91** (Equation 18) <1997JA7579>.



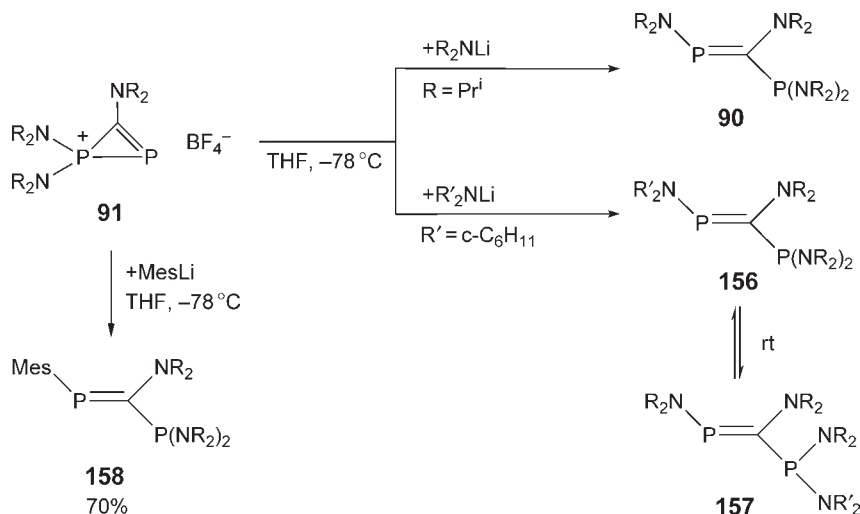
1.16.5.2.2 Anionic ring opening

As already described as a crucial step in the synthesis of diphosphirene **93** from diphosphirenium salt **91** ring opening of the latter species by LiAlH_4 gave phosphalkene $\text{H-P}=\text{C}(\text{NR}_2)\text{P}(\text{NR}_2)_2$ ($\text{R} = \text{Pr}^i$) in 80% yield [\[1999EJI1479\]](#).

Similarly, diphosphirenium complex **104** underwent reaction with LiAlH_4 to afford phosphalkene complex **155**, and subsequently diphosphirene complex **105** (Equation 19) [\[1999EJI1479\]](#).

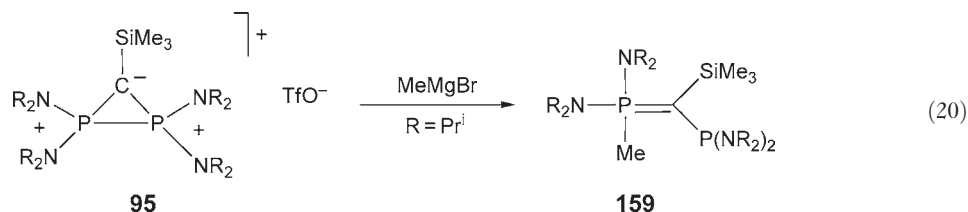


The same type of ring opening was observed when salt **91** was treated with lithium amides or mesityllithium in THF at -78°C . Addition of lithium diisopropylamide to **91** cleanly regenerated phosphalkene **90** in 90% yield. When lithium dicyclohexylamide was used, a 50:50 mixture of *P*-(dicyclohexylamino)phosphalkene **156** and its isomer **157** was isolated. Monitoring this reaction by ^{31}P NMR at -78°C proved the initial formation of **156** with phosphalkene **157** only appeared on warming to room temperature. Lastly, yellow, oily *P*-(mesityl)phosphalkene **158** resulted from the combination of **91** and mesityllithium (70%) [\[1994JA6149\]](#) (Scheme 51).



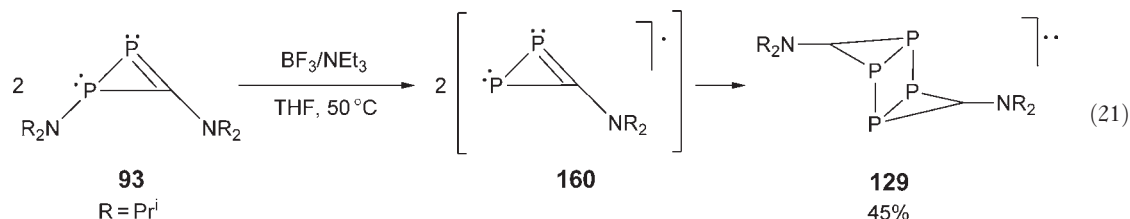
Scheme 51

The phosphorus atoms in the cyclic isomer **95** of a bisphosphinocarocation are markedly positively polarized, and the negative charge is accumulated at the ring carbon atom. In keeping with this, methylmagnesium bromide does not react at the carbon center but at phosphorus leading to phosphorus ylide **159** in near quantitative yield (Equation 20) [\[2000SCI754\]](#).



1.16.5.2.3 Dimerization

The singlet biradical **129**, which is an analogue of the postulated *anti*-tricyclohexylene has been isolated as a red crystalline solid in 45% yield from the reaction of diphosphirene **93** with catalytic amounts of BF_3 (5%) and NEt_3 (5%) in THF at 50°C (Equation 21). Radical **160** was postulated as the initially formed species <1998SCI2080>.

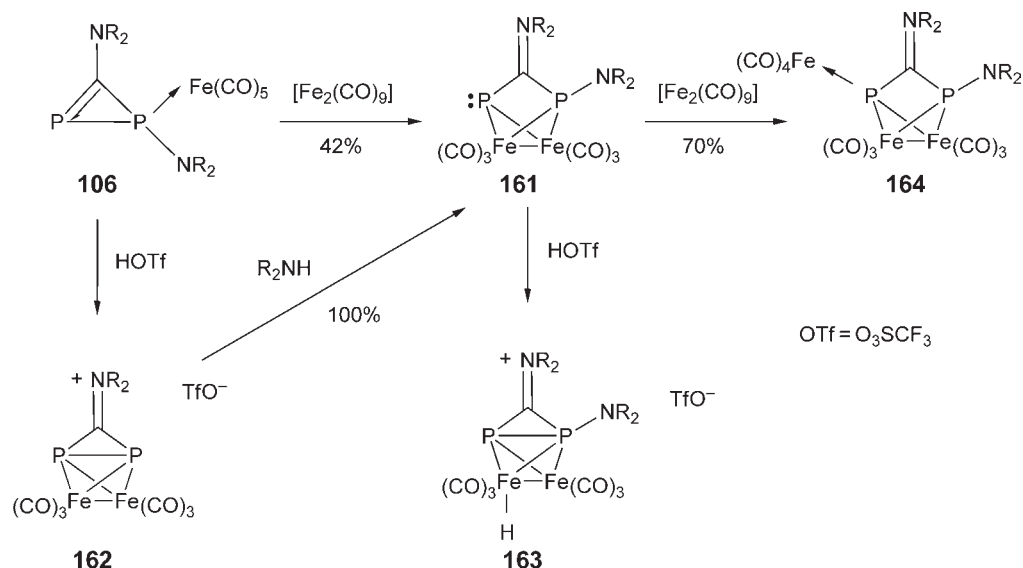


1.16.5.2.4 Reactions with metal carbonyls

In this section reactions of diphosphirene derivatives with transition metal carbonyl complexes, where also the ring skeleton was subject to transformations, are discussed.

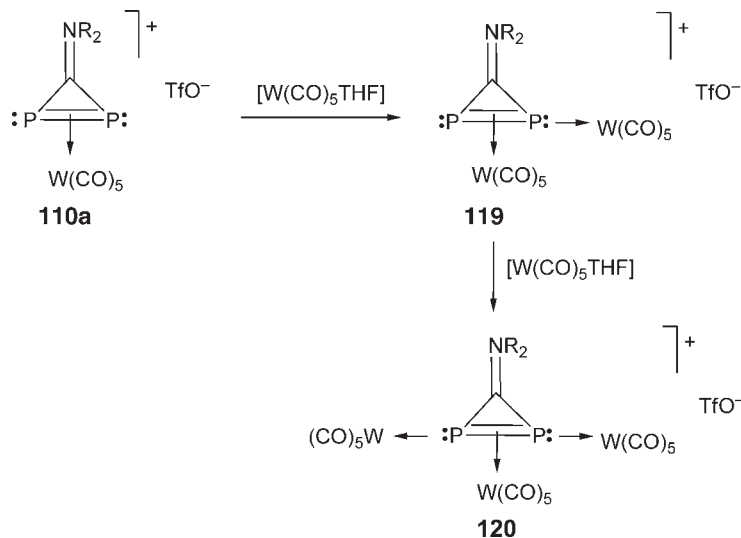
When iron carbonyl complex **106** was treated with 1 equiv of $[\text{Fe}_2(\text{CO})_9]$, the binuclear complex **161** was isolated as red crystals in 42% yield. This complexation was accompanied by the cleavage of the P–P bond.

Interestingly, treatment of the mononuclear 1*H*-diphosphirene complex **106** with 2 equiv of trifluoromethanesulfonic acid at -78°C led to the diphosphirenium binuclear complex **162**. This species was not formed by the protolysis of **161**. Instead, protonation of an iron center occurred leading to the hydridocarbonyl complex **163**. Compound **162** was quantitatively converted into the neutral binuclear complex **161** by exposure to diisopropylamine. The tricoordinate phosphorus atom in **161** imparts ligand properties to the cage. This was substantiated by the synthesis of red trinuclear complex **164** when **161** was combined with an excess of $[\text{Fe}_2(\text{CO})_9]$ in THF at room temperature (70% yield) (Scheme 52) <1999CC1535>.



Scheme 52

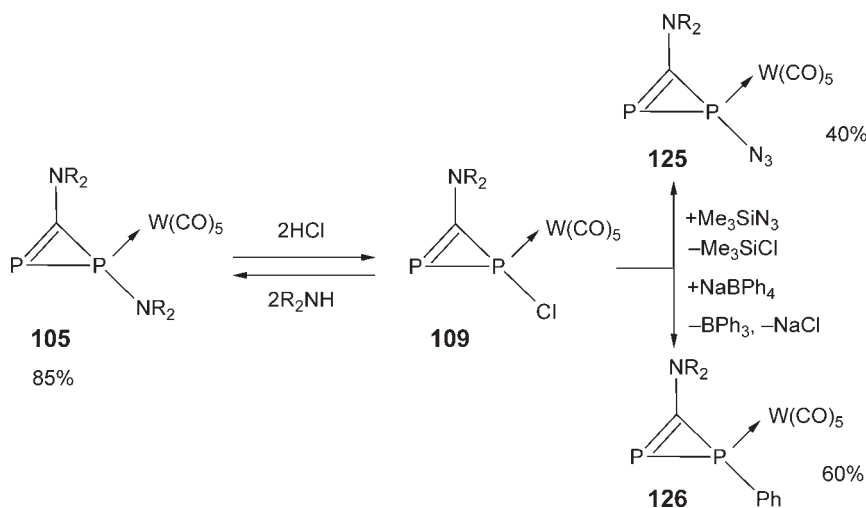
Coordination chemistry of the diphosphirenylium salt **110a** was of interest, since it can potentially add up one or two more $[\text{W}(\text{CO})_5]$ fragments. Thus, on addition of 1 equiv of $[\text{W}(\text{CO})_5(\text{THF})]$ to a solution of **110a** in $\text{ClCH}_2\text{CH}_2\text{Cl}$ dinuclear complex **119** was formed, whereas salt **110a** was converted into trinuclear **120** by an excess of $[\text{W}(\text{CO})_5(\text{THF})]$ (Scheme 53) <1999EJI1479>.



Scheme 53

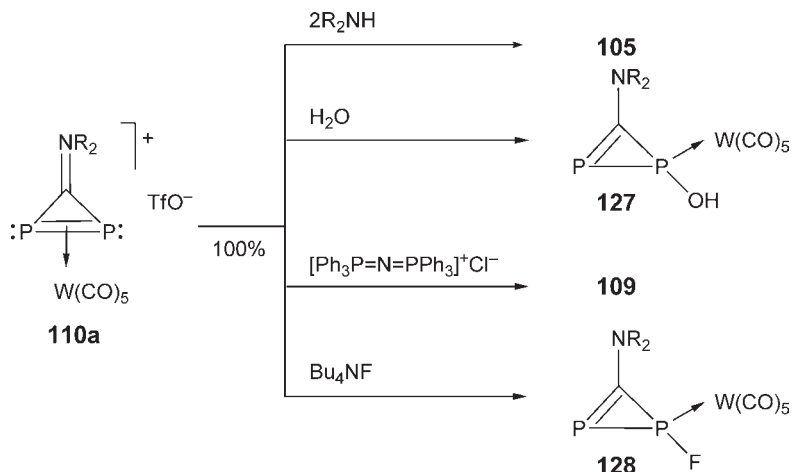
1.16.5.2.5 Substitution reactions

Reactions at the periphery of the ring with exchange of ligands seems a viable approach to a wide variety of diphosphirenes. Thus, reaction of **105** with 2 equiv of hydrogen chloride in pentane gave the *P*-chloro-1*H*-diphosphirene **109** as a yellow oil in 69% yield. The chlorine atom of **109** was easily replaced by an amino, an azido, or a phenyl group. In keeping with this, complex **105** was isolated in 85% yield after treatment of **109** with 2 equiv of diisopropylamine in pentane. On addition of a THF solution of azidotrimethylsilane, this compound underwent facile transformation to yield **125** (40% yield). Treatment of **109** with sodium tetraphenylborate in CH_2Cl_2 at 25°C afforded the *P*-phenyl-1*H*-diphosphirene complex **126** (60% yield). The formation of **126** presumably involved the prior ionization of the $\text{P}-\text{Cl}$ bond of **109** to give a transient diphosphirenylium salt, which then abstracted a phenyl group from the tetraphenylborate counterion (Scheme 54) <1999EJI1479>.



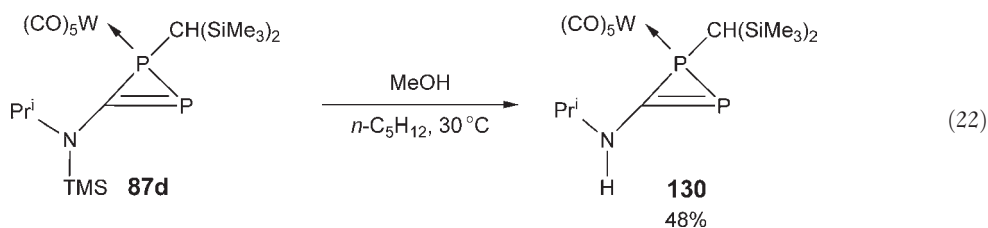
Scheme 54

This idea was supported by the reaction of diphosphirenylium salt **110a** with 2 equiv of diisopropylamine with water and bis(triphenylphosphoranylidene)ammonium chloride, or with tetrabutylammonium fluoride, whereby diphosphirenes **105**, **127**, **109**, and **128** were formed quantitatively (Scheme 55) <1999EJI1479>.



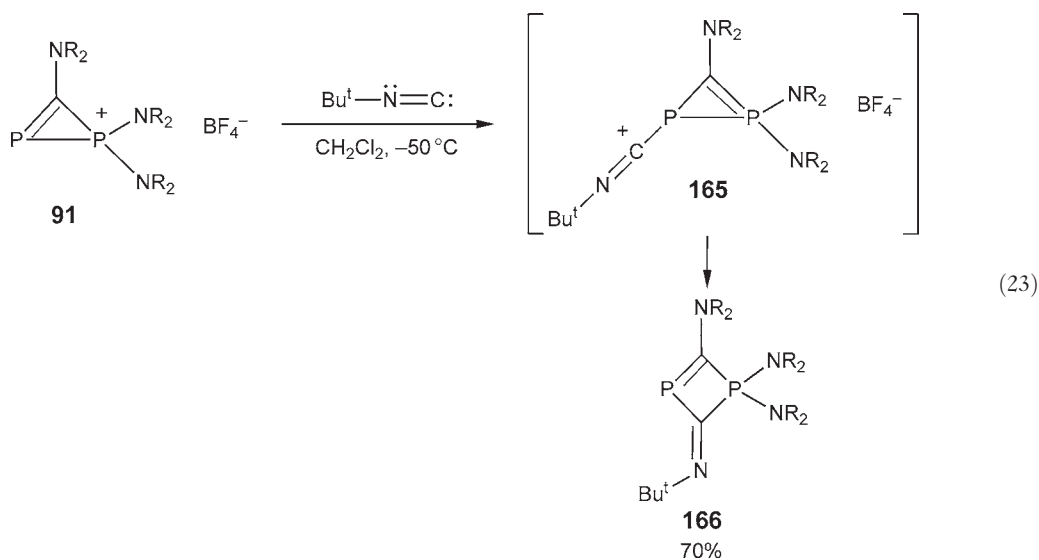
Scheme 55

Methanolysis of the N–Si bond in diphosphirene complex **87d** gave a 48% yield of complex **130** as a yellow solid (Equation 22) <2001AGE2471>.

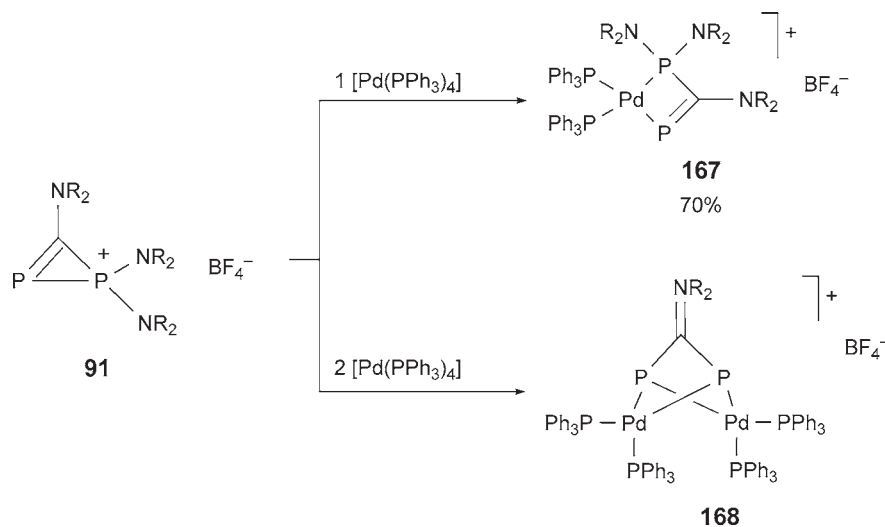


1.16.5.2.6 Ring expansion reactions

Compound **91** was nucleophilically attacked at the dicoordinate phosphorus center when treated with *tert*-butylisocyanide in CH_2Cl_2 at $-50^\circ C$. Ring enlargement of transient **165** afforded product **166**, which was isolated as yellow crystals in 70% yield (Equation 23) <1994CC337>.



Salt **91** cleanly reacts at -40°C with 1 equiv of tetrakis(triphenylphosphane)palladium to complex **167**, which was isolated as a yellow oil in 70% yield. Obviously, the reactive P–P bond of the diphosphirenium ion was oxidatively added onto the zerovalent metal of the coordinatively unsaturated $[\text{Pd}(\text{PPh}_3)_2]$ unit. When a CH_2Cl_2 solution of **91** was heated with 2 equiv of $[\text{Pd}(\text{PPh}_3)_4]$, binuclear complex **168** was obtained (Scheme 56) <1995OM3614, 1996PS53>.



Scheme 56

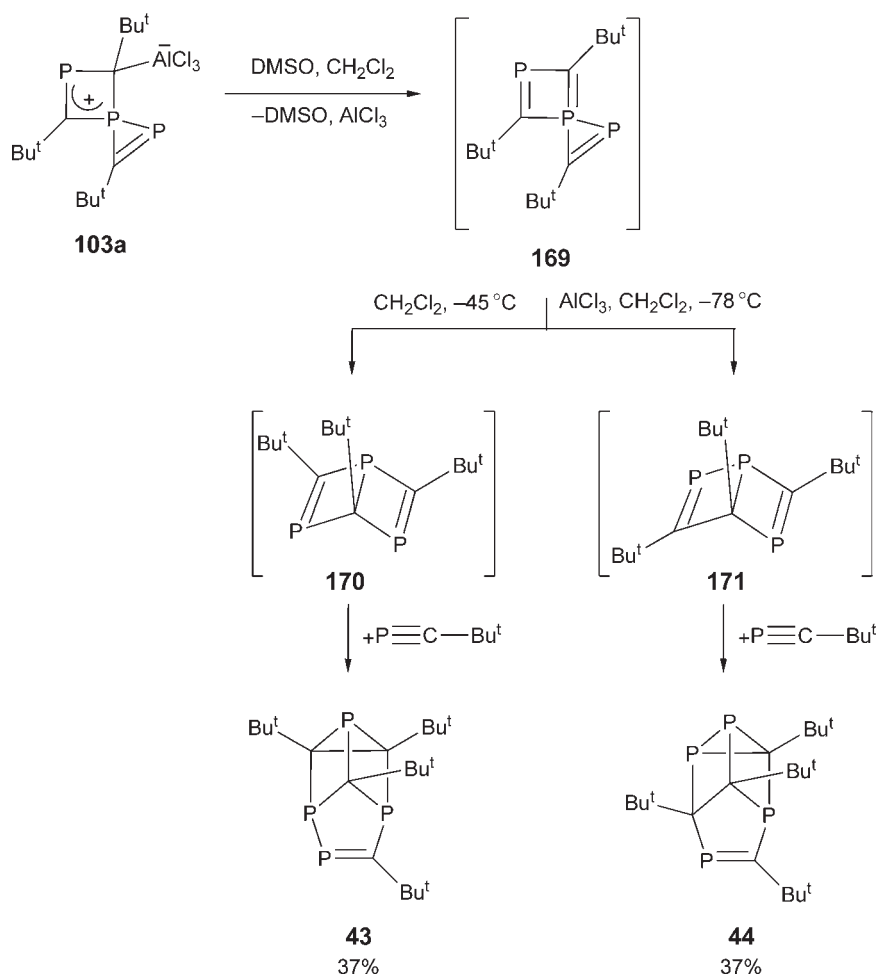
Complex **103a** turned out to be a useful starting material for the generation of various organophosphorus cage compounds, involving the expansion of the three-membered ring. Treatment of **103a** at -45°C with dimethylsulfoxide generated the highly reactive spirocyclic diphosphete **169**, which underwent instantaneous P–P bond cleavage of the diphosphirene unit and ring expansion to the transient 1,3,5-triphospha Dewar benzene **170**. The latter compound was efficiently trapped by phosphalkyne $\text{P}\equiv\text{C}-\text{Bu}^t$ to yield cage **43** in about 37% yield. When, however, the slurry of **103a** in CH_2Cl_2 in the presence of a large excess of aluminium trichloride was treated at -78°C with dimethyl sulfoxide, obviously C–P bond cleavage occurred with the formation of the transient 1,2,5-triphospha Dewar benzene **171**. Again, this species was intercepted by $\text{P}\equiv\text{C}-\text{Bu}^t$ leading to the exclusive generation of cage **44** an isomer of **43** (37% yield) (Scheme 57) <96CB489>.

The first 1,3,4-triphosphole **172** was produced by the thermally induced regiospecific insertion of phosphalkyne $\text{P}\equiv\text{C}-\text{N}(\text{Pr}^i)\text{TMS}$ into the P–P bond of the 1*H*-diphosphirene complex **130** (35% yield). Interestingly, a similar ring expansion was not observed with the sterically more bulky diphosphirene complex **87d**, which is the precursor of **130** (Equation 24) <2001AGE2471>.

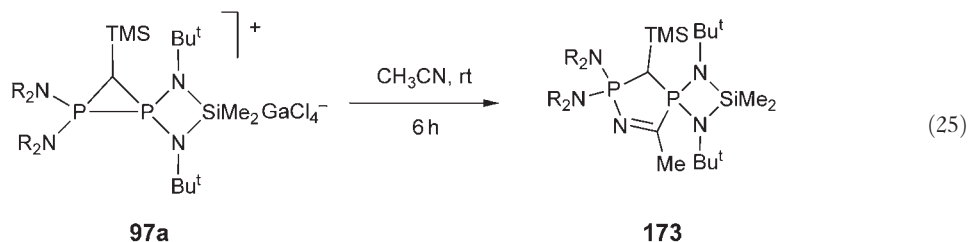
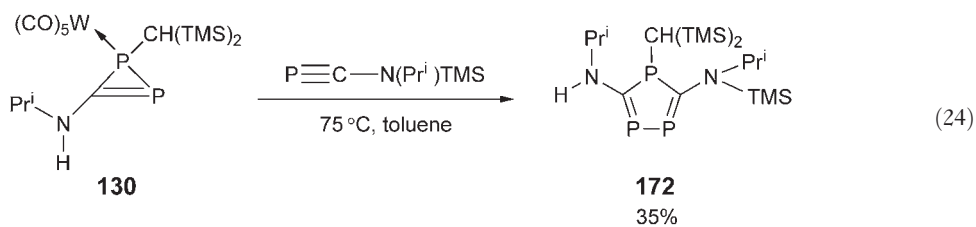
Diphosphirenium derivative **97a** reacted with an excess of acetonitrile at room temperature to give spiro compound **173** as the formal product of a regiospecific insertion of the nitrile into the P–P bond of the precursor. In contrast to this, compound **95** having two diisopropylamino groups at each phosphorus atom did not react with acetonitrile, even when heated at 50°C for 12 h (Equation 25) <2002JA2506>.

1.16.6 Conclusions

Since the previous account on diphosphiranes in this series <1996CHEC-II(1)469>, considerable progress has been made in synthetic, structural, and reactivity studies with polycycles containing the characteristics of diphosphiranes. Here phosphalkynes are often promising precursors in the construction of these molecules. Particularly, exciting was the development of diphosphirenes, diphosphirenium, and diphosphirenium salts within the last decade. Efficient synthetic approaches are based on appropriately functionalized phosphalkenes and phosphalkynes. The great difference in bisphosphino carbenium ions and amidinium ions became evident by the finding that the phosphorus-containing species are cyclic featuring two σ^4 -phosphorus atoms in addition to a carbanionic center in the ring. Moreover, diphosphirenium radicals and dimers thereof are further highlights in the chemistry under discussion. Here careful structural analyses, supported by quantum chemical calculations, provided us with information on the bonding situation of these species.



Scheme 57



The chemistry of three-membered rings with two heteroatoms including arsenic and antimony is still poorly developed. Such species with bismuth atoms remain unknown.

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Biographical Sketch



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1.17

Three-membered Rings with Two Heteroatoms including Other Elements

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1.17.1 Introduction and Tabular Survey of d- and f-Metal-Containing Rings

This chapter covers three-membered cyclic compounds where one atom is carbon, one atom is a metal or metalloid from groups 1 to 14 and the f metals, and the last atom lies in groups 1–17 in the periodic table (except hydrogen). General compound types surveyed include β -metallated, η^2 -heteroynne, and η^2 -heteroene d- and f-metal compounds (heterometallacyclopropenes and cyclopropanes), carbenoids, diborirenes and diboriranes and their heavier congeners, heteroborirenes and heteroboriranes and their heavier congeners, disiliranes, digermiranes, distanniranes, pnictogenametallirenes and pnictogenametalliranes, and chalcogenametalliranes.

To keep the coverage of this broad area manageable, several candidate classes have been neglected or covered minimally. These include compounds containing two d or f metals in the ring, rings formed when two metals are bridged by CCh (Ch = O–Te; e.g., bridging carbonyl compounds) <B-1982COMCI, B-1995COMC-II, B-2000MI7, B-1996MI5>, or isoelectronic CPn[–] and CPn–R (Pn = N–Bi; e.g., bridging cyanide or isocyanide compounds) <B-1987CCDC, B-2004CCDC-II>, cage/cluster compounds like carboranes and homologues/analogues <B-1990MI1, B-1993MI3, B-1990MI2, B-1994MI4>, and rings that arise indirectly from π -complexation of a ring containing multiple bonds to a metal (e.g., η^5 -heterocyclopentadienyl metal complexes) <B-1982COMCI, B-1995COMC-II>. However, some η^2 -heteroalkene or heteroalkyne metal complexes are included, since distinguishing between these and three-membered rings is somewhat arbitrary (as per the Dewar–Chatt–Duncanson model), and since many of the compounds described display ‘ring-like’ physicochemical properties.

Three-membered rings of these types are often suggested as intermediates or transition states in various reactions. In general, this chapter neglects such species, although exceptions that characterize particular issues or mechanisms are included. Typically, if the ring was not observed by some experimental means, or implicated so clearly by experiment or theory that no plausible alternative exists, it is not included within. Consequently, in the sections on theoretical methods, rings predicted by vibrational mode calculations to be transition states are not included. Generally, the computational chemistry literature surveyed is limited to *ab initio*/density functional methods; only a few results from semi-empirical approaches, and no molecular mechanics studies, are included. The term MP4 is used specifically to mean the MP4(SDTQ) perturbation theory model; lower-order models like MP4(SDQ) will be explicitly designated.

Chapter 1.17 in CHEC-II(1996) focused mostly on three-membered ring compounds containing a transition metal, a carbon, and another atom (TM–C–A) appearing in the literature prior to 1995, with emphasis on compounds where A = Si–Sn, N–Sb, and O–Te <1996CHEC-II(1)491>. In keeping with the effort of the CHEC series to present continuous literature reviews, a brief tabular update of work published from 1996 to 2005 is presented here.

Thousands of papers describing the behavior of TM–C–A ring compounds appeared during the decade, so this survey will not attempt to be comprehensive. It generally emphasizes those where the ring compound(s) formed the focus of the paper (as opposed to being one of several classes of compounds discussed), and/or that illustrate important structural or reactivity characteristics involving at least one member of the ring. The restrictions mentioned above apply, as well as the following. Only compounds where A = Si–Sn, N–Sb, and O–Te are included. For readers interested in TM–C–TM ring systems, the *Comprehensive Organometallic Chemistry* series <B-1982COMC, B-1995COMC-II> and the *Science of Synthesis* series <B-2000SOS> represent more exhaustive resources. Also neglected are η^2 -complexes where the carbon has substituents that interact with either the TM or A atoms (i.e., (μ , η)-bridged molecules), and bridging alkyl compounds, where the carbon has three external substituents, as in the well-known Me₂Al–CH₃–TM systems.

Table 1 contains a collection of TM–C–A ring compounds meeting the criteria.

1.17.2 Rings Containing Group 1 (Li–Cs) and/or Group 2 (Be–Ba) Elements

1.17.2.1 Introduction

Elimination of the M–X fragment from the structure shown leaves a carbene; thus, prevailing interest in these heterocycles derives from their characterization as carbenoids. By far, most studies deal with M = Li (α -hetero-organolithiums). In many cases, reactive species could contain three-membered rings, but rarely can this be demonstrated. This section focuses on systems where the presence of such rings is certain or extremely likely. Excellent reviews in the area include <B-2004MI829, 2001CRV697, B-1995MI195>, and <B-1982COMC(2)43> (organo-lithiums), and <B-1996MI6> (Grignard reagents).

Table 1 Papers from 1996 to 2005 containing TM–C–A ring compounds

<i>Ring type</i>	<i>Comment</i>	<i>References</i>
 Ir—Si	Kinetic isomerization and reactivity studies as well as crystal structure	2002OM4648, 2002OM3376
 Pt—Si	Three-coordinate platinum complex	2004AGE745
 Pd—Sn	DFT studies of oxidative addition of C–Sn compounds to Pd complexes	2003OM4286, 2002OM4482
 M—N M = Ti, Zr, Hf	Formed from bis-alkynyl complexes, products contain peripheral cyclopropenium rings as well as heterorings	1999JOM115
 M—N M = Ti, Zr	Several crystal structures	2005OM2424
 Zr—N	Computational studies of the coupling of the η^2 -NC group	2005OM1867
 Zr—N	Propene insertion reactions of a range of η^2 -pyridyl complexes	1997OM5541
 Zr—N	Stereoselective reactions of η^2 -CN moiety	1996JA3479
 M—N M = Zr, Hf	Varied reactivity depending on nature of peripheral groups	1997OM5857
 V—N	Paramagnetic and dimeric ring systems	2004OM5488
 Nb—N	Insertion of isocyanide into Nb–N bonds	2001OM4623
 Nb—A A = N, O	Reactivity of bound ketenimines and ketenes	1997JOM87
 M—N M = Nb, Ta	Formation of rings by unusual mechanisms	2000EJI2047, 2004JOM1304
 Ta—N	Syntheses and reactivities of a diverse set of rings	2005OM848, 2003CJC1137, 1996OM3579
 Ta—A A = N, O	Rings with a variety of spectator ligands, generally formed through insertion reactions	2004OM5030, 2002OM5549, 2000JOM36, 1999CEJ722, 1997OM168
 Mo—N	Reactivity comparison between ring and isomeric nitride complex	2004OM3126
 Mo—N	Alkylation of N atom in ring	2001JCD1732
 Mo—N	Kinetic and reactivity studies of the relationship between peripheral groups on the metal and ring atom behavior	1997JCD3145, 1997OM2263

(Continued)

Table 1 (Continued)

Ring type	Comment	References
 W—N	Experimental and computational studies of η^2 -nitrile complexes	1998OM182, 1997JOM233, 1997JCD3311, 1997OM246
 M—N M = W, Re	η^2 -Pyrrole complexes	2005OM5267
 Re—N	Bis- η^2 -pyridine complexes	2004JA2105
 Fe—N	Two-ring complexes formed from Fe—Fe dimer	2000OM3016
 Ru—N	A series of papers describing η^2 -pyrimidine complexes	1998ICA46, 1998IC1249, 1997IC818
 M—N M = Ru, Os	Insertion of coordinated isocyanide induced by coordination of O ₂	1996JOM267
 Os—N	Cleavage of alkene C=C bonds by Os $\equiv$ N to form C=N bonds	2004OM1932
 Os—N	η^2 -Iminium hydrides formed by β -hydride elimination of amine ligands	1998ICA337
 Co—N	Computational study of effect of peripheral ligands on η^1 vs. η^3 -N—C bonding	2005OM6037
 Ni—N	Poorly stable rings that undergo interesting reactions upon warming	2004OM3997, 2002JA9547
 Pd—N	C—H activation of an amine	2004JA15818
 Pd—N	An unusual fused ring system	2003OM3025
 Pt—N	A number of reactions of a metastable ring	2001JOM671
 M—N M = Sm, Yb	Catalytic behavior of lanthanide imine complexes with varied peripheral ligands	2003T10381, 2003OM3586
 U—N	A remarkable example of a small ring containing U	1999JOM174
 Ta—P	Intermediate in phosphavinyl coupling reaction	2002OM438
 Mo—P	Mo bound to unusual η^5 -thiophene ligand	2002JA4182
 Mo—P	C attached to unusual electron-withdrawing carboxylate groups	2001JOM125, 2000JCS3331
 W—P	Several crystal structures; carbon is sp ² -hybridized	2005OM1351, 2000OM5281
 W—A A = P, As	Both sp ² - and sp ³ -hybridized carbon; several unusual reactions	1999JOM120, 1997OM1875, 1996JOM105

(Continued)

Table 1 (Continued)

<i>Ring type</i>	<i>Comment</i>	<i>References</i>
	A number of complexes built on the (η^6 -arene)Ru template	2004OM3425, 2003JCD441
	Studies of (<i>o</i> -metallated phosphine) (polyphosphine) complexes	2002JA14684, 2002OM2149
	A number of complexes built on the (η^6 -arene)Os template	1999OM1185
	Studies of (<i>o</i> -metallated phosphine) (polyphosphine) complexes	2000OM2310, 2000OM1166
	Experimental and theoretical studies of complexes based on (amino)(phosphino)carbenes	2004JOM1431, 2003CEJ5858, 2002JA11834
 M = Rh, Ir	Experimental and theoretical studies regarding the intermediacy of <i>o</i> -metallated phosphine complexes in C–H activation reactions	1998JA6169, 1997JA11538, 1997JA10793, 1996OM1889
	Phosphorus binds to coinage metals as well	2005IC3275, 2003JCD2889
	From protonation of an alkynylphosphine complex	2001OM980
 M = Ni, Pd	Complexes based on (amino)phosphino)carbenes	2005JOM5541
	Cation formed by loss of acetic acid	2005OM4099
	Carbopalladation of a P–C double bond	1999OM1402
	From protonation of an alkynylphosphine complex	2002JCD226
	An unusual example of a ring containing Y	2002OM1759
	Electrophilic attack of B(Ar) ₃ on metal-bound CO	2003OM1995
	Static and dynamic DFT study of CO insertion	2001JCD1023
	Monomeric and dimeric ring systems	2003OM2080
	Calixarene spectator ligand imparts unusual reactivity	1997JA9709
	Tropocoronand spectator ligand imparts unusual reactivity	1998OM466
	Reactions of η^2 -eneacyls	2000OM901
	Insertion of S into Mo–C acyl bond to form metal-bound xanthate	2000OM261

(Continued)

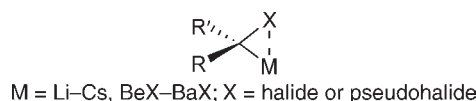
Table 1 (Continued)

Ring type	Comment	References
 M—O M = Mo, W	A range of η^2 -acyl complexes including η^2 -amides	2005OM911
 W—O	Comparison of η^1/η^2 -aldehyde binding	2000OM1540
 W—O	First example of an η^2 -bound aldehyde at a zerovalent tungsten carbonyl center	1996POL2809
 M—O M = W, Fe	Comparison of addition of dialkyl phosphites to free and coordinated cyclopropanone	2004RJO45
 Mn—O	Experimental and theoretical studies on the intermediacy of a cyclic intermediate in migratory insertion reactions	2004JOM2354, 2002IC3553, 2000JA2078
 Re—O	Equilibrium between η^1 - and η^2 -isomers	2003ICA475
 Re—O	Use of rings for enantiofacially selective reactions	2002JA13506, 2001OM3876, 2000OM728
 M—O M = Fe, Mn, Cr	Computational study of relative stabilities of η^1 - and η^2 -acyls	2002PCA11782
 Fe—O	An array of functionalized (<i>E</i>)/(<i>Z</i>)-iron ketene complexes	1998OM960
 Ru—O	Migratory insertion/deinsertion effected by protonation/deprotonation reactions	1997OM5135
 Os—O	Methylation of η^2 -aldehyde complexes forms Fischer carbines	1997JA12772
 Co—O	Experimental and computational studies that include assessment of the importance of η^2 -CO coordination in CO carbonylation reactions	2003IC575, 2005OM2533, 2003OM4665, 2002OM2262, 1996OM2611
 Rh—O	Controllable linkage isomerism in metal-bound ketenes	1999OM5614, 1999AGE156
 M—O M = Rh, Ir	Diffraction and spectroscopic studies of linkage isomerism in metal-bound ketenes	2001JA8260
 Ir—O	Computational studies on aspects of the above	2001OM3938
 Ni—O	Kinetic parameters for CO ₂ association/dissociation and insertion reactions	1998OM98
 U—O	An oxouranirane that does not oligomerize	1997JOM9
 M—S M = Mo, W	Synthesis and reactivity of a range of thioaroyl complexes	2003OM3502
 W—S	Several η^2 -thioaldehyde complexes and their reactions with electro- and nucleophiles	2004ICA1886

(Continued)

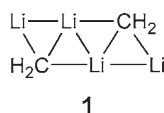
Table 1 (Continued)

Ring type	Comment	References
	Synthesis and reactions of η^2 -thiophene complexes	1999OM2988
	Dimeric thiapalladacyclopropane	1996OM5003
	Formation of a novel ring through C-H activation of bound SCH ₃ ligand	2001OM3698



1.17.2.2 Theoretical Methods

A number of polylithium alkyls that have been examined computationally show short Li-Li interactions and so are visualized as containing Li-Li-C rings <B-1995MI1, B-1995MI45>. One example derived from a simple starting point is the dimer of dilithiomethane, **1**. This planar isomer lies 51.5 kJ mol^{-1} (MP2/6-31G(d)//HF/3-21G level) below the polyhedral form once thought to be the global minimum.



By contrast, in polysodium alkyls, the Na atoms generally lie far apart and so rings do not form <1995JMT317>.

Many studies of polylithium compounds, as in polyboron chemistry, have revolved around finding molecules that contain planar carbon atoms. In addition to cases containing Li₂C rings, molecules containing planar carbon in an Li-C-N ring have been suggested <2001OL1249>. Given the donor properties of N toward Li, it seems likely such molecules will prove easier to prepare and isolate in condensed phase than the Li₂C versions.

Computations at reasonable levels of theory typically predict that cyclic M-C-X structures where M = group 1 metal are more stable than acyclic alternatives. This holds for carbenoids 'LiCH₂X' (X = F, Cl, Br, I, OH; MP2 (full)/6-311++G(d,p) level) <2000T4109, B-1995MI195>. At this level, for example, cyclic LiCH₂OH lies 56.9 and 68.6 kJ mol^{-1} below related acyclic minima. This is consistent with the desire for molecules to delocalize charge in the predominantly ionic C-Li interaction <1995MI1>. The model predicts very slightly shorter Li-C distances (1.92 – $1.97 \text{ \AA}$) in these cycles compared to those predicted for methyllithium ($1.98 \text{ \AA}$), while the C-X and Li-X distances are predicted to increase 7–12% over the values for the corresponding halocarbons and lithium halides. Density functional theory (DFT) approaches give similar results <2002JOC7607>. The sodium carbenoid NaCH₂OH is predicted to lie 31.6 kJ mol^{-1} below the nearest acyclic isomer, with a barrier between the two of $147.7 \text{ kJ mol}^{-1}$ (MP2/6-31+G(d) level) <2000CRCU136>. Cyclic MCH₂OH compounds (M = Li, Na) lie some 150 kJ mol^{-1} above the corresponding methoxides MOCH₃, but barriers of ca. 90 kJ mol^{-1} separate the two, suggesting the former might be observable. Potassium analogues display similar features <2004HX742>. Studies of the potential energy surfaces for the larger C₂H₃OM systems (M = Li, Na) shows that the various isomers can be grouped into non-interconvertible sets: metal enolates, metal acyls, and α -metal vinyl alcohols. Only the second and third of these contain M-C-O rings, but these are the minima for the groups (MP2/6-31+G(d) level). This, combined with their sizable barriers to rearrangement, suggests they might be observable (Section 1.17.2.3) <1998JST207, 1998PCA5816>.

A study of several permutations of halogenated lithiomethanes CF_aH_bX_cX'_dLi (X = Cl, X' = Br; $a = 1$ – 3 ; $b = 0$ – 2 , $c = 0$ – 2 , $d = 0$ – 2) showed a preference for ring formation over acyclic structures, and a preference for the ring to

contain atoms $\text{C-Li-Br} > \text{C-Li-Cl} > \text{C-Li-F}$ (MP2/6-31+G(d,p) level) <2002JFC147>. This agrees with experimental observations of such species (Section 1.17.2.3).

Considerable work suggests that the coordinating properties of the solvent affect cycle stability substantively. While calculations predict that the most stable structure of Li-CH(Cl)Cl is cyclic, they indicate an acyclic, ethane-like structure for solvent-coordinated $(\text{H}_2\text{O})_3\text{Li-CHCl}_2$ <1996AGE1518>. Similarly, coordination of two explicit dimethyl ether molecules to lithium in cyclic $\text{Li-CH}_2\text{-F}$ ($d(\text{Li-F}) = 1.765 \text{ \AA}$) resulted in two minima, one a cycle with $d(\text{Li-F}) = 1.772 \text{ \AA}$ and one linear with $d(\text{Li-F}) = 2.836 \text{ \AA}$. The former is computed to be 13.0 kJ mol^{-1} more stable at 173 K in the gas phase, but the two display essentially identical free energies at this temperature when a dimethyl ether continuum solvent approximation is added. Ether solvation of the cyclic chloro analogue ($d(\text{Li-Cl}) = 2.212 \text{ \AA}$) results in a single acyclic minimum with $d(\text{Li-Cl}) = 2.855 \text{ \AA}$ <2002JOC7607>. The Li-X interaction in these cycles is thus generally weaker than the energy of Lewis base solvent coordination to lithium <2005JOC2294>. Recent work suggests that lithium dialkylamides can act as Lewis bases to alkyllithiums, in some cases disrupting Li-C-X rings, but in others leaving them intact <2005JOC8298>.

Reaction types involving lithium carbenoids examined computationally include dimerization, cyclopropanation, and various substitution and elimination processes <B-2004MI829>. Interestingly, in general, calculations suggest that cyclic alkoxy and amino carbenoids $\text{Li-CH}_2\text{-X}$ ($\text{X} = \text{OR}, \text{NR}_2$) should react as rapidly as the halide analogues. This deviates strongly from experiment in that several examples of these have been isolated and characterized at room temperature, whereas no cyclic halide carbenoids have. In the absence of solvent, dimerization is exceedingly favorable, with most calculations predicting exothermicities greater than 200 kJ mol^{-1} for this process. This is borne out by experimental observation of several dimeric species in the solid state and solution (Section 1.17.2.3). Computational models also predict the experimental observation that ring carbon atoms lie closer to the lithium from the other moiety than to the lithium in their ring (Section 1.17.2.3) <1993CB1887>.

Rearrangements have also been examined. In a study of the stereoselectivity of the reverse Brook rearrangement of α -siloxyalkyl anions, the cycle MCH(R)OSiH_3 ($\text{M} = \text{Li}, \text{Na}$; $\text{R} = \text{H}, \text{CH}_3, \text{CH}=\text{CH}_2$) was shown to be a minimum, and a plausible ‘first-step’ intermediate in the process. Its rearrangement to products is dictated by the electronic nature of R, which controls the barrier energies, consistent with experimental results <1999T12751>.

An early study suggested that cyclic Be_2C , containing two π -electrons, should nonetheless be antiaromatic because the Be-Be ‘bond’ is quite long ($2.235 \text{ \AA}$), so the electrons are poorly delocalized (semi-empirical SINDO1 method) <1984JOC4475>. This was refuted by a higher-level study indicating that the ‘cyclic’ structure, while energetically favored, does not contain a Be-Be bond despite the short distance between the atoms (CASSCF/DZ+P level) <1986JA5732>. In contrast, cyclic Mg_2C is predicted to be a singlet, to contain an Mg-Mg bond, and to be most stable of several structural and spin isomers. However, this isomer is only 2.5 kJ mol^{-1} more stable than a spin triplet, and 7.9 kJ mol^{-1} more stable than a linear isomer, so the prediction must be viewed cautiously (QCISD(T)/6-311+G(2df) level) <1997PCA902>.

Few cyclic carbenoid Grignard reagents have been studied theoretically. In a recent example, models containing correlation effects indicate that for 1-chloro-2-methylpropenyl magnesium chloride, two cyclic isomers differing only in the C(olefin)-C(olefin)-Mg angle lie close in energy (within 1.2 kJ mol^{-1} at the CCSD/6-31+G(d)//MP2/6-31+G(d) level) and appear to be global minima. However, a symmetric, more carbene-like acyclic isomer lies only 8.5 kJ mol^{-1} above the minimum, and solvent effects were not included. Thus the question of the correct structure of the reactive species remains open, although the authors note that a cyclic isomer supports their experimental results (Section 1.17.2.5) <2005T10262>.

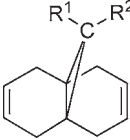
As an aside, it should be noted that calculations suggest that a number of metal cyanide species are predicted to exhibit minima (often ground states) where the metal interacts with the $\text{C}\equiv\text{N}$ π -cloud rather than the lone pair on either. Examples include NaCN, KCN, MgCN, and others <1999PCP2897>. Normally authors characterize them as π -complexes, but obviously one can think of them as MCN cycles as well.

1.17.2.3 Experimental Structural Methods

Seebach *et al.* published seminal studies of observable halocarbenoids <1983HCA308>. They reported that the ^{13}C nuclear magnetic resonance (NMR) chemical shifts of a variety of α -bromolithiohydrocarbons lie markedly downfield of those of the analogous alkyllithiums, alkyl bromides and dibromides, and hydrocarbons. For examples, see Table 2 <1979AGE784>. The dramatic shift was ascribed to a substantial rehybridization of the carbon atom arising from

interaction between the bromine and lithium. Several other studies, including ones on simpler halocarbons such as $\text{CH}_3\text{CBr}_2\text{Li}$, show similar behavior (the downfield shift for this example vs. CH_3CBr_3 and $\text{CH}_3\text{CBr}_2\text{H}$ is over 100 ppm!) [<1979AGE785>](#). This represents compelling evidence for $\text{Li}-\text{C}-\text{X}$ rings in such species; unfortunately, owing to their thermal instability, no solid-state structural studies demonstrating this have appeared.

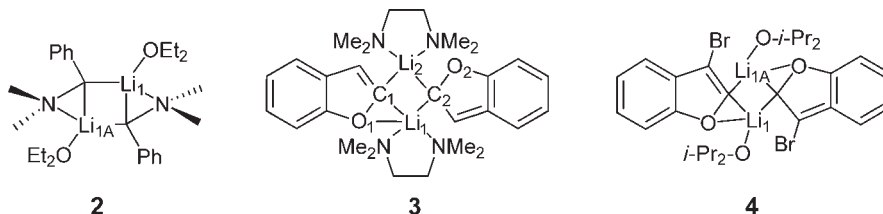
Table 2 ^{13}C NMR chemical shifts for the labeled cyclopropyl carbon atom

R^1	R^2		
		$\delta (^{13}\text{C})$	$\delta (^{13}\text{C})$
H	H	9.6	11.8
H	Li	10.0	11.8
H	Br	24.5	35.4
Br	Br	40.1	53.8
Li	Br	87.0	102.0

Three-membered ring carbenoids have been structurally characterized for species where $\text{X} = \text{OR}$ or NR_2 . The crystal structure of the diethyl ether-solvated α -(dimethylamino)-benzyl lithium dimer **2** shows crystallographically equivalent three-membered $\text{Li}-\text{C}-\text{N}$ rings, with $d(\text{Li}_1-\text{C}) = 2.475(6) \text{ \AA}$, and $d(\text{C}-\text{N}) = 1.469(4) \text{ \AA}$ [<1993CB1887>](#). As predicted by theory, the anionic carbon sits closer to the lithium in the other three-membered ring ($d(\text{Li}_{1A}-\text{C}) = 2.230(7) \text{ \AA}$) than to Li_1 . This seems to present a means for the anionic carbon to delocalize its charge.

The crystal structure of 2-lithiobenzofuran (TMEDA) dimer **3** shows that, despite its expected symmetry, only one $\text{Li}-\text{C}-\text{O}$ group forms a three-membered ring [<1989OM1688>](#). This arises because one of the benzofuryl groups twists substantially with respect to the other. In the cyclic moiety $d(\text{Li}_1-\text{O}_1) = 2.09(1) \text{ \AA}$, while in the acyclic moiety $d(\text{Li}_2-\text{O}_2) = 3.00(1) \text{ \AA}$. As in **2**, carbon C_1 lies asymmetrically between the Li ions, with $d(\text{Li}_1-\text{C}_1) = 2.39(1) \text{ \AA}$ and $d(\text{Li}_2-\text{C}_1) = 2.11(1) \text{ \AA}$, while C_2 is nearly equidistant ($d(\text{Li}_1-\text{C}_2) = 2.23(1) \text{ \AA}$, $d(\text{Li}_2-\text{C}_2) = 2.26(1) \text{ \AA}$). NMR studies demonstrated that **3** is dimeric and C_{2v} -symmetric in toluene- d_8 at low temperature; whether $\text{Li}-\text{C}-\text{O}$ rings were present under these conditions was not determined.

In contrast, diisopropyl ether-solvated 2-lithio-3-bromobenzofuran dimer **4** contains two crystallographically identical $\text{Li}-\text{C}-\text{O}$ cycles, a difference ascribed to monodentate ether versus bidentate TMEDA in **3**. Again the anionic carbon lies ca. $0.3 \text{ \AA}$ closer to the ‘other’ lithium Li_{1A} than to Li_1 . Bond distance $d(\text{Li}-\text{O}) = 1.954(6) \text{ \AA}$ is much smaller than that for unsubstituted **3**, while $d(\text{C}-\text{O}) = 1.470(4) \text{ \AA}$ is almost $0.1 \text{ \AA}$ longer than typical for benzofuran $\text{C}-\text{O}$ bonds.



The dramatic ^{13}C NMR shifts noted above for lithiohalocarbons occur for alkoxy and amino species as well [<B-1995MI195>](#). For example, the shift for the ‘cyclopropyl’ carbon in **3** lies 73.3 ppm downfield of that in the precursor dibromide.

1.17.2.4 Thermodynamic Aspects

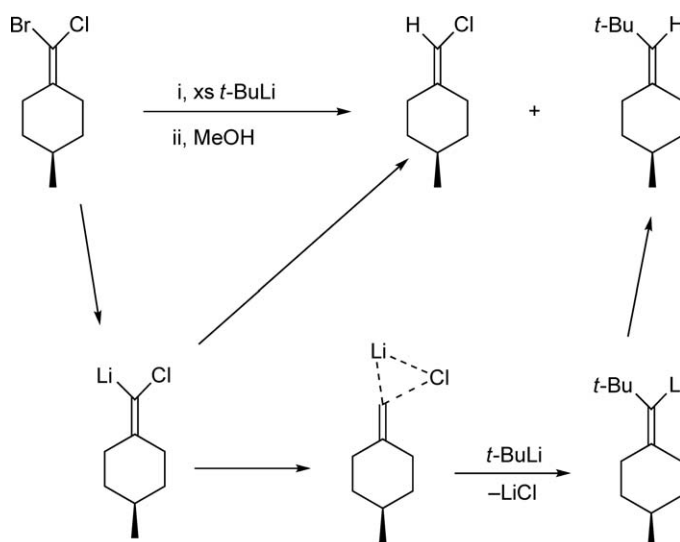
Cyclic lithiohalocarbons have only been studied in solution at low temperature owing to their extreme thermal sensitivity. While most have spectroscopically useful lifetimes at temperatures $\leq -80^\circ\text{C}$, all decompose rapidly above

ca. -40°C . By contrast, alkoxy- and amidolithiocarbon cycles are typically stable at ambient temperature for reasonable periods. Unsurprisingly, no quantitative thermodynamic data have appeared. Solubility properties of carbenoids tend to mimic those of the parents: alkyllithium carbenoids tend to be soluble in polar and nonpolar solvents, and Grignard carbenoids tend to be soluble solely in ethers.

1.17.2.5 Reactivity of Nonconjugated Rings

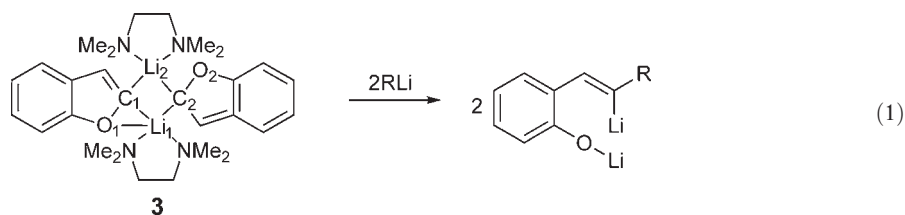
Cyclic (or essentially so) species are implicated in a number of carbenoid reactions processes, although it should be clear from the discussion above that one is rarely certain that a *cyclic* carbenoid is the reactant. In this section and the next, examples will be given of cases where cyclic carbenoids best explain experimental results, employ one of the crystallographically characterized cycles described above, and/or are supported by theory. Reviews in this area include <2004CRV3795, B-2004MI829>, and <2001CRV697>.

Walborsky created the term ‘metal-assisted ionization’ (MAI) for reactions where a carbenoid acts as an electrophile. An example appears in [Scheme 1](#) <1993JOC546>. The *t*-butyl-substituted product is formed with inversion of configuration, supporting the proposed mechanism. While the presence of a three-membered ring in the intermediate is hypothetical, the need to replace the Cl with a Li dictates an interaction between the two.

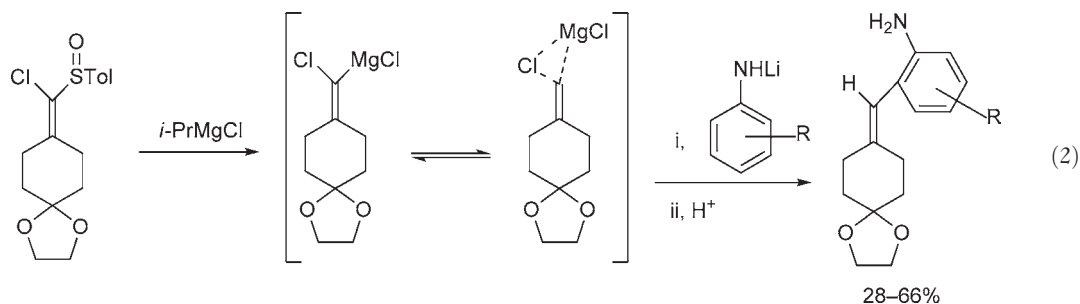


Scheme 1

Compound **3** reacts with alkyllithiums to give products of substitution followed by ring opening ([Equation 1](#)) <1993CB1873>. The regioselectivity of the alkylation supports the mechanism containing an MAI step as above.

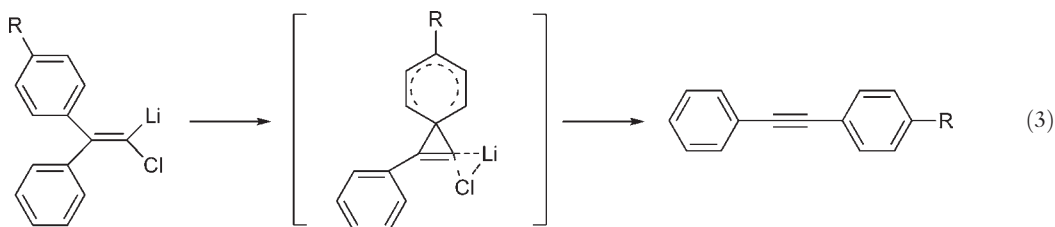


Similarly, the Grignard reagent shown as an intermediate reacts with a variety of lithioanilines to form styrene derivatives ([Equation 2](#)). Deuteration studies support an MAI-type mechanism and by inference a cyclic Grignard intermediate <2005T10262>.



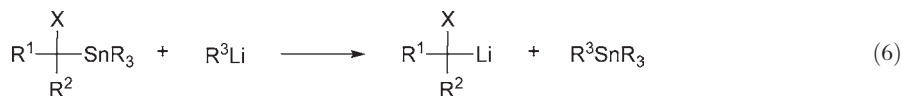
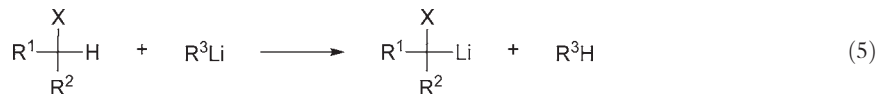
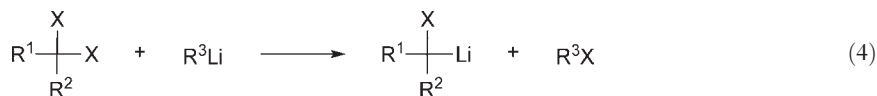
1.17.2.6 Reactivity of Substituents Attached to Ring Carbon Atoms

A classic example of the title reactivity is the Fritsch–Buttenberg–Wiechel rearrangement, involving intramolecular attack of an aryl group on a carbenoid carbon (Equation 3) <2001CRV697, B-2004MI829>. That the migrating group is the one *trans* to the chlorine implicates the ring structure in the intermediate or transition state.



1.17.2.7 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

Cyclic lithium carbenoids, like acyclic versions, are generally formed through halide–lithium exchange reactions (Equation 4). Owing to their limited stability, this represents the only useful route to cyclic lithiohalocarbons, as exploited for the NMR studies described above. Compound **4** was prepared this way. Deprotonation of benzofuran with *n*-BuLi/TMEDA was used to prepare **3** (Equation 5), while lithium–tin exchange was used to prepare **2** (Equation 6). The Grignard reagent thought to contain a ring was prepared as noted in Equation (2).



1.17.3 Rings Containing Group 13 (B–Tl) Elements

1.17.3.1 Introduction

Most of the compounds discussed contain boron, although studies involving Al and Ga have increased. Little indium and thallium chemistry is known, presumably owing to the rarity of the former and the toxicity of the latter. This

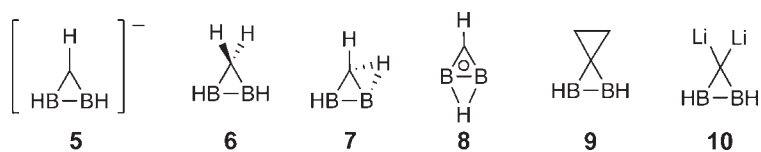
section neglects cage systems such as carboranes containing BBC rings, and rings formed through organometallic ring π -coordination, as in (borabenzene)metal or (carborane)metal complexes.

Since members of this family often form electron-deficient compounds, distinguishing between dielement cyclopropenes and dielement cyclopropanes presents nomenclature challenges. Here the term dielement irene (as in diborirene) is used when the element and the carbon are three coordinate, dielement irane (as in diborirane) is used when the element is three coordinate and the carbon is four coordinate, and dielement cyclopropane signifies a molecule directly analogous to cyclopropane in that all ring atoms are four coordinate. One should note that this approach is not followed in the literature. A classic example is compounds of type **15**, which have variously been termed ‘nonclassical 1,2-diboretanes’ and cryptoborylcarbenes. Other terms, such as azoniboratacyclopropane, should be self-explanatory in context.

1.17.3.2 Theoretical Methods

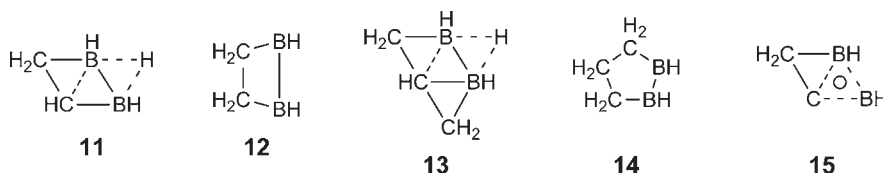
Unbridged diborirenyl anion **5** was studied as an isoelectronic analogue of cyclopropenyl cation. An early study mapped the potential energy surface, finding that **5** lies only 12.5 kJ mol^{-1} below linear $\text{H}_2\text{B}-\text{C}=\text{BH}^-$ (MP2(full)/6-31+G//MP2/6-31+G(d) level) <1995STC225>. However, the barrier of 198 kJ mol^{-1} between the two indicates stability for the anion with respect to ring opening/rearrangement. The short B–C ($1.476 \text{ \AA}$) and B–B ($1.606 \text{ \AA}$) bonds observed are consistent with the presence of delocalization/aromaticity in the ring. Anion **5** is predicted to have an aromatic stabilization energy of 74.5 kJ mol^{-1} (cf. 149 kJ mol^{-1} for cyclopropenyl cation), and to display ^{11}B and ^{13}C NMR chemical shifts of 36 and 147 ppm, respectively. ^{11}B and ^{13}C NMR chemical shifts of 41 and 144 ppm, respectively, were calculated for the permethylated version of **5**; these values match experimental values for **30a** very well (Section 1.17.3.3). A later study supported the anion being aromatic, and showed that an added lithium cation prefers by 47 kJ mol^{-1} to bridge the two borons in the ring plane rather than occupying a ring face (cf. **31**) (MP2(full)/6-311+G(d,p) level) <2001RCB2325>.

Early methods suggested that diborirane **6** and its isomer containing planar carbon represented minima on the potential surface, but more sophisticated models later disproved this. True minima on the B_2CH_4 potential surface contain hydride bridges as in **7** and **8**. Considerable study of bridged and unbridged diborirenes, diboriranes, and similar species followed, often because of cases predicted to contain planar four-coordinate carbon atoms. Examples include spiro-diborirane **9**, more stable than isomers containing tetrahedral carbon by more than 33.1 kJ mol^{-1} , and 3,3-dilithiodiborirane **10**, more stable than isomers containing tetrahedral carbon by more than 75 kJ mol^{-1} (B3LYP/6-311+G(d) level) <1995JST317>. Recent studies have employed **7** and related species (sometimes containing other heteroatoms as well) as tesserae for much larger molecules that should contain planar carbon, creating some esthetically pleasing shapes en route <2005JOC6693, 2005PCA259, 2005PCA4133>. In most cases, such molecules are predicted to be experimentally accessible.



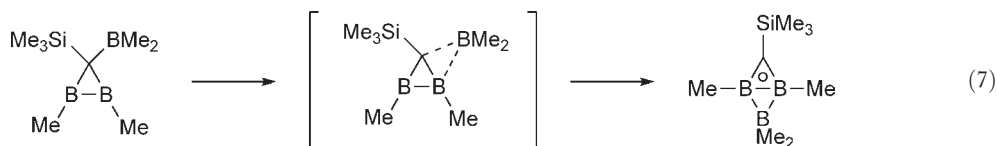
Berndt and co-workers have extensively explored carbon- and boron-bridged diborirenes and diboriranes computationally and experimentally (Sections 1.17.3.5 to 1.17.3.10). Computational studies probing molecular structures and the presence of cross-ring bonding, physical properties, and reaction mechanisms have appeared. Only a few examples of many will be given. A detailed review is <1993AGE985>; a newer mini-review appears in <2000IC4206>. A study dealing solely with the $\text{C}_2\text{B}_2\text{H}_2$ potential energy surface, minima on which show barriers suggesting kinetic stability and display cross-ring bonds forming B–B–C rings, appears in <2003STC325>.

Computational studies of all these bridged systems support their characterization as edge-sharing bicycles. For example, isomer **11** of formula $\text{B}_2\text{C}_2\text{H}_6$ lies 144 kJ mol^{-1} below the trapezoidal four-membered ring **12** (MP2/6-31G(d) level), which the model finds is a transition state. The cross-ring HB–CH distance is $1.709 \text{ \AA}$ (reasonable if slightly long for a B–C bond), while the ring edge HB–CH distance is $1.467 \text{ \AA}$ and the ring edge HB–CH₂ distance is $1.572 \text{ \AA}$. Similarly, for formula $\text{B}_2\text{C}_3\text{H}_8$, the dimethylene-bridged diborirane **13** is 79.1 kJ mol^{-1} more stable than the cyclopentane-like ring **14** <1994AGE2303>. Boron-bridged diboracycles exhibit similar behavior <2003AGE671>. Molecules of type **15** and **33–35** are predicted to exhibit sizable homoaromaticities <2000AGE1272>; this also holds for cases where silicon replaces a ring carbon <2002JOM262>.



Calculated NMR shifts generally agree well with those from experiment, and further support the presence of diborene/diborane rings. The ring carbon shows characteristic deshielding [\[2003AGE671\]](#). The ^1H , ^{11}B , and ^{13}C chemical shifts and associated J_{AB} coupling constants were calculated for methylene-bridged diborene **15** (1,2-diboretane-3-ylidene), several substituted versions, and for similar larger systems. Agreement with experiment for both sets of parameters is quite good. The small, negative $J(^{11}\text{B}-^{13}\text{C})$ predicted for the ‘cross-ring’ B–C interaction in **15** and the substituted versions is consistent with the bonding involving the carbene electron pair in an ‘inverse’ position [\[2004MRC490\]](#).

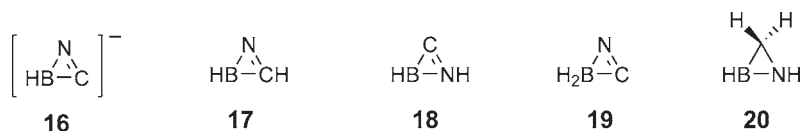
Examination of the mechanism by which the dimethylborane moiety migrates from a C-terminal site to the B–B bridging position in [Equation \(7\)](#) suggests a barrier of 86.2 kJ mol^{-1} to reach the B–C-bridged transition state shown (B3LYP/6-31G(d) model) [\[2003AGE671\]](#).



A multimodel exploration complementing the prediction of planar carbon in systems above predicted that $\text{HB}-\text{CH}_2-\text{MH}_2$ rings ($\text{M}=\text{Si}, \text{Ge}, \text{Sn}$) will contain *pyramidal* three-coordinate boron atoms rather than expected trigonal planar ones [\[2003AGE539\]](#).

A number of cyclic compounds of stoichiometry BCNH_n have been studied. Highly correlated models (various coupled cluster approaches/DZP(p)/MBPT(2)/DZP(p) levels) indicate that $\alpha\text{-HBCN}^-$, **16**, should be a spin singlet (some 100 kJ mol^{-1} more stable than the triplet), ca. 200 kJ mol^{-1} more stable than its BH and CN^- components, but ca. 40 kJ mol^{-1} less stable than linear HBCN^- [\[1996MP247\]](#). Early calculations for formula BCNH_2 suggested that azaborirene **17** and its related azaborirynyl cation should be 2π -aromatic [\[1984JOC4475, 1991JA3689\]](#). Later studies probed the BCNH_2 potential energy surface more broadly. Both perturbation and density functional methods indicated that nitrene-like **17** and carbene-like isomer **18** represent minima on the surface, while ‘cyanide complex’ **19** is a transition state [\[1992JPC10284, 2003PCP4084\]](#). Both minima are substantially less stable than related acyclic species H_2BCN and H_2BNC ($80\text{--}200\text{ kJ mol}^{-1}$ at the CCSD+T/DZP//HF/DZP level). However, the barriers between cyclic and acyclic molecules are substantial (ca. 400 kJ mol^{-1}), suggesting that the cycles might be observable if prepared by means that avoid paths near acyclic BCNH_2 minima. To that end, calculations for a proposed mechanism involving deprotonation of $\text{H}_2\text{BCN}/\text{H}_2\text{BNC}$, followed by rearrangement of linear HBCN^- to **16**, indicated that this path involves lower barriers and so a viable approach to synthesizing **17** [\[1995CPL261\]](#). Optimized structural data for **17** and **18** indicate that donation of π -electron density from the nitrogen and carbon atoms to the boron stabilizes the cycles, supporting the presence of aromaticity. Ring current density calculations for **17** suggest a similar decrease in delocalization for the former compared to cyclopropenium cation as for borazine compared to benzene [\[1997MP401\]](#).

For formula BCNH_4 , azaboriridine **20** was predicted to be slightly more stable than the isomeric acyclic borylimide $\text{H}_2\text{B}-\text{CH}=\text{NH}$, but substantially less stable (151 kJ mol^{-1}) than the acyclic methylborimide $\text{CH}_3-\text{B}=\text{NH}_2$ (HF/6-31G(d) level) [\[1982JOC60\]](#). A more recent study indicated that **20** lies 154.8 kJ mol^{-1} above $\text{CH}_3-\text{B}=\text{NH}$ and 97.9 kJ mol^{-1} above $\text{CH}_3-\text{N}\equiv\text{BH}$, but is separated from them by barriers in excess of 200 kJ mol^{-1} , so such heterocycles should be kinetically stable (MP2/6-31G(d,p) level) [\[2003JH464\]](#).

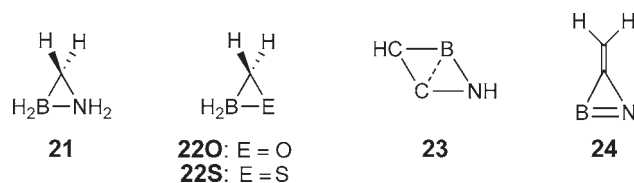


Azoniaboratacyclopropane **21** (formula BCNH_6) was predicted to be 31 kJ mol^{-1} more stable than its acyclic isomer (ROHF/4-31G level) [\[1988JA8164\]](#). Subsequent higher-level calculations confirmed this, as has the experiment

(Section 1.17.3.3). The ring strain energy (RSE) of **21** was predicted to be 92 kJ mol^{-1} , some 20 kJ mol^{-1} smaller than that in cyclopropane (MP4/6-31G(d)//MP2/6-31G(d) level) <1998TL9147>. CCSD(T)/6-311+G(d,p)//B3LYP/6-311+G(d,p) calculations found a value of 53.6 kJ mol^{-1} corresponding to the difference between the B–N bond energy and the RSE (treating both as positive numbers); this suggests the innate B–N dative bond energy equals ca. 146 kJ mol^{-1} <2004JOC3493>. That the B–N bond energy is larger than the RSE supports the stability of cyclic B–N–C species.

In propellane-like azoniaboratacyclopropane **26**, the boron can oscillate between the two nitrogens. The B–N distance is predicted to be $1.539 \text{ \AA}$, indicating a strong bond. Calculations predict this process has a barrier of 47.7 kJ mol^{-1} , suggesting it could be monitored by variable-temperature NMR spectroscopy <1996CPL173>.

A massive computational study of the BC_2NH_2 potential energy surface found a number of BCN rings, both fused and unfused, to be minima <2003JST189>. Acyclic $\text{HC}\equiv\text{C}-\text{B}\equiv\text{NH}$ was found to be the global minimum; fused ring **23** lies 237 kJ mol^{-1} above it and is the lowest-energy cyclic isomer (MP2/6-311G(d,p) level). The resemblance between **23** and **11** and **15** is noteworthy. The B–CH distance in cycle **23** is quite short at $1.497 \text{ \AA}$, while the B–C distance is a more typical $1.691 \text{ \AA}$. The lowest-energy structure containing an unfused ring is **24**, containing the stabilizing exo-olefin function, which lies 336 kJ mol^{-1} above the linear minimum. Cycle **24** contains an unusually long C–N bond ($1.740 \text{ \AA}$) paired with short B–C and B–N bonds, suggesting sizable contributions from a zwitterionic resonance structure that puts negative charge on the nitrogen and positive charge on the exocyclic carbon.



Rings containing boron, carbon, and heavier members of group 15 have been little studied. For formula BC_2P , only C-bridged BCP rings are minima, and they lie $102\text{--}134 \text{ kJ mol}^{-1}$ above global minimum linear PBCC, and $71\text{--}105 \text{ kJ mol}^{-1}$ above $\text{P}-\text{B}-\text{C}-\text{C}$ (G2(P) approach) <2003JMT57>.

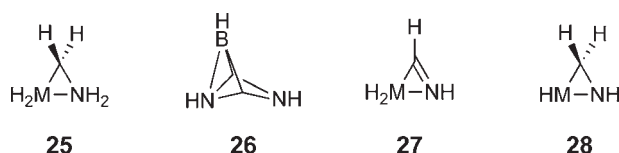
B–C–O ring systems have been examined less often than B–C–N systems, presumably owing to the lack of experimental examples. In contrast to $\alpha\text{-HBCN}^-$, **16**, correlated models predict isoelectronic HBCO to be a spin singlet substantially more stable than acyclic HCBO. A sizable barrier exists between the cycle and its BH/CO components <1996MP247>. However, oxaboriridine **22O** (isoelectronic with **20**), is predicted to be 236 kJ mol^{-1} less stable than isomeric $\text{CH}_3-\text{B}=\text{O}$ (HF/6-31G(d) level) <1982JOC60>. A divergent situation holds for methyl-substituted versions of **22**. C-methyl substituted cyclic $\text{HB}-\text{O}-\text{C}(\text{H})(\text{CH}_3)$ is 59.8 kJ mol^{-1} more stable than acyclic $\text{CH}_3-\text{BH}-\text{CHO}$, but acyclic $\text{CH}_3\text{CH}_2\text{B}=\text{O}$ is 173 kJ mol^{-1} more stable than $\text{CH}_3-\text{B}-\text{CH}-\text{O}$. In the latter case, though, the barrier to rearrangement is 265 kJ mol^{-1} , suggesting that the cycle might be kinetically stable if prepared (MP2/6-31G(d) level) <1992JCC423>. A study of the reaction between nitrones and vinylboranes concluded that the most favored products were 5-borylisoxazolidines containing B–C–O rings. However, the ring-containing products are only $8\text{--}12 \text{ kJ mol}^{-1}$ more stable than isomers where no rings exist and the boron and oxygen are several atoms separated, indicating that the energy benefit of the ring is confined largely to transition states, that is, the ring mostly improves reaction kinetics, not thermodynamics (MP4/aug-cc-PVDZ//B3LYP/aug-cc-PVDZ level) <2001JOC2449>. Both singlet and triplet $:\text{C}=\text{C}=\text{B}=\text{O}:^+$ were predicted to rearrange to singlet or triplet $\text{O}=\text{C}=\text{C}=\text{B}:^+$ through metastable singlet or triplet intermediates containing C-bridged B–C–O rings that lie only 54 and 71 kJ mol^{-1} above $:\text{C}=\text{C}=\text{B}=\text{O}:^+$ (UMP4/aug-cc-pVTZ//UMP2(full)/6-31G(d) level) <2003PCA1181>.

Singlet thiaboriridine **22S** is predicted to be $138.2 \text{ kJ mol}^{-1}$ less stable than isomeric singlet $\text{CH}_3-\text{B}=\text{S}$ (B3LYP/6-311G(d,p) level) <2005JH349>. However, it is separated from singlet $\text{CH}_3-\text{S}=\text{B}$ by a barrier of $262.9 \text{ kJ mol}^{-1}$, which in turn is separated from $\text{CH}_3-\text{B}=\text{S}$ by a barrier of 76.5 kJ mol^{-1} . It is thus likely that kinetically stable thiaboriridines could be prepared.

Studies on rings containing heavier members of group 13 generally find that acyclic molecules are more stable than three-membered cycles <2004JOC3493>. For example, singlet and triplet cyclic structures of stoichiometry AlC_2N containing Al–C–N rings lie $79\text{--}238 \text{ kJ mol}^{-1}$ above the ground-state linear $^3\text{AlCCN}$ (CCSD(T)/cc-pVTZ//B3LYP/6-11G(d) level) <2001JPC6724>. In cases where three-membered cycles are more stable than acyclics, dimerization to six-membered rings appears favored; for instance, dimerizations of azoniometallacyclopropanes **25** (homologues of **21**)

are exothermic by 162 kJ mol^{-1} (Al, 81 kJ mol^{-1} of monomer) and 154 kJ mol^{-1} (Ga), respectively (B3LYP/6-311G(d) level) <2003OM242>.

However, ‘dehydrogenated azoniometallacyclopropanes’ **27** are more stable than dative complexes $\text{H}_3\text{M} \leftarrow \text{C} \equiv \text{NH}$ by 58.3 (M = Al), 25.2 (M = Ga), and 27.2 kJ mol^{-1} (M = In) (B3LYP/pVDZ level). Interestingly, this does not entirely hold for the more symmetric cycles **28** (homologues of **20**), where for M = Al the cycle lies 9.1 kJ mol^{-1} below the dative complex, but for M = Ga the cycle lies 24.2 kJ mol^{-1} above the complex. These observations suggest viewing the cycles as donor–acceptor pairs, in which the interactions weaken progressing down the family. Cyclizations involving breaking the M–N bond followed by oligomerization are quite exothermic <2003JA9998>. Another apparent exception is the digallirenyl anion HGaGaHCH^- (homologous with **5**), studied in the context of cyclotrigallenes. DFT computations suggest considerable localization of negative charge on the carbon, which increases when an alkali metal cation is introduced. Nonetheless, energetic and physical property calculations led the authors to describe the anion as aromatic <1998OM114>.



Molecules of the type $\text{CM}_2\text{M}'_2$ and $\text{CM}_3\text{M}'$ (M = Al, Ga; M' = Si, Ge) contain planar carbon and edge-sharing CMM/CMM' rings. They lie substantially lower in energy than nonplanar isomers, and so are assigned as the species observed in mass spectrometric and photoelectron spectroscopic experiments (Section 1.17.3.3) <2000JA7681, 1998JA7967>.

1.17.3.3 Experimental Structural Methods

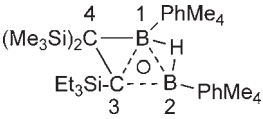
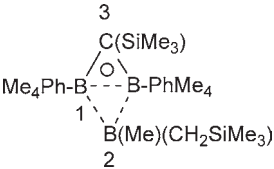
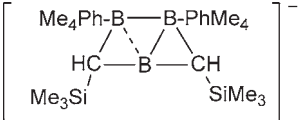
Unbridged diborirene dianions **29a** show ^{13}C NMR chemical shifts for the ring carbon consistent with delocalization of the ring charge ($144\text{--}173$ ppm for various cations; Table 3). The crystal structure of $(\text{K}^+)_2$ **29a** exhibits a planar $\text{B}_2\text{C}_2\text{Si}_2$ core, with short ring B–B and B–C distances of $1.58(1)$ and $1.50(1)$, (average) Å respectively, in keeping with this view. The ^{11}B NMR chemical shifts vary only slightly with different cations ($40\text{--}48$ ppm) <1988ZNB801>. Interestingly, the ^{13}C and ^{11}B chemical shifts for diborirene monoanion **30a** are quite similar to those for **29a**, indicating localization of the exo-anionic charge (Table 3).

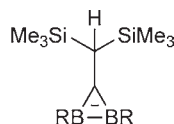
Table 3 ^{11}B and ^{13}C NMR data for diborirenes and diboriranes

	$\delta^{11}\text{B-1}$	$\delta^{11}\text{B-2}$	$\delta^{13}\text{C-3}$	$\delta^{13}\text{C-4}$	Reference
 $(\text{K}^+)_2$	39		161.7		1985AGE788
 (K^+)	45		147.8		1985AGE788
	52.5	18.0	114.8	24.9	2004MRC490

(Continued)

Table 3 (Continued)

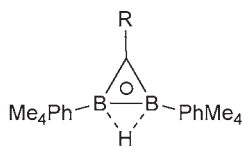
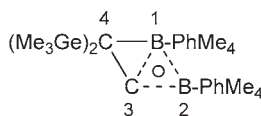
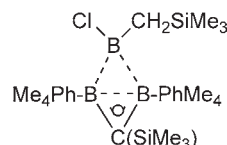
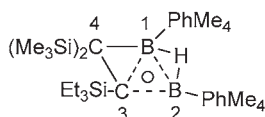
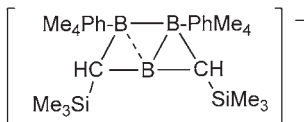
	$\delta^{11}\text{B-1}$	$\delta^{11}\text{B-2}$	$\delta^{13}\text{C-3}$	$\delta^{13}\text{C-4}$	Reference
	3	48	68.2	32.1	1994AGE2303
	40	80	133.0		2003AGE671
	24	24	2.1		2003AGE671

**29a:** R = *t*-Bu**29b:** R = PhMe₄**30a:** R = *t*-Bu**30b:** R = PhMe₄

Berndt and co-workers have demonstrated that many nominally four-membered rings containing two boron atoms should be viewed as edge-sharing three-membered rings, as noted above <1993AGE985>. Key support for this view arises from variable-temperature NMR spectroscopic and crystallographic data. Illustrative NMR data appear in Table 3.

Generally, the ¹³C NMR resonances for ring carbon atoms shift downfield from expected positions, supporting the presence of conjugation. Resonances for ring boron atoms in ¹¹B NMR spectra are less diagnostic, but as noted above, usually may be assigned through computations.

Several bridged diborirenes and diboriranes have been examined by single crystal X-ray diffraction. Hydride-bridged diborirenes **31a** and **31b** represent structurally simple starting points. As for **29**, the B₂C–R atoms are coplanar, and the ring B–C bonds are quite short (average 1.449(4) Å). However, the B–B bond lengthens to 1.743(4) Å because of the presence of the hydrogen bridge <1995AGE327>. Carbon-bridged diborirene **32** shows short B(1)–C(3) and B(2)–C(3) distances of 1.545(9) and 1.351(9) Å, respectively, the latter being exceptionally short for a B–C interaction <1990AGE398>. The C(1)–C(2) (1.475(8) Å), B(1)–B(2) (1.839(9) Å), and B(1)–C(1) (1.617(8) Å) distances fall into typical ranges. Boron-bridged diborirene **33** clearly contains an internal B–B bond, as shown by its distance of 1.695(9) Å, compared with values of 1.926(8) and 1.890(9) Å for the other B–B interactions <2003AGE669>. Diborirane **34** represents an example of a dibridged ring; the internal B(1)–C(3) bond length is 1.723(3) Å <1994AGE2303>. The crystal structure of the polyring diborirane anion **35** shows that it adopts near-*C*_{2v} symmetry with all distances in typical ranges <2000AGE1272>.

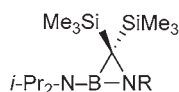
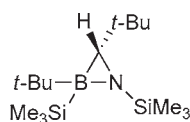
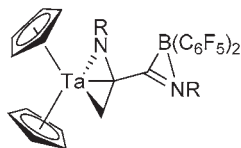
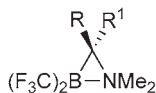
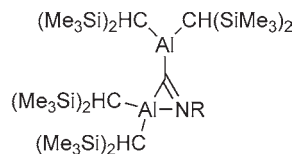
**31a:** R = SiMe₂(PhMe₄)**31b:** R = C(SiMe₃)₂(BEt₂)**32****33****34****35**

Azaboriridines, of which **36a** and **36b** and **37** are examples, exhibit ¹¹B NMR resonances at ca. 21–30 ppm <1985AGE416, 1989CB595, 1993CB(126)1565>. Those with sp³-hybridized ring carbons show ¹³C NMR resonances at ca. 30 ppm (an exception is **37**, at 50.0 ppm), while sp²-hybridized fluorenyl ring carbons show resonances at 52–53 ppm. The unusual tantalum complexes **38** contain peripheral B–C–N azaboriridine rings. The presence of an N=C double bond is supported by its distance of 1.292(7) Å as determined by a single crystal diffraction study of **38a**; this in turn implies that the *exo*-carbon interacts with the tantalum center, giving formally a Ta–N–C ring. (The latter is supported by a Ta–C distance of 2.373(6) Å distance, compared to the Ta–CH₂ distance of 2.231(7) Å.) **38a** and **38b** exhibit ‘upfield’ ¹¹B NMR chemical shifts (ca. –16 ppm) rather than those downfield for **37** and **39**. Intriguingly, given the usual colors of these ring systems, the tantalum complexes are described as purple. This argues either for a limiting characterization of the tantalum in oxidation state +3 (d²) rather than +5 (d⁰), or for an unusually low HOMO–LUMO gap on the (azaboriridinyl)azaallyl ligand (HOMO=highest occupied molecular orbital; LUMO=lowest unoccupied molecular orbital) <2002OM2422>.

Azoniaboratacyclopropane compounds **39** exhibit broad resonances in ¹³C NMR spectra at 51–69 ppm characteristic of the ring carbon, although the resonance lies at 44 ppm for R = H, R¹ = C₆F₅ <1999EJI255>. For comparison, H₃C–B carbons (40–50 ppm), and the carbons in cyclopropane (–4.0 ppm) and aziridine (18.2 ppm), resonate upfield of this range. In neither case are the ¹¹B resonances diagnostic for a ring system; for example, in compounds **32**, they lie at –12 to –17 ppm, in the same range as those for other tetracoordinated boron compounds (for example, –15.3 ppm for (F₃C)₃B–NH₃). Mass spectra of the azoniaboratacyclopropanes show weak signals for M⁺ and stronger signals for [M⁺–CF₃] and [M⁺–C₂F₅].

A single crystal X-ray diffraction study of B(CF₃)₂–NMe₂–C(C₆H₅)₂ (**39**; R = R¹ = Ph) showed several interesting features <1999EJI255>. The B–N bond length was exceptionally short at 1.568(6) Å, whereas the analogous values in larger rings exceed 1.61 Å. By contrast, the N–C distance was 1.556(5) Å, longer than that typically observed for N–C single bonds. The exocyclic C–X–C angles (X = ring C, B, N) averaged 109.1(8)°, nearly tetrahedral despite the presumed large s character in these bonds. Very similar data were observed in a diffraction study of a related azoniaboratacyclopropane (**39**; R = CH₂Ph, R¹ = SiMe₃) <1993AGE384>.

The AlNC compound **40a** showed some disorder in a single crystal diffraction study, but no doubt exists regarding the presence of the ring. The data showed bond distances and angles within normal ranges, and consistent with localization of π-electron density between carbon and nitrogen, despite the presence of the unusual AlR₂ substituent on carbon. Presumably due to their bonding to two aluminium atoms, the ring carbons resonate substantially downfield in the ¹³C NMR spectra (320.2 ppm for **40a**, 302.2 for **40b**). Their ¹H NMR spectra show evidence of hindered rotation of the CH(SiMe₃)₂ groups. Cryoscopic mass determinations in benzene show that both compounds are monomeric in solution. Ultraviolet–visible (UV–Vis) spectroscopy shows a lower energy λ_{max} for phenyl-containing **40a** (**40a**: λ_{max} (ε) = 449 (153); **40b**: λ_{max} (ε) = 437 (60)), indicating some conjugation between the ring double bond and the phenyl ring <1994CB1587>. **40c** also showed crystallographic disorder, which might account for its exhibiting an Al–N distance ca. 0.1 Å longer than that in **40a** <1996ZTFA373>.

**36a:** R = Ph**36b:** R = CH₂Ph**37****38a:** R = α -C₆H₁₁**38b:** R = CH₂Ph**39****40a:** R = Ph**40b:** R = *t*-Bu**40c:** R = Me

Molecules of the type CM₃M' (M = Al; M' = Si, Ge) were observed in mass spectrometric and photoelectron spectroscopic (PES) experiments. They were assigned as containing planar carbon and edge-sharing CMM/CMM' rings by comparison with theory and particularly interpretation of the PES data [<2000JA7681>](#).

1.17.3.4 Thermodynamic Aspects

Most of the diborirene and diborirane derivatives known are stable at ambient temperature, although some rearrange at low temperature [<2003OM1594>](#). Many melt without decomposition, at temperatures generally 130–180 °C. They tend to be soluble in arenes and more polar solvents, and sparingly soluble in alkanes, from which they can be recrystallized at low temperature. Azaboriridines **36** exhibit defined melting points, with fluorenyl-substituted versions (sp²-hybridized ring carbons) melting at substantially higher temperatures than silyl-substituted versions (sp³-hybridized ring carbons). Analogue **37** can be distilled at 40 °C/0.005 Torr. Azoniaboratacyclopropanes (F₃C)₂BNMe₂C(R)(R¹) **39** are solids at room temperature. They are soluble in pentane, and stable enough at elevated temperatures to be volatilized for mass spectrometry.

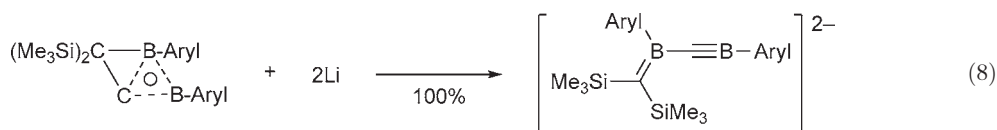
Aluminium-containing compounds **40** melt at temperatures over 100 °C, and are stable in solution to similar temperatures [<1994CB1587>](#).

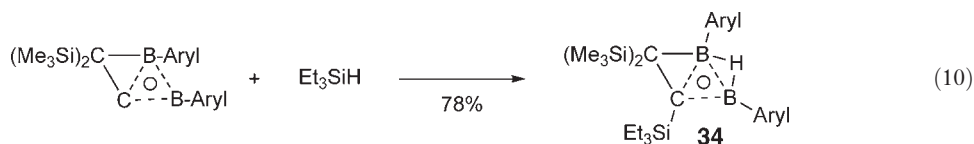
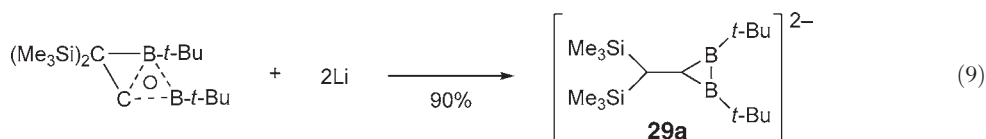
1.17.3.5 Reactivity of Fully Conjugated Rings

Reactions of diborirenes and derivatives were reviewed by Berndt [<1993AGE985>](#). Consequently, this section only describes notable reaction types of these, adding more recent discoveries where appropriate.

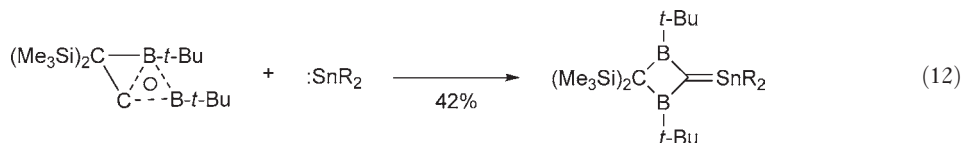
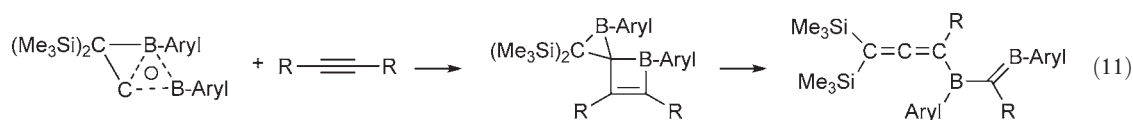
Diborirenides (diborirene anions **30**) react with electrophiles such as hydrogen cation or alkylboron halides to give B–B electrophile-bridged diborirenides of type **31** [<1985AGE788, 2003AGE669>](#). Notably, phosphorus and arsenic electrophiles give isolable products [<2003JOM244>](#).

Carbon-bridged diborirenides containing aryl substituents at boron are reduced by lithium to give ring-opened diborane-ynes (Equation 8) [<1988AGE961>](#). (Note that 'Aryl' denotes that more than one specific aryl substituent is possible.) However, analogues containing *t*-butyl substituents at boron react with alkali metals or magnesium to form dianions containing unbridged diborirenide rings (Equation 9) [<1988ZNB801>](#). Dialkylboranes act as sources of hydride, giving hydride-bridged diborirenides [<1995AGE327>](#), while trialkylhydridoboranes, trialkylsilanes, and stannanes give hydride-bridged diboriranes (Equation 10) [<1994AGE2303, 1996AGE1990>](#).





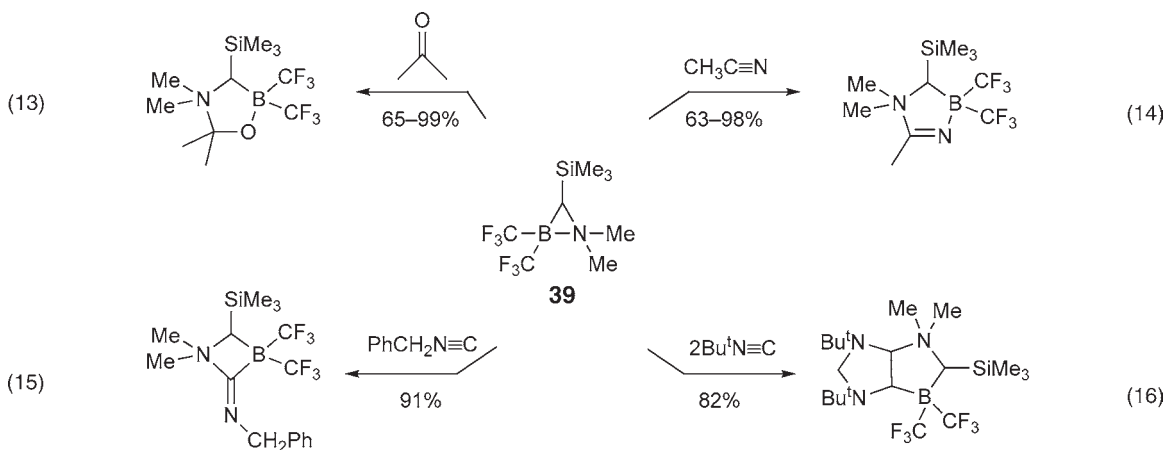
Various intriguing products form when diborirenes react with alkynes. Generally spiro systems form initially; these may undergo ring expansion or ring opening (Equation 11) <1994AGE1487, 1994AGE2306, 1995AGE1340>. Products of ring expansion or ring opening typically result as well from reactions with phenols and silanols, alkyl- and aryllithiums <1993AGE985>, with tetrahalodiboranes <2001EJI387>, and with metal fragments <1995AGE1111, 1997JOM255, 1998CEJ44>. In the last case, reactivity indicative of carbene character often occurs, as shown in Equation (12).



1.17.3.6 Reactivity of Nonconjugated Rings

Water cleaves the B–N bond in azonaboratacyclopropanes **39** except when $\text{R} = \text{R}^1 = \text{Ph}$ and $\text{R} = \text{CH}_2\text{Ph}$, $\text{R}^1 = \text{SiMe}_3$ (i.e., the cases studied crystallographically, which are stable to hydrolysis). Linear zwitterionic aminealkyl-hydroxyboranes $\text{HMe}_2\text{N}-\text{CRR}^1-\text{B}(\text{CF}_3)_2\text{OH}$ form. The stability of the diphenyl compound is ascribed to its low polarity, although it seems likely when compared to the hydrolytically unstable compounds that steric effects of the large phenyl rings play an important role. Other weak acids give similar reactivity; for example, HCN attacks the B–N bond to give $\text{HMe}_2\text{N}-\text{CH}(\text{SiMe}_3)-\text{B}(\text{CF}_3)_2(\text{CN})$ <1996AOM147, 1999EJI255>.

Several ring expansion reactions of azonaboratacyclopropanes have appeared (Scheme 2) <1996AOM147>. All involve, in essence, insertion of substrate into the B–N bond, with attachment of the substrate heteroatom to boron,



Scheme 2

giving five-membered rings (Equations 13 and 14). Ring expansion using carbonyl functions (Equation 13) occurs only with ketones and aldehydes; esters and amides do not react as shown <1994JOM1>. Isocyanides give unexpected reactions, forming four-membered rather than five-membered rings with benzylic isocyanides (Equation 15), and a bicyclic system with *t*-butyl isocyanide (Equation 16) <1994JOM107>.

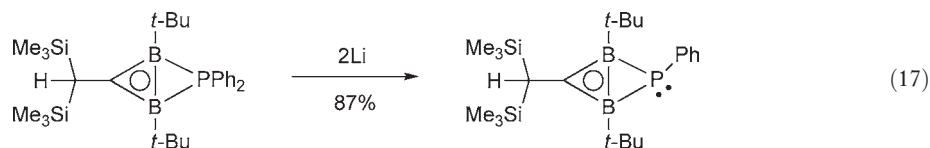
Treatment of $(F_3C)_2BNMe_2$ with the 'CF₂ equivalent' $(F_3C)SiF_3$ at low temperature rapidly gives the acyclic $(F_3C)_2FB-CF=NMe_2$ through the proposed azonaboratacyclopropane $B(CF_3)_2-NMe_2-CF_2$ <1999EJI255>.

1.17.3.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Few examples of this type of reactivity exist, since in bridged diborirenes, for example, no substituents are present on the ring carbon, and more generally, few compounds containing substitutable groups on carbon have been prepared. Two classes of reactivity have been reported. First, diborirenide dianions **29** react with very weak acids such as secondary amines monoanions **30**; protonation occurs exclusively at the *exo*-carbon <1985AGE788, 1993AGE985>. (These further react with electrophiles, as noted in Section 1.17.3.5.) Second, a number of diborirenes show fluxional behavior in solution stemming from bond-breaking/bond-making processes involving the bridging group. Variable-temperature NMR studies indicate exchange barriers of ca. 50 kJ mol⁻¹; computational studies suggest mechanisms involving BC₂ ring transition states and four-membered ring intermediates <1993AGE985>.

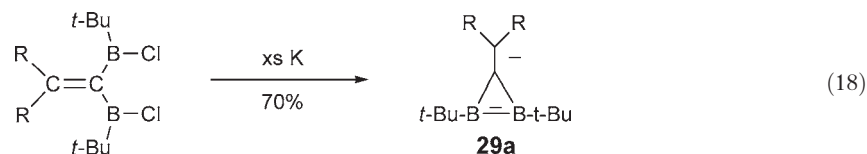
1.17.3.8 Reactivity of Substituents Attached to Ring Heteroatoms

As in the previous section, few cases where substitutable groups are present on the heteroatoms have been prepared. The fluxional behavior mentioned above involves the boron atoms in diborirenes as well as the carbon. In an interesting case, lithium reduces the zwitterionic phosphonium-bridged cation shown to give the phosphine-bridged diborirenide anion (Equation 17) <2003JOM244>.

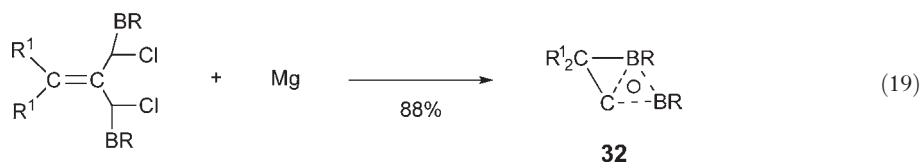


1.17.3.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

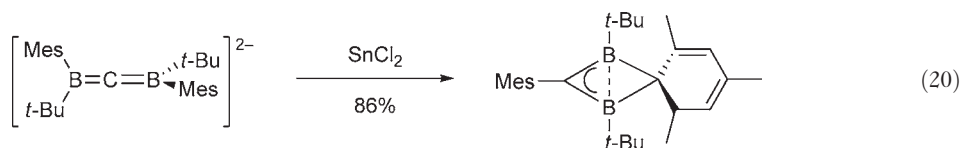
Lithium reduction of 1,1-dichloroborylethenes gives diborirenide dianions of type **29** (Equation 18).



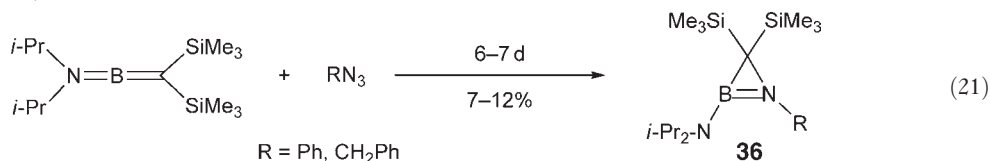
The first synthesis of a diborirene of type **32** involved treatment of a 1,2-dichlorodiborane with bis(trimethylsilyl)ethyne. An improved method analogous to Equation (18) employs magnesium reduction of (diboradichloromethylene)alkenes (Equation 19) <1988ZNB801>.



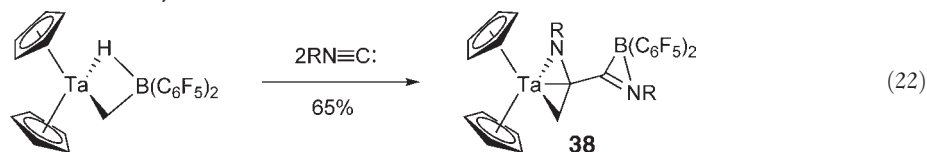
Polyborylalkenes and alkanes represent useful starting materials for phosphorus-bridged diborirenes and bridged diboriranes as well <2003JOM244, 1994AGE2303>. In one unusual reaction, SnCl₂ oxidation of a diboraallene dianion gives a mesitylene-bridged diborirene (Equation 20) <1990AGE399>.



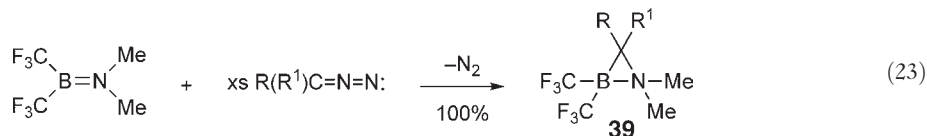
Heteroatom-containing ene analogues react with imine or carbene equivalents to give heterocycles in reactions similar to [2+1] carbene/alkene cyclopropanation. Alkylidenoaminoboranes $\text{R}_2\text{N}=\text{B}=\text{CR}^1_2$ react slowly with various azides with loss of N_2 to form azaboriridines **36** in poor yield. An example appears in Equation (21) ($\text{R} = \text{PhCH}_2$ or Ph) <1985AGE416, 1989CB595>.



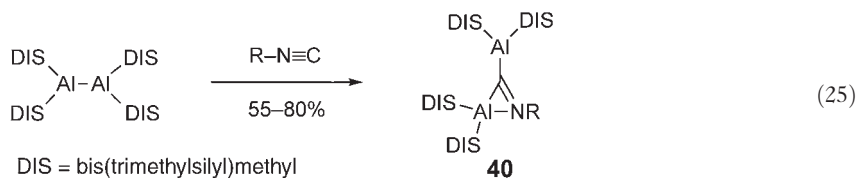
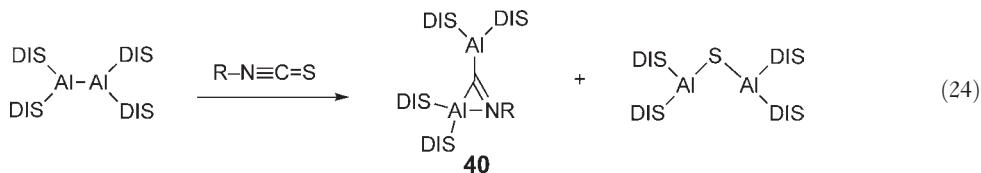
Tantalum complexes **38** were prepared through the reaction in Equation (22). The authors postulate coordination of one isocyanide to the boron with concomitant loss of methane, azaallyl formation, and finally coordination of the second isocyanide to boron followed by its insertion into the B-C bond <2002OM2422>.



Azoniaboratacyclopropanes **39** were prepared using the general carbene cyclopropanation route in Equation (23) <1999EJ1255>. Owing to the reactivity of the aminoborane precursor, only those diazo compounds that can be isolated and purified are appropriate for the reaction.



Aluminium-containing rings **40a** and **40b** were prepared by two routes involving insertion into Al-Al bonds (Equations 24 and 25). The former produces the dialuminium sulfide by-product shown, which is difficult to separate from the ring, so the second method is that of choice <1994CB1587>. Interestingly, synthesis of **40c** uses $\text{CH}_3\text{-N}=\text{C}=\text{S}$ as in Equation (24), but the sulfur is eliminated as the element rather than as the dialuminium sulfide by-product <1996ZFA373>.

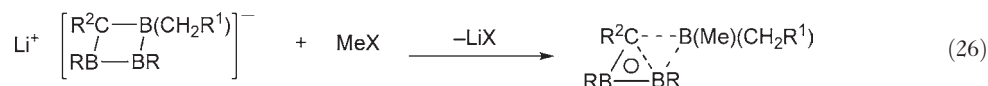


1.17.3.10 Ring Syntheses by Transformations of Another Ring

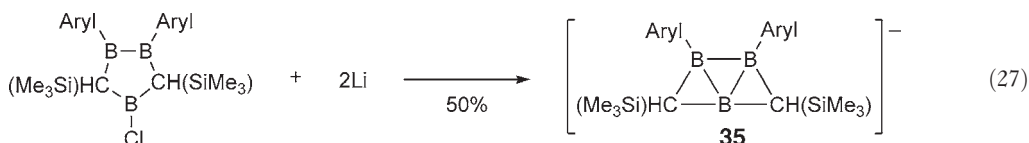
Several instances were described above. As noted (Equation 9), carbon-bridged diborirenes are reduced by alkali metals or magnesium to form dianions containing unbridged diborirene dianions <1988ZNB801>. Rearrangements

involving bridging groups (Sections 1.17.3.5 and 1.17.3.7) interconvert isomers. Addition of trialkylmetal hydrides to diborirenes gives diboriranes (Equation 10).

Treatment of anionic four-membered rings with electrophiles leads to boron-bridged diboriranes (Equation 26). The specific structure varies with the nature of the electrophile, but three-membered rings are always formed <2003AGE669, 2003AGE671>.



Several polyring systems have been prepared via reduction of a larger polyboron ring. Treatment of a 1,3,4-triboracyclopentane with lithium gives the 'triboriranide' containing two diborirane rings (Equation 27) <1997AGE1469>. Similarly, reduction of a 1-oxo-2,4,6-triboracyclohexane gives an oxo-bridged triboriranide <2003JOM244>.



1.17.4 Rings Containing Group 14 (Si–Pb) Elements

1.17.4.1 Introduction

Two excellent review volumes of the chemistry of the elements of this group have recently appeared <B-2001MI8, B-2002MI9>. Sections discussing all types of three-membered rings are spread throughout them. Most studies in this area have involved silicon, and an extensive body of literature exists. Far fewer germanium and tin compounds have been investigated, and while lead compounds have been studied computationally, no examples have been isolated. This last is in keeping with weakness of lead–carbon bonds, and the general instability of lead(IV) with respect to lead(II).

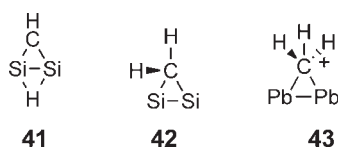
Compounds containing group 16 elements as the third atom, that is, oxasila- and oxagermacyclopropanes, thiasila- and thiagermacyclopropanes, etc., were reviewed in CHEC-II(1996) <1996CHEC-II(1)173, 1996CHEC-II(1)259, 1996CHEC-II(1)457>. Another review from the same author appeared more recently <1998MI2401>. Thus, discussion of such compounds in this section is limited largely, though not entirely, to the years 1996–2005. A few compounds from before 1996 that did not appear in the reviews noted are included here as well.

1.17.4.2 Theoretical Methods

The review volumes mentioned earlier contain chapters discussing computational studies of compounds containing group 14 elements; three-membered rings are dealt with in subsections <B-2001MI(3)1, B-2002MI(2)169>.

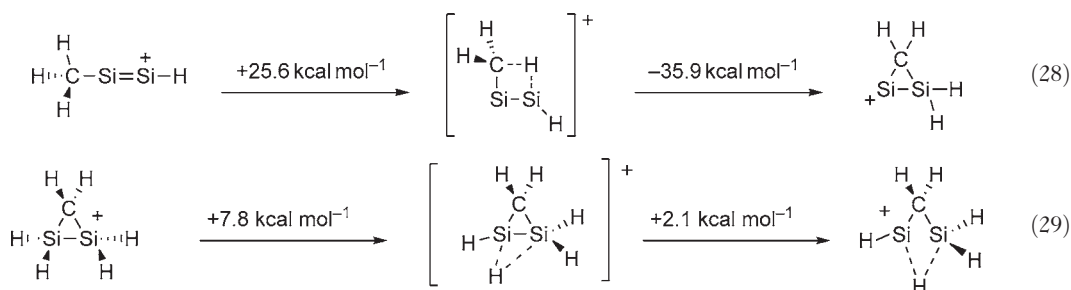
Several species of formula Si_2CH_n have been studied, for both intellectual and astrophysical interest. The cyclic form of Si_2CH^+ has the hydrogen bound to the carbon, is a spin triplet, and lies 119 kJ mol^{-1} above the acyclic isomer lacking an Si–Si bond (MP4/6-31G(d,p)//HF/6-31G(d,p) level) <1988CPL128>. An initial study of minima on the CSi_2H_2 potential surface indicated that the C_{2v} H-bridged cyclic isomer **41** represents the global minimum by 55 kJ mol^{-1} over other isomers, and is stabilized by 2π -electron delocalization (MP2/6-31G(d)//HF/3-21G(d) level) <1990JPC5530>. High-level calculations confirmed and extended this work, indicating that **41** lies $64\text{--}319 \text{ kJ mol}^{-1}$ below other cyclic isomers, and 122 kJ mol^{-1} below the acyclic C_s $\text{H}_2\text{Si}=\text{C}=\text{Si}$: isomer (CCSD(T)/aug-cc-pVTZ level) <2004JMT181>. It adopts a singlet electronic configuration, and contains an exceptionally long Si–Si interaction ($d(\text{Si}-\text{Si}) = 2.557 \text{ \AA}$), presumably due to the presence of the hydrogen bridge. The authors describe the interaction as a two-electron three-center bond. Interestingly, the potential surface for the CSi_2H_2^+ cation is quite different. Here the apparent global minimum is the C_s **42**, a distorted version of the C_{2v} -symmetric cyclopropane-like structure, which is a transition state lying 2.7 kJ mol^{-1} above **42**. The C_{2v} H-bridged cyclic isomer analogous to **41** is also a transition state. Isomer **42** lies 19 kJ mol^{-1} below the next most stable isomers, one cyclic and one acyclic <2004JMT181>.

One of the few studies of cyclic lead compounds suggested that **43** might be observable, being only 11 kJ mol⁻¹ less stable than acyclic Pb–PbMe⁺ (MNDO level) <1990JOM241>.



Surprisingly, no studies of dimetallirenes $\overline{\text{RM=MR-CR}}_2^1$ have appeared. The corresponding cations $\overline{\text{HM=MH-CH}}^+$ (M = Si, Ge) have been studied as possibly aromatic species <2002JCP9543>. Predicted structures of the two dimetal and one Si–Ge cations show distances and angles characteristic of delocalization, and nucleus-independent chemical shift (NICS) calculations give large, negative values indicative of sizable aromaticities in all three.

An extensive investigation of the potential surfaces associated with reaction of Si⁺ with SiH₃(CH₃) provided energetics and barriers associated with reactions of several cyclic species of stoichiometry Si₂CH₄⁺, Si₂CH₅⁺, and Si₂CH₆⁺ <1994JPC6704>. Among several intriguing predictions are those shown in Equations (28) and (29) (PUMP4/6-31G(d,p)//ROHF/6-31G(d) level).



Later study of the Si₂CH₄⁺ surface showed that the cyclic product in Equation (28) is essentially isoenergetic with acyclic H₃C–SiH–Si⁺ (an isomer of the reactant in Equation 28) with only small barriers connecting the two. It should thus be difficult to assign particular reactivity to one or the other <1996OM5391>.

A brief study of the Si₂CH₅⁺ surface showed that the cyclic isomer CH₂SiH₂SiH⁺ lies 35 kJ mol⁻¹ above an acyclic isomer containing a methyl group and 10.5 kJ mol⁻¹ above a silylene-like isomer (B3LYP/6-311G(d,p) level) <2001OM4593>.

Several studies of dimetalliranes $\overline{\text{R}_2\text{M-CR}}_2^1\text{-MR}_2$ (M = Si, Ge, Sn; typically R = R¹ = H) have appeared. Generally, one finds that theoretical methods reproduce reasonably well the structural characteristics of dimetalliranes, even when modest basis sets and correlation-free models are used. For instance, HF/various double- ζ basis sets approaches predict Si–Si and Si–C bonds in $\overline{\text{SiH}_2\text{CH}_2\text{SiH}_2}$ within 0.02 Å of those observed crystallographically in substituted disiliranes (Section 1.17.4.3) <1987JA6577, 1989JPC3025>. Improvements through use of correlated models and larger basis sets are modest at best <2003OM4721>.

Two observations often commented upon are that the M–M bonds are unusually short, and that the geometry around the metal atoms becomes more planar from Si to Ge to Sn. Explanations are typically couched in terms of a Dewar–Chatt–Duncanson model, viewing the ring as a carbene–dimetallene complex. One expects that interaction between fragments decreases down the family, thus increasing the dimetallene character and in turn the planarity of the fragment <1996CHEC-II(1)457>.

This view is supported by calculated fragmentation energies of all combinations of dimetallacyclopropanes $\overline{\text{MH}_2\text{-CH}_2\text{-MH}_2}$ to component methylene and dimetallenes or metalylene and metallene (CCSD/DZ(d)//HF/DZ(d) level) <1992JA2093>. All rings were found to be stable to these decompositions, with expulsion of methylene most endothermic (531 and 448 kJ mol⁻¹ for M = Si and Ge, respectively) and expulsion of digermylene least endothermic (ca. 200 kJ mol⁻¹). The lower endothermicity of the former speaks to the weaker methylene–dimetallene interaction. Calculations of reactions between germynes and phosphathenes point to similar behavior despite the presence of the phosphorus heteroatom <2002RCB1568>.

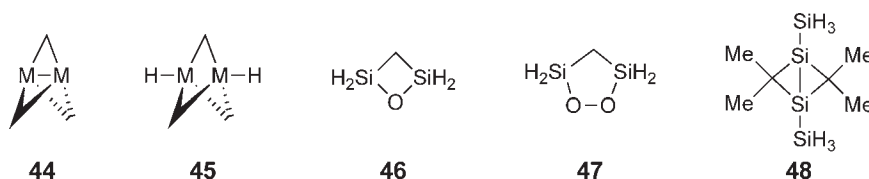
²⁹Si NMR shielding tensors were calculated for $\overline{\text{Me}_2\text{Si-CH}_2\text{-SiMe}_2}$. As is true for cyclotrisilanes, the tensor component perpendicular to the three-membered ring is much larger than those planar, so substantial anisotropy is observed. This does not hold for larger rings <1995CPL393>.

Several studies have probed RSEs of dimetalliranes. While all agree that heterorings contain more strain than does cyclopropane (for which the ring strain is ca. 117 kJ mol^{-1}), they disagree on the presence of trends. Early work using highly correlated energy models but correlation-free optimized structures suggested that RSEs rise regularly from 155 ($\text{M}=\text{M}=\text{Si}$) through 171 ($\text{M}=\text{Si}, \text{Ge}$) to 174 kJ mol^{-1} ($\text{M}=\text{M}=\text{Ge}$) <1992JA2093>. However, a more recent study using correlated structures and energies suggests essentially identical RSEs of 172 (MP2/double- ζ +d) or 155 kJ mol^{-1} (B3LYP/cc-pVTZ) for the homo-dimetallacyclopropanes and for the distanna homologue <2005CEJ5067>. Somewhat surprisingly, the presence of bulky alkyl substituents versus hydrogens appears not to affect the RSEs of disiliranes <2003OM4721>.

1,3-Dimetalla[1,1,1]propellanes **44** ($\text{M}=\text{Si}, \text{Ge}, \text{Sn}$) show M–M distances consistent with the presence of bonds, but do not display the expected critical point in atoms-in-molecules (AIM) electron density projections. Other computational probes left open the question of whether M–M bonds exist here. The propellanes exhibit regularly decreasing RSEs, suggesting sufficient stability for the compounds that they might be observed in the gas phase. However, all three are predicted to oligomerize exothermically, with the disilicon compound likely undetectable in condensed phase and the heavier homologues exhibiting only short lifetimes <2005CEJ5067>.

1,3-Dimetallabicyclo[1,1,1]pentanes **45** ($\text{M}=\text{Si}, \text{Ge}, \text{Sn}$) show only slightly longer ($0.02 \text{ \AA}$) M–M distances than do the unsubstituted analogues **44**, but natural bond orbital calculations suggest that the two M atoms are sp^3 -hybridized and so interact only weakly. In contrast to the situation for compounds **44**, several models predict essentially identical RSEs for the homologues; these are still small enough that the authors suggest the compounds should be isolable. However, they will likely be susceptible to hydrolysis; computed barriers to nucleophilic attack by a single water molecule are 113 (Si), 107 (Ge), and 59 (Sn) kJ mol^{-1} (MP2/6-31G(d), LANL2DZ level), suggesting rapid hydrolysis of the last and slower but regular hydrolysis of the first two <2005CEJ5067>.

Fused di(disilirane) **48** was studied as a model for **77** <2001JA12730>. General structural features and the ^{13}C and ^{29}Si NMR chemical shifts were modeled more successfully using a long Si–Si bond ($2.448 \text{ \AA}$) than using a short one, although both were minima. The longer bond isomer is 49 kJ mol^{-1} more stable (B3LYP/6-311+G(d,p) level). Both isomers are predicted to display a small HOMO–LUMO gap, and so a relatively low energy absorption maximum. This is borne out by experiment (Section 1.17.4.3). Cage compound **78** was modeled similarly using SiH_3 and H to replace larger groups. A structure with an unusually long Ge–C bridge bond proved to be a minimum; the calculations suggest this bond is really represented as a singlet biradical interaction. The ^{13}C NMR spectrum supports this view (Section 1.17.4.3) <2002JA9962>.



Several reactions of dimetalliranes not mentioned above have been studied. Of importance to experiments discussed below (Section 1.17.4.6), thermochemical kinetic modeling suggests small barriers to heterolytic cleavage of the Si–Si bond in disiliranes <1993OM289>. Reactions between excited states of SiH_2 and ground-state $\text{CH}_2=\text{SiH}_2$ are found to be essentially barrierless as well, indicating that photochemical formation and decomposition of disiliranes represent viable pathways <1997PCA10053>. Studies of the mechanism of formation of the oxo **46** and dioxo **47** from disilirane and $^1\text{O}_2$ show that insertion of the latter into the ring Si–Si bond is extremely exothermic (-552 kJ mol^{-1} , MP4/6-31G*//HF/6-31G* level), and that involvement of an ionic peroxo intermediate is energetically plausible. None of the barriers between intermediates exceed $4\text{--}8 \text{ kJ mol}^{-1}$ <1993OM1514>. Disilirane carbenoids with geminal Li,Cl substitution on the ring carbon should eliminate LiCl easily to form ‘disilacarbenes’ that should ring-open to form 1,3-disilaallenes. The crucial transition state barrier, which combines Li–Cl bond formation with Si–Si bond cleavage, requires only 27 kJ mol^{-1} to surmount from the parent carbenoid <2001JOM148>.

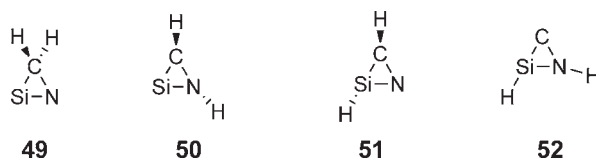
Complementing studies of planar carbon noted in Sections 1.17.2.2 and 1.17.3.2, recent calculations have suggested molecules that should contain planar silicon. Several examples were built from Si–C–B rings <2004JA16227>.

Studies of many compounds of stoichiometry MCN_n ($\text{M}=\text{Si}, \text{Ge}; n=0\text{--}6$) have appeared. Cyclic SiCN lies 54 kJ mol^{-1} above linear SiCN and 44 kJ mol^{-1} above linear SiNC (BLYP/6-311G(d,p) level) <1998EJO1307>. For formula SiCNH, the ground state is acyclic $^1\text{HSiCN}$. Spin singlet HCSiN lies 15.7 kJ mol^{-1} above this, while singlet HNSiC lies 138 kJ mol^{-1} above it (UCCSD/infinite basis set extrapolation//B3LYP/6-311G(d,p) level). The triplet

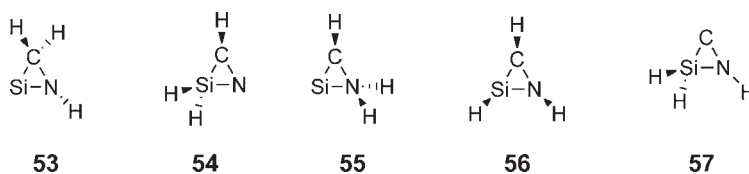
spin isomers are of considerably higher energy <2005CP1, 1998EJO1307>. The vibrational spectrum of the former cycle was calculated, and used to demonstrate its presence as the product of photolysis in a matrix isolation experiment (Section 1.17.4.8) <1998EJO1307>. Substitution of halides (F, Cl, Br) for hydrogen destabilizes the cycles dramatically with respect to acyclics (165–210 kJ mol⁻¹), although such substitution sizably stabilizes singlet spin states with respect to triplets <2005JMT33>.

In contrast, structural predictions for formula GeCNX (X = H, F, Cl, Br) where the germanium is forced to be germylene (i.e., only structures where Ge has a lone pair were considered) are model dependent. However, the data on balance suggest that the lowest-energy state for GeCNH is a cyclic spin singlet $\overline{\text{HCN}}\text{Ge}$, while that for GeCNCl is acyclic ¹Cl–GeCN, with the cyclic some 165 kJ mol⁻¹ higher in energy. For X = F, Br, whether a DFT or perturbation theory model is employed dictates the preference <2005JOM4692>.

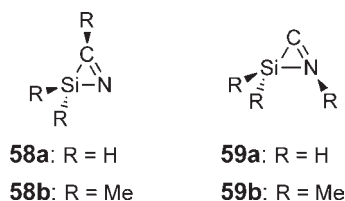
Four cyclic isomers of formula SiCNH₂ are minima on the spin doublet potential surface, 49–52. They lie 87, 124, 140, and 221 kJ mol⁻¹, respectively, above the ground-state ²H₂SiCN, and exhibit low barriers (≤46 kJ mol⁻¹) to ring opening (G3B3 approach). They are thus likely to be kinetically labile and difficult to observe <2005CPH205>.



Five spin singlet cycles 53–57 are predicted to be minima on the SiCNH₃ potential surface. They lie 121, 143, 208, 212, and 255 kJ mol⁻¹, respectively, above ground-state H₃Si–CN (G3B3 approach). However, in contrast to the situation for SiCNH₂ above, all five isomers are predicted to exhibit large barriers to ring opening or other rearrangements, suggesting they should be observable if formed <2004PCA10602>.



To ascertain why azasilirene **79** forms when (TBT)(Mes)Si: reacts with nitriles, but coordination complexes form when the silylene reacts with isocyanides, computed energies of the reaction components and products were determined (Mes = 2,4,6-trimethylphenyl; TBT = 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl). Azasilirene **58b** is 154 kJ mol⁻¹ more stable than carbene-like **59b** (cf. **54** and **57**), and 64 kJ mol⁻¹ more stable than the isomeric coordination complex Me₂Si–NCMe. However, coordination complex Me₂Si–CNMe is 53 kJ mol⁻¹ more stable than **59b** (B3LYP/6-31G(d) level). ¹³C, ²⁹Si, and ³¹P NMR chemical shifts were calculated for the parent and various substituted azasilirenes and phosphasilirenes, including cases with *o*-Xyl (2,6-dimethylphenyl) substituents on Si and a *t*-Bu substituent on carbon. Computed shifts for the parent azasilirene deviated substantially from experimental values for **79**, particularly for silicon, while agreement for molecules with carbon-based substituents was substantially better. It proved impossible to predict the ³¹P NMR shift well (within ±20 ppm) for any phosphasilirene <2002SIC313>.



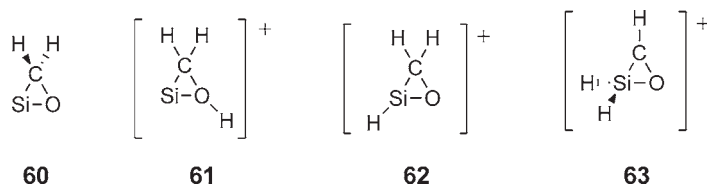
The optimized structure of the parent azasilirane, $\overline{\text{H}_2\text{C}}\text{--SiH}_2\text{--NH}$, shows typical bond lengths and angles (RHF/6-31++G(d,p) level) <1994JPC3154>. The compound is predicted to react exothermically with fluoride ion (–223 kJ mol⁻¹; MP4/6-31++G(d,p)//RHF/6-31++G(d,p) level) to form the diastereomeric anion where the silicon-bound fluoride is oriented toward the nitrogen rather than the carbon. The corresponding phosphasilirane,

$\text{H}_2\text{C}-\text{SiH}_2-\text{PH}$, also shows typical structural parameters, and an RSE of 111 kJ mol^{-1} . This RSE differs substantially from that in silirane (177 kJ mol^{-1}) and is clearly not the average of this value and that of phosphirane (93 kJ mol^{-1}).

Since siliranes of all types containing exocyclic double bonds are more common (and so presumably more stable) than those without, an extensive study of the phenomenon for azasiliranes was undertaken. Azasilirane $\text{H}_2\text{C}=\text{C}-\text{SiH}_2-\text{NH}$ is more stable than other tricyclic isomers by $33\text{--}100 \text{ kJ mol}^{-1}$ (QCISD(T)/6-31G(d,p)//MP2/6-31G(d,p) level). This arises directly from the presence of the exocyclic methylene, which lowers the RSE. The mechanism by which the silirane might be formed from $\text{HN}\equiv\text{C}$: and $\text{CH}_2=\text{SiH}_2$ remained elusive, as the transition states located lay too high energetically to be appropriate for a reaction that occurs at low temperature (Section 1.17.4.8). In this regard, it was found that decomposing the azasilirane requires crossing a barrier of 136 kJ mol^{-1} to form a four-membered cyclic carbene; this argues for experimental stability for rings with exocyclic double bonds <1994JOC8015>.

A number of studies have probed rings containing Si-C-O and Si-C-S atoms. Examination of the SiCOH_2 potential energy surface allowed the prediction that cyclic **60** lies only 2.5 kJ mol^{-1} above the global minimum, an $\text{H}_2\text{Si}\cdot\text{CO}$ complex. Barriers of $>165 \text{ kJ mol}^{-1}$ separate this isomer from rearrangement products (B3LYP/6-31G(d,p) level). Vibrational calculations were used to confirm formation of the cyclic isomer in a matrix (Section 1.17.4.3) <1999OM2155>.

The SiCOH_3^+ surface was examined as part of a mass spectrometric study. Two non-interconvertible classes of cations were found. One, with acyclic CH_3OSi^+ as the global minimum, contained minima **61** (184 kJ mol^{-1} higher in energy) and **62** (236 kJ mol^{-1} higher in energy) (G2 approach). While these energies argue for limited stability, the latter sits in a fairly deep well and so might be observable. The authors indeed suggest it as a product of electron ionization of $\text{Me}_3\text{SiCH}_2\text{OH}$ (Section 1.17.4.8). Cyclic $\text{H}_3\text{C}-\text{Si}-\text{O}$ was found to be a transition state. The other class showed acyclic H_3SiCO^+ as the minimum (this lies 87 kJ mol^{-1} above global minimum CH_3OSi^+). Only cyclic **63** was found to be a minimum here, lying 233 kJ mol^{-1} above H_3SiCO^+ . Similar to the first case, cyclic $\text{H}_3\text{Si}-\text{C}-\text{O}$ was found to be a transition state <1996J(P)2389>.



Frequency calculations on oxasilirane **64** (SiCOH_4) and its 1-methyl-substituted congener were used to identify them as products of reactions between Si atoms and $\text{CH}_3\text{OH}/\text{CH}_3\text{OCH}_3$, respectively, in an argon matrix at 12–15 K (Section 1.17.4.3). Energetic calculations suggest that **64** forms through insertion of intermediate silylene $:\text{Si}(\text{OCH}_3)(\text{H})$ into the C-H bond of the methyl group (B3LYP/6-311G(d,p) level) <2000JOM248>. Both Si-C-O and Si-C-S rings appear plausible intermediates in the complex reaction between silaformyl anion HSiO^- and CS_2 . While none are global minima (which appears to be acyclic $\text{SSiOCH}(\text{S})^-$), some exhibit barriers to rearrangement sufficiently large to suggest they might be observable <2000PCA5799>.

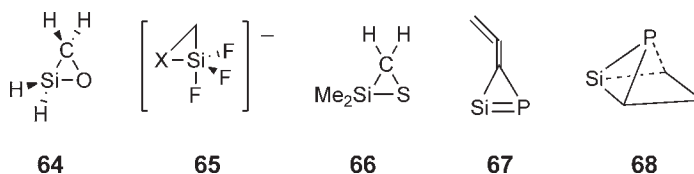
3-Methyl-substituted oxasiliranes were examined in studies of gas-phase reactions between silylene and carbonyl-containing molecules formaldehyde, acetaldehyde, and acetone. The rings lie $72\text{--}75 \text{ kJ mol}^{-1}$ higher in energy than global minima silaoxetanes, and $59\text{--}63 \text{ kJ mol}^{-1}$ higher than 2-siloxyalkenes, but are separated from both by barriers in excess of 100 kJ mol^{-1} (G2 or G2Q approaches). RRKM calculations were used to model the pressure dependence of the reactions; the computational data as a set match experiments well <1999PCA4457, 2001PCP2343>.

Rings containing hypervalent silicon have been studied as well. An $\text{H}_3\text{Si}-\text{C}-\text{O}$ ring was suggested as an intermediate for the reverse Brook rearrangement of α -siloxyalkyl anions (Section 1.17.2.2) <1999T12751>. Anionic Si-C-N and Si-C-O rings containing trigonal bipyramidal silicon were examined as a complement to the syntheses of thiasiliranides (Section 1.17.4.6). Isomers **65** with electronegative NH or O in the equatorial plane and ring carbon axial lie ca. 12.5 kJ mol^{-1} below those with ring carbon equatorial and heteroatom axial. This results from better interaction of N/O lone pairs with Si-F σ^* -orbitals when the heteroatom is equatorial. Isomers with both ring atoms equatorial are transition states corresponding to barriers of $84\text{--}126 \text{ kJ mol}^{-1}$ (MP2/6-311+G(d,p) level) <2001JPC(A)10711>.

Dimerization of dimethylthiasilirane **66** is predicted to be exothermic by 163 kJ mol^{-1} (PBEPBE/ca. triple- ζ level) This apparently stems from considerable ring strain, as denoted by the unusually small Si-C-S angle of 69.1° <2001RCB771>.

Several minima of stoichiometry SiC_2N contain Si–C–N rings. The lowest-energy isomer contains a C-bridged ring, and lies 117 kJ mol^{-1} above ground-state linear ${}^2\text{SiCCN}$. However, its barrier to rearrangement to the linear isomer is quite large (130 kJ mol^{-1}), indicating it could be observed if prepared <2001JPC5896>.

For formula SiC_3P , two spin doublet structures **67** and **68** are viewed as kinetically stable minima. They lie 152 and 238 kJ mol^{-1} above the global minimum, linear ${}^2\text{SiCCCP}$, but exhibit barriers to rearrangement in excess of 42 kJ mol^{-1} (CCSD(T)/6-311G(2d)/B3LYP/6-311G(d) level), and thus might be observed at low temperatures (and/or in interstellar space). Pseudo-square-pyramidal **68** is plausibly stabilized by several resonance structures; the authors suggest one containing a vinyl radical contributes most to the overall bonding picture <2004JPC11828>.



In stark contrast to much of the above, for formula SiC_2S , all singlet or triplet SiCS rings that are minima are of very high energy and sit in shallow potential energy wells, indicating they are unlikely to be observed <2003JPC6859>. The same holds for SiCN rings in SiC_3N <2004JPC6919>.

1.17.4.3 Experimental Structural Methods

Several single crystal X-ray diffraction studies of dimetalliranes have appeared; selected data appear in **Table 4**. Enough disiliranes have been so characterized to allow trends to be discerned. The Si–Si and Si–C bond lengths fall into two classes, depending upon the hybridization of the ring carbon. When this carbon is sp^3 -hybridized, the bond lengths are short, with the Si–Si length exceptionally short compared to values (ca. 2.4 Å) found in cyclotrisilyl compounds and to acyclic Si–Si bond lengths of $2.34\text{--}2.35\text{ Å}$. When the ring carbon is sp^2 -hybridized, the Si–Si bond definitely lengthens and the Si–C bonds appear to. The Ge–Ge and Sn–Sn bonds in their respective rings are also exceptionally short; typical values are 2.55 and 2.44 Å for Ge, and 2.94 and 2.84 Å for Sn (cyclotrimetallanes and acyclics, respectively). In both cases, the M–C bond distances fall into expected ranges.

Table 4 Selected bond distances (Å) and angles (deg) from single crystal X-ray diffraction studies of dimetalliranes. In several cases related quantities were averaged

	$M\text{--}M$	$M\text{--}C$	$\angle M\text{--}C\text{--}M$	Σ Angles around M	Reference
69a	2.272(2)	1.887(6)	74.1(2)		1983JA7776
70	2.275(1)	1.879(3) (Si_1) 1.980(3) (Si_2)	72.2(1)	357.76 354.99	2004OM2848

(Continued)

Table 4 (Continued)

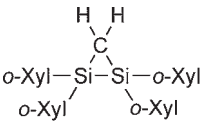
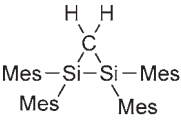
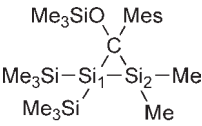
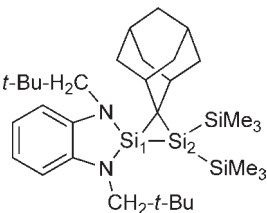
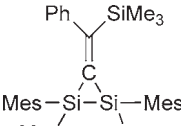
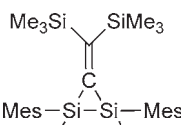
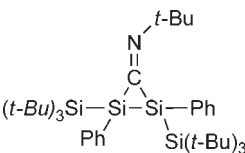
	<i>M–M</i>	<i>M–C</i>	<i>∠M–C–M</i>	<i>Σ Angles around M</i>	<i>Reference</i>
71a	2.327(2)	1.907(4)	75.2(2)	355.1	1983OM174
72	2.328(3)	1.924(7)	74.5(2)	357.5 354.9	1987CC1605
73a	2.379(1)	1.970(1) 1.984(3)	74.3(1)	356.9 358.2	1990OM2061
74	2.777(2)	2.203(12)	78.2(4)	353.1	2004JA11792

Comparing homologues, one sees that the M–C–M angle appears to increase for M = Si–Sn, as one expects since the M–M bond lengthens, but the change is modest. The sum of the angles around the metal atoms is very close to 360°, even for M = Si. As mentioned in Section 1.17.4.2, this is typically ascribed to a bonding situation represented by a Dewar–Chatt–Duncanson methylene–dimetallene interaction, with the near-planarity of metal atom and substituents suggesting a weak interaction between the fragments. Curiously, while the data are too limited to confirm this, the metal atoms appear to be *more* pyramidal for Sn than for Si, contrary to expectation.

All isolable dimetalliranes have been characterized by NMR spectroscopies. In general, ring carbons resonate in expected ranges in ^{13}C NMR spectra. For instance, the sp^3 -hybridized ring carbons in **69a/b** and **70** appear at δ 6.1 and 31.5, respectively, while the sp^2 -hybridized ring carbons in **71a/b** and **72** resonate at δ 150–170 (since these do not experience nuclear Overhauser effect (NOE) upon ^1H decoupling, they are difficult to distinguish from the other olefinic carbons and so are typically not assigned to a particular peak).

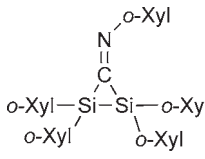
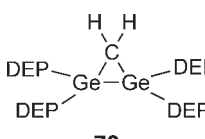
^{29}Si NMR spectroscopy has been used as a diagnostic for disilirane rings, although some anomalous assignments have been made. Collected data appear in Table 5. As one can see, ring Si atoms generally resonate sizably upfield of TMS. However, Si_2 in **70** does not, even though its substitution pattern is similar to that of Si_1 in **75**, which shows a more typical shift. That this Si exhibits a markedly long Si–C bond distance may indicate that it has unusual electronic characteristics. The authors suggest it may be exceptionally influenced by the N_2 substitution on Si_1 . The resonance for the silicons in **72** is exceptionally anomalous, perhaps because of the imide group. These observations dictate caution when assigning resonances in disiliranes with unusual substituents.

Table 5 ^{29}Si NMR chemical shifts (ppm) of ring silicon atoms in disiliranes (with respect to SiMe_4), and values of λ_{max} (nm) and $\log \varepsilon$ (ε in $\text{M}^{-1} \text{cm}^{-1}$) for dimetalliranes

	$\delta^{29}\text{Si}$	λ_{max} ($\log \varepsilon$)	Reference
 69a		302 (4.11)	1983JA7776
 69b	−65.97		1993OM1514
 75	−118.5 (Si_1), −35.6 (Si_2)		1985OM1487
 70	−86.9 (Si_1), 0.9 (Si_2)		2004OM2848
 71a	−56.0, −63.3	382 (3.75)	1985JA7706
 71b	−48.4	415 (3.75)	1985JA7706
 76	−60.88		2002CEJ2730

(Continued)

Table 5 (Continued)

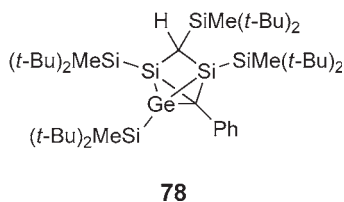
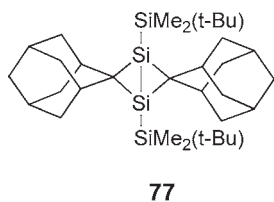
	$\delta^{29}\text{Si}$	$\lambda_{\text{max}} (\log \epsilon)$	Reference
 72	+37.2	510 (2.25)	1987CC1605
 73a		300 (4.24)	1990OM2061

Distannirane **74** exhibits a resonance at -365.3 ppm in the ^{119}Sn NMR spectrum, with $J(^{119}\text{Sn}-^{117}\text{Sn}) = 4674$ Hz <2004JA11792>.

Owing to their use in photochemical M–M bond cleavage reactions (Section 1.17.4.5), absorption spectra of several dimetalliranes have been collected. Values of λ_{max} and $\log \epsilon$ appear in Table 5. The compounds display a range of absorption maxima, with those containing olefinic/imidic moieties exhibiting red shifts (fluorenyl-containing distannirane **39** is described as red as well <2004JA11792>). It seems likely that the transition associated with these is largely localized in the double-bonded fragment. In keeping with this, photochemistry has been reported only for dimetalliranes containing sp^3 -hybridized carbon, implying that molecules with unsaturated ring carbons do not readily distribute photoenergy into the ring.

As part of their studies of reactions between fullerenes and dimetalliranes (Section 1.17.4.5), Ando *et al.* determined oxidation potentials for disilirane **34b** (+0.81 V vs. saturated calomel electrode (SCE)) <1993OM1514> and digermirane **38a** (0.72 V vs. SCE) <1990OM2061>.

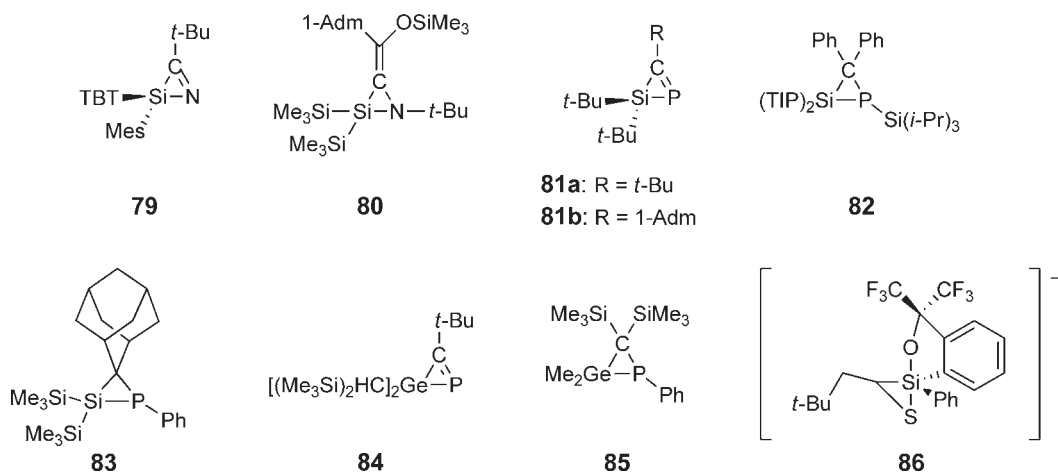
Two dimetalliranes containing fused dimetallirane rings have been reported and characterized crystallographically. Di(disilirane) **77** shows a rather long Si–Si distance (2.412(1) Å), and so was described as a long-bridge isomer. The planes of the fused rings form an angle of $141.1(1)^\circ$. The ring silicons exhibit the ^{29}Si NMR resonance at -104.2 ppm, in keeping with the values in Table 5 but generally farther upfield. Its absorption maximum of 420 nm ($\epsilon = 6500$) is sizably red-shifted compared to other disiliranes containing sp^3 carbon atoms, a result consistent with theory <2001JA12730>. Cage compound **78** exhibits a very long Ge–C bridge bond (2.242(3) Å), and the carbon resonates at 60.8 ppm in the ^{13}C NMR spectrum. Both features were interpreted to mean that the Ge–C interaction has considerable singlet biradical character. The ring silicon atoms resonate at -28.0 ppm, upfield as expected, but less so than is typical <2002JA9962>.



Several compounds containing carbon–silicon/germanium–group 15 atom rings have been reported. The only known azasilirene, **79** was characterized crystallographically. Though afflicted with disorder, the structural data include distances consistent with Si–N and Si–C single bonds, and a C=N bond. As in the disiliranes, the Si exhibits an upfield ^{29}Si chemical shift (-107 ppm); this suggests that observation of an upfield ^{29}Si NMR shift is diagnostic for

a three-membered ring containing silicon, and most workers have identified heterosilirenes and siliranes on this basis. The ^{13}C chemical shift (224 ppm) is consistent with the presence of a $\text{C}=\text{N}$ bond <2002SIC313>.

Azasilirane **80** was characterized by a single crystal X-ray diffraction study. It shows long $\text{Si}-\text{C}$ (1.830(15) Å) and $\text{Si}-\text{N}$ (1.764(13) Å) bonds, and in contrast to the disiliranes studied above, the $\text{Si}-\text{C}-\text{N}$ angle is quite small at $64.3(8)^\circ$. **80** and three analogues differing in the substituents at the ring nitrogen or the olefinic carbon show resonances in their ^{29}Si NMR spectra at -89.5 ± 0.5 ppm for the ring silicon <1988OM2245>. Phosphasilirenes **81** exhibit ^{31}P NMR resonances at 273–274 ppm, consistent with the presence of $\text{P}=\text{C}$ bonds. (The phosphorus homologue of **79** shows this resonance at 287 ppm <2002SIC313>.) Phosphasilirene **81b** was characterized crystallographically as its $\text{W}(\text{CO})_5$ adduct to confirm the ring structure <1987AGE776>. Phosphasilirane **82** was not isolated, but identified by ^{29}Si NMR spectroscopy (-54.4 ppm, $J_{\text{P,Si}} = 49.7$ Hz) <1992AGE751>. Another phosphasilirane, **83**, was characterized crystallographically as the $\text{W}(\text{CO})_5$ adduct to confirm the three-membered ring structure. This complex exhibits a resonance in the ^{29}Si NMR spectrum at -97.9 ppm ($J_{\text{SiP}} = 22.9$ Hz), which appears to support the characterization of **82** given the substituent differences <2000AGE4127>. Phosphagermirene **84** was characterized by single crystal X-ray diffraction <1988CC753>. The $\text{P}-\text{C}$ bond distance is consistent with the presence of a double bond; the presence of two resonances in the ^1H NMR spectrum for the $\text{CH}(\text{SiMe}_3)_2$ groups indicates diastereotopy. Phosphagermirene **85** was too unstable to isolate, but was characterized by ^{13}C (23.0 ppm, $J_{\text{PC}} = 68.9$ Hz for ring carbon) and ^{31}P NMR spectroscopies (-137.1 ppm) <2002RCB1568>. An arasilirane was characterized solely by high-resolution mass spectrometry, as it was thermally unstable and difficult to separate from by-products <1996OM1845>.

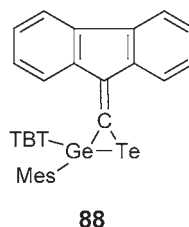
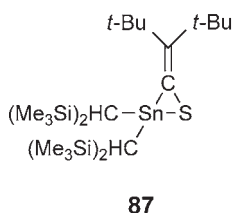


Seventeen IR vibrational bands (Ar matrix, 12–15 K) were observed and assigned to oxasiliranylidene **60** on the basis of their similarity to calculated values (Section 1.17.4.2). Isotopic shifts were measured for the $^2\text{H}_2$ homologue and were consistent with the assignments <1999OM2155>. IR vibrational bands at 1024, 942, 826, 763, and 729 cm^{-1} were assigned to oxasilirane **64** on the basis of their similarity to calculated values (Section 1.17.4.2). The methyl-substituted version showed bands at 2110, 1006, and 935 cm^{-1} (Ar matrix, 12–15 K) <2000JOM248>.

The crystal structure of trigonal bipyramidal thiasiliranide **86** shows the two most electronegative atoms, O and S, in axial positions, as one would expect from theory. The $\text{Si}-\text{S}$ bond is fairly long at $2.569(9)$ Å, and the $\text{Si}-\text{C}-\text{S}$ angle large at $87(1)^\circ$. There appears to be a substantial interaction between the sulfur and the potassium cation, which may contribute to the long $\text{Si}-\text{S}$ bond observed. The anion as formed is a mixture of diastereomers, so two resonances appear in the ^{29}Si NMR spectrum, at -61.2 and -69.9 ppm <2002JOM504, 2003BCJ471>. The upfield ^{29}Si chemical shift appears diagnostic for thiasiliranes, and has been used to identify such a ring fused to a naphthalene fragment (-67.6 ppm) <1999JA11336>.

The crystal structure of thiaastannirane **87** shows no unusual features save that the $\text{C}-\text{Sn}-\text{S}$ angle is exceptionally acute at $45.7(4)^\circ$. The NMR spectra demonstrate that **87** partially dissociates into its stannylene and thiaallene components in solution at room temperature, but the equilibrium is such that resonances can be assigned to **87**. The ring Sn and C atoms resonate at -365 and 137 or 149 ppm in the ^{119}Sn and ^{13}C NMR spectra, respectively; variable-temperature ^1H NMR studies gave $\Delta H^\ddagger = 81.6\text{ kJ mol}^{-1}$ and $\Delta S^\ddagger = 197\text{ J mol}^{-1}\text{ K}^{-1}$. That **87** is colorless supports the idea noted above that the fluorenyl group in distannirane **74** is the reason the latter is red <1993OM4>.

The crystal structure of the remarkable telluragermirane **88** shows a large Ge–C–Te angle of 80.6(7)° and a nearly planar environment around the Ge atom, supporting viewing the ring formally as a complex between a carbene and R₂Ge=Te. The compound exhibits a resonance at 13.8 ppm in the ¹²⁵Te NMR spectrum. The sulfur and selenium analogues were reported; the Se analogue has a resonance at 127.6 ppm in the ⁷⁷Se NMR spectrum. Although absorption spectra were not reported, the colors are consistent with charge-transfer bands in that they change from yellow (S) to pale orange (Se) to orange (Te) <1997OM5127>.



1.17.4.4 Thermodynamic Aspects

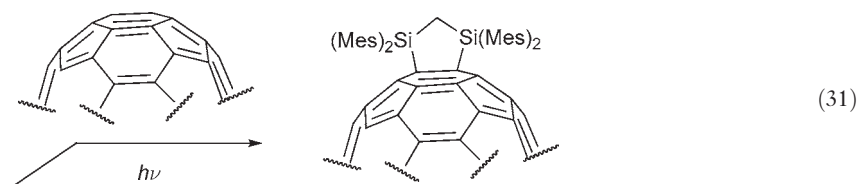
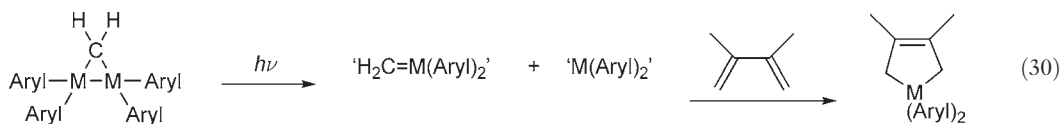
Nearly all the isolable compounds mentioned in Section 1.17.4.3 are sufficiently stable in the gas phase for their mass spectra to be obtained; azasilirane **80** sublimes intact at 70 °C (0.1 mm) <1988OM2245>. While they tend to decompose upon excessive heating, some exhibit reversible melting points, including disiliranes **70** (139–141 °C) and **72** (171–173 °C), 1,1,2,2-tetrakis(TIP)digermirane **73b** (the TIP analogue of **73a**, 202–203 °C) <1990OM2061>, and even distannirane **74** (185 °C) <2004JA11792> and azasilirane **80** (74 °C) (TIP = 2,4,6-triisopropylphenyl). That **70** and **73b** melt without decomposing indicates that the exo-olefinic function is not required to stabilize dimetallirane rings to decomposition pathways, but it clearly imparts additional stability as denoted by the number of stable compounds containing one.

While most dimetalliranes are crystallized from solution, some are stable to chromatographic methods, and so are isolated this way. Examples include disiliranes **69a** and **69b**, and digermirane **73b**. As solids, they tend to be air stable for short periods, but some hydrolyze slowly. That disiliranes and digermiranes undergo photoreactions with oxygen (Section 1.17.4.5) demands long-term storage in the dark if air is present. Azasilirane **80**, for comparison, decomposes rapidly in air. Phosphasilirenes **81** survive chromatography, although **81a** is thermally unstable. Both are sufficiently stable to be characterized by mass spectrometry.

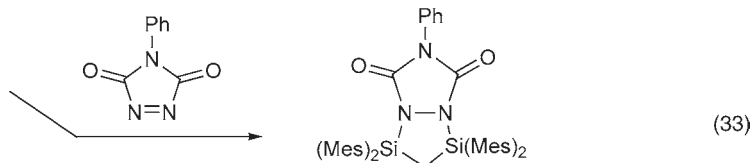
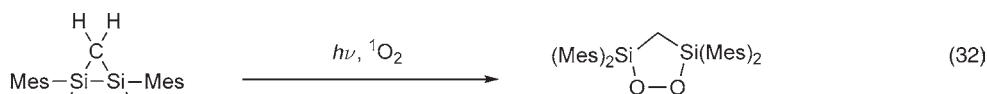
Oxa- and thiasiliranes oligomerize or decompose at ambient temperatures, and so have not been well characterized thermodynamically. Thiastannirane **87** decomposes at 70 °C, but can be chromatographed on Florisil under inert atmosphere <1993OM4>. The sulfur and selenium analogues of telluragermirane **88** are stable above 200 °C, while **88** itself decomposes at this temperature. The telluragermirane is however stable to chromatography, and to air, light, and moisture in the solid state <1997OM5127>.

1.17.4.5 Reactivity of Nonconjugated Rings

Initial photoreactions of **69a** indicated that :Si(*o*-Xyl)₂ and H₂C=Si(*o*-Xyl)₂ formed, and these underwent typical cyclization and insertion reactions, with or without trapping agents <1983JA7776>. Later experiments showed digermiranes behave similarly <1990OM2061>. One general reaction is that shown in Equation (30). More controlled photoreactivity has been exploited through studies of photochemical reactions between disiliranes or digermiranes and various fullerenes and metal–fullerene complexes. Si–Si/Ge–Ge bond scission occurs, and the putative diradicals cyclize with fullerene double bonds, giving fused five-membered rings on the fullerene surface (Equation 31). In several cases, the exact position of the ring is unknown, <2002MI(12)324>, but combining spectroscopic and computational tools can help by providing ‘best guesses’ <2000OL2671>. Reactivities of disila- and digermiranes toward fullerenes/metal–fullerenes correlate with the reduction potential of the fullerenes, suggesting electron transfer from the dimetallirane as a first step in the process. An excellent overview of aspects of this area is <2000JOM74>. Heterometalliranes and metalliranes can also act as sources of metalylenes, although this is less well studied and apparently less common; an example appears in <2002SIC313>.

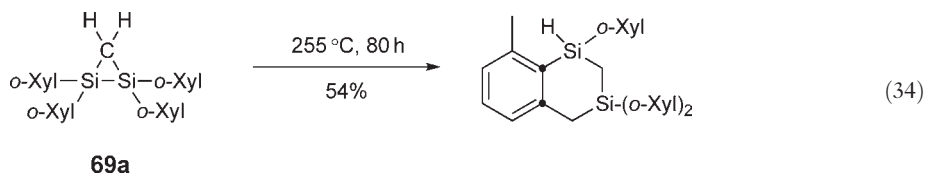


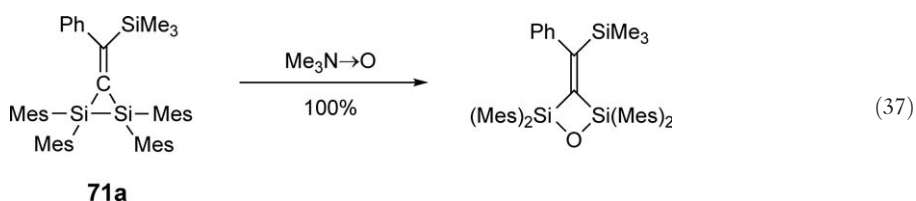
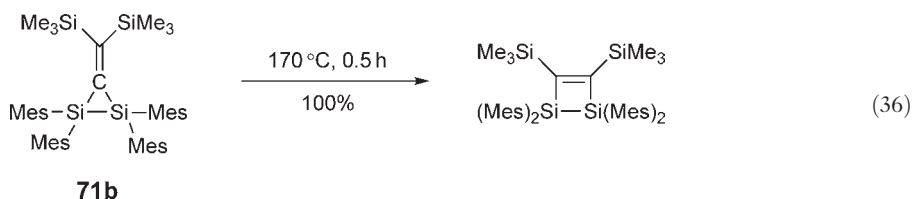
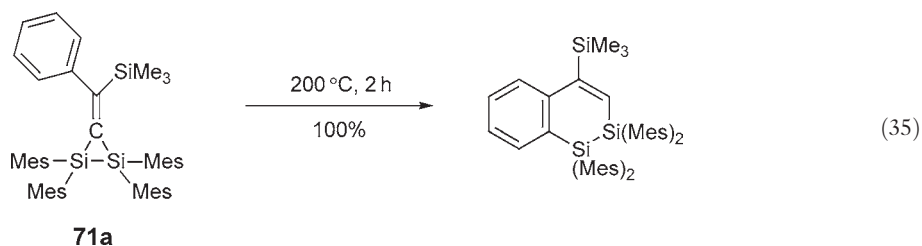
Mesityl-substituted disilirane **69b** reacts with oxygen under irradiation to form a five-membered peroxo ring (Equation 32) <1989TL6705>. Careful studies, particularly the use of quenching agents, determined that this process involves formation of $^1\text{O}_2$ <1990JA7804, 1993OM1514>. The computational studies mentioned above suggest this reagent inserts one oxygen into the Si–Si bond, and then the second oxygen inserts into an Si–O bond in a second step. This mechanism is supported by the facts that: (1) in the presence of sulfoxides, the four-membered ring $\text{Mes}_2\text{SiCH}_2\text{SiMes}_2\text{O}$ also forms; (2) when stereoisomeric oxodisilanes undergo the same reaction, they form the analogous trioxodisila rings stereospecifically; and (3) when **69b** reacted with the triazoline dione shown to form a bicyclic in 38% isolated yield (Equation 33), an intermediate with ^{13}C NMR resonances consistent with its characterization as an azetidinium imide was observed at low temperature <1991JA6286>. Oxidation of **69b** to the four- and/or five-membered rings occurs through thermal reaction with organic peroxides as well (Scheme 3) <1993OM1514>.



Scheme 3

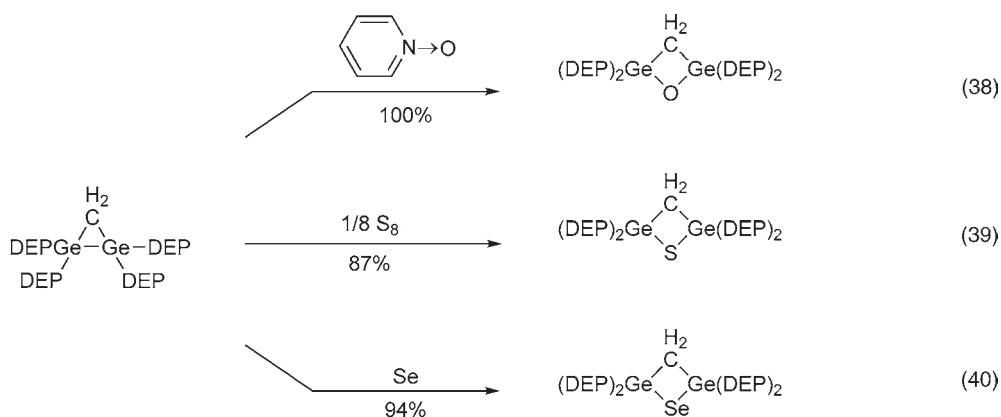
The first thermal reaction of a dimetallirane involved pyrolysis of **69a** in C_6D_6 ($255 \pm 5^\circ\text{C}$, sealed tube). This resulted in the disilatetralin product shown (Equation 34), arising formally from ring opening, hydride transfer from a xylyl methyl group to silicon, and silicon–carbon bond formation <1983JA7776>. Thermolysis of **71a**, on the other hand, led to activation of the olefin-bound phenyl group rather than the silicon-bound mesityl groups (Equation 35); the product forms quantitatively <1985JA7706>. Both reactions are included in this section because the authors suggest ring C–Si bond breaking precedes C–H activation; however, they represent reactions of substituents and so are also referred to in Sections 1.17.4.6 and 1.17.4.7. Interestingly, when the phenyl substituent of **71a** is replaced by trimethylsilyl in **71b**, thermolysis of the latter gives the four-membered ring product shown in Equation (36) <1985JA7706>.





Some of the reactions between dimetalliranes and fullerenes/metal–fullerenes occur thermally, again depending upon the relationship between oxidation/reduction potential between the reactants <2002MI(12)324>, <2000JOM74>.

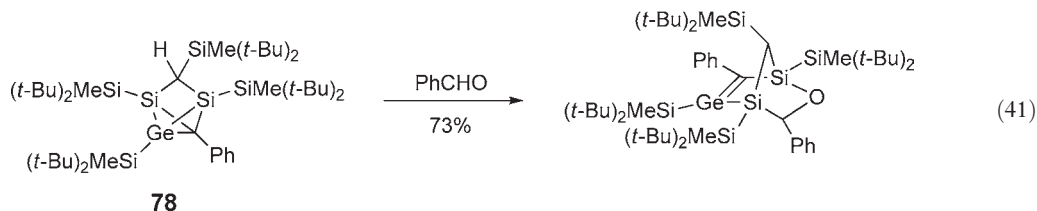
As noted above, singlet oxygen reacts with disiliranes to form larger rings. This propensity to react with chalcogenide sources has often been exploited, as shown in Equation (37) and Scheme 4 (Equations 38–40) <1985JA7706, 1990OM2061>. The digermirane reactions all provide exceptionally high yields (87–100%).



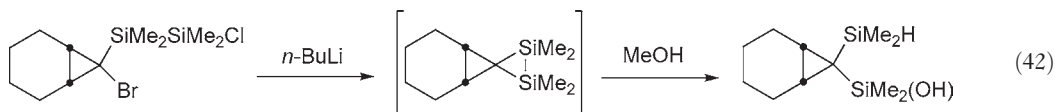
Scheme 4

Ring expansion also occurs when digermirane **73a** reacts with alkynes in the presence of Pd and Ni catalysts to form 1,3-digermacyclopentenes in fair yield. Mechanistic studies suggest the role of the catalyst is to break the Ge–Ge bond <1989OM2286>.

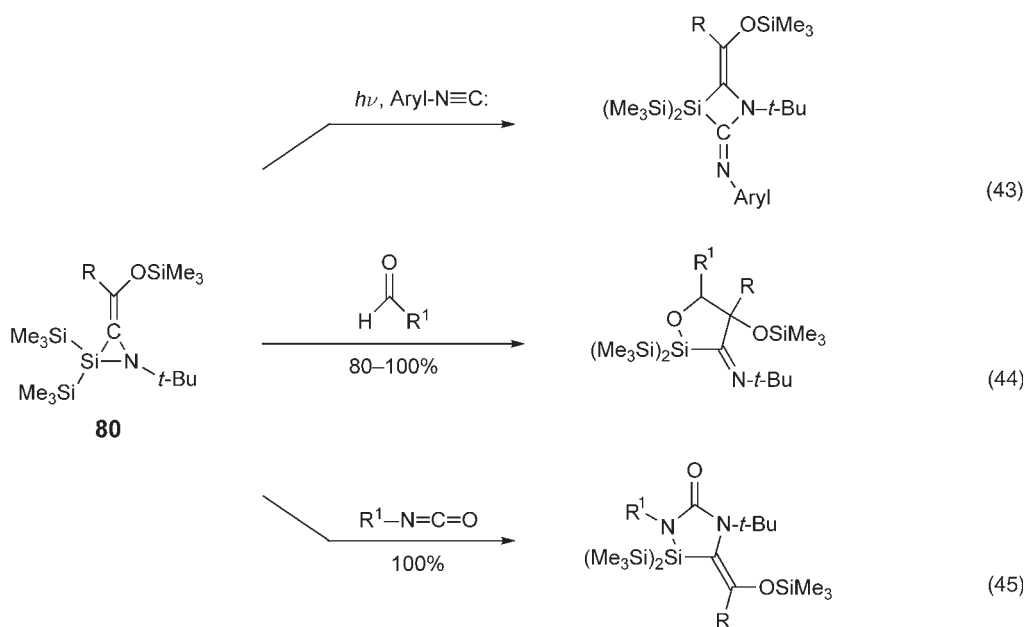
Cage compound **78** reacts with PhCHO to form a product with a norbornene skeleton, as shown in Equation (41) <2002JA9962>. It is notable that the extremely long Ge–C bond in **78** is maintained in the product.



In addition to the above, disiliranes and digermiranes are implicated in several ring opening processes from which they were not isolated. The first report of the preparation of a disilirane actually resulted in isolation of an α,α -disilylcompound (Equation 42) <1976JOMC21>. The product distribution from pyrolysis of Me₃SiSiH₂SiMe₃ with 1,3-butadiene strongly suggests the intermediacy of disiliranes that interconvert through Si–Si bond breaking/ring opening <1986OM698>.



In a 12 K argon matrix, photolysis ($\lambda > 395$ nm) of cyclic HCNSi leads to formation of acyclic isocyanosilylene HSiNC, identified by its vibrational spectrum <1998EJO1307>. Ring-opening reactions have also been reported for azasiliranes (Scheme 5). When the substrate is an isocyanide, the products formed are analogous to those in Equations (37)–(40), with specific Si–N bond breaking opening the ring (Equation 43) <1989OM850>. However, when the substrate is either an aldehyde or nitrosobenzene, five-membered rings with exocyclic imide groups form, indicating rapid olefin–imide electron reorganization and Si–C bond rotation in an intermediate (Equation 44) <1993OM529, 2003CJC1164>. When the substrate is an isocyanate, five-membered rings with exo-olefinic groups form; the reaction is analogous to that in Equation (43) but is a [3+2] rather than a [3+1] process (Equation 45) <1993OM529>.

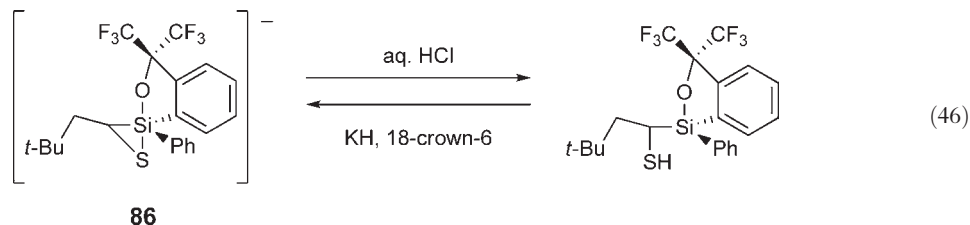


Scheme 5

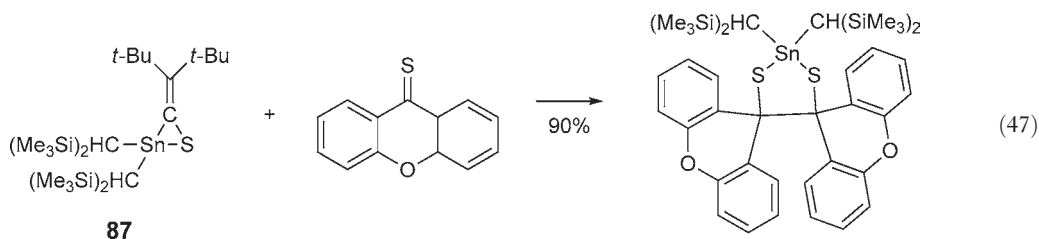
Azagermiranes, though not isolated, appear to undergo Ge–N bond scission/ring-opening processes easily, leading to a variety of cyclic and acyclic products <1979JOM43>.

Photolysis of matrix-isolated oxasiliranylidene **60** with 366 nm light causes ring opening and hydrogen transfer, forming dative complex $\text{H}_2\text{Si}\cdot\text{CO}$. However, use of higher-energy 313 nm light causes insertion of Si into the C–O bond, giving $\text{H}_2\text{C}=\text{Si}=\text{O}$ <1999OM2155>.

Thiasiliranide **86** reacts with water to form 3,3-dimethylbutanethiol and unidentified silicon products. However, it reacts with aqueous HCl to form a silyl thiol that retains the ring atoms, though not the ring (Equation 46). This reagent is the starting material for the preparation of **86** (Section 1.17.4.8) <2002JOM504>.



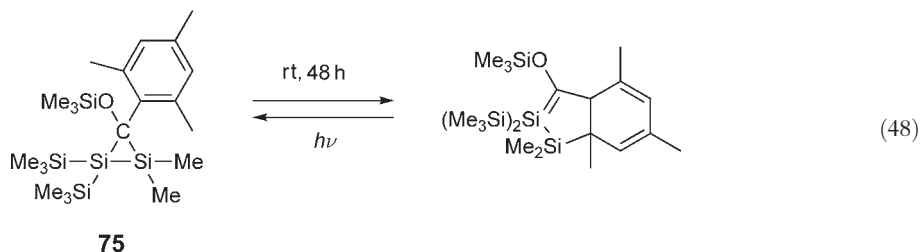
As noted in Section 1.17.4.3, thiastannirane **87** partially dissociates to its stannylene and thiaallene components in solution at room temperature. **87** reacts with thioketones with apparent displacement of the thiaallene and formation of a new thiastannirane/stannylene–thioketone equilibrium. This system then reacts with more thioketone to give five-membered ring products (Equation 47) <1993OM4>.



Similarly, the tellurium atom in **88** reacts with $\text{P}(\text{NMe}_2)_3$ to generate the germaallene theorized to be an intermediate in its preparation (Equation 58). This allowed isolation of the germaallene <1998CL811>.

1.17.4.6 Reactivity of Substituents Attached to Ring Carbon Atoms

Relatively few examples of the title reaction type exist, since employing unreactive substituents is a design methodology for these systems. The reaction in Equation (35) involves C–H activation of an exo-olefinic phenyl substituent, while that in Equation (44) involves cyclization using the exo-olefinic carbon itself. Disiliranide **75** undergoes silylation of the carbon-bound mesityl group with concomitant ring Si–C bond cleavage to form the bicyclic shown at room temperature in the dark over 2 days (Equation 48) <1985OM1487>.



When heated at 110 °C for 48 h, phosphasilirane **82** undergoes metallation of a phenyl ring, hydrogen transfer, and C–Si bond cleavage to form a five-membered ring product <1992AGE751>.

1.17.4.7 Reactivity of Substituents Attached to Ring Heteroatoms

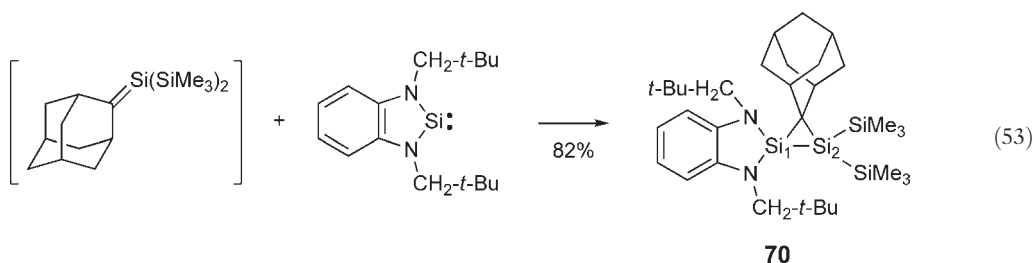
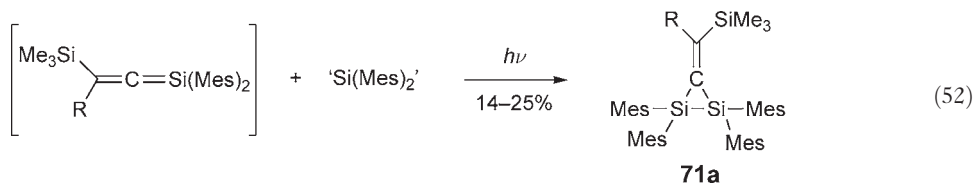
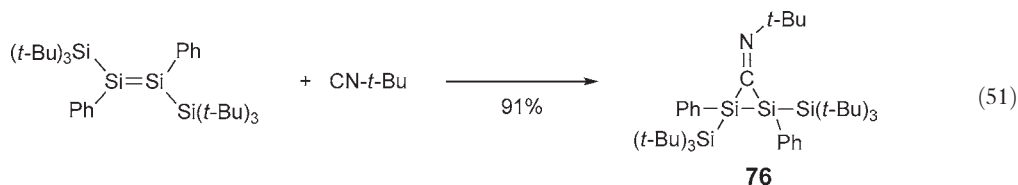
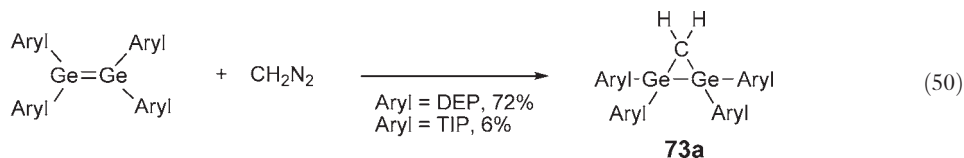
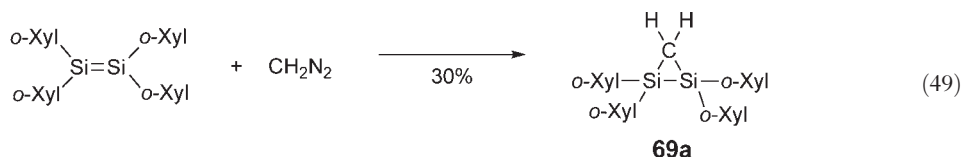
As stated in Section 1.17.4.6, substituents on the heteroatoms are typically chosen specifically to be unreactive, so few examples of this category exist. That said, as noted above, Equation (34) involves C–H activation of a silicon-bound

o-xyl substituent <1983JA7776>. Processes within the framework of pyrolysis of $\text{Me}_3\text{SiSiH}_2\text{SiMe}_3$ involve transfer of hydrogen or methyl groups from one silicon to another in putative disilirane rearrangements <1986OM698>.

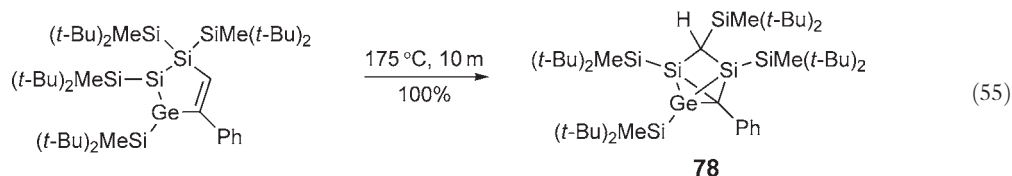
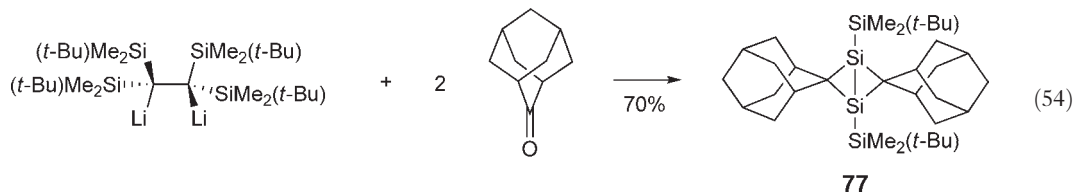
While not technically the reaction of a substituent, lone pairs on heteroatoms can act as Lewis bases toward Lewis acids. Two examples among several are the coordination of phosphasiliranes and phosphasilirenes to $\text{W}(\text{CO})_5$, employed both to stabilize the ring thermally and to allow formation of crystalline materials <1987AGE776, 2000AGE4127>.

1.17.4.8 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

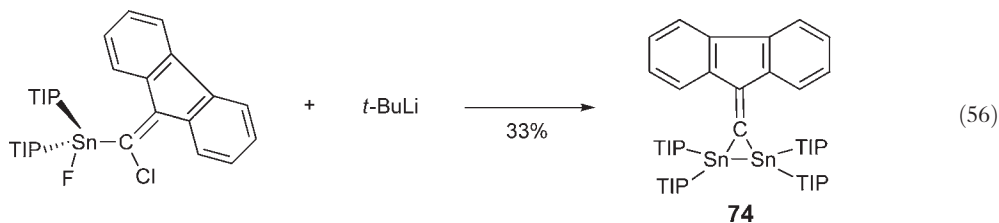
By far the most common preparation of metalliranes and dimetalliranes involves [2+1] cyclization. The two-atom component can be a metallene, a dimetallene, or a metallaallene; the one-atom component can be a carbene equivalent, either a diazo compound or an isocyanide, or a metalylene. It should be noted that the dimetallenes used are typically prepared *in situ* through photodegradation of a trimetallirane (Equations 49–53); thus these preparations also fit into Section 1.17.4.9. Examples include Equations (49), (50), and (52) <1983JA7776, 1990OM2061, 2002CEJ2730, 1985JA7706>. Yields vary wildly, with no obvious pattern, although it appears that having larger substituents on the dimetallene tends to lower the yield of dimetallirane. For instance, in Equation (50), the digermirane **73a** with 2,6-diethylphenyl (DEP) substituents forms in 72% yield, while **73b** with bulkier TIP substituents forms in only 6% yield. In variations on the theme, disiliranes were prepared by treating silylenes with transient silenes (e.g., Equation (53) for **70**) <1985OM1487, 2004OM2848>.



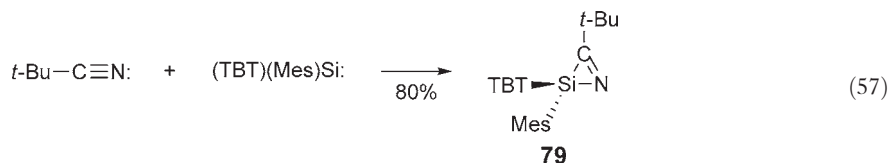
An alternative approach exploited in the preparation of **77** is Equation (54), which takes advantage of the large Si–O bond energy and probably does not involve a carbene or silylene intermediate <2001JA12730>. Equation (55) involves a remarkable rearrangement of the neat starting material that takes place rapidly at 175 °C in a sealed tube, forming cage compound **78** <2002JA9962>.



Distannirane **74**, however, containing a stabilizing fluorenylvinylidene function, was prepared by addition of *t*-BuLi to a halotin vinyl halide as shown (Equation 56). The authors posit a mechanism involving Li–Cl exchange, followed by loss of LiF to form a stannaallene, which in turn provides a stannylene fragment that attacks other stannaallenes to form **74**; in other words, the mechanism mimics that of Equation (52). This view is supported by the reaction yield of 33% (i.e., less than half) and that only 1 equiv of *t*-BuLi is required <2004JA11792>. The di-dehalogenation reaction itself recalls the first report of the preparation of a disilirane, which was not isolated but identified by implication <1976JOMC21>.



In a 12 K argon matrix, photolysis of acyclic HCNSi with light of $\lambda > 700$ nm leads to formation of cyclic HCNSi, identified by its vibrational spectrum <1998EJO1307>. Azasilirene **79** and its phosphasilirene homologue were prepared using Equation (57), a special heteroatom-containing case of Equations (52) and (53) <2002SIC313>. Azasilirane **80** and its analogues were prepared by reactions similar to that in Equation (51), wherein *in situ*-generated silenes $(\text{Me}_3\text{Si})_2\text{Si}=\text{C}(\text{OSiMe}_3)(\text{R})$ ($\text{R} = t\text{-Bu}$ or 1-adamantyl) were treated with *t*-butyl- or isooctylisocyanide <1988OM2245>. Initially formed unstable silacyclopropanimines rearrange rapidly to form the azasiliranes. Equation (57) was used to prepare phosphasilirenes **81**, employing $t\text{-BuC}\equiv\text{P}$ in place of the nitrile <1987AGE776>; phosphagermirene **84** was prepared similarly from isolated $\text{Ge}[\text{CH}(\text{SiMe}_3)_2]$ and $t\text{-BuC}\equiv\text{P}$ <1988CC753>. Equation (53) was used to prepare $\text{W}(\text{CO})_5$ -bound phosphasilirane **83** <2000AGE4127>. Phosphasilirane **82** was prepared by a reaction similar to that in Equation (50), wherein phosphasilene $(\text{TIP})_2\text{Si}=\text{P}-\text{Si}(\text{i-Pr})_3$ was treated with diphenyldiazomethane <1992AGE751>. A similar procedure employing phosphalkene $(\text{Me}_3\text{Si})_2\text{C}=\text{PPh}$ and *in situ*-generated GeMe_2 produced **85** <2002RCB1568>.

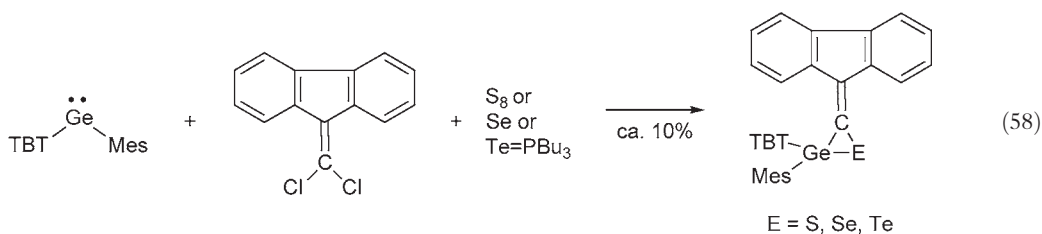


Oxasiliranylidene **60** is apparently formed upon deposition of silicon atoms and formaldehyde in an argon matrix at 12 K. It is also formed upon low-energy irradiation ($\lambda = 435$ nm) of $\text{H}_2\text{C}=\text{Si}=\text{O}$ in the matrix <1999OM2155>.

Oxasilirane **64** and its 1-methyl congener form upon photolysis of the complex $\text{Si-O}(\text{CH}_3)(\text{R})$ ($\text{R} = \text{CH}_3, \text{H}$) in an argon matrix, presumably through a silylene intermediate (Section 1.17.4.2). **64** and its 3-methyl congeners also form through gas-phase reactions analogous to that in Equation (57) between photolytically generated silylene and carbonyl-containing molecules formaldehyde, acetaldehyde, and acetone <1999JPCA4457, 2001PCCP2343>.

As noted in Equation (46), thiasiliranide **86** was prepared through deprotonation of a silyl thiol. The reagent was prepared by sulfuration of an α -silyl anion and quenching with aqueous NH_4Cl <2002JOM504>. Thiastannirane **87** was prepared by a reaction analogous to Equation (52) <1993OM4>.

The chalcogenagermiranes of type **88** were prepared by the unusual reactions in Equation (58). The authors hypothesize a mechanism wherein the germylene inserts into a C–Cl bond of the fluorenyl compound, whereupon another germylene dechlorinates the first to form a germaallene, which is subsequently chalcogenated. The mechanism is consistent with the by-products isolated and the poor yield of ring products <1997OM5127>. The mechanism is further supported by the fact that the isolated germaallene (Section 1.17.4.5) forms chalcogenagermiranes when treated with sulfur or $\text{R}_3\text{P}=\text{Te}$ <1998CL811>. A variation of this reaction employs a bulky thioketene in place of the fluorenyl compound and sulfur <1997H(44)149>.



Ratios of ions observed suggest that electron ionization of $\text{Me}_3\text{SiCH}_2\text{OH}$ may give rise to cyclic oxasila cation **61** in the gas phase <1996JP22389>.

Aza-, oxa-, and thiastanniranes containing exocyclic double bonds were prepared by the approach in Equation (57), using ketenes, ketenimines, thioketenes, and the stannylenes $[\text{2,4,6-(CF}_3)_3\text{C}_6\text{H}_2]_2\text{Sn}$. Yields were below 50%, but this appears to be a remarkably general route to heterostanniranes <1997JFC29>.

1.17.4.9 Ring Syntheses by Transformations of Another Ring

As shown in Equation (48), the bicyclic compound converts to disilirane **75** upon brief photolysis with low-energy light. The authors report this conversion pair may be cycled repeatedly without side reactions <1985OM1487>.

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Biographical Sketch



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